RISK ASSESSMENT OF ACUTE KIDNEY INJURY USING BIOMARKERS OF KIDNEY STRESS
Selection of publications
2021 EDITION

TIMP-2
IGFBP-7
“AKI* occurs in **13.3 million** people every year”¹

“More than **50%** of ICU patients have AKI”²

“Hospital mortality rises from **28%** to **57%** in sepsis patients with AKI”³

“**23.5%** of AKI patients receive RRT** – representing a significant healthcare burden”⁴

Current diagnostic tools are inadequate for assessing the risk of AKI.⁵,⁶

Urinary biomarkers, [TIMP-2•IGFBP-7]***, are produced during kidney stress and may support earlier intervention before significant kidney injury occurs.⁷

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* AKI: Acute Kidney Injury
** RRT: Renal Replacement Therapy
*** TIMP-2•IGFBP-7: Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein-7
Acute kidney injury (AKI) remains a global challenge affecting about 13.3 million people per year and more than 50% of patients in the intensive care unit (ICU).\textsuperscript{6,9} Independent of the etiology, AKI is associated with serious short and long-term complications, including the development of non-renal organ failure, a longer stay in hospital and increased mortality.\textsuperscript{10,11} Survivors of AKI are at risk of premature chronic kidney disease (CKD), cardiovascular morbidity, infections, and reduced survival, even if kidney function initially recovers.\textsuperscript{12} The risk is highest in patients with more severe AKI, a longer duration of AKI, recurrent episodes and pre-existing CKD. Complete and sustained reversal of AKI within 48–72 hours of the onset is associated with better outcomes than persistent AKI. Not surprisingly, the diagnosis of AKI and long-term kidney disease has a significant impact on well-being and quality of life of patients and their families. Finally, the health care costs for managing AKI exceed those of common cancers.\textsuperscript{10,13}

In the absence of a specific therapy for AKI, prevention and mitigation of progression remain high priority to overcome the challenges. For any prevention strategies to be effective, high-risk patients need to be identified before they are exposed to potentially nephrotoxic insults, and \textbf{AKI needs to be diagnosed as early as possible}, ideally before any structural damage or functional impairment has occurred. There is increasing evidence that this is possible, thanks to the discovery of new biomarkers which have not only improved our understanding of AKI but also provided opportunities for effective interventions.

The \textbf{cell cycle arrest markers tissue inhibitor of metalloproteinases–2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7)} have emerged as effective tools to identify kidney stress before serum creatinine rises or urine output declines.\textsuperscript{14} They allow the identification of high-risk surgical patients in whom the application of protocolized goal-directed management can effectively prevent progression to severe AKI.\textsuperscript{15–17} Importantly, both positive and negative biomarker results are valuable and may change processes of care and outcomes, especially if combined with traditional investigations and tested repeatedly.\textsuperscript{18,19}

For years, serum creatinine has been used to optimize drug dosing despite the fact that creatinine concentrations are influenced by age, sex, race, muscle mass, and dietary intake. Data are accumulating for a refined approach to estimate glomerular function, including the utilisation of new biomarkers.\textsuperscript{20}

Based on existing data, a recent international expert committee recommended the \textbf{integration of new AKI biomarkers into routine clinical practice}.\textsuperscript{21} In particular, it was suggested to combine clinical assessment and validated biomarkers in order to improve the diagnostic accuracy of AKI, to identify different sub-types of AKI, to assess AKI severity and to direct clinical management. At last, there is a prospect of better patient care and improved outcomes.
ACUTE KIDNEY INJURY (AKI)

**Acute kidney injury.**
Ronco C, Bellomo R, Kellum JA.  
*Lancet* 2019;394:1949-1964

**Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study.**  
*Intensive Care Medicine* 2015;41:1411–1423

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Meersch M, Volmering S, Zarbock A.  
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**Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment.**  
Peerapornratana S, Manrique-Caballero CL, Gomez H, Kellum JA.  
*Kidney International* 2019;96(5):1083-1099

**URINARY BIOMARKERS [TIMP-2•IGFBP-7]**

**Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury.**  
*Critical Care* 2013;17(1):R25

**Clinical use of [TIMP-2]•[IGFBP-7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel.**  
*Critical Care* 2019;23(1):225

**Serial Urinary Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 and the Prognosis for Acute Kidney Injury over the Course of Critical Illness.**  
*CardioRenal Medicine* 2019;9(6):358-369

**Urinary [TIMP-2] × [IGFBP7] and serum procalcitonin to predict and assess the risk for short-term outcomes in septic and non-septic critically ill patients.**  
*Annals of Intensive Care* 2020;10:46

**Kinetics of Urinary Cell Cycle Arrest Markers for Acute Kidney Injury Following Exposure to Potential Renal Insults.**  
*Critical Care Medicine* 2018;46(3):375-383

**Using urinary biomarkers to reduce acute kidney injury following cardiac surgery.**  
Engelman DT, Crisafi C, Germain M, Greco B, Nathanson BH, Engelman RM, Schwann TA.  
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Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial.


INTENSIVE CARE MEDICINE 2017;43(11):1551-1561

HEALTH ECONOMICS AND OUTCOMES STUDIES

Economic and clinical benefits of early indication of acute kidney injury using a urinary biomarker.


JOURNAL OF MEDICAL ECONOMICS 2019;22(12):1281-1289

Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury.


CRITICAL CARE MEDICINE 2019;47(10):e820-e826

Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study.


ANNALS OF SURGERY 2018;267(6):1013-1020

GUIDELINES AND CONSENSUS STATEMENTS

Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference.

Ostermann M, Zarbock A, Goldstein S.


Nadim M, Forni L, Mehta R.

NATURE REVIEWS NEPHROLOGY 2020;16(12):747-764

ADDITIONAL RECOMMENDED READING

KDIGO Clinical Practice Guideline for Acute Kidney Injury.


KIDNEY INTERNATIONAL SUPPLEMENTS 2012;2:S1–S138


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International Society of Nephrology’s 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology.
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Cell-cycle arrest and acute kidney injury: the light and the dark sides.
Kellum JA, Chawla LS.
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EPILAT-IRA Study: A contribution to the understanding of the epidemiology of acute kidney injury in Latin America.
Lombardi R, Ferreiro A, Claure-Del Granado R, et al., EPILAT-ITA Study Group
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Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery.
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Global epidemiology and outcomes of acute kidney injury.
Hoste EAJ, Kellum JA, Selby NM, et al.
NATURE REVIEWS NEPHROLOGY. 2018;14(10):607-625

Alishaikh HN, Katz NM, Gani F, et al.
ANNALS OF THORACIC SURGERY 2018;105(2):469-475
## ABBREVIATIONS & ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE-I</td>
<td>angiotensin-converting-enzyme inhibitor</td>
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<td>ADQI</td>
<td>Acute Dialysis Quality Initiative</td>
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<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<td>AKI</td>
<td>acute kidney injury</td>
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<td>AKI-EPI</td>
<td>Acute Kidney Injury-Epidemiological Prospective Investigation</td>
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<td>AKIN</td>
<td>Acute Kidney Injury Network</td>
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<td>AKRT</td>
<td>Acute Kidney Response Team</td>
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<td>APACHE</td>
<td>Acute Physiology And Chronic Health Evaluation</td>
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<td>ARB</td>
<td>angiotensin II receptor blocker</td>
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<td>AUC</td>
<td>area under the curve</td>
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<td>BUN</td>
<td>blood urea nitrogen</td>
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<td>CDSS</td>
<td>Computer Decision Support System</td>
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<td>CHF</td>
<td>congestive heart failure</td>
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<td>CI</td>
<td>cardiac index</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CKD</td>
<td>chronic kidney disease</td>
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<td>COPD</td>
<td>chronic obstructive pulmonary disorder</td>
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<td>CSA-AKI</td>
<td>cardiac surgery-associated acute kidney injury</td>
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<tr>
<td>CVP</td>
<td>central venous pressure</td>
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<td>EMR</td>
<td>electronic medical record</td>
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<td>GFR</td>
<td>glomerular filtration rate</td>
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<td>HR</td>
<td>heart rate</td>
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<tr>
<td>HVCC</td>
<td>Heart &amp; Vascular Critical Care (Unit)</td>
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<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>IGFBP</td>
<td>insulin-like growth factor-binding protein</td>
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<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
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<tr>
<td>LOS</td>
<td>length of stay</td>
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<td>MAKE</td>
<td>major adverse kidney events</td>
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<td>NGAL</td>
<td>neutrophil gelatinase-associated lipocalin</td>
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<td>NHS</td>
<td>National Health Service (UK)</td>
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<td>NIS</td>
<td>National Inpatient Sample</td>
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<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>PAD</td>
<td>pulmonary artery diastolic pressure</td>
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<td>PCT</td>
<td>procalcitonin</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>RIFLE</td>
<td>Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease</td>
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<td>RR</td>
<td>relative risk</td>
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<td>RRT</td>
<td>Renal Replacement Therapy</td>
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<td>S-AKI</td>
<td>sepsis-associated acute kidney injury</td>
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<td>SAPS</td>
<td>Simplified Acute Physiology Score</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<td>SCr</td>
<td>serum creatinine</td>
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<td>SOC</td>
<td>standard of care</td>
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<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
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<td>STS</td>
<td>Society of Thoracic Surgeons</td>
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<td>SVO2</td>
<td>mixed venous oxygen saturation</td>
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<tr>
<td>TIMP</td>
<td>tissue inhibitor of metalloproteinases</td>
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<tr>
<td>UB</td>
<td>urinary biomarker</td>
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<td>UO</td>
<td>urine output</td>
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ACUTE KIDNEY INJURY (AKI)
Acute kidney injury (AKI) is a syndrome and an important complication that occurs in approximately 10–15% of patients admitted to hospital. In intensive care, its incidence has been reported in more than 50% of patients. Epidemiology studies show that the incidence of AKI is rising, but this is partly due to improved clinical evaluation and detection methods. General risk factors for AKI include advanced age and underlying chronic kidney disease (CKD). AKI rates and causes are found to be highly variable in different countries depending on specific local resources and healthcare systems. The epidemiology of AKI is shown in Figure 1. A major challenge to AKI diagnosis and treatment is that AKI often coexists with other syndromes, such as sepsis, cardiorenal or hepatorenal syndromes. Early and rapid diagnosis and treatment of AKI is therefore an important part of the overall management of patients with such syndromes.

**DIAGNOSTIC CRITERIA AND CLINICAL JUDGMENT**

Diagnosing AKI requires the clinician to interpret the changes in kidney function in the context of the clinical picture, which is both challenging and complex. International consensus criteria have been developed (ADQI), and later refined (RIFLE, KDIGO) to provide guidance on the diagnosis and staging of AKI, and help standardize the way AKI is reported in clinical trials and epidemiological studies.

**CLINICAL COURSE**

Nearly two-thirds of AKI cases resolve within 7 days. When a case does not resolve or relapse occurs, substantially worse clinical outcomes are expected. Patients with stage 2–3 AKI who resolve within 7 days and remain free of renal dysfunction by hospital discharge have a 1-year survival of >90%. Patients who do not resolve have a 47% hospital mortality rate and, among those who are discharged, 1-year survival is only 77%. It is therefore important to prevent clinical relapse in patients who have recovered.

**DIAGNOSTIC METHODS**

When assessing kidney function, changes in serum creatinine (SCr) or urinary output (UO) currently remain the cornerstone of the diagnostic approach, although neither is sensitive or specific for AKI. The discovery of AKI biomarkers and the implementation of computer decision support systems (CDSS) have substantially improved the diagnostic approach to and treatment of AKI. More recently, a second generation of biomarkers has been developed using modern definitions of AKI. Two markers of cell cycle arrest, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) have been incorporated into the first diagnostic test for critically ill patients with AKI approved by the US FDA (NEPHROCHECK®). Such biomarkers of kidney injury or stress are new tools for risk assessment and could possibly guide therapy.

**PREVENTION AND MANAGEMENT OF AKI**

Treating the cause of AKI and avoiding further kidney damage are essential to AKI prevention. Adequate fluid administration and the avoidance of other nephrotoxic drugs are critical. Additionally, the use of urinary biomarkers for early risk assessment to prevent AKI before kidney damage occurs has led to the implementation of specific biomarker-driven care bundles derived from KDIGO recommendations. And a more structured organization of nephrology rapid response teams has contributed to substantially reducing the occurrence of severe AKI cases and the need for Renal Replacement Therapy (RRT).

**CONCLUSIONS**

The management of patients with AKI has improved alongside improvements in hospital and intensive care quality, supported by more standardized and protocoled management of AKI, the availability of new biomarkers and CDSS, and the demonstrated effectiveness of bundling several interventions on improved patient outcomes.

Near-future challenges include the need for more widespread access to new technologies, and a more sustainable, affordable and effective approach to AKI management in certain geographical areas.
ACUTE KIDNEY INJURY (AKI)

Figure 1. Epidemiology of AKI per hospital admission and corresponding incidence by region
Adapted from Ronco C. et al. Lancet 2019;394:1949-1964

“New biomarkers and advanced diagnostic techniques represent an important advancement in the field, leading to implementation of timely and effective preventive and protective measures.”

KEY FINDINGS

- AKI occurs in approximately 10–15% of patients admitted to hospital. In intensive care, it has been reported in more than 50% of patients.
- International consensus criteria have been developed for the diagnosis and staging of AKI in order to standardize the way AKI is reported in clinical trials and in epidemiological studies.
- The discovery of new AKI biomarkers, informing clinicians much earlier than historical functional markers (e.g. SCr and UO), and the application of computer decision support systems, have the potential to substantially improve the diagnostic approach to and the treatment of AKI.
Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study.


OBJECTIVE
The Acute Kidney Injury-Epidemiological Prospective Investigation (AKI-EPI) was a multicenter international study of the global occurrence and outcomes of AKI in intensive care units (ICUs).

STUDY DESIGN
Investigators at participating ICUs recorded incidence of AKI during the first week of admission in ten or more consecutively admitted ICU patients using a consensus definition of AKI based on the complete KDIGO criteria. A total of 97 ICUs reported on 1,802 patients originating from 33 different countries.

RESULTS
AKI occurred in 57.3% of ICU patients on day one of the ICU stay. KDIGO stage 1 occurred in 18.4% of patients; KDIGO stage 2 in 8.9% and KDIGO stage 3 (the maximum AKI severity) in 30% of patients. Renal Replacement Therapy was used in 13.5% of all patients and 23.5% of patients with AKI during the whole 1-week study period. Increasing AKI severity was associated with increased length of ICU stay, increased length of hospital stay, poorer renal function at time of hospital discharge, and increased mortality. Comorbidities were present in 71.5% of patients, and 37.6% of patients had two or more comorbidities, such as cancer, hypertension, chronic heart failure, cirrhosis, AIDS, COPD, or diabetes mellitus. Sepsis and hypovolemia were the most frequently reported causes of AKI, followed by nephrotoxic drugs. Hypertension, diabetes, cardiovascular cause of admission, neurosurgery, and SAPS 3 score were all associated with AKI.

CONCLUSIONS
Patients with AKI were older, more often Caucasian, more severely ill, and had worse kidney function at baseline and at the time of ICU admission. After adjustments were made for income, healthcare spending and baseline risk factors, rates of AKI and AKI-related mortality were similar worldwide.

“AKI severity was associated with increased mortality, and this association remained after correction for covariates that may explain mortality. After adjusting for baseline risk there was little variation in AKI occurrence and mortality between different regions in the world.”

KEY FINDINGS
- AKI occurred in over half of patients admitted to ICUs.
- Patients who developed AKI had longer lengths of hospital and ICU, and had worse renal outcomes.
- Rates of AKI and mortality for AKI patients were found to be nearly identical between different continents.
Acute kidney injury (AKI) is a sudden incidence of kidney failure or kidney dysfunction that occurs over several hours or days. It is a reversible condition that can occur in individuals with normal kidney function and in those suffering from chronic kidney disease (CKD). Risk factors include older age, CKD, diabetes, chronic obstructive pulmonary disease, heart failure, sepsis, and shock. Surgical and interventional measures, such as major cardiovascular and abdominal surgery, inotropic support, vasopressors, selective renal ischemia, ischemia-reperfusion injury, administration of nephrotoxic drugs and blood transfusion, have been linked to the development of AKI.

AKI is frequently underdiagnosed, and estimates of incidence vary. Incidence may be as high as 22% in hospitalized patients, and up to 60% in ICU patients. AKI is associated with increased in-hospital mortality, and increased AKI severity is associated with a greater risk of death. Patients who survive an episode of AKI have an almost eight-fold increased risk of CKD and development of end-stage renal disease.

**DIAGNOSING AKI**

Traditionally, diagnosis and classification of kidney injury severity have been based on serum creatinine levels and urine output over a number of hours. However, these clinical markers are influenced by numerous factors other than renal function, and are lagging indicators of damage. In recent years, new urinary biomarkers have been identified that can detect subclinical AKI during the tubular damage phase prior to functional deterioration. These biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor-binding protein-7 (IGFBP-7). Measurement of the combination biomarker [TIMP-2•IGFBP-7] has recently been recommended to assess risk of AKI in high-risk patients (ICU patients, age >21 years with one further risk factor for AKI, after cardiac bypass or other major high-risk surgery or with sepsis).

**AKI GUIDELINES**

The KDIGO guidelines recommend supportive measures in high-risk patients: close monitoring of serum creatinine and urine output, optimization in monitoring, discontinuation of nephrotoxic agents, avoidance of hyperglycemia, and remote ischemic preconditioning to reduce AKI. Renal Replacement Therapy (RRT) is currently the only therapeutic choice for treating severe AKI. Early initiation of RRT improves patient outcomes and is associated with a shorter ICU length stay and decreased 28-day mortality.

“A complex multimodal approach including a detailed risk assessment and the implementation of new biomarkers is advisable to prevent and manage AKI.”

**KEY FINDINGS**

- AKI is an underdiagnosed condition that is associated with increased in-hospital morbidity and mortality.
- Use of new biomarkers will provide more rapid detection, risk stratification and earlier intervention in treating AKI in high-risk patients.
Sepsis-associated acute kidney injury (S-AKI) is a common complication of critically ill patients, and is associated with high morbidity and mortality. Prevention of S-AKI is particularly challenging as it is extremely difficult to determine the exact onset of AKI in patients with sepsis, since most patients developing S-AKI will already have AKI on presentation. Early diagnosis and timely intervention are therefore crucial to provide supportive treatment and limit further damage. This review aimed to define the syndrome, determine the role of biomarkers and discuss recent advances in the pathophysiology and treatment of S-AKI.

**EPIDEMIOLOGY & PATHOPHYSIOLOGY**

Although the global incidence of S-AKI is largely unknown, it is estimated that around 1 in 3 patients with sepsis will develop AKI, and that the annual global incidence might be between 6 and 10 million cases. In the ICU, sepsis is found in about 40%-50% of patients with AKI, and is strongly associated with a poor clinical outcome: higher risk of in-hospital death (odds ratio: 1.48) and longer hospital stay compared with AKI from any other cause (37 vs. 21 days).

Renal replacement therapy (RRT) requirement was strongly associated with hospital mortality, and patients with renal recovery after S-AKI have significantly improved survival rates. Relapse of AKI is common after initial recovery and long-term outcomes of S-AKI patients is determined by AKI severity and recovery status on hospital discharge. Patients with even partial recovery appear to have a similar prognosis to those without AKI, whereas patients who do not recover have a worse prognosis (44% mortality in moderate to severe S-AKI cases). AKI severity, RRT requirement and recovery status during hospitalization have been shown to be the three key determinants in the risk of progression to chronic kidney disease (CKD).

Although the principal pathophysiologic model currently attributes S-AKI to decreased global renal blood flow and secondary tubular epithelial cell death, or acute tubular necrosis, it is becoming increasingly clear that multiple mechanisms are involved. Recent evidence shows that 3 fundamental mechanisms may play a role in the development of S-AKI: microvascular dysfunction, inflammation, and metabolic reprogramming.

**ROLE OF BIOMARKERS**

Novel biomarkers of kidney stress and damage have been recently validated for risk prediction and early diagnosis of S-AKI. Urinary tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) are two proteins involved in cell cycle arrest. These urinary biomarkers have been shown to outperform other biomarkers for prediction of AKI with an area under the curve (AUC) of 0.80 (Kashani et al., *Critical Care*, 2013;17(1):R25 - see study summary page 16). Furthermore, unlike many biomarkers, [TIMP-2•IGFBP-7] levels did not increase in non-renal organ failures in sepsis.

**PREVENTION AND TREATMENT**

As most patients developing S-AKI will already have it at presentation, AKI is most often impossible to prevent. Early recognition of AKI in the setting of sepsis is therefore vital to provide optimal treatment and avoid further kidney injury. Early appropriate antibiotic administration, fluid resuscitation and source control are the staples of sepsis treatment, and may also prevent further kidney injury. Several new drugs for AKI are currently being investigated, but only a few are focused specifically on S-AKI.

The survival advantage for early initiation of RRT in patients with severe AKI is debatable. Although some studies have shown that early initiation of RRT may result in a significantly reduced rate of major adverse kidney events, mortality, and enhanced renal recovery at 1-year follow-up, further studies are need to provide more conclusive evidence.

**CONCLUSIONS**

Further research is needed to achieve greater understanding of the underlying mechanisms of S-AKI, as well as more effective interventions for its prevention and treatment. The value of biomarkers to improve early detection of S-AKI has been established as complementary to clinical judgment and functional tests, and can potentially guide patient management and monitor recovery.
ACUTE KIDNEY INJURY (AKI)

Figure 1. Metabolic reprogramming during S-AKI, with re prioritization of energy consumption
Adapted from Peerapornratana S, et al. Kidney International 2019;96(5):1083-1099

REPRIORITIZATION OF ENERGY CONSUMPTION
Decreased ATP consumption for nonvital functions

* Endocytosis and decreased expression of ion transporters decreases ion transport

Paracrine signaling ([TIMP-2•IGFBP-7]?)

Tubular solute concentration

Induction of cell cycle arrest

Biomarkers predictive of AKI

ATP: adenosine triphosphate; G0–G2: phases of the cell cycle; IGFBP-7: insulin-like growth factor-binding protein-7; TIMP-2: tissue inhibitor of metalloproteinases-2; TNF: tumor necrosis factor
**ACUTE KIDNEY INJURY (AKI)**

Importantly unlike many biomarkers, non-renal organ failures in sepsis did not result in increased [TIMP-2•IGFBP-7].

S-AKI is a common complication in ICU patients with high morbidity and mortality. Early detection is essential for appropriate patient management and to prevent further organ damage.

The pathophysiology of this syndrome is complex and a better understanding of the multiple mechanisms causing S-AKI is needed.

Novel biomarkers of kidney stress, including urinary biomarkers [TIMP-2•IGFBP-7], have been recently validated for risk prediction and early diagnosis of S-AKI.

**KEY FINDINGS**

- S-AKI is a common complication in ICU patients with high morbidity and mortality. Early detection is essential for appropriate patient management and to prevent further organ damage.
- The pathophysiology of this syndrome is complex and a better understanding of the multiple mechanisms causing S-AKI is needed.
- Novel biomarkers of kidney stress, including urinary biomarkers [TIMP-2•IGFBP-7], have been recently validated for risk prediction and early diagnosis of S-AKI.
URINARY BIOMARKERS

[TIMP-2•IGFBP-7]
Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury.


OBJECTIVE
Two multicenter observational studies (discovery and validation) were performed in critically ill patients at risk for acute kidney injury (AKI). The objective was to identify and validate novel biomarkers of AKI.

STUDY DESIGN
In the discovery phase, 522 adult patients with sepsis, shock, major surgery, and trauma were enrolled at three sites. Blood and urine samples from these patients were used to identify the best biomarkers among 340 proteins, some previously characterized and some novel. Biomarkers were ranked by their ability to predict AKI RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) stage within 12-36 hours.

The top two markers from the discovery study were then validated in a second study (Sapphire) and compared to a number of previously described biomarkers. In the validation study, 744 adult subjects were enrolled with critical illness and without evidence of AKI at enrollment; the final analysis cohort was a heterogeneous sample of 728 critically ill patients. The primary endpoint was moderate to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection.

RESULTS
Among all permutations of biomarkers tested, the combination of urine insulin-like growth factor-binding protein-7 (IGFBP-7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) best distinguished patients who developed moderate to severe AKI within 12 hours from those who did not. [TIMP-2•IGFBP-7] exhibited an area under the curve (AUC) of 0.80, outperforming all other markers (Figure 1). Both biomarkers are inducers of G1 cell cycle arrest, a key mechanism implicated in the pathogenesis of AKI.

The risk of AKI increased sharply above [TIMP-2•IGFBP-7] 0.3 (Figure 2). When biomarker values were divided into tertiles, the middle tertile had a 3-fold greater risk of AKI and the highest tertile had a nearly 10-fold risk (p<0.001) as compared to patients with the lowest tertile values. Further, these biomarkers improved risk prediction when added to a 9-parameter clinical risk assessment model.

CONCLUSIONS
[TIMP-2•IGFBP-7] has been validated in independent multicenter cohorts as a novel biomarker for AKI. The combination biomarker has been shown to be superior to existing markers, providing additional information over clinical variables and a greater understanding of the mechanisms involved in the development of AKI.

“… this new test should significantly improve the ability of physicians caring for critically ill patients to identify risk of impending AKI.”

KEY FINDINGS
- [TIMP-2•IGFBP-7] is shown to be a superior combination biomarker for assessing acute kidney stress compared to other candidate biomarkers for AKI.
- [TIMP-2•IGFBP-7] demonstrates specificity to AKI and are not elevated with other acute or chronic conditions.
- [TIMP-2•IGFBP-7] shows a quantitative relationship between the test result and level of risk for AKI.
Figure 1. Comparison of Areas under the ROC curve (AUCs) for novel urinary biomarkers and existing biomarkers of AKI for the primary Sapphire study endpoint (KDIGO stage 2 or 3 within 12 hours of sample collection)
Adapted from Kashani et al. Critical Care 2013;17(1):R25

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Figure 2. Discrimination between non-AKI conditions and AKI of different severities for urine [TIMP-2•IGFBP-7]
Adapted from Kashani et al. Critical Care 2013;17(1):R25

*The AUC is a single measure of diagnostic test accuracy that combines sensitivity and specificity.

CI: confidence interval; IGFBP-7: insulin-like growth factor-binding protein-7; IL-1β: interleukin-1β; KIM-1: kidney injury marker-1; L-FABP: liver fatty acid-binding protein; NGAL: neutrophil gelatinase-associated lipocalin; pi-GST: pi-Glutathione S-transferase; TIMP-2: tissue inhibitor of metalloproteinases-2

CI: confidence interval; IGFBP-7: insulin-like growth factor-binding protein-7; IL-1β: interleukin-1β; KIM-1: kidney injury marker-1; L-FABP: liver fatty acid-binding protein; NGAL: neutrophil gelatinase-associated lipocalin; pi-GST: pi-Glutathione S-transferase; TIMP-2: tissue inhibitor of metalloproteinases-2


OBJECTIVE
A working group of clinical experts convened meetings to discuss their collective experience with the practicalities of implementing the NEPHROCHECK® test, a combination biomarker of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein (IGFBP-7), known as [TIMP-2•IGFBP-7]. The work group sought to understand how the biomarker test was being used at sites that have adopted it.

STUDY DESIGN
Experts in critical care, nephrology, and surgery who had significant clinical experience with the biomarker were invited to 2 meetings conducted in 2018. One meeting was held in the US and another in the EU.
Prior to the meetings, invitees completed a questionnaire on [TIMP-2•IGFBP-7] testing at their sites. Participants were also encouraged to provide their individual institution protocols and/or written instructions they had developed or with which they were familiar. These protocols were analyzed for common elements, and then rank-ordered by all participants.

RESULTS
Clinical experts from Europe and North America agreed on target testing populations, how to interpret a quantitative test result, and what actions to take based on test results, but achieved less of a consensus on timing of testing. Priority patient populations for measuring kidney stress were patients undergoing major surgery (both cardiac and non-cardiac), patients with hemodynamic instability or with sepsis. Among patients whose values indicated moderate to high risk of AKI, clinicians identified the highest priority actions to be 1) discontinue all nonessential potential nephrotoxins; 2) avoid vancomycin alone or in combination or dose adjust; 3) perform goal-directed fluid management; and 4) discontinue angiotensin-converting-enzyme inhibitors (ACEs) and angiotensin II receptor blockers (ARBs).

CONCLUSIONS
Clinicians reported ordering the NEPHROCHECK test when there was concern that the kidneys were under threat for any reason and there was agreement that testing is especially useful within the first 72 hours of ICU admission. Those patients who tested negative were considered to be excellent candidates for “fast-track” protocols and rapid de-escalation of monitoring.

“By instituting an AKI biomarker protocol, hospitals have the opportunity to develop and test metrics that can enhance quality improvement initiatives.”

KEY FINDINGS
- Types of patients being tested and the types of recommended interventions based on the test result were similar. More variation was seen in terms of when to test.
- A negative test result was also considered informative as patients could benefit from treatments best avoided in high-risk patients and monitoring could be de-escalated more rapidly.
Figure 1. Protocol for [TIMP-2•IGFBP-7] testing
Serial Urinary Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 and the Prognosis for Acute Kidney Injury over the Course of Critical Illness.


OBJECTIVE
This is a secondary analysis of data from the previously published Sapphire trial – the prospective, blinded, observational, international study of patients admitted to intensive care units - which demonstrated that initial urine [TIMP-2•IGFBP-7] predicted stage 2/3 AKI within 12 hours and before a rise in serum creatinine (see pages 16-17). This analysis was done to evaluate the utility of serial measurements of [TIMP-2•IGFBP-7] to anticipate the occurrence of AKI over the first 7 days of critical illness.

STUDY DESIGN
Urine samples from 530 patients collected every 12 hours up to 3 days were analyzed. The first 3 measurements (baseline, 12 and 24 hours) were evaluated and if any of these results were >0.3 (ng/mL)^2/1,000, additional results were evaluated. Patient stratification was done based on number of results >0.3 (ng/mL)^2/1,000 and number of results >2.0 (ng/mL)^2/1,000. The primary endpoint was stage 2/3 AKI defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

RESULTS
This analysis demonstrated that serial urinary [TIMP-2•IGFBP-7] at baseline, 12, 24 hours, and up through 3 days are prognostic for the occurrence of stage 2/3 AKI over the course of critical illness (Figures 1, 2, 3).

For patients testing negative <0.3 (ng/mL)^2/1,000 for the first 3 tests, the incidence of de novo KDIGO stage 2/3 AKI at 7 days was 13.0%. However, for those with one, two, or three strongly positive values >2.0 (ng/mL)^2/1,000, the incidence of stage 2/3 AKI at 7 days was 57.7, 75.0, and 94.4%, respectively (p<0.001 for trend).

CONCLUSIONS
Critically ill patients have frequent and ongoing exposures that can cause AKI. Thus, serum creatinine and blood-urea-nitrogen (BUN) are usually measured daily. This analysis was done to mimic a clinician-driven serial testing strategy. Persistently negative results <0.3 (ng/mL)^2/1,000 are associated with very low incidence of stage 2/3 AKI while persistently positive or strongly positive results >2.0 (ng/mL)^2/1,000 are associated with progressively higher stage 2/3 AKI rates.

This study was the first to assess serial measurements of [TIMP-2•IGFBP-7] in a large multicenter international cohort of heterogeneous critically ill patients.

“Our results show that sequential measurement of [TIMP-2•IGFBP-7] can complement the information given by serum creatinine in the anticipation of subsequent stage 2/3 AKI.”

**KEY FINDINGS**

- Serial measurement of urine [TIMP-2•IGFBP-7] in critically ill patients every 12 hours for at least 3 samples provided an approach to predict the progressive risk of stage 2/3 AKI up to 7 days in the ICU.
- Three consecutive negative values <0.3 (ng/mL)^2/1,000 are associated with very low (13.0%) incidence of stage 2/3 AKI over the course of 7 days.
- Emerging or persistent, strongly positive results >2.0 (ng/mL)^2/1,000 predict very high incidence rates (up to 94.4%) of stage 2/3 AKI.
Figure 1. Cumulative incidence of stage 2/3 AKI over 1 week for patients stratified by number of consecutive [TIMP-2•IGFBP-7] above the 0.3 (a) and 2.0 (ng/mL)^2/1,000 (b) cutoffs
Adapted from McCullough PA, et al. Cardiorenal Medicine 2019;9(6):358-369

Figure 2. Incidence of stage 2/3 AKI within 1 week of enrollment by number of [TIMP-2•IGFBP-7] values ≤0.3 (a) and >2.0 (ng/mL)^2/1,000 (b) among the first 7 measurements collected approximately 12 h apart
Adapted from McCullough PA, et al. Cardiorenal Medicine 2019;9(6):358-369

Figure 3. Evolution of patients with [TIMP-2•IGFBP-7] values >0.3 to ≤2.0 (ng/mL)^2/1,000 over the first 7 consecutive [TIMP-2•IGFBP-7] measurements collected approximately 12 h apart
Adapted from McCullough PA, et al. Cardiorenal Medicine 2019;9(6):358-369

Box shadings show number of patients who started within each [TIMP-2•IGFBP-7] level (1st column) or decreased to ≤0.3 (ng/mL)^2/1,000 (gray), remained at >0.3 to ≤2.0 (ng/mL)^2/1,000 (white), or increased to >2.0 (ng/mL)^2/1,000 (black).
**Urinary [TIMP-2] × [IGFBP7] and serum procalcitonin to predict and assess the risk for short-term outcomes in septic and non-septic critically ill patients.**


**OBJECTIVE**

This study assessed the combination of biomarkers [TIMP-2•IGFBP-7] and procalcitonin (PCT) for AKI prediction and risk stratification in ICU patients. The hypothesis was that the addition of an AKI biomarker with a sepsis biomarker may lead to early identification of patients with sepsis-induced AKI, and measurement of [TIMP-2•IGFBP-7] and PCT on admission may help assess risk of short-term adverse renal outcomes in septic and non-septic patients.

**STUDY DESIGN**

This retrospective cohort analysis included critically ill adult patients admitted to a multidisciplinary ICU from June 2016–February 2018 and who received [TIMP-2•IGFBP-7] and PCT measurements on ICU admission. The primary endpoint assessed [TIMP-2•IGFBP-7] and PCT measurements, alone and combined, on ability to predict AKI development within 48 hours. The secondary endpoint assessed the utility of combining results from both biomarkers for risk assessment of AKI within 48 hours, and acute kidney disease (AKD) and mortality at 7 days. To evaluate the utility of combining [TIMP-2•IGFBP-7] and PCT results for risk assessment, the predictive value for single-biomarker positivity was compared to double-biomarker positivity using cut-offs of 0.3 (ng/mL)/1000 for [TIMP-2•IGFBP-7] and 0.5 µg/L for PCT. Primary and secondary endpoints were studied in both septic and non-septic patient groups.

**RESULTS**

Four hundred and thirty-three (433) patients were included in the study, of whom 168 (38.8%) developed AKI within 48 hours (93 septic and 65 non-septic patients). The combination of [TIMP-2•IGFBP-7] and PCT showed a good predictive ability to predict AKI occurrence (AUC\(^1\) 0.81, 95% CI 0.77–0.86, \(p<0.001\), Sensitivity 78%, Specificity 73%). The presence of at least one of the two biomarkers was significantly associated with AKI development (OR\(^2\) 4.1, 95% CI 1.9–8.8, \(p<0.001\)) – a 4-fold risk increase for single-marker positivity (Table 1). When both biomarkers were positive, the risk of AKI occurrence increased 26-fold (OR 26.4, 95% CI 12.3–56.62, \(p<0.001\)).

**CONCLUSIONS**

The combination of biomarkers showed good predictive ability for patients at risk of developing AKI. The combined results enabled risk stratification for AKI development within 48 hours. The double-marker positivity was significantly associated with mortality within 7 days in the septic subgroup and with AKD at 7 days in non-septic patients (Table 2). Data should be confirmed in a larger prospective study.

1 AUC: Area Under the Curve; 2 OR: Odds Ratio

**KEY FINDINGS**

- Combining [TIMP-2•IGFBP-7] and PCT with cut-offs of 0.3 and 0.5 respectively, may help in stratifying ICU patients at high risk of developing AKI (regardless of sepsis).
- The positivity of the two biomarkers showed a 26-fold odds of AKI development, compared with a 4-fold risk increase with only single-marker positivity.
- The double-marker positivity also indicated an elevated risk for AKD at 7 days in non-septic patients and for mortality within 7 days in patients with suspected or confirmed sepsis.

“Combining the results of [TIMP-2•IGFBP-7] and PCT may be a useful tool to identify and stratify ICU patients at high risk for septic AKI and short-term adverse outcomes.”
### Table 1. Risk assessment for primary and secondary outcomes in the entire population and in septic and non-septic subgroups


<table>
<thead>
<tr>
<th>Variables</th>
<th>Analysis cohort</th>
<th>Sepsis</th>
<th>Non-sepsis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI within 48 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[TIMP-2•IGFBP-7] &gt; 0.3</td>
<td>3.93a</td>
<td>2.14–7.20</td>
<td>&lt; 0.001</td>
<td>5.92a</td>
</tr>
<tr>
<td>PCT &gt; 0.5</td>
<td>3.67a</td>
<td>2.17–6.19</td>
<td>&lt; 0.001</td>
<td>2.74a</td>
</tr>
<tr>
<td>Single-marker positivity</td>
<td>4.08</td>
<td>1.90–8.76</td>
<td>&lt; 0.001</td>
<td>2.27</td>
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<tr>
<td>Double-marker positivity</td>
<td>26.41</td>
<td>12.32–56.62</td>
<td>&lt; 0.001</td>
<td>19.5</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI at 7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-marker positivity</td>
<td>4.73</td>
<td>1.04–21.60</td>
<td>0.045</td>
<td>2.28</td>
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<tr>
<td>Double-marker positivity</td>
<td>15.92</td>
<td>3.67–68.97</td>
<td>0.001</td>
<td>4.57</td>
</tr>
<tr>
<td>Mortality within 7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-marker positivity</td>
<td>1.16</td>
<td>0.51–2.65</td>
<td>0.724</td>
<td>0.86</td>
</tr>
<tr>
<td>Double-marker positivity</td>
<td>2.75</td>
<td>1.34–5.65</td>
<td>0.006</td>
<td>4.1</td>
</tr>
</tbody>
</table>

A single-marker positivity was defined by the presence of [TIMP-2•IGFBP-7] above the cut-off of 0.3 or PCT above the cut-off of 0.5; the double-marker positivity was defined by the presence of [TIMP-2•IGFBP-7] measurements above 0.3 and the concomitant presence of PCT levels above 0.5

### Table 2. Patients’ outcomes in the overall population and in septic and non-septic subgroups


<table>
<thead>
<tr>
<th>Variables</th>
<th>Analysis cohort</th>
<th>Sepsis</th>
<th>Non-sepsis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI at ICU admission</td>
<td>26 (6.0)</td>
<td>14 (7.7)</td>
<td>12 (4.8)</td>
<td>0.001a</td>
</tr>
<tr>
<td>Stage 1</td>
<td>14 (3.2)</td>
<td>8 (4.4)</td>
<td>6 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>5 (1.1)</td>
<td>2 (1.1)</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>7 (1.6)</td>
<td>4 (2.2)</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>AKI within 24 h</td>
<td>149 (34.4)</td>
<td>82 (45.3)</td>
<td>67 (26.6)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Stage 1</td>
<td>46 (10.6)</td>
<td>25 (13.8)</td>
<td>21 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>38 (8.8)</td>
<td>19 (10.5)</td>
<td>19 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>65 (15.0)</td>
<td>38 (21.0)</td>
<td>27 (10.7)</td>
<td></td>
</tr>
<tr>
<td>AKI within 48 h</td>
<td>168 (38.8)</td>
<td>93 (51.4)</td>
<td>75 (29.8)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Stage 1</td>
<td>55 (12.7)</td>
<td>31 (17.1)</td>
<td>24 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>44 (10.2)</td>
<td>22 (12.2)</td>
<td>22 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>69 (15.9)</td>
<td>40 (22.1)</td>
<td>29 (11.5)</td>
<td></td>
</tr>
<tr>
<td>RRT need</td>
<td>33 (7.6)</td>
<td>18 (9.9)</td>
<td>15 (6.0)</td>
<td></td>
</tr>
<tr>
<td>AKI at 7 days</td>
<td>47 (10.8)</td>
<td>26 (14.4)</td>
<td>21 (8.3)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Stage 0</td>
<td>15 (3.5)</td>
<td>10 (5.5)</td>
<td>5 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>9 (2.1)</td>
<td>5 (2.8)</td>
<td>4 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>7 (1.6)</td>
<td>4 (2.2)</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>16 (3.7)</td>
<td>7 (3.9)</td>
<td>9 (3.6)</td>
<td></td>
</tr>
<tr>
<td>RRT need</td>
<td>14 (3.2)</td>
<td>7 (3.9)</td>
<td>7 (2.8)</td>
<td></td>
</tr>
<tr>
<td>7 days mortality</td>
<td>65 (15.0)</td>
<td>37 (20.4)</td>
<td>28 (11.1)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>100 (23.1)</td>
<td>50 (27.6)</td>
<td>50 (19.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Days in ICU</td>
<td>4 (2–11)</td>
<td>4 (2–10)</td>
<td>4 (2–11)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>128 (29.6)</td>
<td>64 (35.4)</td>
<td>64 (25.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>15 (7–31)</td>
<td>13 (6–30)</td>
<td>15 (7–31)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Data are reported as numbers (percentages) as categorical variables and median (interquartile range) for continuous variables. * identified a p-value <0.005

AKI: acute kidney injury; AKD: acute kidney disease; RRT: renal replacement therapy; ICU: intensive care unit.
URINARY BIOMARKERS [TIMP-2•IGFBP-7]

CRITICAL CARE MEDICINE 2018;46(3):375-383

Kinetics of Urinary Cell Cycle Arrest Markers for Acute Kidney Injury Following Exposure to Potential Renal Insults.


OBJECTIVE
This study is an ancillary analysis of the multicenter Sapphire study, which examined the impact of exposure to common renal insults, such as major surgery, IV radiocontrast, vancomycin, nonsteroidal anti-inflammatory drugs, and piperacillin/tazobactam on the kinetics of the urinary biomarker [TIMP-2•IGFBP-7].

STUDY DESIGN
The kinetics of [TIMP-2•IGFBP-7] and serum creatinine were analyzed in 723 critically ill patients from the day prior to exposure up to 5 days after exposure.

RESULTS
Among these patients, 679 (94%) had at least one, 70% had more than one, and 35% had three or more exposures to a known renal insult.

CONCLUSIONS
There was a significant association between cumulative number of exposures up to study day 3 and risk of AKI (p=0.02), but no association between the specific type of exposure and AKI (p=0.22). With the exception of radiocontrast, patients who developed stage 2/3 AKI after one of the five exposures had a clear rise and fall of [TIMP-2•IGFBP-7] from the day of exposure to 24-48 hours later (Figure 1).

“Urinary [TIMP-2•IGFBP-7] exhibit a characteristic rise and fall around various exposures but importantly, only in patients who ultimately develop AKI.”

KEY FINDINGS
- Exposure to multiple nephrotoxic insults is common during critical illness and associated with an increased risk of AKI.
- Serum creatinine is not altered during the early hours after exposure to a renal insult, but [TIMP-2•IGFBP-7] is typically elevated in patients who develop AKI.
Figure 1. Biomarker kinetics in association with specific exposures
Adapted from Ostermann M, et al. Critical Care Medicine 2018;46(3):375-383

Time course of urinary [TIMP-2•IGFBP-7] concentrations relative to the time or day of exposure by acute kidney injury (AKI) stage for patients exposed to (A) major surgery, (B) IV contrast, (C) vancomycin, (D) nonsteroidal anti-inflammatory drugs (NSAIDs) or (E) piperacillin/tazobactam.

Symbols show median urinary [TIMP-2•IGFBP-7] concentrations for patients who had no AKI (circles), stage 1 AKI (squares), and stage 2/3 AKI (triangles) within 3 days post-exposure.

Vertical and horizontal lines through the symbols show the interquartile range of bootstrap medians for the [TIMP-2•IGFBP-7] concentrations and the time from exposure, respectively.

Median urinary [TIMP-2•IGFBP-7] concentrations are shown by day for drug exposures because only the day and not the time of exposure was recorded. The width of the shaded area indicates the day of the first dose of each drug.
Objective
The objective of this study was to determine if therapeutic interventions driven by elevated urinary biomarkers reduce post cardiac surgical stage 2/3 acute kidney injury (AKI).

Study Design
A quality improvement initiative was undertaken based on adding urinary biomarkers (UB) and an Acute Kidney Response Team (AKRT) to standard of care patient management.

The study used cell cycle arrest urinary biomarkers: tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7). Cell cycle arrest is described as “kidney stress” and occurs before kidney damage.

All adult patients >18 years old with a preoperative serum creatinine level <2.0 mg/dL undergoing a cardiac operation with cardiopulmonary bypass between July 2016 and June 2018 were included. Data from the Society of Thoracic Surgeons (STS) Adult Cardiac Database were retrospectively reviewed.

Outcomes were compared between patients undergoing cardiac surgery before the use of UB (pre-UB) between July 2016 and June 2017 and after implementation of the quality improvement initiative (instituted on July 1, 2017) for the following year: July 2017 to June 2018 (post-UB). The primary study endpoint was the development of stage 2 or 3 AKI.

Urinary biomarkers were measured in the morning after cardiac surgery. In the post-UB period, the multidisciplinary AKRT, composed of intensivists, nephrologists, cardiac surgeons, nurses, and advanced practitioners, was triggered in UB-positive (>0.3) patients. AKRT used a predetermined algorithm based on the KDIGO cardiac surgery care bundle. This bundle includes targeted goal-directed fluid management, liberalizing transfusion thresholds, continued invasive hemodynamic monitoring, and avoidance of nephrotoxins. A pocket card was used by the multidisciplinary team to guide the systematic response to the UB results (Figure 1).

Results
A total of 435 patients in the pre-UB group were compared to 412 patients in the post-UB cohort with respect to incidence of stage 2/3 AKI. Of the post-UB patients, 55% had a moderate or high UB score (≥0.3 ng/dL). In the pre-UB group, 10 (2.30%) had stage 2/3 AKI vs 1 (0.24%) post-UB, representing an 89% relative reduction (p=0.01) (Figures 2 and 3). Total and postoperative length of stay, cost, mortality, and readmissions were found to be similar between groups. The negative predictive value for AKI of UB <0.3 ng/dL was 100%.

Conclusions
A multidisciplinary AKRT triggered by urinary biomarkers for kidney stress reduced acute kidney injury following cardiac surgery. Findings suggest that routine measurement of UB values may be useful in identifying cardiac surgery patients at risk for perioperative AKI, and the subsequent activation of an AKRT with implementation of an AKI bundle may be a beneficial adjunct to routine clinical care in preventing stage 2/3 AKI. While labor-intensive, these interventions were not associated with increased length of stay or higher costs.

“.... UB [urinary biomarkers] may alert clinicians to implement preventative and protective measures in patients at high-risk for AKI long before clinical AKI manifests.”

Key Findings
- Early urinary biomarkers [TIMP-2•IGFBP-7] triggered implementation of an Acute Kidney Response Team utilizing a KDIGO “cardiac surgery care bundle”, which resulted in an 89% relative decrease in the incidence of moderate or severe AKI within 7 days of surgery compared to routine post-operative clinical care.
- The routine measurement of urinary biomarkers and subsequent activation of an acute kidney response team are useful additions to the conventional post-cardiac surgery therapy.
URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Figure 1. Pocket card for the acute kidney response team: urinary biomarker (UB) (NEPHROCHECK®) values and corresponding response

Acute Kidney Response Team Pocket Card

THE NEPHROCHECK® TEST

Intended to aid in assessing the risk of moderate to severe AKI.

WHO TO TEST
All cardiac surgery patients on post-op day 1 at 05:30.

WHO NOT TO TEST
Pre-op creatinine >2, on dialysis or received methylene blue.

STAGE OF ACUTE KIDNEY INJURY (AKI)

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of 2.0 - 2.9 x baseline</td>
<td>&lt;0.5 ml/kg/h for 12 hours</td>
</tr>
<tr>
<td>Increase of &gt;3x baseline or increase of SCR to &gt;4 mg/dL or initiation of RRT</td>
<td></td>
</tr>
</tbody>
</table>

WHEN & HOW TO TEST
1. Patient meets test inclusion: at 05:30 am PO D1 collect fresh urine specimen from Foley bag (at least 10 ml).
2. Results will show up in EMR chemistry section under urine miscellaneous - click for value range. Lab will report results in time for HVCC 07:00 team rounds.

Response to Urinary Biomarker (UB) Drawn the Morning after Cardiac Surgery

UB neg (<0.3):
“Fast-track recovery”

UB low positive (0.3-2.0):
- Discontinue nephrotoxic medications
- Monitor hourly urine output
- Transfer to telemetry after 4pm
- Convert to high positive protocol if patient becomes oliguric

UB high positive (>2.0):
- Activate acute kidney response team
- Goal-directed fluid therapy
- Maintain hemodynamic monitoring overnight
- Raise transfusion threshold to hemoglobin >8.0

Stage 2/3 AKI reduced by 89%

Figure 2. Prevalence of cardiac surgery–associated AKI before and after use of the urinary biomarker (NEPHROCHECK®), demonstrating an 89% reduction in moderate/severe AKI after introducing the biomarker

Figure 3. Responses to negative (<0.3), low positive (0.3-2.0), and high positive (>2.0), urinary biomarker values (NEPHROCHECK®) on the morning after surgery and the resultant decrease in stage 2/3 acute kidney injury

Stage 2/3 AKI reduced by 89%
Investigators tested the hypothesis that intraoperative concentrations of urinary [TIMP-2•IGFBP-7] are associated with postoperative AKI.

This was a prospective cohort study from a previously published trial of statin therapy for prevention of AKI in cardiac surgery. The Statin AKI Cardiac Surgery trial was a randomized, double-blinded, placebo-controlled trial to test the efficacy of perioperative atorvastatin administration for reducing cardiac surgery-associated AKI (CSA-AKI).

Adult patients undergoing elective coronary bypass grafting, valvular heart surgery, or ascending aortic surgery at Vanderbilt University Medical Center were eligible for inclusion. Eight perioperative measurements of [TIMP-2•IGFBP-7] were performed. The primary endpoint was stage 2/3 (moderate-severe) AKI occurring within 48 hours of surgery, defined by changes in serum creatinine according to KDIGO criteria.

The study included 400 patients, of whom fourteen patients (3.5%) developed stage 2/3 AKI within 48 hours of surgery, and a further 77 patients (19.3%) developed stage 1 AKI.

Patients who developed stage 2/3 AKI displayed 2 elevation peaks of [TIMP-2•IGFBP-7] - intraoperatively and six hours postoperatively. The time course was characterized by [TIMP-2•IGFBP-7] that increased significantly immediately after the end of CPB or off-pump coronary artery bypass (OpCAB), returned towards baseline at ICU admission, and then subsequently increased considerably more six hours after ICU admission. [TIMP-2•IGFBP-7] levels then remained elevated into postoperative day 1 before decreasing towards baseline on postoperative day 2 in stage 2/3 AKI patients compared to patients with stage 1 or no AKI (Figure 1).

Each 10-fold increase in intraoperative [TIMP-2•IGFBP-7] was found to be independently associated with a 290% increase in the odds of stage 2/3 AKI (p=0.01), and each 10-fold increase in six hours postoperative [TIMP-2•IGFBP-7] with a 650% increase (p<0.001). The maximum [TIMP-2•IGFBP-7] between these two time points provided an area under the curve (AUC) of 0.82 (95% CI: 0.73–0.90), 100% sensitivity, and 100% negative predictive value using the >0.3 cutoff to predict stage 2/3 AKI.

No elevations in [TIMP-2•IGFBP-7] were observed in patients who did not develop AKI.

Increased intraoperative concentrations and increased early postoperative concentrations of [TIMP-2•IGFBP-7] are independently associated with development of moderate-severe AKI. Perioperative [TIMP-2•IGFBP-7] is a highly sensitive predictor of postoperative AKI and could provide the opportunity to alter postoperative management to prevent kidney injury.

“If either the intraoperative or the early postoperative [TIMP-2•IGFBP-7] is >0.3, we recommend instituting renal supportive measures such as the KDIGO bundle.”
In patients who were later diagnosed with stage 2/3 AKI, there was a bimodal elevation where initial urinary [TIMP-2•IGFBP-7] was increased during surgery followed by a decrease at ICU admission and then a sharp increase within six hours.

If neither the intraoperative nor the early postoperative test is positive (>0.3), the treating clinician may be confident the patients will not develop moderate-severe AKI (the “double-negative” [TIMP-2•IGFBP-7]).

The negative predictive value using this sampling strategy in the study was 100% and sensitivity of 100% using the >0.3 cutoff.
OBJECTIVE
This single-center randomized controlled trial (RCT) investigated whether the “KDIGO bundle” could reduce the occurrence and severity of acute kidney injury (AKI) in patients post cardiac surgery.

STUDY DESIGN
Control patients received standard care treatment and intervention patients received the care “bundle,” consisting of optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and prevention of hyperglycemia. High-risk patients were defined as those with urinary biomarker [TIMP-2•IGFBP-7] >0.3. The primary endpoint was the rate of AKI defined by KDIGO criteria within the first 72 h after surgery. Secondary endpoints included AKI severity, need for dialysis, length of stay, and major adverse kidney events (MAKE) at days 30, 60, and 90.

RESULTS
Overall incidence of AKI was 63.4% (175/276). The intervention group had significantly lower rates of AKI (55.1%) compared to controls [71.7%; \(p=0.004\)] (Figure 1). Rates of moderate to severe AKI were also significantly reduced by the intervention compared to controls. The implementation of the bundle resulted in significantly improved hemodynamic parameters at different time points \(p<0.05\), less hyperglycemia \(p<0.001\) and reduced use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) \(p<0.001\) compared to controls. Other secondary outcomes did not vary significantly between groups.

CONCLUSIONS
This study observed that by identifying high-risk patients using the urinary biomarker [TIMP-2•IGFBP-7], a bundle of supportive measures could be implemented which reduced the occurrence of AKI within 72 hours compared to standard care.

**KEY FINDINGS**
- In this RCT of patients undergoing cardiac surgery, the urinary [TIMP-2•IGFBP-7] biomarker identified high-risk patients, which allowed for the implementation of a bundle of protective measures and reduced the occurrence of AKI within 72 hours compared to standard care.
- In high-risk cardiac surgery patients, implementing the KDIGO care bundle guidelines compared with standard care may reduce the frequency and severity of AKI after cardiac surgery in high-risk patients.
HEALTH ECONOMICS
AND OUTCOMES
STUDIES
OBJECTIVE
The purpose of this study was to evaluate the incremental budget impact of adding a novel diagnostic test, [TIMP-2•IGFBP-7], which identifies patients at risk of moderate to severe acute kidney injury (AKI), to the current standard of care (SOC) in a hospital setting. Through more rapid identification of AKI risk and treatment, overall AKI severity and healthcare utilization could be reduced.

STUDY DESIGN
A budget impact model was developed from the perspective of a hypothetical US hospital system serving 10,000 inpatients annually. Using published data and expert opinion, the model estimated the effect of adding the US Food and Drug Administration approved assay [TIMP-2•IGFBP-7] to SOC on healthcare utilization and costs over a 1-year time horizon. Other factors that had cost implications included payer mix among patients, diagnostic efficacy, and provider adoption rates as well as biomarker costs.

RESULTS
As compared to SOC alone, adding [TIMP-2•IGFBP-7] to SOC was associated with a $1,855 reduction in uncompensated care per patient tested, which, after accounting for the additional costs of the test, resulted in annual net savings of $1,578 per patient tested and hospital savings of $789,104 (2017 USD) (Table 1). In varying model parameters, net cost savings to the hospital ranged from $50,308 to $3,971,514, or $101 to $7,943 per tested patient (mean $1,710; 95% confidence interval $1,691–$1,729).

CONCLUSIONS
Adding [TIMP-2•IGFBP-7] to SOC risk assessment for AKI could lead to substantial cost-savings for the hospital, largely by resulting in shorter ICU and non-ICU lengths of stay and fewer 30-day readmissions (Table 2). Prospective real-world studies are needed to evaluate the effect of [TIMP-2•IGFBP-7] on patient outcomes and healthcare costs.

“The introduction of [TIMP-2•IGFBP-7] as a novel tool in the identification of AKI risk may result in considerable cost savings from a hospital perspective under this model’s base-case assumptions.”
**Table 1. Annual net savings by level of AKI severity (overall and per tested patient)**  
Adapted from Berdugo MA, et al. *Journal of Medical Economics* 2019;22(12):1281-1289

<table>
<thead>
<tr>
<th></th>
<th>No AKI</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Per tested patient</td>
<td>-$1,227</td>
<td>$0</td>
<td>$2,126</td>
<td>$956</td>
<td>$1,578</td>
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<tr>
<td>Overall</td>
<td>-$613,311</td>
<td>$0</td>
<td>$1,063,149</td>
<td>$477,766</td>
<td>$789,104</td>
</tr>
</tbody>
</table>

Total cost is inclusive of the incremental per-usage estimate for [TIMP-2•IGFBP-7]. Monetary values are in 2017 United States dollars.

Abbreviations. AKI: acute kidney injury.

**Table 2. Reduction in overall clinical burden and resulting budget impact by AKI severity (overall and per patient)**  
Adapted from Berdugo MA, et al. *Journal of Medical Economics* 2019;22(12):1281-1289

<table>
<thead>
<tr>
<th>Overall reduction in health care resource utilization among target population</th>
<th>No AKI</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Total ICU bed under SOC</td>
<td>181</td>
<td>264</td>
<td>146</td>
<td>70</td>
<td>661</td>
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<tr>
<td>Total ICU bed with SOC and [TIMP-2•IGFBP-7]</td>
<td>232</td>
<td>264</td>
<td>50</td>
<td>24</td>
<td>570</td>
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<tr>
<td>Decrease in ICU bed with [TIMP-2•IGFBP-7]</td>
<td>-51</td>
<td>0</td>
<td>96</td>
<td>46</td>
<td>91</td>
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<tr>
<td>Total non-ICU bed under SOC</td>
<td>465</td>
<td>775</td>
<td>319</td>
<td>136</td>
<td>1,696</td>
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<tr>
<td>Total non-ICU bed with SOC and [TIMP-2•IGFBP-7]</td>
<td>597</td>
<td>775</td>
<td>109</td>
<td>46</td>
<td>1,527</td>
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<tr>
<td>Decrease in non-ICU bed with [TIMP-2•IGFBP-7]</td>
<td>-131</td>
<td>0</td>
<td>211</td>
<td>90</td>
<td>170</td>
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</table>

<table>
<thead>
<tr>
<th>Resulting budget impact due to reduced uncompensated care among target population</th>
<th>No AKI</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ICU costs under SOC</td>
<td>$905,100</td>
<td>$1,322,475</td>
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<td>$349,590</td>
<td>$3,306,840</td>
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<td>Total ICU costs with SOC and [TIMP-2•IGFBP-7]</td>
<td>$1,160,085</td>
<td>$1,322,475</td>
<td>$248,164</td>
<td>$118,896</td>
<td>$2,849,619</td>
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<td>ICU savings with addition of [TIMP-2•IGFBP-7] to SOC</td>
<td>-$254,985</td>
<td>$0</td>
<td>$481,511</td>
<td>$230,694</td>
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<td>Total non-ICU costs under SOC</td>
<td>$1,163,700</td>
<td>$1,937,513</td>
<td>$798,413</td>
<td>$341,205</td>
<td>$4,240,830</td>
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<tr>
<td>Total non-ICU costs with SOC and [TIMP-2•IGFBP-7]</td>
<td>$1,491,538</td>
<td>$1,937,513</td>
<td>$271,541</td>
<td>$116,044</td>
<td>$3,816,636</td>
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<tr>
<td>Non-ICU, inpatient savings with addition of [TIMP-2•IGFBP-7] to SOC</td>
<td>-$327,838</td>
<td>$0</td>
<td>$526,871</td>
<td>$229,161</td>
<td>$424,194</td>
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<tr>
<td>Total readmission costs under SOC</td>
<td>$108,224</td>
<td>$167,360</td>
<td>$82,993</td>
<td>$33,205</td>
<td>$391,781</td>
</tr>
<tr>
<td>Total readmission costs with SOC and [TIMP-2•IGFBP-7]</td>
<td>$138,713</td>
<td>$167,360</td>
<td>$28,226</td>
<td>$11,293</td>
<td>$345,591</td>
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<td>Savings on 30-day readmissions with addition of [TIMP-2•IGFBP-7] to SOC</td>
<td>-$30,489</td>
<td>$0</td>
<td>$54,767</td>
<td>$21,912</td>
<td>$46,188</td>
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<tr>
<td>Total cost of uncompensated care under SOC</td>
<td>$2,177,024</td>
<td>$3,427,347</td>
<td>$1,611,080</td>
<td>$724,000</td>
<td>$7,939,451</td>
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<td>Total cost of uncompensated care with SOC and [TIMP-2•IGFBP-7]</td>
<td>$2,790,335</td>
<td>$3,427,347</td>
<td>$547,931</td>
<td>$246,233</td>
<td>$7,011,846</td>
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<tr>
<td>Savings on uncompensated care with addition of [TIMP-2•IGFBP-7] to SOC</td>
<td>-$613,311</td>
<td>$0</td>
<td>$1,063,149</td>
<td>$477,766</td>
<td>$927,604</td>
</tr>
<tr>
<td>Per-tested-patient savings on uncompensated care with addition of [TIMP-2•IGFBP-7] to SOC</td>
<td>-$1,227</td>
<td>$0</td>
<td>$2,126</td>
<td>$956</td>
<td>$1,855</td>
</tr>
</tbody>
</table>

Monetary values are in 2017 United States dollars. Abbreviations. AKI: acute kidney injury; ICU: intensive care unit; SOC: standard of care.
**OBJECTIVE**
This paper describes a secondary analysis of the Sapphire trial, an international, prospective, observational study which evaluated two biomarkers of G1 cell cycle arrest, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) for AKI risk assessment. In the primary analysis, these two biomarkers were found to be superior to other existing biomarkers, provide additional information over clinical variables and add mechanistic insight into AKI.

The purpose of this secondary analysis was to evaluate whether adding [TIMP-2•IGFBP-7] to serum creatinine (SCr), and urine output (UO) improves risk prediction for development of stage 3 AKI, need for dialysis, or death within one week of enrollment. Longer-term outcomes were also examined: the relationship between [TIMP-2•IGFBP-7] measurements and death or dialysis within nine months in patients who progressed to stage 2-3 AKI within one week.

**STUDY DESIGN**
This study included subjects from the prospective Sapphire trial who did not have stage 2-3 AKI at enrollment. Among 661 subjects eligible for this analysis, urine samples for testing with biomarkers [TIMP-2•IGFBP-7] were collected at enrollment and at 12-hour intervals up to 30 hours. AKI status based on SCr and UO were determined within ±12 hours of biomarker sample collection.

**RESULTS**
Among the 79 patients (10.9%) who died or had stage 3 AKI, including dialysis over the first week, 50 patients died; and 41 had stage 3 AKI, of whom 26 received dialysis. These patients were more likely to be surgical patients and to have higher non-renal APACHE II scores, which measures hospital mortality risk in critically ill patients.

Among patients who had more than one positive variable indicating AKI, (stage 1 SCr, stage 1 UO and [TIMP-2•IGFBP-7] results (2.0)), the risk of stage 3 AKI or death doubled for patients with two positive results indicating AKI and rose by over 16 times when all 3 variables were positive (Figures 1 and 2).

**CONCLUSIONS**
Biomarkers of cell cycle arrest, [TIMP-2•IGFBP-7], in conjunction with SCr and/or UO, improve risk stratification for severe outcomes among patients with stage 1 AKI. Patients with [TIMP-2•IGFBP-7] values above 2.0 had increased risk of death or dialysis at 9 months (Figure 3).

**KEY FINDINGS**
- Patients who develop stage 1 AKI are at high risk of progressing to stage 3 AKI.
- Risk for stage 3 AKI or death increases with each indicator of AKI: SCr, UO and [TIMP-2•IGFBP-7] measurement greater than 2.0.
Figure 1A and 1B. Stage 3 acute kidney injury (AKI) or death by AKI status by SCr and [TIMP-2•IGFBP-7] level relative to the 0.3 (A) and 2.0 (B) cutoffs.

Figure 2A and 2B. Stage 3 acute kidney injury (AKI) or death by AKI status by UO and [TIMP-2•IGFBP-7] level relative to the 0.3 (A) and 2.0 (B) cutoffs.

Figure 3. Death or dialysis within 9 months among patients who were alive and dialysis free at 7 days after enrolment.
**OBJECTIVE**

This prospective, randomized single-center study assessed the impact of renal biomarker-guided implementation of the Kidney Disease: Improving Global Outcomes (KDIGO) care bundle on acute kidney injury (AKI) incidence in patients admitted to the intensive care unit (ICU) after major non-cardiac surgery.

**STUDY DESIGN**

Patients who had intraoperatively received a jugular central venous line and a urinary catheter and had at least one additional risk factor for AKI were screened with the urine biomarker [TIMP-2•IGFBP-7]. Other risk factors included age >75 years, critical illness, pre-existing chronic kidney disease or intraoperative use of an intravenous radiocontrast agent.

One hundred and twenty-one (121) patients with a [TIMP-2•IGFBP-7] value above 0.3 within 4 hours of ICU admit were randomized 1:1 to standard care treatment (n=61) or the KDIGO care bundle (n=60). Patients were stratified by [TIMP-2•IGFBP-7] level: >0.3-2.0 and >2.0. The control group received standard of care treatment including a weekly assessment of medications. Patients in the intervention group received the KDIGO care bundle, including continuous intravenous fluid administration for 6 hours along with nephrology consultation.

The primary endpoint was incidence of AKI during the first 7 days after surgery. Severity of AKI, length of stay (LOS), major kidney events at discharge, and cost effectiveness were also evaluated.

**RESULTS**

In the intervention group, 31.7% of patients were classified as having AKI versus 47.5% in the control group. This difference was not statistically significant. However, in the 0.3-2.0 cohort receiving the care bundle, reduction in AKI incidence was statistically significant compared to controls (27.1% versus 48%, \( p = 0.03 \)).

Biomarker guided care also significantly reduced the incidence of moderate and severe AKI in the intervention group (6.7% versus 19.7%, \( p = 0.04 \)). Median ICU LOS decreased by 1 day in the intervention group and median hospital LOS declined by 5 days. Reducing the ICU LOS by 1 day was associated with a cost savings of £2,031 per patient. Additionally, the relative decrease in urinary biomarker levels 12 hours after surgery was significantly greater in the intervention group, with the greatest declines in the 0.3-2.0 level group.

**CONCLUSIONS**

Early implementation of the KDIGO care bundle based on biomarker-based prediction of imminent AKI significantly reduced the incidence of moderate and severe AKI. Furthermore, postoperative creatinine increases were reduced, along with shorter length of ICU and hospital stay in patients after major non-cardiac surgery, resulting in ICU cost-savings.

“Reducing the incidence and severity of AKI... was caused by prediction of imminent AKI at the very early stage.”

**KEY FINDINGS**

- Early identification of AKI risk and use of the KDIGO care bundle significantly reduces AKI severity and hospital and ICU LOS.
- Intervening early in patients with [TIMP-2•IGFBP-7] levels 0.3-2.0 showed the greatest impact on outcomes, possibly because patients in this range had preventable AKI while patients with higher [TIMP-2•IGFBP-7] levels may have established AKI.
GUIDELINES AND CONSENSUS STATEMENTS
GUIDELINES AND CONSENSUS STATEMENTS

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
2020;3(10):E2019209

Recommendations on Acute Kidney Injury Biomarkers
From the Acute Disease Quality Initiative Consensus Conference.

Ostermann M, Zarbock A, Goldstein S.

This 23rd edition of Acute Disease Quality Initiative (ADQI) is a follow-up consensus meeting from the 10th ADQI in 2011, where the consensus was that there was limited data on novel biomarkers and their use in practice. Since then, new AKI biomarkers have been discovered, evaluated in clinical trials, and some biomarkers have gained official regulatory approval. These include urinary biomarkers, [TIMP-2•IGFBP-7], which are early indicators of kidney injury or stress. There was therefore a need to review this new evidence and develop appropriate recommendations for the use of these AKI biomarkers in routine clinical practice.

This 23rd edition utilized the work of a panel of 23 experts from the fields of nephrology, critical care medicine, surgery, anesthesia, pediatrics and pharmacy. A wide array of publications were assessed and recommendations were made from a 90% consensus amongst the panelists. The panel produced 11 consensus statements for biomarker use each with an associated grade using the Grading of Recommendations, Assessment, Development and Evaluation system. Consensus statements include recommendations related to the following:

• Biomarkers for AKI risk assessment
• Biomarkers for AKI prediction and prevention
• Biomarkers for AKI diagnosis, etiology and management
• Biomarkers to assess AKI progression and kidney recovery.

Specifically regarding urinary biomarkers, [TIMP-2•IGFBP-7], the Consensus Statement recommends:

• using these biomarkers to identify patient populations at risk of developing AKI and for whom preventive interventions have been shown to improve outcomes. Trials (PrevAKI, BigpAK) have demonstrated that initiating timely preventive strategies in patients with positive stress biomarker results after a kidney insult can be effective at preventing AKI.

• using both functional and stress/damage biomarkers concomitantly to optimize dosing and duration of treatment with life-saving, but potentially nephrotoxic drugs and to prevent AKI.

• combining clinical assessment and these newly validated biomarkers to triage patients, improve risk stratification in critically ill patients, and optimize the timing and type of interventions designed to improve patient management and outcomes. This combined approach provides information that may support changes in care processes and guide therapy.

CONCLUSIONS

Progress made in the field of AKI biomarkers over the past decade has led to improved outcomes through biomarker-guided algorithms and goal-directed management protocols. Evidence from clinical trials substantiates the routine use of new biomarkers for AKI prevention and management. By indicating kidney stress before permanent damage occurs, these new biomarkers support the possibility of reversing AKI and positively impacting patient recovery. The consensus recommendations of this 23rd ADQI meeting aim to support clinicians in the use of these biomarkers in their daily practice. Gaps in knowledge remain and more research is needed to further improve management of AKI.

“... the prospect of clearer identification of high-risk patients and different AKI sub-phenotypes and the integration of appropriately selected biomarkers in routine clinical practice hold the key to further improvement in AKI care.”

KEY FINDINGS

- Current evidence from clinical trials support the use of biomarkers for management and prevention of AKI.
- Several novel biomarkers can detect AKI earlier and with more sensitivity when compared to serum creatinine.
- The integration of such novel biomarkers in routine clinical practice has the potential to improve acute kidney injury care.
- The use of validated biomarkers is recommended to identify patient populations for whom preventive interventions have been shown to improve outcomes.
Figure 1. Refined Staging System for the diagnosis of Acute Kidney Injury (AKI).

A - CURRENT DIAGNOSTIC AKI CRITERIA

| AKI stage 1 | Increase in SCr level OR Decrease in UO |

B - EXPANDED DIAGNOSTIC AKI CRITERIA

| AKI stage 1S | BM positive AND No increase in SCr level AND No decrease in UO |
| AKI stage 1A | BM negative AND Increase in SCr level OR Decrease in UO |
| AKI stage 1B | BM positive AND Increase in SCr level OR Decrease in UO |

C - REASSESSMENT DIAGRAM

Resolution

| BM negative: no increase in SCr level or decrease in UO | BM positive: no increase in SCr level or decrease in UO |
| BM negative: increase in SCr level or decrease in UO | BM positive: increase in SCr level or decrease in UO |

AKI stage 1S

AKI stage 1A

Progression

AKI stage 1B

AKI: acute kidney injury; BM: biomarker; SCr: serum creatinine; UO: urine output

Patients with a biomarker of injury positivity without increase or decrease in SCr level and not reaching UO criteria should be classified as 1S. Reassessment should be performed according to patient clinical context and temporal trends. Patients reaching SCr and UO criteria with no increase on BM are defined as stage 1A, and those reaching SCr and UO criteria with increased BM are reclassified as stage 1B. BM positivity should be based on its mechanism defined threshold.

Figure 2. Proposed new definition of Acute Kidney Injury.

<table>
<thead>
<tr>
<th>FUNCTIONAL CRITERIA</th>
<th>STAGE</th>
<th>DAMAGE CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change or SCr level increase &lt;0.3 mg/dL and no UO criteria</td>
<td>1S</td>
<td>Biomarker positive</td>
</tr>
<tr>
<td>Increase of SCr level by &gt;0.3 mg/dL for ≤48 h or &gt;150% for ≤7 days and/or UO &lt;0.5 mL/kg/h for &gt;6 h</td>
<td>1A</td>
<td>Biomarker negative</td>
</tr>
<tr>
<td>Increase of SCr level by &gt;200% and/or UO &lt;0.5 mL/kg/h for &gt;12 h</td>
<td>1B</td>
<td>Biomarker positive</td>
</tr>
<tr>
<td>Increase of SCr level by &gt;300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO &lt;0.3 mL/kg/h for &gt;24 h or anuria for &gt;12 h and/or acute KRT</td>
<td>3A</td>
<td>Biomarker negative</td>
</tr>
<tr>
<td>Increase of SCr level by &gt;300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO &lt;0.3 mL/kg/h for &gt;24 h or anuria for &gt;12 h and/or acute KRT</td>
<td>3B</td>
<td>Biomarker positive</td>
</tr>
</tbody>
</table>

KRT: kidney replacement therapy; SCr: serum creatinine; UO: urine output

Functional markers include SCr and UO but new functional markers may also be included.

Nadim M, Forni L, Mehta R.

The novel Corona virus first identified in December of 2019 (COVID-19) has evolved into a global pandemic resulting in countless deaths and impacting the global healthcare system severely. One of the many sequelae associated with COVID-19 is acute kidney injury (AKI). Rapidly evolving data has shown that AKI occurs in over half of critically ill COVID-19 patients. The ADQI panel consists of experts in nephrology and critical care from around the world. This latest convention of the group met with the purpose of providing consensus positions on COVID-19 and AKI, using the recognized ADQI methodology and format. These statements center around recommendations for diagnosis, prevention and management of COVID-19 AKI and areas identified for future research.

The consensus statements included positions on the pathophysiology, epidemiology and clinical course of COVID-19-associated AKI, as well as prevention and management strategies, Renal Replacement Therapy (RRT), optimized anticoagulation strategies and use of extracorporeal blood purification (EBP) techniques.

**DIAGNOSIS**

Specifically regarding the diagnosis of COVID-19-associated AKI (COVID-19 AKI), the Consensus Statement recommends use of the Kidney Disease: Improving Global Outcomes (KDIGO) consensus definition for AKI. This includes the use of serum creatinine level and urine output in clinical practice, as well as kidney-specific tests and measures of kidney function to characterize clinical presentations, course and outcomes of AKI.

The Statement reported several studies in which urinalysis and biomarkers of AKI were frequently found to be abnormal in COVID-19 patients and could therefore be useful to characterize AKI in such patients.

It was also observed that patients with COVID-19 AKI and high levels of urinary biomarkers [TIMP-2•IGFBP-7], were more likely to progress to RRT than patients with AKI but with low [TIMP-2•IGFBP-7]. Furthermore, higher levels of systemic markers of inflammation, particularly ferritin, C-reactive protein, procalcitonin and lactate dehydrogenase, have been reported in patients with COVID-19 AKI.

**CLINICAL COURSE AND PROGNOSIS**

Further study of the mechanism, timing and clinical implications of traditional markers of AKI (proteinuria and haematuria) as well as novel biomarkers for the diagnosis and prognosis of AKI is needed.

**CONCLUSIONS**

COVID-19 AKI is more common than initially thought and is associated with high mortality. Although rates of COVID-19 AKI vary considerably between studies and regions, an incidence of over 20% in hospitalized patients is widely observed. The pathogenesis of AKI in patients with COVID-19-AKI is likely multifactorial. Given that the risk factors, mechanisms and patient outcomes are similar between COVID-19 AKI and AKI of non-viral origin in the ICU, the treatment recommendations and preventative measures proposed in this Consensus Statement are therefore frequently common to both.

“Patients with COVID-19 AKI and high levels of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein-7 [TIMP-2•IGFBP-7] were more likely to progress to RRT than patients with AKI but with low [TIMP-2•IGFBP-7].”

**KEY FINDINGS**

- AKI is now a recognized complication of SARS-CoV-2 infection.
- COVID-19 AKI is associated with adverse outcomes and a greater use of healthcare resources.
- Consensus recommends using KDIGO criteria for diagnosing and staging AKI in practice.
- Use of traditional markers and novel biomarkers are recommended in clinical practice to characterize clinical presentations, course and outcomes of AKI, as per KDIGO consensus definition.
Figure 1. Pathogenesis of COVID-19 AKI*.

*The pathogenesis of AKI in patients with COVID-19-AKI is likely multifactorial, involving both the direct effects of SARS-CoV-2 virus on the kidney and the indirect mechanisms resulting from systemic consequences of viral infection or effects of the virus on distant organs including the lung, in addition to mechanisms relating to the management of COVID-19.
REFERENCES

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