BIOMÉRIEUX

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

TIMP-2
IGFBP-7

PIONEERING DIAGNOSTICS

"AKI* occurs in 13.3 million people every year"[1]
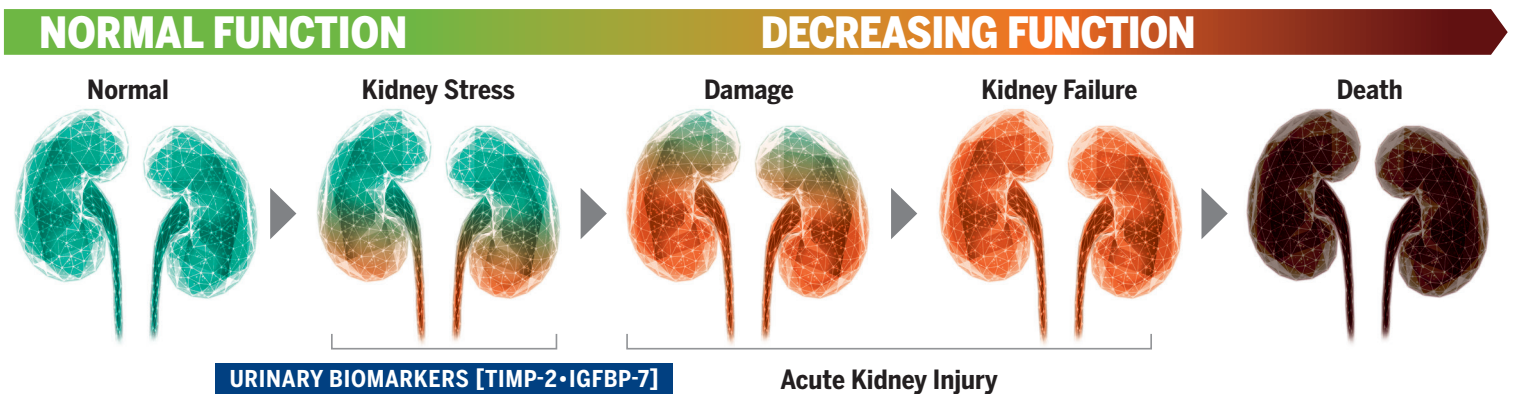
"More than 50% of ICU patients have AKI"[2]

"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]

NORMAL FUNCTION   **DECREASING FUNCTION**

| Normal | Kidney Stress | Damage | Kidney Failure | Death |

URINARY BIOMARKERS [TIMP-2•IGFBP-7]   Acute Kidney Injury

* 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

PREFACE

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).[8,9] 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.[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.[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.[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 **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 **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.[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.[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.[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.[20]

Based on existing data, a recent international expert committee recommended the **integration of new AKI biomarkers into routine clinical practice**.[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.

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ADDITIONAL RECOMMENDED READING (continued)

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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The impact of biomarkers of acute kidney injury on individual patient care.

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Acute Kidney Stress and Prevention of Acute Kidney Injury.

Katz NM, Kellum JA, Ronco C.
CRITICAL CARE MEDICINE 2019;47(7):993-996

Perioperative Acute Kidney Injury: Risk Factors and Predictive Strategies.

Hobson C, Ruchi R, Bihorac A.
CRITICAL CARE CLINICS 2017;33(2):379-396

Cell-cycle arrest and acute kidney injury: the light and the dark sides.

Kellum JA, Chawla LS.
NEPHROLOGY DIALYSIS TRANSPLANTATION 2016;31(1):16-22

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
PLOS ONE 2019;14(11):e0224655

Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery.

Husain-Syed F, Ferrari F, Sharma A, et al.
NEPHROLOGY DIALYSIS TRANSPLANTATION 2019;34(2):308-317

Global epidemiology and outcomes of acute kidney injury.

Hoste EAJ, Kellum JA, Selby NM, et al.
NATURE REVIEWS NEPHROLOGY 2018;14(10):607-625.

Financial Impact of Acute Kidney Injury After Cardiac Operations in the United States.

Alshaikh HN, Katz NM, Gani F, et al.
ANNALS OF THORACIC SURGERY 2018;105(2):469-475

ABBREVIATIONS & ACRONYMS

ACE-I	angiotensin-converting-enzyme inhibitor
ADQI	Acute Dialysis Quality Initiative
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
AKI-EPI	Acute Kidney Injury-Epidemiological Prospective Investigation
AKIN	Acute Kidney Injury Network
AKRT	Acute Kidney Response Team
APACHE	Acute Physiology And Chronic Health Evaluation
ARB	angiotensin II receptor blocker
AUC	area under the curve
BUN	blood urea nitrogen
CDSS	Computer Decision Support System
CHF	congestive heart failure
CI	cardiac index
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disorder
CSA-AKI	cardiac surgery-associated acute kidney injury
CVP	central venous pressure
EMR	electronic medical record
GFR	glomerular filtration rate
HR	heart rate
HVCC	Heart & Vascular Critical Care (Unit)
ICU	Intensive Care Unit
IGFBP	insulin-like growth factor-binding protein
KDIGO	Kidney Disease: Improving Global Outcomes
LOS	length of stay
MAKE	major adverse kidney events
NGAL	neutrophil gelatinase-associated lipocalin
NHS	National Health Service (UK)
NIS	National Inpatient Sample
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	odds ratio
PAD	pulmonary artery diastolic pressure
PCT	procalcitonin
RCT	randomized controlled trial
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RR	relative risk
RRT	Renal Replacement Therapy
S-AKI	sepsis-associated acute kidney injury
SAPS	Simplified Acute Physiology Score
SBP	systolic blood pressure
SCr	serum creatinine
SOC	standard of care
SOFA	Sequential Organ Failure Assessment
STS	Society of Thoracic Surgeons
SVO2	mixed venous oxygen saturation
TIMP	tissue inhibitor of metalloproteinases
UB	urinary biomarker
UO	urine output

ACUTE KIDNEY INJURY (AKI)

ACUTE KIDNEY INJURY (AKI)

Acute kidney injury.

Ronco C, Bellomo R, Kellum JA..

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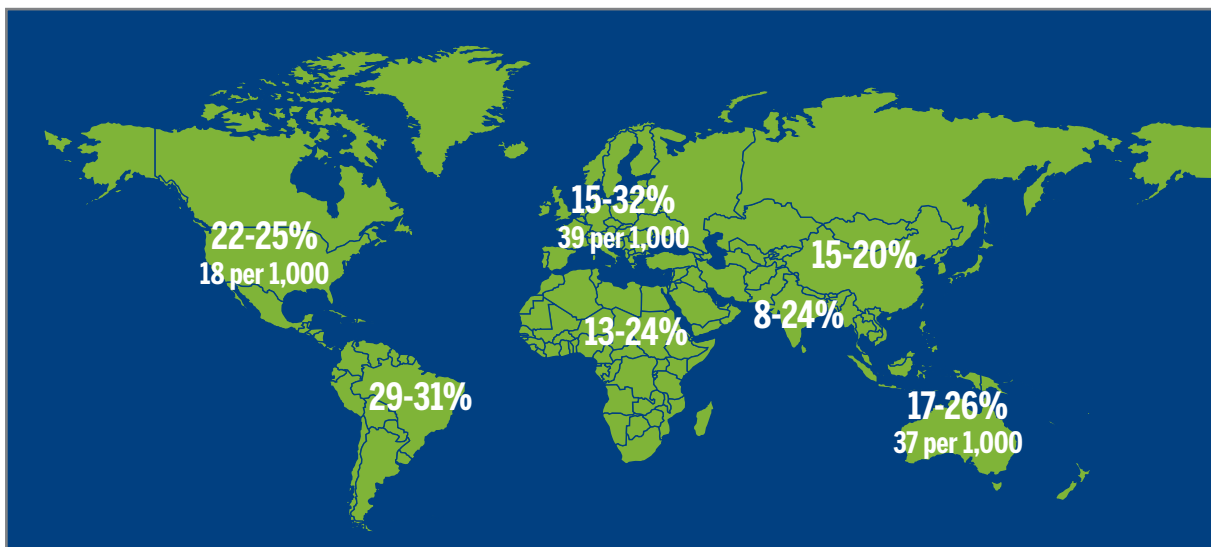
"New biomarkers and advanced diagnostic techniques represent an important advancement in the field, leading to implementation of timely and effective preventive and protective measures."

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.

ACUTE KIDNEY INJURY (AKI)

Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study.

Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA.

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)

Prevention of acute kidney injury.

Meersch M, Volmering S, Zarbock A.

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.

Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment.

Peerapornratana S, Manrique-Caballero CL, Gomez H, Kellum JA..

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. S-AKI 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.

Metabolic reprogramming involves reprioritizing energy to meet vital metabolic needs by maintaining survival at the expense of cell function **(Figure 1)**. For example, during the cell cycle, if the cell does not have sufficient energy to replicate, it will undergo cell cycle arrest to avoid cell death. Cell cycle arrest is therefore one of the mechanisms used in metabolic reprogramming to defend the body against sepsis.

ROLE OF BIOMARKERS

Novel biomarkers of kidney stress and damage have been recently validated for risk prediction and early diagnosis of S-AKI **(Figure 2)**. 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 reprioritization of energy consumption
Adapted from Peerapornratana S, et al. *Kidney International* 2019;96(5):1083-1099
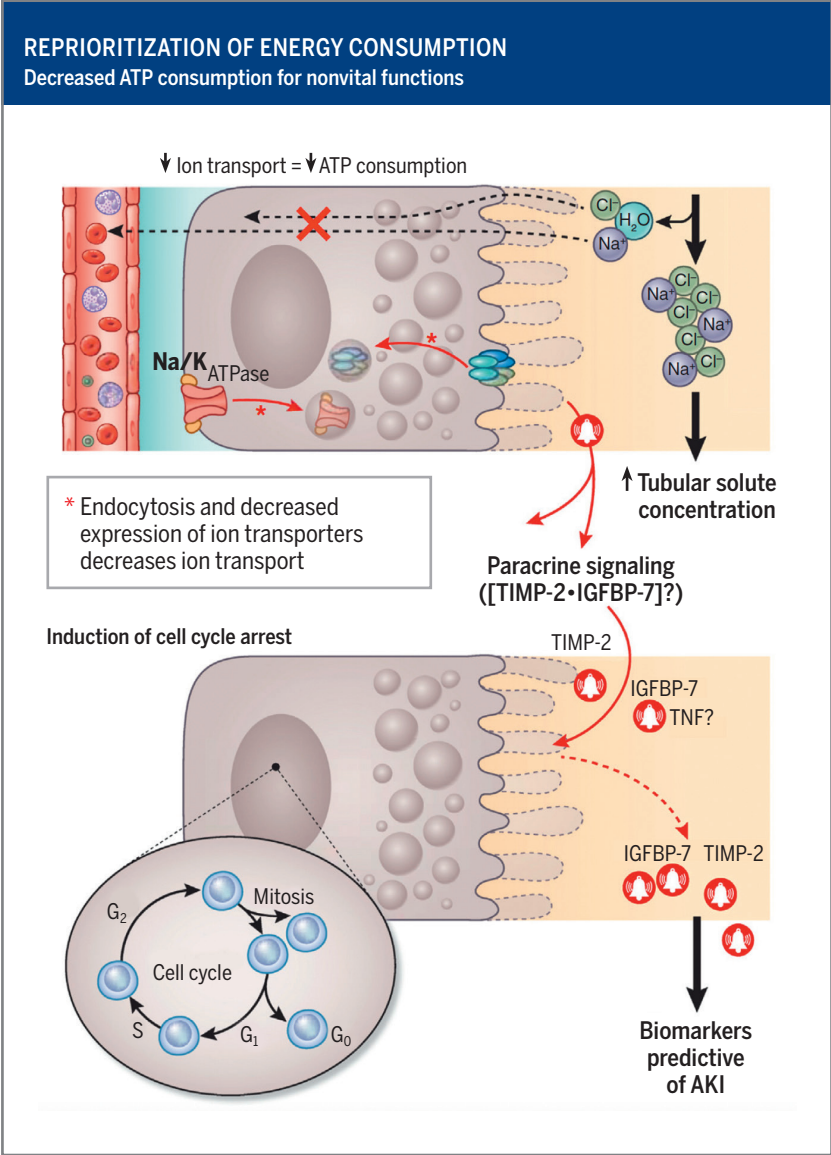
ATP: adenosine triphosphate; G0–G2: phases of the cell cycle; IGFBP-7: insulin-like growth factor-binding protein-7; TIMP-2: tissue inhibitor of metalloproteinases-2; TNF: tumor necrosis factor

ACUTE KIDNEY INJURY (AKI)

Figure 2. Clinical course and outcomes of S-AKI, with management and potential roles of biomarkers
Adapted from Peerapornratana S, et al. *Kidney International* 2019;96(5):1083-1099
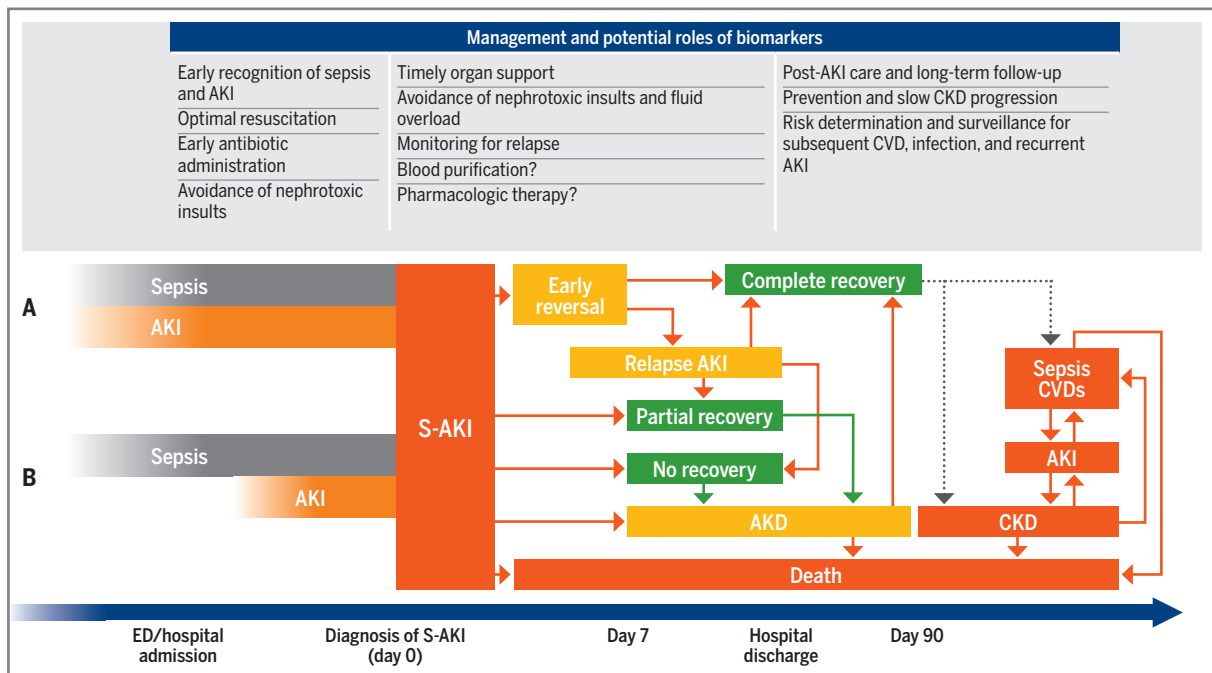
AKI: acute kidney injury; AKD: acute kidney disease; CKD: chronic kidney disease; CVD: cardiovascular disease; S-AKI: sepsis-associated acute kidney injury; ED: emergency department

The exact onset of AKI in sepsis is not well elucidated. AKI may present simultaneously with sepsis at hospital admission **(A)** or develop during hospitalization **(B)**. Novel biomarkers have a place in the early risk assessment of S-AKI, and can guide resuscitation which ultimately can prevent the adverse outcomes associated with S-AKI. Those adverse outcomes include; increased hospital mortality, and post discharge complications such as development of AKD which can subsequently lead to CKD. These post-discharge complications may still arise in patients who have been discharged in seemingly good health, highlighting the need for more intense monitoring and avoidance of renal insults even after early reversal from S-AKI.

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

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]

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury.

Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA.

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.**

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

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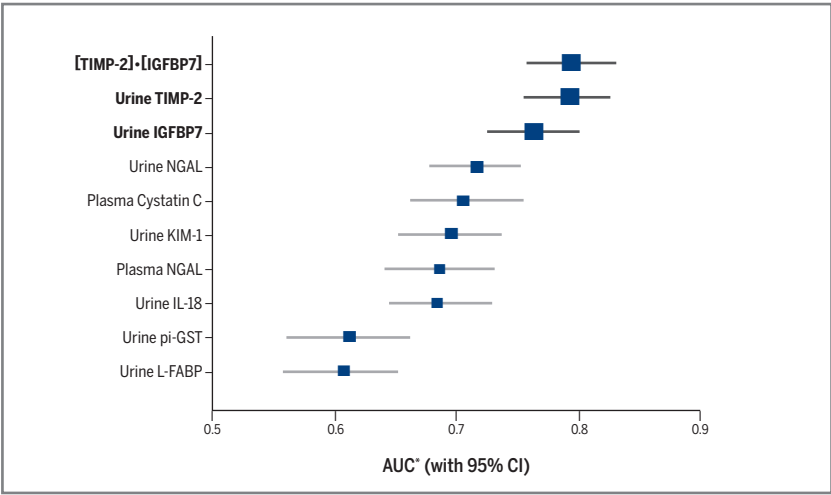
*The AUC is a single measure of diagnostic test accuracy that combines sensitivity and specificity.

CI: confidence interval; IGFBP-7: insulin-like growth factor-binding protein-7; IL-18: interleukin-18; 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

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
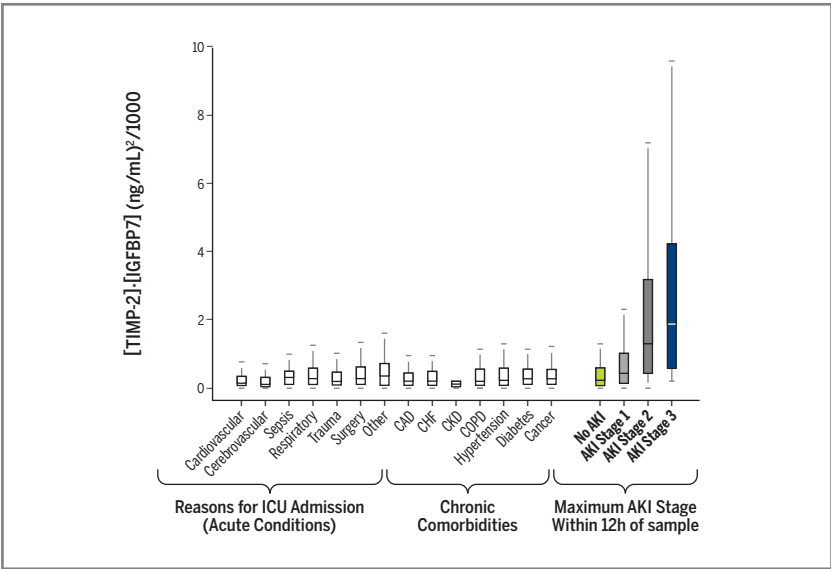
CI: confidence interval; IGFBP-7: insulin-like growth factor-binding protein-7; IL-18: interleukin-18; KIM-1: kidney injury marker-1; L-FABP: liver fatty acid-binding protein; NGAL: neutrophil gelatinase-associated lipocalin; pi-GST: pi-Glutathione S-transferase; TIMP-2: tissue inhibitor of metalloproteinases-2

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel.

Guzzi LM, Bergler T, Binnall B, Engelman DT, Forni L, Germain MJ, Gluck E, Göcze I, Joannidis M, Koyner JL, Reddy VS, Rimmelé T, Ronco C, Textoris J, Zarbock A, Kellum JA.

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

Adapted from Guzzi LM, et al. *Critical Care* 2019;23(1):225. doi:10.1186/s13054-019-2504-8

Potential AKI Risk Patients

- Cardiovascular/respiratory compromise <24 h (~21 y)
- Shock
- Sepsis (suspicion/confirmation)
- Post-operative major/cardiac surgery
- Trauma with cardiac/respiratory compromise
- Other

>0.3 Moderate/Severe AKI Risk

≤0.3 Low AKI Risk

0.3

AKI Risk Score

Nephroprotective Bundle

- Discontinue all nonessential nephrotoxins (e.g., NSAIDs)
- Avoid vancomycin or dose-adjust
- Goal-directed fluid/diuretic management*
- Discontinue all ACEs and/or ARBs
- Maintain close UO monitoring
- Review meds with clinical pharmacist
- Retain invasive hemodynamic monitoring
- Avoid saline
- Consult Nephrology
- Repeat [TIMP-2•IGFBP-7] test in 12-24h
- Consult Intensive Care

AKI Risk Increase: Kidney Stress Origin

What is causing increased kidney stress?

- Additional patient evaluation
- Consider existing or additional treatments/consults

Standard of Care

- Standard of care or fast-track
- Repeat [TIMP-2•IGFBP-7] test if additional exposures occur
- Consider diuretics to maintain fluid balance

AKI Prevented: Standard of Care

Triage/Fast-Track/Step-Down

- Continue monitoring

Golden Hours of AKI Prevention†   4   12   24   48

[TIMP-2•IGFBP-7] Testing
6-12 h post /CU admission or deemed critically ill

* Includes bedside ultrasound and functional hemodynamic monitoring.
† Consider additional testing with any significant change in patient condition or insult.

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.

McCullough PA, Ostermann M, Forni LG, Bihorac A, Koyner JL, Chawla LS, Shi J, Kampf JP, McPherson P, Kellum JA.

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.

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

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

Among the first 3 values									
3 consecutive >0.3		211	161	139	132	123	113	99	88
2 consecutive >0.3		76	63	57	50	48	45	40	37
1 consecutive >0.3		128	117	110	103	95	90	61	68
None >0.3		115	113	107	100	88	82	74	69

Starting from the first value >0.3									
3 consecutive >2.0		18	5	1	1	1	1	1	1
2 consecutive >2.0		12	4	3	3	3	3	2	2
1 consecutive >2.0		66	44	35	30	29	26	25	25
None >2.0		314	283	263	247	229	214	188	162
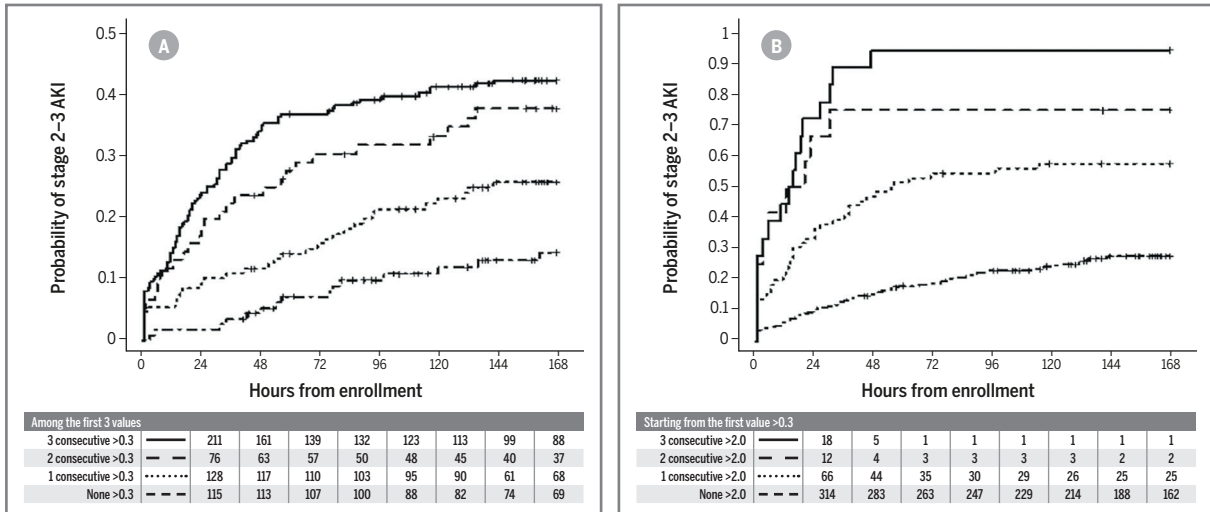
Figure 2. Incidence of stage 2/3 AKI within 1 week of enrollment by number of [TIMP-2•IGFBP-7] values ≤0.3 (a) and >2.0 (ng/mL)^2/1,000 (b) among the first 7 measurements collected approximately 12 h apart

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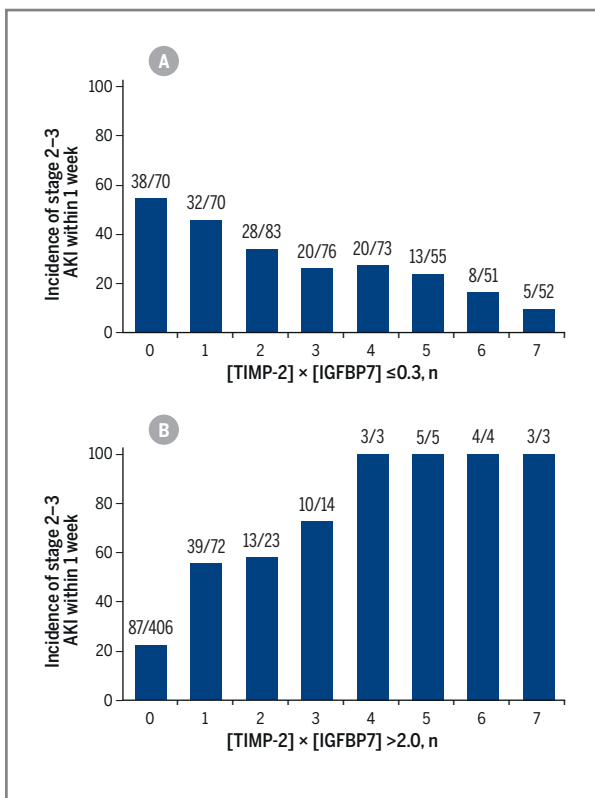
Figure 3. Evolution of patients with [TIMP-2•IGFBP-7] values >0.3 to ≤2.0 (ng/mL)^2/1,000 over the first 7 consecutive [TIMP-2•IGFBP-7] measurements collected approximately 12 h apart

Adapted from McCullough PA, et al. *Cardiorenal Medicine* 2019;9(6):358-369
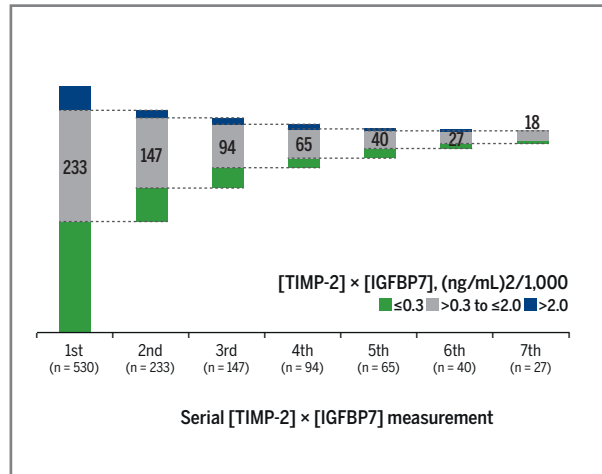
Box shadings show number of patients who started within each [TIMP-2•IGFBP-7] level (1st column) or decreased to ≤0.3 (ng/mL)^2/1,000 (gray), remained at >0.3 to ≤2.0 (ng/mL)^2/1,000 (white), or increased to >2.0 (ng/mL)^2/1,000 (black).

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.

Godi I, De Rosa S, Martino F, Bazzano S, Martin M, Boni E, Carta MR, Tamayo Diaz C, Mari G, Lorenzin A, de Cal M, Corradi V, Caprara C, Giavarina D, Ronco C.

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 $(ng/mL)^2/1000$ 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

"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."

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.

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Table 1. Risk assessment for primary and secondary outcomes in the entire population and in septic and non-septic subgroups
Adapted from Godi I, et al. *Annals of Intensive Care* 2020;10:46

Variables	Analysis cohort			Sepsis			Non-sepsis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Primary outcome									
AKI within 48 h									
[TIMP-2•IGFBP-7] > 0.3	3.93[a]	2.14–7.20	< 0.001	5.92[a]	2.53–13.82	< 0.001	3.27[a]	1.53–6.97	< 0.001
PCT > 0.5	3.67[a]	2.17–6.19	< 0.001	2.74[a]	0.87–8.57	0.083	4.85[a]	2.37–9.94	< 0.001
Single-marker positivity	4.08	1.90–8.76	< 0.001	2.27	0.45–11.23	0.316	4.93	2.05–11.82	< 0.001
Double-marker positivity	26.41	12.32–56.62	< 0.001	19.5	4.20–90.44	< 0.001	25.11	9.58–65.79	< 0.001
Secondary outcomes									
AKD at 7 days									
Single-marker positivity	4.73	1.04–21.60	0.045	2.28	0.26–20.02	0.15	3.24	0.65–16.20	0.151
Double-marker positivity	15.92	3.67–68.97	0.001	4.57	0.48–36.25	0.15	15.36	3.21–73.57	0.001
Mortality within 7 days									
Single-marker positivity	1.16	0.51–2.65	0.724	0.86	0.77–2.75	0.494	1.59	0.63–4.05	0.329
Double-marker positivity	2.75	1.34–5.65	0.006	4.1	1.41–11.78	0.001	2.01	0.75–5.40	0.166

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
[TIMP-2•IGFBP-7]: tissue inhibitor metalloproteinases-2 and insulin-growth factor-binding protein-7 product; PCT: procalcitonin
a) Odds ratios (OR) were adjusted for Sequential Organ Failure Assessment (SOFA) and estimated glomerular filtration rate (eGFR) at the time of admission

Table 2. Patients' outcomes in the overall population and in septic and non-septic subgroups
Adapted from Godi I, et al. *Annals of Intensive Care* 2020;10:46

	Analysis cohort	Sepsis	Non-sepsis	*p*-value
Patients	433	181	252	
AKI at ICU admission	**26 (6.0)**	**14 (7.7)**	**12 (4.8)**	**0.001***
Stage 1	14 (3.2)	8 (4.4)	6 (2.4)	
Stage 2	5 (1.1)	2 (1.1)	3 (1.2)	
Stage 3	7 (1.6)	4 (2.2)	3 (1.2)	
AKI within 24 h	**149 (34.4)**	**82 (45.3)**	**67 (26.6)**	**<0.001***
Stage 1	46 (10.6)	25 (13.8)	21 (8.3)	
Stage 2	38 (8.8)	19 (10.5)	19 (7.5)	
Stage 3	65 (15.0)	38 (21.0)	27 (10.7)	
AKI within 48 h	**168 (38.8)**	**93 (51.4)**	**75 (29.8)**	**<0.001***
Stage 1	55 (12.7)	31 (17.1)	24 (9.5)	
Stage 2	44 (10.2)	22 (12.2)	22 (8.7)	
Stage 3	69 (15.9)	40 (22.1)	29 (11.5)	
RRT need	33 (7.6)	18 (9.9)	15 (6.0)	
AKD at 7 days	**47 (10.8)**	**26 (14.4)**	**21 (8.3)**	**<0.01***
Stage 0	15 (3.5)	10 (5.5)	5 (2.0)	
Stage 1	9 (2.1)	5 (2.8)	4 (1.6)	
Stage 2	7 (1.6)	4 (2.2)	3 (1.2)	
Stage 3	16 (3.7)	7 (3.9)	9 (3.6)	
RRT need	14 (3.2)	7 (3.9)	7 (2.8)	
7 days mortality	**65 (15.0)**	**37 (20.4)**	**28 (11.1)**	**<0.01***
ICU mortality	**100 (23.1)**	**50 (27.6)**	**50 (19.8)**	**0.57**
Days in ICU	**4 (2-11)**	**4 (2–10)**	**4 (2–11)**	**0.77**
Hospital mortality	**128 (29.6)**	**64 (35.4)**	**64 (25.4)**	**0.37**
Days in hospital	**15 (7–31)**	**13 (6–30)**	**15 (7–31)**	**0.27**

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.

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

Ostermann M, McCullough PA, Forni LG, Bagshaw SM, Joannidis M, Shi J, Kashani K, Honore PM, Chawla LS, Kellum JA.

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.

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Figure 1. Biomarker kinetics in association with specific exposures

Adapted from Ostermann M, et al. *Critical Care Medicine* 2018;46(3):375-383
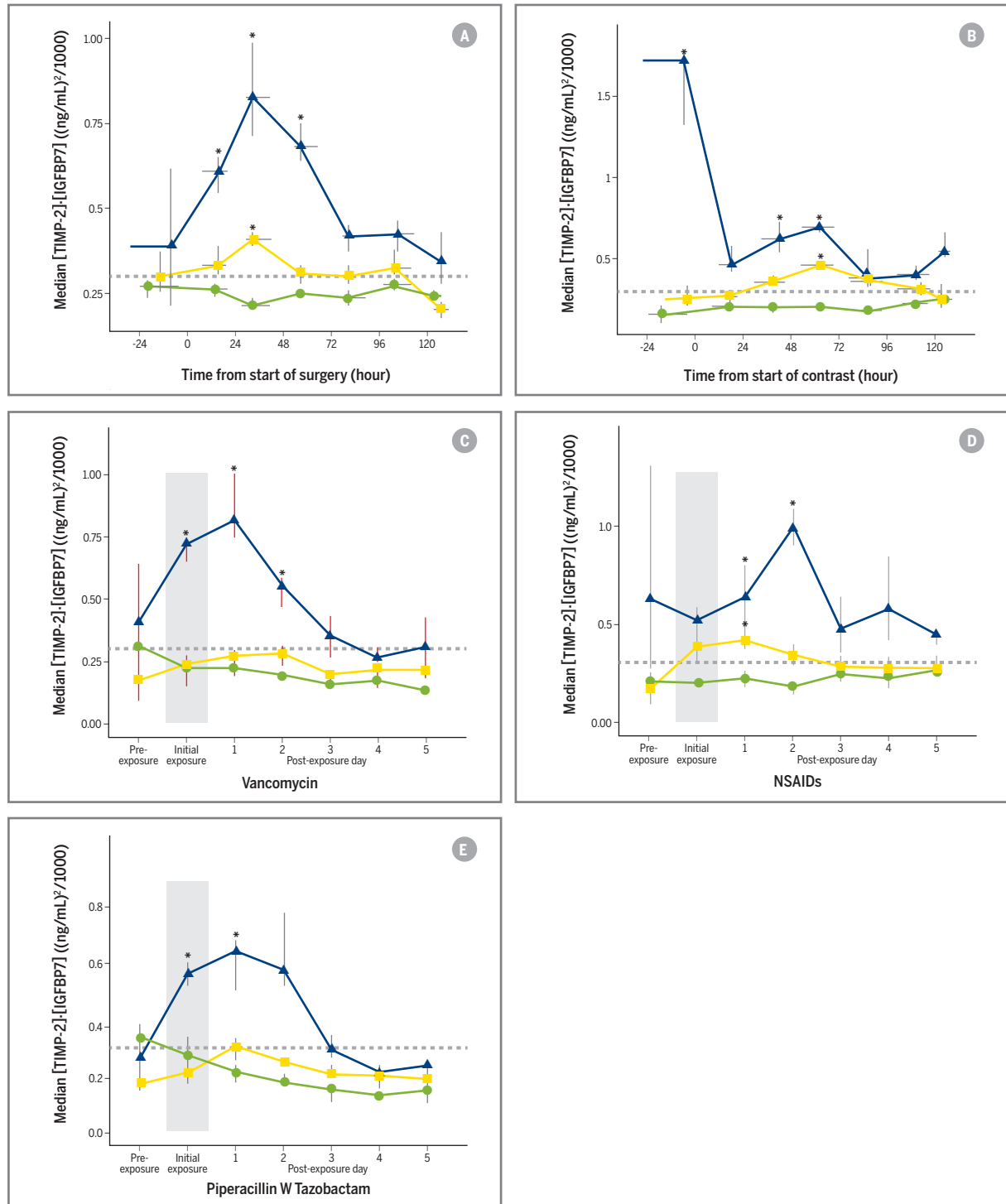
Time course of urinary [TIMP-2•IGFBP-7] concentrations relative to the time or day of exposure by acute kidney injury (AKI) stage for patients exposed to **(A)** major surgery, **(B)** IV contrast, **(C)** vancomycin, **(D)** nonsteroidal anti-inflammatory drugs (NSAIDs) or **(E)** piperacillin/tazobactam.

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.

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

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.

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

Adapted from Engelman DT, et al. *Journal of Thoracic and Cardiovascular Surgery* 2020;160(5):1235-1246.e2

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)

	Serum Creatinine	Urine Output
2	Increase of 2.0 - 2.9 x baseline	<0.5 ml/kg/h for 12 hours
3	Increase of >3x baseline or increase of SCr to >4 mg/dL or initiation of RRT	<0.3 ml/kg/h for 24 h or anuria for 12 hours

WHEN & HOW TO TEST

1. Patient meets test inclusion: at 05:30 am PO DI 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.

AKI: Acute kidney injury; SCr: serum creatinine; RRT: renal replacement therapy; EMR: electronic medical record; HVCC: Heart&Vascular Critical Care Unit; AKRT: acute kidney response team; CI: cardiac index; HR: heart rate; ARB: angiotensin II receptor blocker; ACE-I: angiotensin-converting-enzyme inhibitor; GFR: glomerular filtration rate; NSAIDS: nonsteroidal anti-inflammatory drugs; CVP: central venous pressure; PAD: pulmonary artery diastolic pressure; CHF: congestive heart failure; SBP: systolic blood pressure; SVO$_2$: mixed venous oxygen saturation.

NC/ACUTE KIDNEY RESPONSE TEAM (AKRT) 2.0		
NEG <0.3	(+) 0.3-2.0	HIGH (+) >2.0
FAST TRACK	TELE UNIT @ 4PM	ACTIVATE AKRT
Remove Foley, arterial line, central line. Transfer to telemetry if meeting all other criteria (CI/HR/Resp. fxn) liberal diuretics.	Keep Foley and monitor hourly UO until afternoon rounds. Transfer to telemetry (alter 4PM) if all other transfer criteria are met (CI/HR/Resp. fxn) and no oliguria treatment was required.	Keep Foley and monitor hourly UO. Maintain hemodynamic monitoring.
MAY USE: ARBs/ACE-I, Toradol prn (if pre-op GFR>60) Consider holding diuretics if Toradol given.	**AVOID NEPHROTOXINS** NSAIDS, ARBs/ACE-I, Vanco/Gentamycin Transfusion threshold hemoglobin <7.0 unless oliguric.	**AVOID NEPHROTOXINS** NSAIDS, ARBs/ACE-I, Vanco/Gentamycin Renal dosing of medications.
Transfusion threshold hemoglobin <7.0 Check SCr daily	**IF PT BECOMES OLIGURIC:** (UO <0.5 cc/kg/hr X 3 hours) activate AKRT/Nephrology consult. Use lactated ringers boluses if CVP<8; PAD<14; Hold Lasix unless pulmonary edema. Repeat NC in 24hr	Goal directed therapy (keep PAD>14 with LR, No diuretics unless PAD>20 or CHF), reassess transfusion threshold. CI >2.5, SBP>130. Monitor SVO$_2$, Echo if <55% Nephrology Consult Repeat NC in 24hr

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

Adapted from Engelman DT, et al. *Journal of Thoracic and Cardiovascular Surgery* 2020;160(5):1235-1246.e2

Moderate to Severe AKI (Stage 2 or 3) reduced by 89%

p=0.01

Percent of Cardiac Surgery Patients with Stage 2 or 3 Acute Kidney Injury

- Pre-Urinary Biomarkers (UB)
- Post-Urinary Biomarkers (UB) Whith an Acute Kidney Response Team
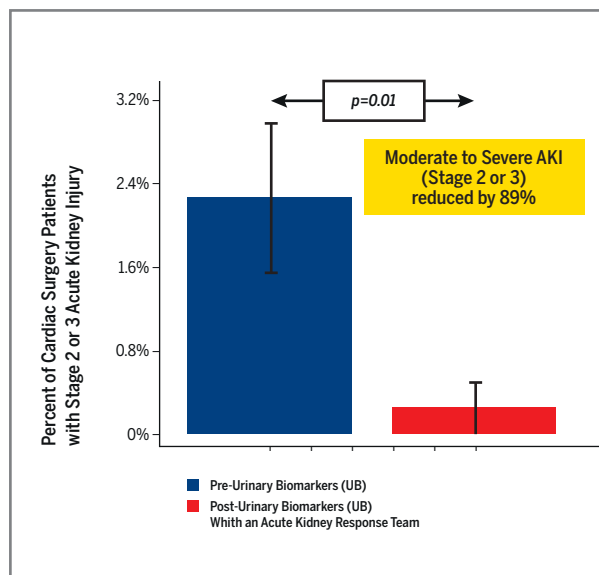
Figure 3. Responses to negative (<0.3), low positive (0.3-2.0), and high positive (>2.0), urinary biomarker values (NEPHROCHECK®) on the morning after surgery and the resultant decrease in stage 2/3 acute kidney injury

Adapted from Engelman DT, et al. *Journal of Thoracic and Cardiovascular Surgery* 2020;160(5):1235-1246.e2

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%

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Intraoperative prediction of cardiac surgery-associated acute kidney injury using urinary biomarkers of cell cycle arrest.

Cummings JJ, Shaw AD, Shi J, Lopez MG, O'Neal JB, Billings FT.

OBJECTIVE

Investigators tested the hypothesis that intraoperative concentrations of urinary [TIMP-2•IGFBP-7] are associated with postoperative AKI.

STUDY DESIGN

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.

RESULTS

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.

CONCLUSIONS

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."

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Figure 1. Median perioperative urinary [TIMP-2•IGFBP-7] and serum creatinine concentrations in patients with No AKI (green), Stage 1 AKI (blue), and Stage 2/3 AKI (red)

Adapted from Cummings JJ, et al. *Journal of Thoracic and Cardiovascular Surgery* 2018;157(4):1545-1553.e5

Intraoperative elevations of [TIMP-2•IGFBP-7] can predict moderate-severe AKI and could provide opportunity to alter post-operative management to prevent kidney injury.

Vertical lines through the symbols show the interquartile range of bootstrap medians for the [TIMP-2•IGFBP-7] and creatinine concentrations.
*$p<0.05$ for comparing the distributions of [TIMP-2•IGFBP-7] or creatinine values to the distributions among patients without AKI.
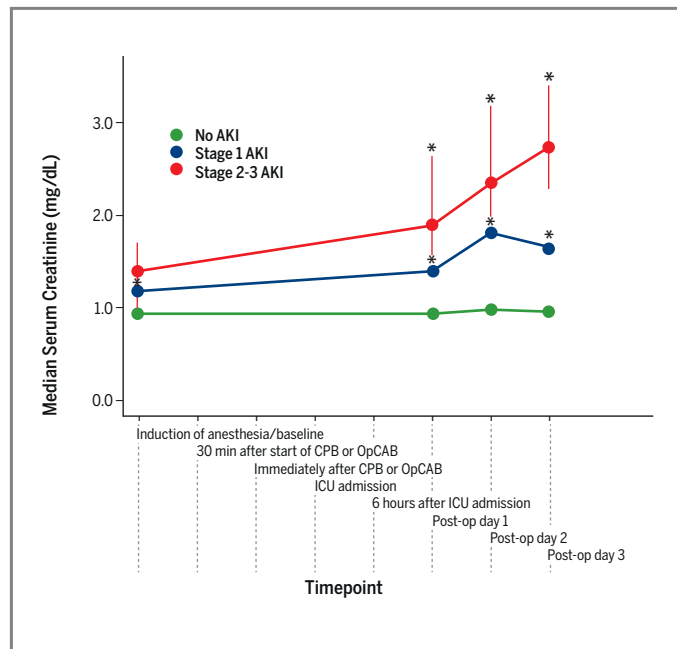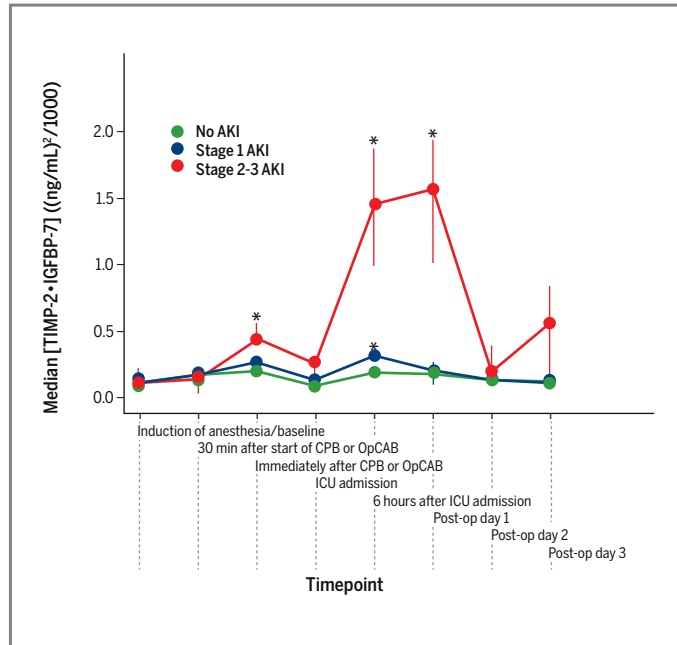
KEY FINDINGS

→ 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.

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial.

Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A.

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.
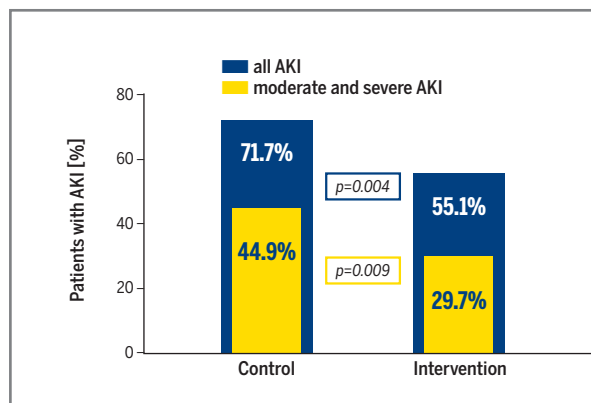
Figure 1. Occurrence of cardiac surgery-associated AKI (CSA-AKI) and rate of CSA-AKI in control and intervention groups
Adapted from Meersch et al. *Intensive Care Medicine* 2017;43(11):1551-1561

"Biomarkers may allow one to implement preventive and protective measures well before clinical AKI becomes manifest according to well-established definitions."

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

HEALTH ECONOMICS AND OUTCOMES STUDIES

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

Berdugo MA, Noam Y. Zimmer L, Beyhaghi H, Toback S, Scarpati LM, Stone MN, Dember R, Tseng-Tham J, Wen J, Miller M.

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."

KEY FINDINGS

➡ The use of [TIMP-2•IGFBP-7] to identify acute kidney injury risk may reduce costs for hospitals by approximately $1,578 per patient tested.

➡ Adding [TIMP-2•IGFBP-7] as a novel tool may decrease time to identification of AKI risk, treatment and may result in shorter lengths of stay, fewer 30-day readmissions and overall hospital costs.

HEALTH ECONOMICS AND OUTCOMES STUDIES

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

	No AKI	Mild	Moderate	Severe	Total
Per tested patient	-$1,227	$0	$2,126	$956	**$1,578**
Overall	-$613,311	$0	$1,063,149	$477,766	**$789,104**

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

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

Resulting budget impact due to reduced uncompensated care among target population	No AKI	Mild	Moderate	Severe	Total
Total ICU costs under SOC	$905,100	$1,322,475	$729,675	$349,590	**$3,306,840**
Total ICU costs with SOC and [TIMP-2•IGFBP-7]	$1,160,085	$1,322,475	$248,164	$118,896	**$2,849,619**
ICU savings with addition of [TIMP-2•IGFBP-7] to SOC	- $254,985	$0	$481,511	$230,694	**$457,221**
Total non-ICU costs under SOC	$1,163,700	$1,937,513	$798,413	$341,205	**$4,240,830**
Total non-ICU costs with SOC and [TIMP-2•IGFBP-7]	$1,491,538	$1,937,513	$271,541	$116,044	**$3,816,636**
Non-ICU, inpatient savings with addition of [TIMP-2•IGFBP-7] to SOC	- $327,838	$0	$526,871	$225,161	**$424,194**
Total readmission costs under SOC	$108,224	$167,360	$82,993	$33,205	**$391,781**
Total readmission costs with SOC and [TIMP-2•IGFBP-7]	$138,713	$167,360	$28,226	$11,293	**$345,591**
Savings on 30-day readmissions with addition of [TIMP-2•IGFBP-7] to SOC	-$30,489	$0	$54,767	$21,912	**$46,189**
Total cost of uncompensated care under SOC	$2,177,024	$3,427,347	$1,611,080	$724,000	**$7,939,451**
Total cost of uncompensated care with SOC and [TIMP-2•IGFBP-7]	$2,790,335	$3,427,347	$547,931	$246,233	**$7,011,846**
Savings on uncompensated care with addition of [TIMP-2•IGFBP-7] to SOC	-$613,311	$0	$1,063,149	$477,766	**$927,604**
Per-tested-patient savings on uncompensated care with addition of [TIMP-2•IGFBP-7] to SOC	-$1,227	$0	$2,126	$956	**$1,855**

Monetary values are in 2017 United States dollars. Abbrevations. AKI: acute kidney injury; ICU: intensive care unit; SOC: standard of care.

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

Joannidis M, Forni LG, Haase M, Koyner J, Shi J, Kashani K, Chawla LS, Kellum JA, on behalf of the Sapphire Investigators.

OBJECTIVE

This paper describes a secondary analysis of the Sapphire trial, an international, prospective, observational study[1] 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[2] III 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)**.

1. Kashani K, et al. Critical Care 2013;17(1):R25 (see page 16)   2. APACHE: Acute Physiology and Chronic Health Evaluation

"Cell cycle arrest biomarkers, TIMP-2 and IGFBP-7, improve risk stratification for severe outcomes in patients with stage 1 acute kidney injury by urine output, serum creatinine or both, with risk increasing with each acute kidney injury indicator."

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.

HEALTH ECONOMICS AND OUTCOMES STUDIES

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.
Adapted from Joannidis M, et al. *Critical Care Medicine* 2019;47(10):e820-e826

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.
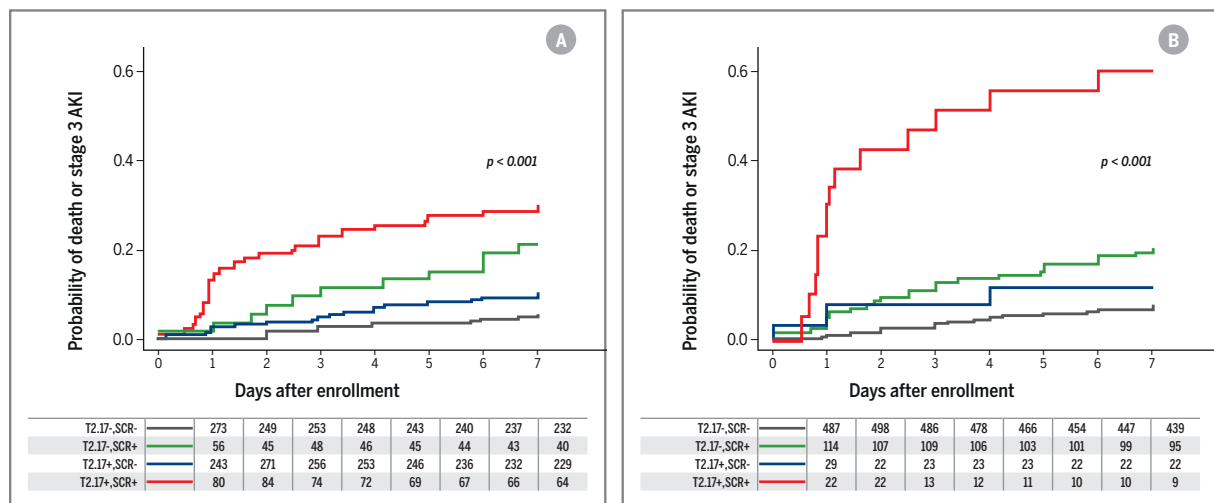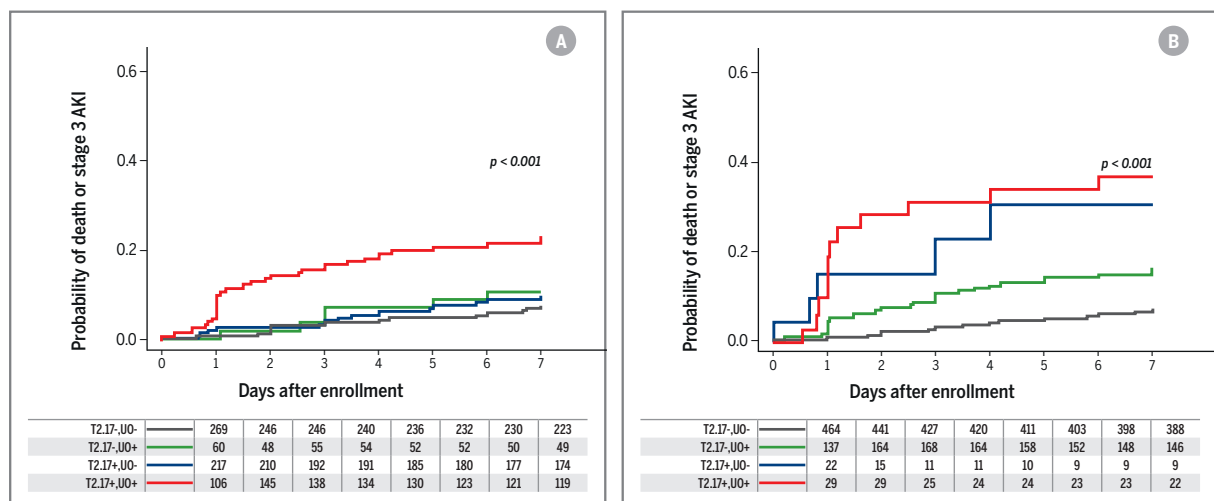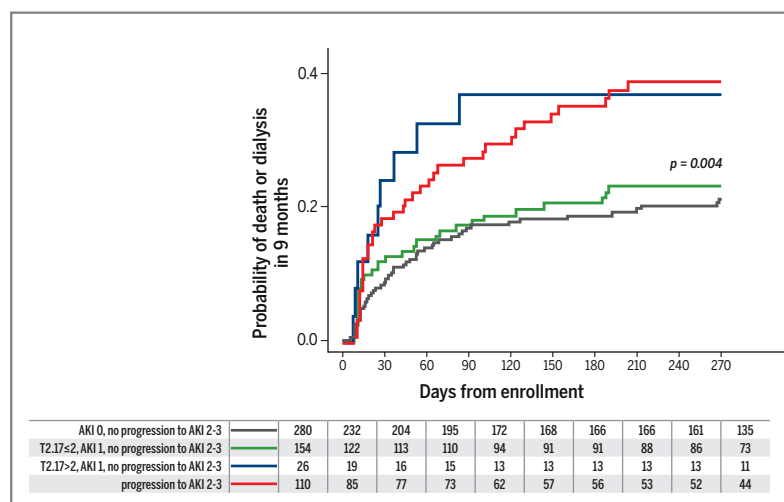Adapted from Joannidis M, et al. *Critical Care Medicine* 2019;47(10):e820-e826

Figure 3. Death or dialysis within 9 months among patients who were alive and dialysis free at 7 days after enrolment.
Adapted from Joannidis M, et al. *Critical Care Medicine* 2019;47(10):e820-e826

HEALTH ECONOMICS AND OUTCOMES STUDIES

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

Göcze I, Jauch D, Götz M, Kennedy P, Jung B, Zeman F, Gnewuch C, Graf BM, Gnann W, Banas B, Bein T, Schlitt HJ, Bergler T.

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

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.

GUIDELINES AND CONSENSUS STATEMENTS

Figure 1. Refined Staging System for the diagnosis of Acute Kidney Injury (AKI).
Adapted from Ostermann M, et al. *The Journal of the American Medical Association* 2020;3(10):e2019209

A - CURRENT DIAGNOSTIC AKI CRITERIA

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

B - EXPANDED DIAGNOSTIC AKI CRITERIA

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

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 — AKI stage 1S

BM negative; increase in SCr level or decrease in UO ↔ BM positive; increase in SCr or decrease in UO — AKI stage 1B

AKI stage 1A

Progression

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 an defined threshold.

Figure 2. Proposed new definition of Acute Kidney Injury.
Adapted from Ostermann M, et al. *The Journal of the American Medical Association* 2020;3(10):e2019209

FUNCTIONAL CRITERIA	STAGE	DAMAGE CRITERIA
No change or SCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of SCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of SCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of SCr level by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

KRT: kidney replacement therapy; SCr: serum creatinine; UO: urine output
Functional markers include SCr and UO but new functional markers may also be included.

COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup.

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.

GUIDELINES AND CONSENSUS STATEMENTS

Figure 1. Pathogenesis of COVID-19 AKI*.

Adaped from Nadim M, et al. *Nature Reviews Nephrology* 2020;16(12):747-764
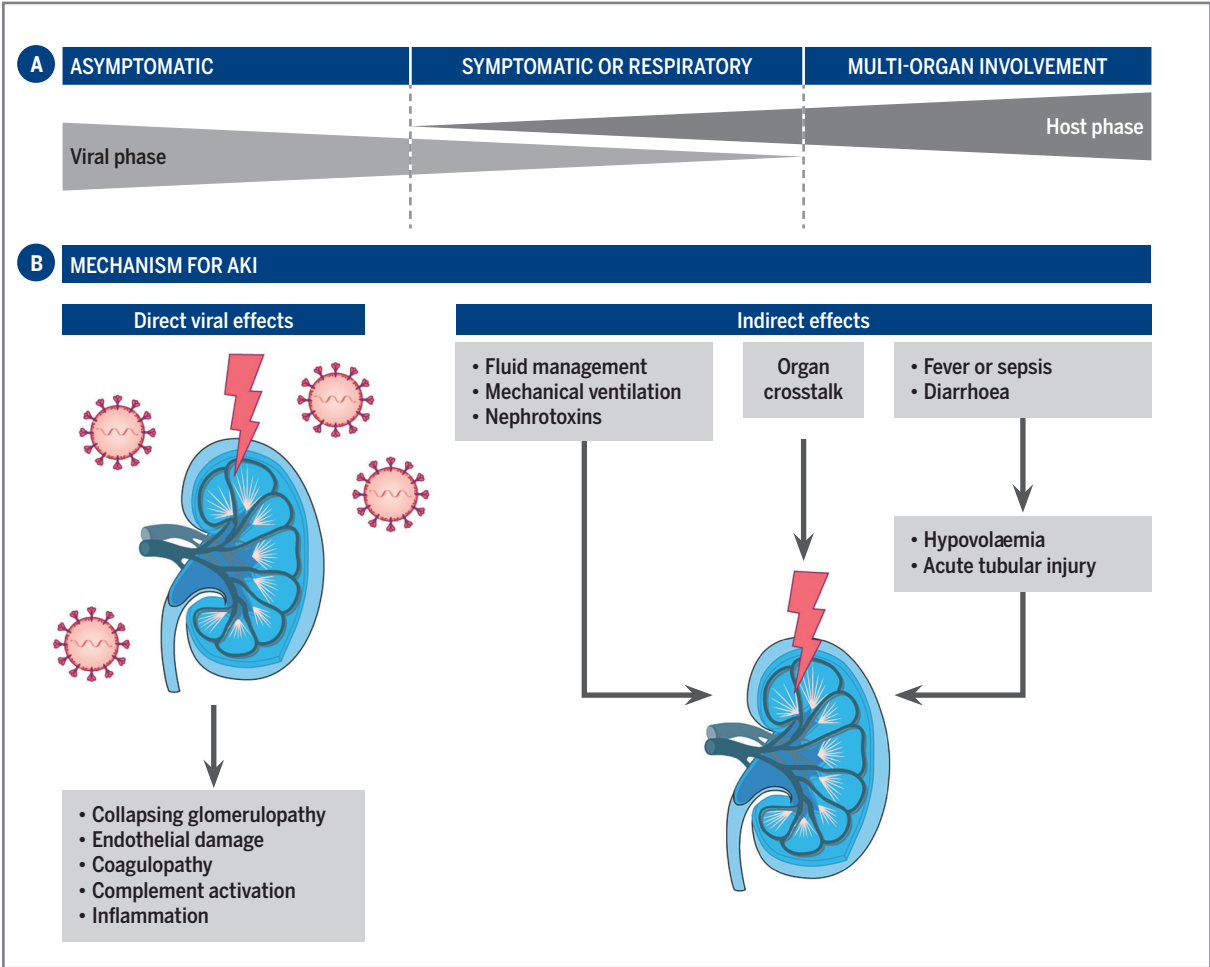
*The pathogenesis of AKI in patients with COVID-19-AKI is likely multifactorial, involving both the direct effects of SARS-CoV-2 virus on the kidney and the indirect mechanisms resulting from systemic consequences of viral infection or effects of the virus on distant organs including the lung, in addition to mechanisms relating to the management of COVID-19.

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NOTES

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