



Clinical Use of the Urine Biomarker [TIMP-2] × [IGFBP7] for Acute Kidney Injury Risk Assessment

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Acute kidney injury (AKI) is a serious complication, commonly occurring in the critically ill population, with devastating short- and long-term consequences. Despite standardization of the definition and staging of AKI, early recognition remains challenging given that serum creatinine level is a marker, albeit imperfect, of kidney function and not kidney injury. Furthermore, the delay in increase in serum creatinine level after loss of glomerular filtration also prevents timely detection of decreased kidney function in patients with AKI. During the past decade, numerous clinical investigations have evaluated the utility of several biomarkers in the early diagnosis and risk stratification of AKI. In 2014, the US Food and Drug Administration approved the marketing of a test based on the combination of urine concentrations of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 ([TIMP-2] × [IGFBP7]) to determine whether certain critically ill patients are at risk for developing moderate to severe AKI. The optimal role of this biomarker in the diagnosis, management, and prognosis of AKI in different clinical settings requires further clarification. In this perspective, we summarize the biological actions of these 2 cell-cycle arrest biomarkers and present important considerations regarding the clinical application, interpretation, and limitations of this novel test for the early detection of AKI. *Am J Kidney Dis.* 68(1):19-28. © 2016 by the National Kidney Foundation, Inc.

INDEX WORDS: Acute kidney injury (AKI); biomarker; [TIMP-2] × [IGFBP7]; diagnosis; critically ill; tissue inhibitor of metalloproteinase 2; insulin-like growth factor binding protein 7; NephroCheck; early detection; risk assessment; renal dysfunction; decreased kidney function.

Overview of Biomarker Development in AKI

Acute kidney injury (AKI) is a common but complex clinical syndrome in hospitalized patients associated with substantial inpatient complications, increased risk for end-stage renal disease, and significant mortality.¹⁻⁴ The field of AKI biomarkers started in the nascent phase early in the 21st century and was further propelled by recommendations from the American Society of Nephrology Renal Research Group in 2005.⁵ Biomarkers were prioritized to decrease reliance on serum creatinine (Scr) level and urine output because these 2 long-standing

“gold-standard” functional markers are insensitive for the early recognition of kidney injury and real-time evaluation of AKI.^{6,7} This search for the “renal troponin” was aided by the development of consensus definitions of AKI over the past decade, which allowed for standardization across biomarker trials.⁸⁻¹¹ As a result, numerous AKI clinical investigations have been conducted evaluating biomarkers such as plasma and urine neutrophil gelatinase-associated lipocalin (NGAL), urine interleukin 18 (IL-18), urine liver-type fatty acid binding protein (L-FABP), and urine kidney injury molecule 1 (KIM-1) in

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*The members of the American Society of Nephrology Acute Kidney Injury Advisory Group are listed in the Acknowledgements.

Received August 13, 2015. Accepted in revised form December 26, 2015. Originally published online March 4, 2016.

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<http://dx.doi.org/10.1053/j.ajkd.2015.12.033>

high-risk patients.⁸⁻¹² A few of these biomarkers have been approved for clinical use outside the United States (Table 1). However, it was not until September 2014, following the publication of 2 multicenter intensive care unit (ICU) cohort studies, that the combination of urine tissue inhibitor of metalloproteinase 2 and insulin-like growth factor (IGF) binding protein 7, known as [TIMP-2] × [IGFBP7], was allowed for marketing by the US Food and Drug Administration (FDA). This is the first biomarker for risk assessment of AKI to become available for clinical use in the United States.^{11,13,14}

Biological Functions of TIMP-2 and IGFBP7

TIMP-2 and IGFBP7 are cell-cycle arrest proteins expressed in renal tubular cells during periods of cellular stress or injury. TIMP-2 inhibits matrix metalloproteinase activity and exhibits a number of matrix metalloproteinase-independent effects, many centering on regulation of the cell cycle. TIMP-2 binds to the $\alpha_3\beta_1$ integrin on the surface of endothelial cells, thus potently blocking endothelial cell proliferation and angiogenesis.¹⁵ This effect is mediated by the induction of p27^{KIP1} expression, a cyclin-dependent kinase inhibitor that induces G₁ cell-cycle arrest.¹⁶ TIMP-2 is also capable of stimulating cell division, emphasizing that the cellular effects of TIMPs are highly context dependent.¹⁷ In kidneys, TIMP-2 is strongly expressed in renal cell carcinoma, indicating that renal epithelia are capable of expressing it.¹⁸ IGFBP7 is a secreted protein that is a member of the IGFBP superfamily, also known as IGFBP-related proteins.¹⁹ IGFs exhibit pleiotropic effects in development and disease, and IGFBP7 regulates the bioavailability of IGFs through direct low-affinity binding.¹⁹ Several IGF-independent effects, such as tumor suppression in melanoma and colon cancer and induction of cell senescence in breast cancer lines, are also ascribed to IGFBP7.^{20,21}

Upregulation of TIMP-2 and IGFBP7 in patients with AKI has been proposed to reflect their growth-inhibitory functions because G₁ cell-cycle arrest is a known consequence of AKI.¹¹ Certainly p27^{KIP1} and p21 can be induced by TIMP-2 and IGFBP7, respectively, and this would potently induce G₁ arrest. However, there is much that remains poorly understood regarding the biological role for these proteins in AKI beyond their utility as biomarkers. Their presumed role as inducers of G₁ cell-cycle arrest in the kidney remains speculative given that these proteins are capable of inducing a wide variety of cellular responses.

Premarketing Clinical Trials

Although multiple plasma and urine biomarkers have been studied for prediction of AKI in critically ill patients, prior to 2014, no biomarker had been allowed to be marketed in the United States for either diagnosis or risk assessment of AKI.²²⁻³⁰ The 4 premarketing [TIMP-2] × [IGFBP7] studies are: (1) Discovery (discovery study to identify novel biomarkers), (2) Sapphire (multicenter validation study), (3) Opal (analysis to determine appropriate cutoffs), and (4) Topaz (multicenter study using clinical platform for [TIMP-2] × [IGFBP7] measurement and 3 experts for clinical adjudication).^{11,14,31} To better understand the appropriate use of this biomarker, these studies are summarized next and in Table 2.

In the Discovery study, 340 candidate biomarkers were assessed for their ability to predict risk for AKI in a cohort of 522 critically ill adults. Urine TIMP-2 and IGFBP7 were identified as the best-performing biomarkers.¹¹ The subsequent multicenter validation Sapphire study prospectively enrolled 728 critically ill adults with respiratory and/or cardiovascular impairment. Patients were enrolled within 24 hours of ICU admission, and those with KDIGO (Kidney Disease: Improving Global Outcomes) stage 2 or 3 AKI were excluded.³² The performance of urine concentrations

Table 1. Urine Biomarker Performance for Prediction of AKI

Urine Biomarker	Clinical Trial Setting					Clinical Use
	ICU	CPB Surgery	Kidney Tx	IV Contrast	ED	
NGAL ^{12,66-68}	+	+	+	+	+	Approved in Europe and Canada
IL-18 ^{12,66,67,69,70}	+	+	+	?	?	Not approved for clinical use
L-FABP ^{12,71-74}	+	+	?	?	+	Approved in Japan
KIM-1 ^{12,68,75-78}	?	+	–	?	+	Not approved for clinical use
[TIMP-2] × [IGFBP7] ^{14,31,36,37}	+	+	?	?	?	Approved in United States and Europe

Abbreviations and definitions: +, associated with risk for AKI in clinical trials; –, did not correlate with AKI; ?, data are inconclusive or biomarker has not been extensively studied in that setting; AKI, acute kidney injury; CPB, cardiopulmonary bypass; ED, emergency department; ICU, intensive care unit; IGFBP7, insulin-like growth factor binding protein 7; IL-18, interleukin 18; IV, intravenous; KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloprotease 2; Tx, transplantation.

Table 2. Overview of [TIMP-2] × [IGFBP7] Trials Leading to FDA Approval

Study Name	Purpose of Study	Patient Population	N	Result	Other
Discovery	Identify novel protein biomarkers for AKI	ICU patients with sepsis or 1 risk factor for AKI	522	TIMP-2 and IGFBP7 were the best-performing markers (AUROCs of 0.75 and 0.77, respectively)	340 potential biomarkers were tested, including urine NGAL, KIM-1, IL-18, and L-FABP
Sapphire	Validation study	ICU patients older than 21 y with either respiratory or CV impairment; patients with moderate or severe AKI were excluded	728	14% reached primary end point of moderate or severe AKI; risk for AKI was significantly elevated with [TIMP-2] × [IGFBP7] > 0.3	Risk for major adverse kidney event significantly elevated with [TIMP-2] × [IGFBP7] > 0.3
Opal	Derivation and validation study to confirm accuracy and clinical utility of 2 different cutoff values	ICU patients older than 21 y; most had respiratory or CV impairment; indwelling Foley catheters	154	18% reached primary end point of moderate or severe AKI; AUROC was 0.79; for 0.3 cutoff, NPV was 97%, PPV was 49%	0.3 is highly sensitive but has very low specificity; baseline Scr was elevated in patients who reached primary end point
Topaz	Validation study with clinical adjudication of primary end point	ICU patients older than 21 y; all had either respiratory or CV impairment; indwelling Foley catheters; 83% had nephrotoxic medication exposure	420	17.4% reached primary end point of moderate or severe AKI; AUROC was 0.82; at cutoff of 0.3, sensitivity was 92% and specificity was 46%; at cutoff of 2.0, sensitivity was 46% and specificity was 95%	[TIMP-2] × [IGFBP7] remained significant even when combined with clinical model

Abbreviations: AKI, acute kidney injury; AUROC, area under the receiver operating characteristic curve; CV, cardiovascular; FDA, US Food and Drug Administration; ICU, intensive care unit; IGFBP7, insulin-like growth factor binding protein 7; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NPV, negative predictive value; PPV, positive predictive value; Scr, serum creatinine; TIMP-2, tissue inhibitor of metalloprotease 2.

of TIMP-2 and IGFBP7, measured within 24 hours of ICU admission, was tested against a panel of existing biomarkers in predicting the primary end point of KDIGO stage 2 or 3 AKI within 12 hours. TIMP-2 concentration multiplied by IGFBP7 concentration ([TIMP-2] × [IGFBP7]) was superior to the other biomarkers ($P < 0.002$), with an area under the receiver operating characteristic curve (AUROC) of 0.80. Of note, an AUROC of 0.70 is generally considered to be the cutoff for a clinically useful biomarker.³³ [TIMP-2] × [IGFBP7] values were not elevated at baseline among patients with chronic kidney disease, and the biomarker performed well in patients with sepsis (AUROC, 0.82) and high-risk surgery (AUROC, 0.85). In the Sapphire study, [TIMP-2] × [IGFBP7] was superior for risk assessment of KDIGO stage 2 or 3 AKI (AUROC, 0.80; 95% confidence interval [CI], 0.76-0.88) when compared to simultaneously measured plasma and urine NGAL (AUROCs of 0.69 [95% CI, 0.64-0.73] and 0.72 [95% CI, 0.68-0.76], respectively), plasma cystatin C (AUROC, 0.71; 95% CI, 0.66-0.75), urine IL-18 (AUROC, 0.69; 95% CI, 0.65-0.73), KIM-1 (AUROC, 0.70; 95% CI, 0.65-0.74), and L-FABP (AUROC, 0.61; 95% CI, 0.56-0.66).

Using data from the Sapphire study, 2 cutoffs for [TIMP-2] × [IGFBP7], 0.3 (ng/mL)²/1,000 and 2.0 (ng/mL)²/1,000, were developed based on sensitivity

and specificity for assessment of risk for AKI. These thresholds were prospectively tested and verified in the multicenter Opal study. The Opal study enrolled 154 critically ill adults, of whom 18% developed KDIGO stage 2 or 3 AKI within 12 hours of testing.³¹ This study confirmed the high sensitivity and high negative predictive values of 89% and 97%, respectively, for the cutoff of 0.3 and the high specificity and moderate positive predictive values of 95% and 49%, respectively, for the cutoff of 2.0.³¹

Topaz was a multicenter prospective study of 420 critically ill patients conducted in the United States. Unlike prior AKI biomarker studies, the end point was independently adjudicated by 3 nephrologists who were blinded to test results. The preselected high sensitivity value cutoff for [TIMP-2] × [IGFBP7] of 0.3 was validated for the prediction of clinically adjudicated KDIGO stage 2 or 3 AKI within 12 hours of testing. Urine [TIMP-2] × [IGFBP7] had an AUROC of 0.82 in this population, and the proposed threshold of 0.3 discriminated between patients at high and low risk for AKI.¹⁴ Approximately 25% of patients with [TIMP-2] × [IGFBP7] > 0.3 developed AKI, whereas only 4% with [TIMP-2] × [IGFBP7] < 0.3 developed AKI. The absolute risk for AKI with [TIMP-2] × [IGFBP7] > 0.3 was 7 times higher than the absolute risk among patients with values below this cutoff.

Other Clinical Trials

Additional studies have examined the use of $[\text{TIMP-2}] \times [\text{IGFBP7}]$ to predict increased risk for AKI in patients after cardiopulmonary bypass (CPB) and other major noncardiac surgeries. Patients undergoing CPB surgery constitute one of the highest risk populations for the development of AKI.³⁴ A recent clinical trial in 240 patients undergoing CPB surgery found that elevated values ($[\text{TIMP-2}] \times [\text{IGFBP7}] \geq 0.5$) 4 hours after surgery correlated with postoperative AKI development.³⁵ An additional smaller study among CPB surgery patients showed sensitivity of 0.92 and specificity of 0.81 for a cutoff value of 0.5 measured within 24 hours postoperatively.³⁶ In both these studies, a value of 0.5 (not 0.3) was used as a predictor of developing AKI. In another small study with 42 participants, in patients who went on to develop AKI, $[\text{TIMP-2}] \times [\text{IGFBP7}]$ levels were not significantly elevated 4 hours postoperatively and did not become elevated until postoperative day 1.³⁷ This demonstrates that in addition to the test result, timing of measurement is very important in its interpretation.

In the pediatric population, a prospective cohort study explored the ability of $[\text{TIMP-2}] \times [\text{IGFBP7}]$ to predict risk for AKI in 51 children undergoing CPB surgery. The study compared $[\text{TIMP-2}] \times [\text{IGFBP7}]$, NGAL, and KIM-1 levels in 12 children with AKI (defined as a decrease in estimated creatinine clearance by 25% from baseline) and 39 without AKI.³⁸ The AUROC for $[\text{TIMP-2}] \times [\text{IGFBP7}]$ was 0.85 (95% CI, 0.72-0.94) at 4 hours after CPB, similar to NGAL (AUROC, 0.87; 95% CI, 0.74-0.95) and better than KIM-1 (AUROC, 0.64; 95% CI, 0.49-0.77). Interestingly, baseline $[\text{TIMP-2}] \times [\text{IGFBP7}]$ levels were high (~ 1.0) in all children. Unexpectedly, $[\text{TIMP-2}] \times [\text{IGFBP7}]$ values of those without AKI decreased at 4 hours after surgery, and the best cutoff to predict AKI at 4 hours was 0.7 (lower than the baseline value and higher than the approved cutoff of 0.3). The reason for the elevated baseline levels and subsequent decline in the biomarker levels in children without AKI is unclear. At present, the biomarker is not approved for use in those younger than 21 years.

The utility of $[\text{TIMP-2}] \times [\text{IGFBP7}]$ has also been investigated in high-risk patients undergoing major noncardiac surgery. In a recent single-center study, this biomarker was measured in 107 high-risk patients on ICU admission approximately 4 hours after undergoing major surgery, with a predefined cutoff value of $[\text{TIMP-2}] \times [\text{IGFBP7}] > 0.3$ to predict risk for AKI. In this cohort, the AUROC for predicting risk for developing AKI was 0.85 and that for predicting need for renal replacement therapy within 48 hours was 0.83.³⁹

The furosemide stress test has been investigated for its utility to predict outcomes in AKI. Urine output < 200 mL in the first 2 hours after administration of 1 to 1.5 mg/kg of furosemide has been shown to predict AKI progression with sensitivity of 87.1% and specificity of 84.1%.⁴⁰ The combination of $[\text{TIMP-2}] \times [\text{IGFBP7}]$ and furosemide stress test has demonstrated synergy in prognosticating progression of AKI, need for renal replacement therapy, and in-patient mortality in patients with early AKI. In a 77-participant cohort, $[\text{TIMP-2}] \times [\text{IGFBP7}]$ alone performed modestly in predicting these outcomes (AUROCs of 0.61-0.69)⁴¹; however, when furosemide stress test results were analyzed in 32 participants with prefurosemide $[\text{TIMP-2}] \times [\text{IGFBP7}] > 0.3$, the stress test provided an AUROC of 0.90 ($P < 0.001$) for AKI progression and 0.91 for inpatient renal replacement therapy.⁴¹ Using an elevated $[\text{TIMP-2}] \times [\text{IGFBP7}]$ value as the renal troponin trigger for a “kidney stress test” may improve risk stratification in patients with early AKI.

Clinical Application of $[\text{TIMP-2}] \times [\text{IGFBP7}]$

The FDA allowed Astute Medical to market the $[\text{TIMP-2}] \times [\text{IGFBP7}]$ test under the brand name NEPHROCHECK on September 5, 2014.⁴² The package insert specifies that the test is to be used in ICU patients older than 21 years with cardiovascular and/or respiratory compromise within the prior 24 hours.⁴³ The test is “an aid in the risk assessment for moderate or severe acute kidney injury” (emphasis added). The FDA letter also states that “test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods.”⁴² The FDA decision summary clarifies that $[\text{TIMP-2}] \times [\text{IGFBP7}]$ is not a stand-alone test and should not be used as point-of-care testing in the United States.⁴⁴ The FDA also requires that the manufacturer provide appropriate end-user training to “mitigate the risk of failure to correctly interpret test results.”⁴⁴

As noted, $[\text{TIMP-2}] \times [\text{IGFBP7}] > 0.3$ had sensitivity of 92% for moderate or severe AKI in the next 12 hours and was associated with approximately 7 times the risk compared with values < 0.3 in the Topaz study.¹⁴ Importantly, the specificity of this cutoff to detect AKI was only 46% (95% CI, 41%-52%), with a positive predictive value of 27% (95% CI, 21%-32%). Therefore, false-positive results will be common and will be magnified if the test is used inappropriately in low-risk patients. Like other tests with high sensitivity and low specificity, the predictive value of the test is dependent on the likelihood that disease is present. For example, serum troponin is useful to assess for the presence of myocardial

infarction when tested in the appropriate clinical setting (eg, chest pain and known clinical risk factors) and is likely to predict myocardial infarction if positive; however, in a low-risk patient, a positive test result is less meaningful. Similarly, a [TIMP-2] \times [IGFBP7] value > 0.3 will have greater predictive value in patients at high risk for AKI, but will be less useful in patients at low risk for AKI. To put this into clinical context, cardiac surgery is associated with an $\sim 18\%$ incidence of AKI and might be an appropriate setting in which to use this biomarker.⁴⁵

Clinicians should be mindful of using [TIMP-2] \times [IGFBP7] in settings in which it has not been studied (Box 1). This biomarker should not be used in ambulatory practices and it is not beneficial in patients with established KDIGO stage 2 or 3 AKI because it is unknown how long elevations in [TIMP-2] \times [IGFBP7] might persist and therefore whether levels would predict worsening of AKI or kidney recovery.

Box 1. Summary of [TIMP-2] \times [IGFBP7] Use in the Clinical Setting

Appropriate patient population

ICU patients aged ≥ 21 y:

- With 1 other risk factor for AKI
- After cardiac bypass or other major high-risk surgery
- With sepsis

Appropriate use

- On admission to ICU or sudden deterioration of a critically ill patient
- Can be used in conjunction with furosemide stress test

Unapproved uses and limitations

- Patients aged < 21 y
- Ambulatory setting
- Minor surgery
- Low-risk patients in the hospital and emergency department
- In patients with established KDIGO stages 2 and 3 AKI
- Daily or serial measurement
- As a substitute for serum creatinine measurement
- Proteinuria: urine albumin > 125 mg/dL interferes with result; $> 3,000$ mg/dL invalidates it
- Bilirubinuria: urine bilirubin concentrations > 7.2 g/dL interfere with the result

Implications of positive test (> 0.3)

- Test should be interpreted along with other clinical factors
- High risk for KDIGO stage 2 or 3 AKI within 12 h (27% absolute risk)
- Consider nephrology consultation
- Consider preventive strategies: optimize volume status and hemodynamics, avoid nephrotoxins, closer monitoring of urine output

Note: Turnaround time for the test is approximately 30 to 60 minutes.

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; IGFBP7, insulin-like growth factor binding protein 7; KDIGO, Kidney Disease: Improving Global Outcomes; TIMP-2, tissue inhibitor of metalloprotease 2.

The [TIMP-2] \times [IGFBP7] test should not be considered as a substitute for Scr measurement. Serial measurements of the biomarker have not been established as a means of assessing AKI progression and therefore routine daily measurements are not recommended. A subsequent measurement in a critically ill patient may be considered if a change in clinical situation in a stable patient (eg, hypotension or blood loss) puts him or her at risk for AKI. Higher [TIMP-2] \times [IGFBP7] values are more specific for assessing kidney injury; in a secondary analysis of the Topaz study, a cutoff of 2.0 was associated with specificity for moderate to severe AKI of 95%, although sensitivity decreased to 37%.¹⁴ High urine bilirubin and albumin levels interfere with the test, and clinicians should be aware of this limitation because many critically ill patients have significant comorbid conditions such as diabetic nephropathy and end-stage liver disease that lead to proteinuria and bilirubinuria (Box 1).⁴³

Testing Process and Cost

According to the manufacturer, 10 mL of fresh urine should be collected in a sterile container and centrifuged by the laboratory within an hour of collection.⁴³ Approximately 100 μ L of urine is placed in the ASTUTE140 Meter (Astute Medical) and the readout is printed after 20 minutes. Thus, with prompt handling, results may reasonably be expected within 1 hour of sample collection. The result is reported as a single value (calculated by the machine) referred to as the “AKIRISK Score,” which is TIMP-2 concentration (ng/mL) multiplied by IGFBP7 concentration (ng/mL) divided by 1,000. The result is reported without units or the concentrations of the individual biomarkers. A value > 0.3 identifies patients with a high likelihood to have moderate to severe AKI within 12 hours, whereas a value ≤ 0.3 identifies patients with low risk to develop moderate to severe AKI within 12 hours. In Europe, a second cutoff of 2.0, which is associated with higher specificity, has been approved.⁴⁶

Currently, the machine that runs the biomarker test costs \sim \$5,000.⁴⁶ The cost to the hospital for the cartridge for 1 [TIMP-2] \times [IGFBP7] test is listed at \$85, but a \$15 discount is expected to be given to centers with “high usage.”⁴⁶ When comparing reagent cost alone, it is significantly higher than i-STAT system test cartridges (Abbott) for creatinine (\$4), the i-STAT basic metabolic panel (\sim \$10), and troponin (\$3). The cost of the test will be included in the inpatient diagnosis-related group because it does not have a separate code.⁴⁶ An important logistical issue with the current [TIMP-2] \times [IGFBP7] testing kit is that one machine can perform only one test at a time, so at 20 minutes per test, only 3 tests can be done in an hour. This might change if [TIMP-2] \times [IGFBP7] is integrated into large chemistry platforms.

The cost benefit of [TIMP-2] × [IGFBP7] testing is unknown. It is well established that AKI contributes substantially to the cost of clinical care. In one analysis, the cost attributable to mild and severe post-operative AKI using the RIFLE (Risk Injury Failure Loss End-Stage Renal Disease) score was \$10,700 in RIFLE-R versus \$21,400 in RIFLE-I.⁴⁷ Thus, if early recognition and treatment led to reduced severity of AKI, a favorable cost-benefit ratio of [TIMP-2] × [IGFBP7] might be anticipated. Currently, there are no data to support the premise that early recognition of kidney injury with [TIMP-2] × [IGFBP7] or other AKI biomarkers will prevent the progression of AKI or be associated with a cost benefit to the patient or institution. In addition, a false-positive test result may lead to unnecessary and expensive diagnostic and therapeutic evaluations.

Management Options for Patients With a Positive Result

Nephrologists may not be involved in ordering [TIMP-2] × [IGFBP7] testing, but they must be

familiar with the use and interpretation of the results because positive results are likely to lead to nephrology consultation (Box 1). In patients with values > 0.3, clinicians should consider standard preventative approaches similar to those taken with increasing Scr values, as recommended in the KDIGO clinical guideline for prevention and treatment of AKI (Fig 1).⁴⁸ These may include early renal consultation, volume resuscitation, maintenance of adequate blood pressure, and judicious avoidance of nephrotoxins such as aminoglycosides and iodinated contrast. The overall goal is to reduce further kidney injury and potentially prevent progression of AKI.

Newer standardized AKI definitions have enabled the use of electronic alert systems for early detection of AKI with the goal to warn clinicians early and optimize intervention.⁴⁹⁻⁵¹ In a recent randomized single-blind study in a large US teaching hospital, electronic alert systems using Scr results were not associated with improved outcomes in patients with AKI.⁵² Possible reasons for the disappointing result include alert fatigue, physicians already aware of

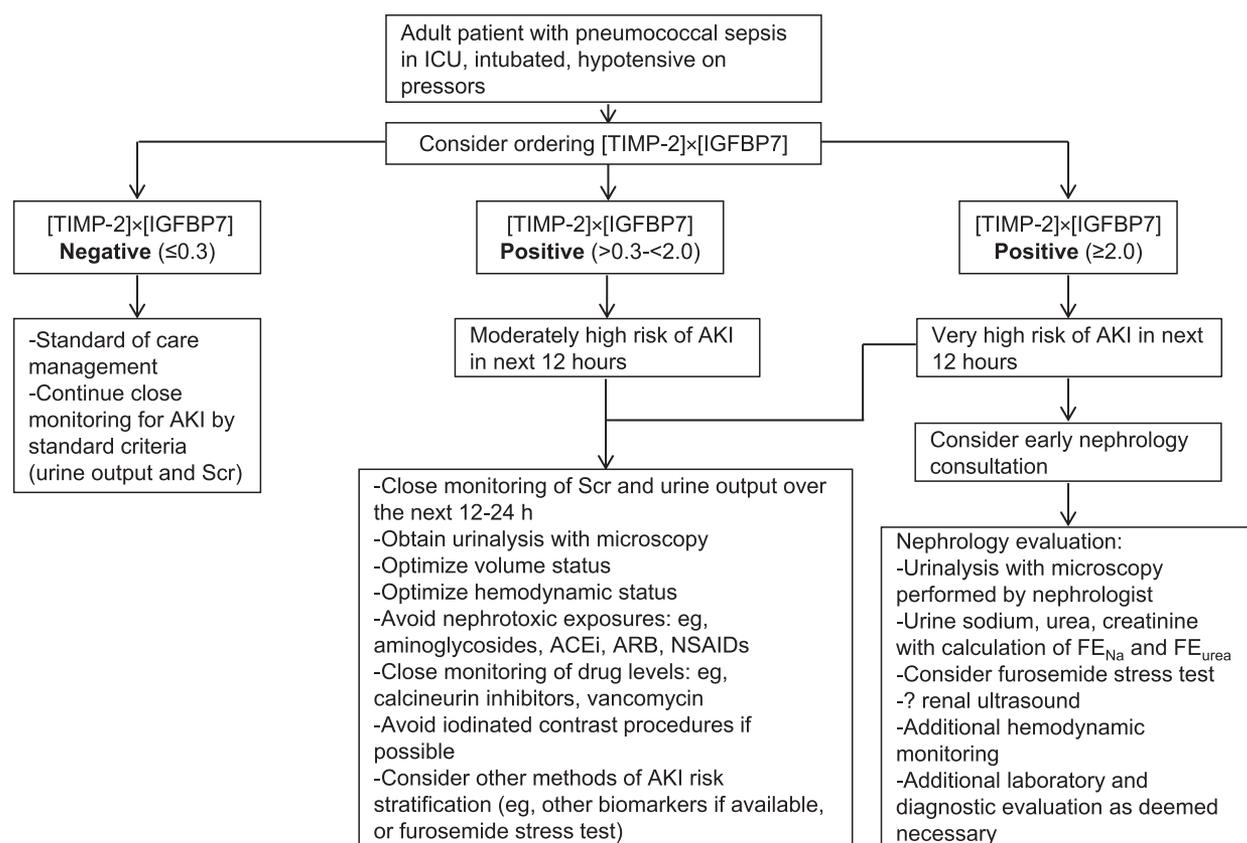


Figure 1. Hypothetical clinical scenario shows a potential use for [TIMP-2] × [IGFBP7] (combination of urine concentrations of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7) in a critically ill patient. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; FE_{Na}, fractional excretion of sodium; FE_{urea}, fractional excretion of urea; ICU, intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs; Scr, serum creatinine. Note: The authors have presented this hypothetical case illustration to demonstrate a possible use for this biomarker. To date, this algorithm has not been standardized and is not in use at any of medical centers that are affiliated with the authors. We recommend that each center institute its own protocol to ensure the appropriate use of this test.

increasing Scr levels, and the fact that the alert was not associated with specific management recommendations. Because [TIMP-2] \times [IGFBP7] is a novel biomarker that can detect kidney injury early, an elevated value might trigger early renal consultation, similar to cardiology consultation for patients with elevated troponin levels. There are data to suggest that early nephrology involvement is associated with improved outcomes in patients with AKI.⁵³⁻⁵⁶ Thus, we believe that it is essential for nephrologists to be involved in the interpretation and response to an [TIMP-2] \times [IGFBP7] test. Numerous actions could be taken, including optimizing fluid balance, discontinuation of nephrotoxic medications, and earlier diagnostic evaluation (Fig 1). Nephrologists are trained to perform urine microscopy, and the presence of granular casts and tubular epithelial cells calculated as urine sediment score has been shown to be of diagnostic and prognostic benefit.⁵⁷ The combination of urine sediment score and a positive [TIMP-2] \times [IGFBP7] result could potentially have higher sensitivity and specificity compared with their individual results.⁵⁸

For institutions exploring the option of adding [TIMP-2] \times [IGFBP7] to their laboratory panel, we suggest that center-specific protocols be created and implemented to ensure appropriate response to the test result. The protocol should ensure collaboration among nephrologists, surgeons, and critical care physicians in appropriate interpretation of the test and management of the patient, not just to use appropriate preventive measures, but also to avoid unnecessary additional testing. Nephrologists in turn should become familiar with the validity and utility of the test and pursue appropriate management strategies, such as urine microscopy and furosemide stress test.

Future Directions

Drug-induced nephrotoxicity has been implicated in up to 20% of in-hospital and community-acquired AKI and 25% of AKI cases occurring in the ICU.^{59,60} Early detection of nephrotoxicity is critical so that the responsible agent may be discontinued and supportive therapy begun in order to minimize kidney damage. Although 83% of patients in the Topaz study had nephrotoxicity contributing to AKI, there have been no clinical studies demonstrating the utility of [TIMP-2] \times [IGFBP7] in detecting drug toxicity when it might be the sole cause for AKI. Given that TIMP-2 and IGFBP7 are involved in cell-cycle arrest of renal tubular cells in response to injury, it is possible that they may be useful for monitoring the development of nephrotoxicity related to known tubular toxins such as aminoglycosides, amphotericin B, cisplatin, calcineurin inhibitors, and iodinated contrast. However, the use of [TIMP-2] \times [IGFBP7] to detect drug-induced nephrotoxicity outside the ICU

cannot be recommended at this time and should be considered as a potential area for future research.

The lack of efficacy of various nondialytic interventions for AKI has been attributed to several factors, including heterogeneity of AKI, a complex patient population, poor trial design, and delay in recognition of AKI using Scr measurements.⁶¹ Trials evaluating IGF-1, anaritide, and fenoldopam have used elevation in Scr level or the development of oliguria as an entry criterion.⁶²⁻⁶⁴ By the time Scr level becomes elevated, AKI is fully established in the extension or maintenance phase, and delayed interventions may not be particularly beneficial in restoring tubular function. The NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) Kidney Research National Dialogue recommended the pursuit of discovery efforts of biomarkers that can not only help clinical decision making, but also guide therapeutic interventional trials in AKI.⁶⁵ Future interventional trials in AKI may consider using an elevated [TIMP-2] \times [IGFBP7] value as a criterion for early enrollment.

In conclusion, the approval of the novel biomarker combination of [TIMP-2] \times [IGFBP7] is a positive step in the search for robust and accurate means of early diagnosis of kidney injury. However, it is imperative that clinicians and laboratory directors understand the utility and limitations of this test before deciding whether to make it available at their institution. To translate this advancement in AKI biomarkers to meaningful improvement in clinical outcomes, standardization of care and early nephrology involvement will be important. Additional trials to study the role of this biomarker in preventive strategies and interventional trials are needed to assess its effectiveness in improving outcomes in AKI.

ACKNOWLEDGEMENTS

The American Society of Nephrology AKI Advisory Group (AKIAG) comprises Sarah Faubel, MD (through 2016), David J. Askenazi, MD, MPH (2016), Rajit K. Basu, MD (2018), Udayan Y. Bhatt, MD, MPH (2018), Azra Bihorac, MD (2017), Jorge Cerda, MD (2017), Michael J. Connor Jr, MD (2018), Alan J. Davidson, PhD (2016), Mark P. de Caestecker, MBBS, PhD (2017), Kent Doi, MD, PhD (2018), William H. Fissell, MD (2016), Ladan Golestaneh, MD (2018), Michael Heung, MD (2017), Benjamin D. Humphreys, MD, PhD (2017), Jay L. Koyner, MD (2018), Kathleen D. Liu, MD, PhD (2016), Girish K. Mour, MD, MBBS (2017), Prabhleen Singh, MD, MPH (2018), Charuhas V. Thakar, MD (2018), and Anitha Vijayan, MD (2017).

Support: None.

Financial Disclosure: Dr Vijayan was a clinical adjudicator for the Topaz trial and has research support from Spectral Medical Inc and AM-Pharma. Dr Askenazi is a speaker for the AKI Foundation. Dr Heung reports receiving grant funding from Astute Medical Inc, the manufacturer of NEPHROCHECK. Dr Humphreys is a Co-Principal Investigator on an NIH grant to develop novel biomarkers of chronic kidney disease (CKD) (U01DK104308). Dr Koyner reports receiving grant funding from Abbott and Astute

Medical Inc for enrolling patients in observational AKI biomarker studies and consulting fees from Astute Medical Inc. Dr Liu was a clinical adjudicator for the Topaz trial and reports consultancy agreements with Achaogen Inc, Astute Medical Inc, Chemocentryx Inc, and Durect Corporation. She is a Co-Principal Investigator on an NIH grant to test novel biomarkers of CKD (U01DK085649). Dr Nolin is member of the Independent Data Monitoring Committee for Thrassos Innovation Inc. Dr Bihorac is supported by Center for Sepsis and Critical Illness Award P50 GM-111152 from the National Institute of General Medical Sciences and has received research grants from the Society of Critical Care Medicine, Astute Medical Inc, and the I. Heermann Anesthesia Foundation Inc. The remaining authors declare that they have no relevant financial interests.

Peer Review: Evaluated by 2 external peer reviewers, a Co-Editor, the Education Editor, and the Editor-in-Chief.

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