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Current Status of Novel Biomarkers for the Diagnosis of Acute Kidney Injury: A Historical Perspective

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Abstract

Acute kidney injury (AKI) is a common and serious medical condition associated with significant increases in morbidity, mortality, and cost of care. Because of the high incidence and poor outcomes associated with AKI, there has been significant interest in the development of new therapies for the prevention and treatment of the disease. A lack of efficacy in drug trials led to the concern that AKI was not being diagnosed early enough for an effective intervention and that a rise in serum creatinine itself is not a sensitive-enough marker. Researchers have been searching for novel biomarkers that can not only assess a decline in kidney function but also demonstrate structural damage to the kidney and at time points earlier than increases in serum creatinine measurements allow. Over the past 10 years, there have been 3300 new publications and hundreds of new biomarkers investigated, yet concern still remains regarding AKI biomarker performance. The AKI biomarkers are yet to be widely utilized in clinical practice, leading some to question whether AKI biomarkers will ever reach their initial promise. However, we believe that biomarkers are an important part of current and future AKI research and clinical management. In this review, we compare the historical contexts of acute myocardial ischemia and AKI biomarker development to illustrate the progress that has been made within AKI biomarker research in a relatively short period of time and also to point out key differences between the disease processes that have been barriers to widespread AKI biomarker adoption. Finally, we discuss potential paths by which biomarkers can lead to appropriate AKI treatment responses that lower morbidity and mortality.

Keywords

acute kidney injury; biomarkers; NGAL; TIMP2 IGFBP7

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Introduction

Acute kidney injury (AKI) is a common and serious medical condition associated with significant increases in morbidity, mortality, and cost of care. The AKI complicates 20% of general inpatient admissions,¹ 27% of pediatric intensive care unit (ICU) admissions,² and 30% to 50% of adult ICU admissions.³ It is an independent risk factor for death with mortality rates of 25% overall¹ and as high as 50% in the adult ICU setting.⁴ In addition, patients with AKI are more likely to develop significant morbidity including increased rates of infection, respiratory failure, functional impairment requiring discharge to short- or long-term care facilities, chronic kidney disease (CKD), and end-stage renal disease (ESRD).⁵ Finally, AKI is expensive, costing the US health-care system an estimated US\$10 billion annually.⁶ Unfortunately, the rate and complications of AKI are increasing. Even after adjusting for severity of illness, the odds of developing AKI in adult patients undergoing cardiac surgery are currently 3.3 times greater than in 1999, with an increase in attributable mortality of 50%.⁷

Because of the high incidence and poor outcomes associated with AKI, there has been significant interest in the development of new therapies for prevention and treatment of the disease. Several notable drug trial failures raised concerns that AKI was not being diagnosed early enough for an effective intervention and that a rise in serum creatinine lacked sufficient sensitivity for renal damage.⁸ Thus, the search began in earnest for novel biomarkers that could not only assess a decline in estimated glomerular filtration rate (GFR) but also demonstrate structural damage to the kidney and at time points earlier than those allowed by increases in serum creatinine.^{9–12}

Over the past 10 years there have been over 3300 new publications and 15 AKI biomarkers investigated.¹³ However, despite these large investments of time, money, and effort, results of many biomarker trials have been perceived as disappointing, leading some to despair that biomarkers will achieve their initial promise.¹⁴ We believe that biomarkers still have the potential to improve clinical kidney care; however, it is important to recognize that biomarkers in AKI face a number of barriers that will still take time and effort to overcome.

The primary purpose of this review is to identify and explain the major barriers to AKI biomarker development and implementation. To do this, we will compare the process of biomarker development within AKI to the historical development of biomarkers for acute myocardial infarction (AMI). The quest for the ideal AKI biomarker is often likened to the development of troponin for detection of AMI; however, we often forget how long it took troponin to become the reliable marker it is today.¹⁵ Troponin was first discovered in 1965,¹⁶ but it took several decades to achieve its current status as the model biomarker for myocardial infarction. We believe a careful examination of the historical timelines and recognition of similarities and differences between AKI and AMI will illustrate the unique barriers faced by AKI researchers and show why these barriers have been difficult to overcome. However, we also suggest that the timeline of expectations for AKI biomarkers has been unrealistic, and AKI biomarker development is on pace to deliver on at least a portion of its immense promise. Finally, we will discuss steps that can be taken now to improve AKI outcomes in the context of AKI biomarkers.

History of Biomarker Development in AMI

A Brief History of Troponin Development

Prior to the 1950's there were no biomarkers for AMI, and diagnosis was based on physical symptoms in the form of chest pain, radiating numbness to the arm or jaw, and shortness of breath. Treatment consisted of bed rest and morphine, and mortality rates were high.^{15,17,18} Two major steps forward were taken in 1954, when the 12-lead electrocardiogram (ECG) as we know it today came into being,¹⁹ and when the first serum biomarker, serum glutamic oxaloacetic transaminase (SGOT), was originally described.²⁰ For the first time, physicians had access to data besides physical symptoms to make a rapid diagnosis of AMI. Incremental biomarker progress was made through the 1960s and 1970s in the forms of lactate dehydrogenase (LDH) and creatinine phosphokinase (CPK), which were more sensitive for myocardial damage than SGOT but still lacked sufficient specificity.^{21–23}

A major step forward came in 1976 when Chazov et al demonstrated that streptokinase could be used to lyse cardiac clot.²⁴ For the first time, AMI had a pharmacologic treatment that could address the pathophysiologic cause of disease, rather than the downstream effects of ischemia. Subsequent trials demonstrated that early coronary reperfusion, first with lytic agents and later with direct percutaneous intervention, was associated with prolonged survival as well as salvage of even severely ischemic myocardium.²⁵

With the arrival of a viable treatment, early intervention became of paramount importance. As a result, there was renewed interest in the identification of biomarkers that could identify AMI with high specificity as early as possible in the course of the disease.

Biopharmaceutical companies, which viewed lytics as a source of potential revenue, began to invest in biomarker research as well. Myoglobin was identified in 1978 and had better specificity for AMI than either LDH or CPK.^{26,27} In the early 1980s, advances in laboratory techniques allowed for detection of more cardio-specific isoenzymes of CPK and LDH in the forms of creatine kinase MB and LDH 1 and 2.²⁸ These assays soon replaced myoglobin and their unfractionated predecessors and became the main biomarkers used in AMI detection until the mid-1990s.²⁹

Troponin was originally discovered in 1965.¹⁶ However, its utility as a clinical marker of cardiac ischemia wasn't realized until the late 1980s.³⁰ The assays for troponin were refined over the course of the 1990s, and by the end of the decade, serial troponin had sensitivity and specificity to predict AMI in the range of 95% to 100%.^{30,31} Advances in differentiating subtypes of troponin were made in the 2000s, leading to the "fourth-generation" troponin assays, which came into widespread use by the 2010s.³² Recently, "fifth-generation" assays were approved by the Food and Drug Administration (FDA). These can detect troponin at concentrations 10- to 100-fold lower than prior assays,^{33,34} giving negative predictive values of nearly 100% when patients are tested on arrival to the emergency department and again 3 hours thereafter.³⁵ The timely identification of AMI by high-sensitivity troponin allowed for earlier and more effective cardiac interventions that led to major improvements in patient outcomes.³⁶

Impact of AMI Biomarkers on Treatment and Outcomes

The ultimate purpose of biomarkers is to improve patient outcomes. The AMI biomarkers were able to contribute to significant reductions in mortality even from their early stages, which greatly aided in their development. It is important to note that mortality benefits were derived from biomarkers even in the absence of a specific pharmacologic treatment. Despite the fact that SGOT was not particularly sensitive or specific relative to later biomarkers,³⁷ its widespread adoption by the mid-1960s paved the way for the cardiac care unit (CCU),³⁸ a major advancement in AMI treatment. The CCUs were specialized wards where patients were continuously monitored and treated under the care of nurses and doctors with expertise in management of AMI. Although there were no medications available that could treat the underlying cause (ie, coronary artery occlusion), through implementation of best practices, these units contributed to a decrease in absolute mortality from 30% to 15% by the late 1960s.¹⁷

After the discovery of lytic therapy to treat AMI, there was even more emphasis on the early identification of AMI. Markers that are highly sensitive and specific for AMI, like troponin, augmented the efficacy of lytic therapy and stent placements by allowing for earlier intervention in the disease process, further reducing mortality. As a result, 28-day mortality for ST-segment elevation myocardial infarction (STEMI) has fallen from 9% to 5% since 1987,³⁹ and non-STEMI mortality has fallen to 4%,⁴⁰ far from the highs seen prior to biomarker development.

History of Biomarkers in AKI and Barriers to Development

Functional Markers: Creatinine and Cystatin C

Unlike AMI, AKI is typically painless, and physical signs such as decreased urine output, fatigue, and shortness of breath are neither sensitive nor specific. Physicians have long relied on creatinine, a serum marker of kidney function, to diagnose kidney failure. Creatinine was first identified in 1847, and an increase in creatinine was first noted to correlate with a decrease of GFR in 1926.⁴¹ Serum creatinine reflects muscle mass, and thus rates of production tend to be stable from day to day. It is unbound to serum proteins and freely filtered at the glomerulus with tubular manipulation that is mild. Because of these advantages, serum creatinine became the go-to test for clinical GFR estimation by the early 1950s, a distinction it has held essentially ever since.

Compared to AMI biomarkers, creatinine most resembles the first AMI marker described, SGOT. SGOT is itself a liver enzyme and is not found within cardiac myocytes. Its increase after AMI is attributed to a decrease in cardiac output causing liver ischemia, and so it acts as a marker of cardiac function rather than cardiac injury. Cardiac output must fall to the point that liver ischemia is present, which introduces a time lag before SGOT is elevated and also makes it an insensitive marker for mild to moderate disease. Because any cause of reduced cardiac output can cause liver ischemia, SGOT can be elevated in a number of disease processes, making it also a relatively nonspecific marker. Similarly, creatinine is not found within the tissues of the kidney but rather is produced in muscle before being released into the blood stream. It therefore does not directly detect damage to the cells of the kidney

but rather only a decrease in overall kidney function. Just as a significant degree of cardiac dysfunction is needed to cause liver damage, a significant amount of kidney function must be lost before creatinine begins to rise. Also, because creatinine is produced at a relatively constant rate, accumulation is not instantaneous, and creatinine can lag several days behind the initial insult. Finally, all causes of kidney injury that inhibit function will cause a rise in creatinine, so this marker is unhelpful when determining AKI etiology. Prerenal states, obstruction, and intrinsic renal injury have different underlying mechanisms but cannot be reliably differentiated by creatinine.⁴²

Serum cystatin-C arose as a possible alternative to creatinine in 1985.⁴³ It is a nuclear protein produced in all cells and excreted at a constant rate, freely filtered at the glomerulus, and completely degraded by the proximal tubular cells.⁴⁴ Studies over the course of the 1990s showed that while its accuracy is adversely affected by thyroid function ^{45,46} and inflammation,⁴⁶ it correlates more closely with EDTA clearance ⁴⁷ and increases in the serum earlier in the course of AKI than creatinine. Cystatin-C is thus often considered a “better creatinine,”⁴⁸ but because it too is a marker of kidney function rather than injury, it is subject to many of the same limitations.

The Impact of Pharmacologic Failures and the Search for Markers of Kidney Damage

In 2002, the Acute Dialysis Quality Initiative convened to codify a consensus definition of AKI, which was ultimately released in 2004.⁴⁹ A rise in creatinine or a decrease in urine output were the only diagnostic criteria for AKI, which seemed to firmly cement creatinine’s place as the dominant AKI biomarker. It was also around this time that human testing began for a number of promising therapeutic agents such as recombinant human IGF-I, atrial natriuretic peptide, and others which had proven effective in animal models for the treatment of AKI. Hopes within the AKI field were high that a pharmacologic agent, like streptokinase in AMI, would finally be available. Unfortunately, all these drug trials failed to show clinical benefit.^{8,50,51} While there are several potential explanations for the lack of success seen in these trials, including problems with clinical design, a major issue was thought to be the inability to recognize AKI early enough in its course to impact outcomes. In animal studies, treatment is often initiated at or near the time of the renal insult. Because a rise in creatinine is often seen well after the onset of injury, creatinine was deemed too insensitive and too late a marker for effective drug development.

The impetus for further biomarker development in AKI, unlike AMI, stemmed from the hope that a better biomarker would allow for the development of a treatment, as opposed to increased efficacy of a demonstrated treatment, which has limited pharmaceutical investment in AKI biomarkers relative to that seen in AMI. Even in biomarkers that have shown promise in the early diagnosis of AKI (as discussed below), the lack of a clear pharmacologic intervention has hindered adoption within hospital systems.

Just as AMI began looking for direct markers of cardiac injury, the AKI field began looking for renal-specific markers that would rise immediately following kidney damage. In 2005, the American Society of Nephrology Renal Research Report assigned the highest research priority to the discovery and validation of new AKI biomarkers in different patient populations and clinical settings.¹² In AMI, it took over 30 years to move from SGOT to

troponin; however, the nephrology community was optimistic that new “-omics”-based technology would dramatically decrease the time it would take to identify and develop novel biomarker candidates. This initially seemed to be the case, with well over 300 new aspirants reported in the literature between 1995 and 2011.^{52,53} Some of the earliest novel biomarkers were identified through transcriptome profiling techniques, which used complementary DNA microarrays and subtractive hybridizations to identify highly upregulated genes and their downstream products following episodes of ischemic AKI.^{54,55} Two of these biomarkers were kidney injury molecule 1 (KIM-1)⁵⁶ and neutrophil gelatinase-associated lipocalin (NGAL),⁹ both of which continue to show promise in certain patient populations. Many other candidates discovered in this fashion showed initial potential but did not perform well in subsequent studies.^{57–60}

Early Biomarker Trials

One of the earliest major biomarker trials was The Translational Research Investigating Biomarker Endpoints (TRIBE) trial, which was a large, prospective, multicenter trial with a cohort of 1219 adult patients undergoing cardiac surgery. Results were published in 2011, and urine interleukin 18 (IL-18), plasma NGAL, and urine NGAL did not perform as well as expected. Urine IL-18 and plasma NGAL had areas under the curve (AUC) values to predict AKI of 0.76 and 0.75, respectively, and urine NGAL did not improve upon a predictive clinical model.⁶¹ A parallel trial by the TRIBE-AKI Consortium showed similar results in 311 pediatric patients, with urine IL-18 and urine NGAL AUCs of 0.72 and 0.71, respectively.⁶² The authors concluded that while these biomarkers did correlate with important clinical outcomes, the prognostic significance of these markers was less impressive than previous studies had reported.

Another large study, the Discovery trial, sought to evaluate all identified biomarkers to that point in a large, heterogeneous pool of critically ill patients. The authors meticulously evaluated all biomarker data published before 2013 and identified 340 candidate biomarkers. All identified biomarkers were tested in 522 patients from 3 cohorts including patients with sepsis, major surgery, and trauma. The AUC values for previously promising markers such as urine NGAL, urine cystatin C, IL-18, and KIM-1 were disappointing, with only IL-18 at 0.76 having an AUC above 0.70. However, tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7), 2 markers of cell cycle arrest, individually and in combination outperformed all other biomarkers and biomarker combinations with a combined AUC of 0.80.

Acute Kidney Injury is a Heterogeneous and Complicated Disease

The poor performances of AKI biomarkers when using 3 different populations demonstrates a major barrier to development, which is the complicated and heterogeneous nature of AKI. In AMI, the mechanism is an obstruction of blood flow in the coronary arteries leading to downstream ischemia with resultant impairment in myocardial function. Inhibition of and relief from coronary artery obstruction are therefore the main avenues of prevention and treatment, respectively. AKI, in contrast, can differ significantly depending on the insult.⁶³ For example, AKI due to sepsis is quite different mechanistically from AKI due to ischemia or AKI from a nephrotoxic agent, and these differences in pathophysiology affect biomarker

performance. Even within a category of AKI like cardiac surgery-associated AKI, the pathophysiology is very complex and may be attributed to several factors that occur alone or in combination, including renal hypoperfusion, inflammation and oxidative stress, nephrotoxin exposure, neurohormonal activity, and cholesterol emboli.⁶⁴ In addition to these traditional risk factors, a number of genetic polymorphisms have recently been identified that can predispose to the development of AKI, suggesting that genetic makeup plays an important role in the renal response to traditional insults. Finally, a recent study using metabolomics suggests that as many as 58% of plasma metabolite levels are altered in patients due to AKI,⁶⁵ a finding that warrants further investigation. Studies like these show that we are only at the cusp of understanding the genomic, biologic, and enzymatic determinants of renal injury.

It is not surprising in light of the enormous heterogeneity within AKI that a biomarker will often perform well in one patient population and poorly in another. For instance, serum NGAL is upregulated in sepsis and severe inflammation regardless of the degree of AKI, blurring the utility of NGAL in critically ill patients with highly inflammatory processes.^{66,67} However, NGAL performed well in predicting AKI in a study of 635 patients presenting to the emergency department,⁶⁸ suggesting that the best uses of NGAL may be very early in the disease course or outside the medical ICU setting altogether.⁶⁹ A “one-size-fits-all” biomarker, used in a manner similar to troponin for AMI, is unlikely to be identified, and so determining the proper role for each biomarker, and for combinations of biomarkers, is a challenge that will take time and experience to overcome.

Acute Kidney Injury biomarkers are Expected to Fulfill Multiple Roles

Because troponin is a molecule found inside cardiac myocytes, its presence in the systemic circulation indicates necrosis of cardiac tissue. Troponin is therefore primarily expected to indicate the presence of myocardial ischemia. Biomarkers in AKI, on the other hand, are expected to play a number of roles. The AKI biomarkers are used to estimate GFR, to predict the development of AKI early in the disease course, to determine whether renal replacement therapy will be needed, to predict rates of renal recovery, and to determine the etiology of AKI, among other uses. Not surprisingly, biomarkers fulfill some roles better than others, and no single biomarker can perform all of these tasks at a high level.

Identification and FDA Approval of TIMP2*IGFBP7 and Methodologic Study Issues

Tissue inhibitor of metalloproteinases-2 and IGFBP7, the 2 most promising biomarkers in the Discovery trial, were validated in the SAPPHERE study that enrolled 728 ICU patients, and again demonstrated a combined AUC of 0.80 for the prediction of AKI in a heterogeneous population. Subgroup analysis indicated that these makers performed well in sepsis (AUC 0.82) and in post-surgical patients (AUC 0.85). Finally, an additional validation study known as Topaz was able to show that a cut point of 0.3 mg/mL²/1000 was able to successfully identify patients at imminent risk of AKI with an AUC of 0.82.⁷⁰ Following the Topaz trial, the TIMP2*IGFBP7 assay, known commercially as Nephrocheck, was approved for marketing by the FDA in 2014, which represented a significant milestone in biomarker development. TIMP2*IGFBP7 can be used with fresh or thawed samples, provides results in

20 minutes, and is increasingly becoming integrated into research trials and clinical practice.⁷¹

Although TIMP2*IGFBP7 has been a success within AKI biomarker research, its story highlights some of the methodologic issues with AKI biomarker studies to date. Because AKI has few physical symptoms, and because of the limitations of creatinine, it is often difficult to determine the time of AKI onset. In AMI, accurate timeframes for biomarker increases and decreases following AMI could be described based on the onset of chest pain. The AKI biomarker timeframes have been more difficult to determine, and as a result, the appropriate time to test AKI biomarkers has not been established and is often not uniform in trials. In the SAPPHIRE and TOPAZ trials, biomarkers were measured at 12 hours after admission. In contrast, the TRIBE-AKI trial reported outcomes based on values drawn soon after admission to the ICU following surgery (supplementary data included additional time points). The Biomark trial evaluated biomarker levels at 1 day, 7 days, and 14 days after renal replacement therapy (RRT) initiation. A troponin at 1, 7, and 14 days, for instance, would be of very little value, indicating that proper testing intervals need to be identified to improve performance.

The AKI biomarkers are also hampered by comparison against the current gold standard, creatinine.⁷² Creatinine is an imperfect measure as described earlier. Because AKI is defined by a rise in creatinine; however, the performances of biomarkers are often inextricably linked to the performance of creatinine. Theoretical exercises have shown that even a perfect biomarker will perform poorly when compared to an imperfect gold standard.⁷³ This has led some investigators to eschew serum creatinine-based definitions entirely, choosing to link elevations in biomarkers to outcomes such as the need for RRT or death.⁷⁴ Using alternative definitions of AKI has recently led to the delineation of “subclinical AKI,” which is defined as biomarker positive but creatinine negative disease.⁷⁵ These patients have greater risk of complications including longer hospital length of stay and increased mortality compared to patients without a biomarker rise.^{76,77} As the phenomenon of subclinical AKI becomes better described, it is possible that newer definitions of AKI based on rises in biomarkers other than creatinine will be developed and standardized.

The identification of “biomarker-only” AKI also raises the possibility of using changes in biomarkers as end points in clinical trials. Indeed, 7 urinary AKI biomarkers (KIM-1, albumin, total protein, β 2-microglobulin, clusterin, trefoil factor-3 [TFF-3], and cystatin C) have already been approved by the FDA and European Medicines Agency for detection of drug-induced kidney injury in nonclinical and clinical drug development,⁷⁸ and can be used to monitor for injury in preclinical studies and on a case-by-case basis in clinical trials.⁷⁹ Further research is needed before AKI biomarker changes can seriously be considered for use as primary outcomes. However, we would advocate for the use of biomarkers as secondary end points in current studies with the hope that knowledge and familiarity gained from such studies will someday allow for an AKI definition based on biomarker combinations rather than creatinine alone.

Current Steps that Can be Taken to Improve AKI Outcomes: Incorporation of Biomarkers into an AKI Response Network

Lessons From Cardiac Care Units

While the use of streptokinase to relieve coronary artery obstruction was a pivotal advance in the treatment of AMI, it is notable that mortality rates had been falling significantly even before the widespread availability of lytic agents. Cardiac care units were created 1 to 2 decades before a pharmacologic AMI treatment was available. Doctors and nurses with expertise in AMI management implemented best practices and carefully monitored for known complications such as arrhythmias. With these nonpharmacologic interventions alone, mortality was reduced by 50%.¹⁷ While AKI management would benefit tremendously from a new drug or procedure that directly reversed the underlying disease process, the importance of best practice implementation should not be overlooked.

Mehta and colleagues first looked into the benefits of early nephrology consultation in 2002. In a retrospective study of 215 ICU patients, renal consults placed more than 48 hours after the development of AKI were associated with increased mortality, ICU length of stay, and hospital length of stay.⁸⁰ While the results were somewhat attenuated in the multivariate analysis, the study spawned multiple retrospective and prospective follow-up studies.^{80–85} A recently published meta-analysis of these shows a clear and statistically significant mortality benefit to early nephrology consultation.⁸⁶ Another report has shown that even the relatively simple act of documenting AKI appropriately, a surrogate for recognition of AKI, was associated with reduced 30-day mortality.⁸⁷

Biomarkers for Identification of High-Risk Patients

Like early AMI biomarkers, current AKI biomarkers can play an important role in identifying high-risk patients. When using biomarkers to predict AKI occurrence, it is instructive to note that troponin in AMI is always interpreted as part of a larger clinical framework. In patients without chest pain or ECG changes, for instance, troponin elevations become much less meaningful. Recent developments in AKI have thus sought to place biomarker use into proper clinical context.

Renal angina (RA) is a concept designed to identify patients at high risk of AKI based on the idea of cardiac angina. Risk factors including susceptibilities (advanced age, hypertension, diabetes, and CKD) and exposures (volume depletion, nephrotoxins, and sepsis) are combined with symptoms (decreased urine output, volume overload, and creatinine elevation) to give greater context to a patient's clinical situation.⁸⁸ The renal angina index (RAI) is a scoring system designed to quantify renal angina and was initially derived and validated in the pediatric population.⁸⁹ In the initial pediatric studies, the RAI demonstrated a high negative predictive value of 92% to 99% for subsequent severe AKI (KDIGO stage 2 or 3) on day 3.⁹⁰

Not surprisingly, incorporation of AKI biomarkers into RAI-positive patients dramatically improves the predictive performance.⁹¹ A recently published study by Basu et al incorporated urine NGAL results in a study of critically ill pediatric patients with an RAI

score of .8. While the RAI at day 0 alone predicted day 3 AKI with an AUC of 0.80, adding in urine NGAL in patients who met the RAI threshold increased the AUC to an impressive 0.97,⁹² which again illustrates that using biomarkers in patients with a high pretest probability for AKI dramatically increases efficacy.

Another prediction tool that has gained popularity recently is the furosemide stress test (FST).⁹³ Akin to a cardiac stress test, it is a functional test used to further stratify patients at intermediate risk of AKI progression. In the FST, a patient is given 1.0 mg/kg of IV furosemide if furosemide naive and 1.5 mg/kg if previously exposed. A urine output less than 200 mL over the next 2 hours was shown to have 87% sensitivity and 84% specificity to predict progression to stage 3 AKI. Once again, when combined with AKI biomarkers, in this case plasma NGAL, the AUC increased to 0.91 for prediction of RRT requirement and 0.90 for progression to stage 3 AKI.^{93,94}

Recently, clinicians have begun to employ machine learning in order to identify patients at high risk to develop AKI or the need for RRT, with impressive results. Koyner et al published an AKI risk prediction model utilizing electronic health record data devised using machine learning algorithms. The risk model was able to predict the development of stage 2 or greater AKI at 24 and 48 hours with AUC of 0.90 and 0.87, respectively.⁹⁵ Using biomarkers selectively within a group identified by these algorithms as high risk is expected to significantly increase the predictive power and efficacy of existing AKI biomarkers.

Efficacy of Best-Practice Implementation

The ultimate purpose of biomarkers is to improve patient outcomes. Although there is no streptokinase equivalent to pharmacologically treat AKI, recent studies have demonstrated that the implementation of best practices alone is sufficient to meaningfully improve clinical outcomes. For example, the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) program uses the electronic health record to identify non-critically ill pediatric patients at risk for nephrotoxic medication-associated AKI.⁹⁶ When studied prospectively, this automated alert system decreased nephrotoxin exposure rate by 38% and the overall rate of AKI by 64%.⁹⁷ This initiative has now been implemented across many pediatric hospitals in the United States and continues to prove effective in reducing rates of AKI.

Best practice implementation has also been shown to effectively reduce rates of AKI in adults following cardiac surgery. In the recently published PrevAKI⁷¹ trial, patients who underwent cardiac surgery requiring cardiopulmonary bypass were randomized to receive usual care or a “KDIGO-based care bundle” which consisted of the following measures: (1) avoidance of nephrotoxic agents, (2) discontinuation of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) for the first 48 hours after surgery, (3) close monitoring of serum creatinine and urinary output, (4) avoidance of hyperglycemia (glucose >150 mg/dL) for the first 72 hours after surgery, (5) consideration of alternatives to radio contrast, and (6) close hemodynamic monitoring by using a pulse contour cardiac output catheter with an optimization of the volume status and hemodynamic parameters according to a prespecified algorithm. Rates of AKI were dramatically reduced by use of the bundle compared to standard care alone (55.1% vs 71.1%, 95% confidence interval 5.5–27.9%, $P = .004$).⁷¹ This study was also notable because it was able to enrich

the population at risk of AKI by stratifying based on postoperative TIMP2*IGFBP7 levels. Patients were required to have a level >0.3 mg/mL²/1000 for enrollment, and as a result over 70% of patients in the usual care arm developed AKI, a rate much higher than the 20% seen in the general cardiac surgery population.⁹⁸ Use of TIMP2*IGFBP7 was successfully able to select for high-risk patients, thus increasing the impact of the interventions and decreasing the study population needed to demonstrate clinical efficacy.

The importance of timely and specialized AKI care led Drs Rizo-Topete, Rosner, and Ronco to propose the creation of a nephrology rapid response team (NRRT).⁹⁹ The NRRT would quickly evaluate patients with AKI or at high risk for AKI and begin an appropriate workup while also implementing mitigation strategies including discontinuation of nephrotoxic medications, avoidance of contrast media, volume status evaluation and optimization, and hemodynamic stabilization. This concept of NRRT appropriately captures the urgency with which providers should respond to AKI. It is also important to note that these additional responsibilities shouldn't be tasked to already overburdened primary teams.¹⁰⁰ Dedicated Nephrology involvement and guidance will be critical to the success of AKI response systems in the future. Just as CCUs with expertise in AMI were able to impact outcomes with best practices, new systems built around early alerts and rapid nephrology intervention will need to be implemented for a biomarker-based system of AKI prevention to be effective.

Conclusion

The “troponin for AKI” that is broadly applicable across clinical populations with an AUC >0.9 has not yet been identified. The AKI biomarkers face a number of barriers that make clinical applicability more difficult than troponin, including the complexity and heterogeneity of AKI, the variety of clinical aims in AKI biomarker use, and a lack of pharmacologic interventions for established AKI. However, it is important to keep in mind that even after troponin was identified as a useful biomarker for cardiac disease in the 1990s, it took almost 20 years to develop into the model biomarker it is today. The processes of changing attitudes toward AKI, redefining the disease using biomarkers, and developing institutional infrastructure and know-how take time. While awaiting the ideal AKI biomarker panel, we strongly advocate that providers and hospital systems begin now to develop alert systems and AKI response protocols which have the potential even in the present to reduce AKI morbidity and mortality. The AKI biomarkers continue to show tremendous promise but need to be approached with patience.

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