Using Kidney Biomarkers for AKI: Risk Assessment, Diagnosis, and Staging

Rajit K. Basu
Patrick Murray
Jay L. Koyner
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“Starting the Fast Break”

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Disclosures

• Research Funding from
  – NIH/NIDDK

• Consulting
  – Baxter-Gambro Renal Products
  – La Jolla Pharmaceuticals
Proper Positioning → ↑ Scoring Probability

How does this relate to AKI and biomarkers?
It is 1966.

Gabriel Stallman is a 65 year old overweight smoker. After getting into a heated argument with his son 25 year-old son Bob about his career choices and not working in the factory like the rest of his family, he sits down to read the paper. He begins to feel tightness in his chest and abdomen and tells his wife. Concerned, his wife takes him to the hospital. After a few hours in the smoke filled ED of their local hospital, the doctors take a full history, draw some blood and determine this is not indigestion or abdominal pain. They perform an ECG and are concerned about heart injury but his pain progresses and he develops shortness of breath. He goes unconscious and amidst a flurry of sudden activity, including consultation with a cardiologist and treatment with aspirin, he dies in the ED – 8 hours after arriving.
pensa – what is.

• It is 2016.
• Robert Stallman is a 65 year old overweight smoker. After getting into a heated argument with his son 25 year-old son Jay about his career choices and having to move back into the house, he sits down to read the paper. He begins to feel tightness in his chest and abdomen and tells his wife. He remembers watching his father die 50 years earlier of a heart attack. Concerned, his wife takes him to the hospital. After a few minutes in the ED of their local hospital, the doctors perform an ECG, are concerned about coronary syndrome, and draw some blood for serum troponin. The clock is started and the interventional cardiologists are called as he is given oxygen and morphine. This is not indigestion or abdominal pain. Within 8 hours after arrival, a catheterization and stent placement is performed, he is recovered in post-anesthesia, and he wakes up in his cardiac ICU bed and resumes reading his paper.
agenda

• Troponin, The Cherry Picking Biomarker
• AKI Biomarkers, Finally Usable?
• Risk stratification and Renal Angina
• Risk Assessment and Moving the Needle
agenda

• Troponin, The Cherry Picking Biomarker
• AKI Biomarkers, Finally Usable?
• Risk stratification and Renal Angina
• Risk Assessment and Moving the Needle
Epidemiological Approaches to Disease: The Framingham Stu

THOMAS R. DAWBER, M.D.; GILCIN F. MEADOR, M.P.H.; AND FELIX E. MOORE, JR.

National Heart Institute, National Institutes of Health, Public Health Service, Washington, D. C.

The use of the word "epidemiology" and the concept of what epidemiology as a discipline may encompass have varied widely since the days of Peter Panum and John Snow. There are today many differing definitions of the word, but nearly all workers in the field will agree on one element of the definition: The word "epidemiology" by etymology refers to the study of something which is thrust upon the people. There are still some who insist that epidemiology deals only with epidemics of infectious diseases, but current usage suggests that most workers now agree that epidemiology deals with clinical diagnosis. Thus, today, epidemiology is used in a relatively broad way, which, with present technic, cannot be observed in addition to the many studies on communicable diseases, there have been epidemiological studies in embryology, nutrition, imbalance, and social, occupational hazards, cancer, and rheumatic fever.

In the field of cardiovascular studies using the epidemiological method have led to findings of clinical importance for treatment. Mention may, for example, be made of the studies of diseases, such as beriberi, pellagra, and of the infective diseases, such as syphilis, hemolytic infections, and streptococcal pneumonia. The findings of these studies have been implications of the epidemiological method in the prevention of these diseases. The adoption of control measures by the health authorities has led to the adoption of control measures by the health authorities.

These facts have long been known to Sir James Mackenzie, one of the pioneers in cardiology, over 30 years ago. He warned that the adoption of control measures would be of great benefit.

...
### Table 2. Regression Coefficients and Hazard Ratios

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta^*$</th>
<th>P</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women [So(10)=0.95012]</td>
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</tr>
<tr>
<td>Log of age</td>
<td>2.32888</td>
<td>$&lt;0.0001$</td>
<td>10.27</td>
<td>(5.65–18.64)</td>
</tr>
<tr>
<td>Log of total cholesterol</td>
<td>1.20904</td>
<td>$&lt;0.0001$</td>
<td>3.35</td>
<td>(2.00–5.62)</td>
</tr>
<tr>
<td>Log of HDL cholesterol</td>
<td>-0.70833</td>
<td>$&lt;0.0001$</td>
<td>0.49</td>
<td>(0.35–0.69)</td>
</tr>
<tr>
<td>Log of SBP if not treated</td>
<td>2.76157</td>
<td>$&lt;0.0001$</td>
<td>15.82</td>
<td>(7.86–31.87)</td>
</tr>
<tr>
<td>Log of SBP if treated</td>
<td>2.82263</td>
<td>$&lt;0.0001$</td>
<td>16.82</td>
<td>(8.46–33.46)</td>
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<tr>
<td>Smoking</td>
<td>0.52873</td>
<td>$&lt;0.0001$</td>
<td>1.70</td>
<td>(1.40–2.06)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.69154</td>
<td>$&lt;0.0001$</td>
<td>2.00</td>
<td>(1.49–2.67)</td>
</tr>
<tr>
<td>Men [So(10)=0.88936]</td>
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<td></td>
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</tr>
<tr>
<td>Log of age</td>
<td>3.06117</td>
<td>$&lt;0.0001$</td>
<td>21.35</td>
<td>(14.03–32.48)</td>
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<tr>
<td>Log of total cholesterol</td>
<td>1.12370</td>
<td>$&lt;0.0001$</td>
<td>3.08</td>
<td>(2.05–4.62)</td>
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<tr>
<td>Log of HDL cholesterol</td>
<td>-0.93263</td>
<td>$&lt;0.0001$</td>
<td>0.39</td>
<td>(0.30–0.52)</td>
</tr>
<tr>
<td>Log of SBP if not treated</td>
<td>1.93303</td>
<td>$&lt;0.0001$</td>
<td>6.91</td>
<td>(3.91–12.20)</td>
</tr>
<tr>
<td>Log of SBP if treated</td>
<td>1.99981</td>
<td>$&lt;0.0001$</td>
<td>7.38</td>
<td>(4.22–12.92)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.65451</td>
<td>$&lt;0.0001$</td>
<td>1.92</td>
<td>(1.65–2.24)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.57367</td>
<td>$&lt;0.0001$</td>
<td>1.78</td>
<td>(1.43–2.20)</td>
</tr>
</tbody>
</table>

So(10) indicates 10-year baseline survival; SBP, systolic blood pressure.
*Estimated regression coefficient

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D'Agostino, Circulation 2008
Dawber, Am J Pub Health 1959
Risk Factors Enough?

Age-Adjusted Death Rates for Coronary Artery Disease in the US 1950-2004

1960 First CABG performed in US
1967 CK test¹
1967 CCUs Widely adopted²
1977 CABG widely adopted
First PTCA
1982 Streptokinase FDA Approval
1987 tPA Approved

Vital Statistics US, NCHS


*Courtesy of Kellum JA, 2012*
The Gold Standard

Troponin to predict MI is optimized because of context dependent use

Early Dx
Early Tx
Early Recovery
Gold Standard?

Frontiers in cardiovascular medicine

Troponin elevation in disease

S. Agewall¹*, E. Giannitsis³, T. Jernbe

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Reasons for acutely elevated troponins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td></td>
<td>Acute heart failure</td>
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<tr>
<td></td>
<td>Pulmonary embolism</td>
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<td>Stroke</td>
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<td></td>
<td>Acute aortic dissection</td>
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<tr>
<td></td>
<td>Tachyarrhythmias</td>
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<tr>
<td></td>
<td>Hypotension / Shock</td>
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<tr>
<td></td>
<td>Sepsis</td>
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<tr>
<td></td>
<td>ARDS</td>
</tr>
<tr>
<td></td>
<td>Perimyocarditis</td>
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<tr>
<td></td>
<td>Endocarditis</td>
</tr>
<tr>
<td></td>
<td>Tako-tsubo cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Radiofrequency catheter ablation</td>
</tr>
<tr>
<td></td>
<td>Cardiac contusion</td>
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<td></td>
<td>Strenuous exercise</td>
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<td></td>
<td>Sympathomimetic drugs</td>
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<td></td>
<td>Chemotherapy</td>
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</tbody>
</table>
Troponin – Value Analysis

• San Diego County: 16 Major medical centers
  – Average of 100 ER visits/day
  – = 16 * 100 * 365 = 584000 ER visits/year
  – Cost of Troponin-I (~ $15/sample)
  – Cost of one Troponin per visit SD County EDs - $8,760,000

• Context Dependent Troponin Testing
  – If number of ED patients with chest pain, EKG changes is less..

<table>
<thead>
<tr>
<th>% Pts with Acute Coronary Syndrome</th>
<th># pts</th>
<th>Troponin cost per pt (millions)</th>
<th>Cost savings (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>438000</td>
<td>6.57</td>
<td>2.11</td>
</tr>
<tr>
<td>50</td>
<td>292000</td>
<td>4.48</td>
<td>4.38</td>
</tr>
<tr>
<td>25</td>
<td>146000</td>
<td>2.19</td>
<td>6.57</td>
</tr>
</tbody>
</table>
Pre- / Post- Test Probability

Cherry Picking
agenda

- Troponin, The Cherry Picking Biomarker
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- Risk Assessment and Moving the Needle
Risk Stratification Continuum

A Kidney injury continuum

- Normal
- Increased risk
- Damage
- ↓ GFR
- Kidney failure
- Death

Biomarkers
Biomarkers for early diagnosis of AKI in the ICU: Are We Ready for Prime Time?

Prasad Devarajan a, Patrick Murray b

aNephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; bSchool of Medicine and Medical Science, Health Sciences Centre, University College Dublin, Dublin, Ireland

Abstract

Novel biomarkers are required to improve the timely detection of early acute kidney injury (AKI) and to improve the differential diagnosis, prognostic assessment, and management of AKI cases. It is anticipated that novel biomarkers of early structural AKI (“acute kidney damage”) will provide critical diagnostic and prognostic stratification and complement functional markers such as serum creatinine. Further studies are required to conclusively demonstrate the association between early kidney damage biomarkers and clinical outcomes, both with and independently of functional markers, and to discern whether or not randomization to a treatment for AKI based on high structural/damage biomarker levels results in an improvement in kidney function and clinical outcomes.

Key Words

Biomarker · Acute kidney injury · Kidney damage · Kidney function

Review

Introduction

Accurate diagnosis of AKI in an ICU setting is challenging. Indeed, the characteristic symptom of AKI, i.e., a rise in serum creatinine, is often preceded by an increase in glomerular filtration rate, which is difficult to measure in critically ill patients. AKI is characterized by a decrease in urine output and/or an increase in serum creatinine. Although serum creatinine is the current standard for measuring kidney function, it is a late marker of kidney injury, and thus, a delay in initiating appropriate and timely therapy of AKI may still occur, has gained considerable attention in the literature published between 1999 and 2011 on potential early biomarkers for acute renal failure/kidney injury. As a consequence, the delay in initiating appropriate and timely therapy of AKI has increased, and hence, the need to identify biomarkers that are capable of detecting AKI early in the course of the disease. In the issue of the American Journal of Kidney Diseases, Devarajan et al utilize unbiased proteomics and biomarker techniques to identify α₂-microglobulin, α₁-antitrypsin, and albumin as diagnostic and prognostic markers of AKI in children undergoing CPB.

Ischemic AKI represents a sequence of events that are conceptually separated into initiation, extension, maintenance, and repair phases. The initiation and extension phases are characterized by alteration of microvascular hemodynamics and activation of inflammatory pathways in response to ischemic insult. Tubular epithelial injury resulting from these insults can induce apoptosis and necrosis, luminal sloughing of epithelial cells, tubular obstruction, and back leak. Sublethally injured tubular cells can lose their cytoskeletal integrity, brush border membranes, and cell polarity. Mislocalization of adhesion molecules leads to loss of viable epithelial cells into the tubular lumen. In the repair phase, surviving epithelial cells undergo dedifferentiation and proliferation, and subsequently redifferentiation leading to restitution of normal tubular epithelium (reviewed in detail [1]).

Although this paradigm has provided a framework for possible therapeutic interventions in animal models of AKI, similar interventions in human AKI are still to be determined. Our long-standing reliance on serum creatinine measurements has clearly hindered progress in acute kidney injury (AKI), the incidence of which is increasing globally [1]. This condition accounts for 3–5% of admissions in general hospitals, with devastating adverse outcomes that have not changed significantly in the past several decades. Serum creatinine, the current standard for measurement of kidney function and dysfunction, is a flawed AKI marker for many reasons. First, a single measurement of serum creatinine cannot distinguish true structural (intrinsic) AKI (with acute renal tubular damage) from chronic kidney disease or from functional, and potentially hemodynamically reversible, AKI (“prerenal azotemia”) [2]. It is critical to make these distinctions, since the management of each is distinct and mismanagement is deleterious. Second, creatinine levels are dramatically influenced by several nonrenal factors such as age, gender, muscle mass, muscle metabolism, medication use, hydration status, and nutrition status. Third, an increase in serum creatinine is delayed in AKI due to a number of factors, including: significant renal functional reserve (in many patients, but not necessarily in those with chronic kidney disease), the obligatory requirement for the accumulation of circulating creatinine before a new steady-state serum concentration is reached, and the masking and further delay of serum creatinine increments by a...
What about biomarkers to predict AKI?

Vanmassenhove, NDT 2012

### Table 1. Biomarkers considered in this review

<table>
<thead>
<tr>
<th>Acronym/abbreviation</th>
<th>Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>$\alpha_1$MG</td>
<td>Alpha 1 microglobulin</td>
</tr>
<tr>
<td>$\alpha_1$acidGP</td>
<td>Alpha 1 acid glycoprotein</td>
</tr>
<tr>
<td>$B_2$MG</td>
<td>Beta 2 microglobulin</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>FENA</td>
<td>Fractional excretion of sodium</td>
</tr>
<tr>
<td>GGTP</td>
<td>Gamma glutamyl transpeptidase</td>
</tr>
<tr>
<td>$\alpha$GST</td>
<td>Alpha glutathione S transferase</td>
</tr>
<tr>
<td>$\pi$GST</td>
<td>Pi glutathione S transferase</td>
</tr>
<tr>
<td>HGF</td>
<td>Hepatoocyte Growth Factor</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>IL-8</td>
<td>Interleukin 8</td>
</tr>
<tr>
<td>IL-10</td>
<td>Interleukin 10</td>
</tr>
<tr>
<td>IL-18</td>
<td>Interleukin 18</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Kidney injury molecule 1</td>
</tr>
<tr>
<td>NFABP</td>
<td>Liver-type fatty acid-binding protein</td>
</tr>
<tr>
<td>NGAL</td>
<td>Neutrophil gelatinase-associated lipocalin</td>
</tr>
<tr>
<td>NAG</td>
<td>N-Acetyl beta glucosaminidase</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Plasminogen activator inhibitor 1</td>
</tr>
<tr>
<td>PCX</td>
<td>Podocalyxin</td>
</tr>
<tr>
<td>RBP</td>
<td>Retinol-binding protein</td>
</tr>
<tr>
<td>sTNFR-I</td>
<td>Soluble tumour necrosis factor receptor I</td>
</tr>
<tr>
<td>sTNFR-II</td>
<td>Soluble tumour necrosis factor receptor II</td>
</tr>
<tr>
<td>TNF$\alpha$</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>11k-TXB$_2$</td>
<td>11-keto-Thromboxane B$_2$</td>
</tr>
<tr>
<td>vWF</td>
<td>Von Willebrand factor</td>
</tr>
</tbody>
</table>

**Abstract**

**Background.** Acute kidney injury (AKI) remains associated with high morbidity and mortality, despite progress in medical care. Although the RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease) and AKIN (Acute Kidney Injury Network) criteria, based on serum creatinine and urine output, were a step forward in diagnosing AKI, a reliable tool to differentiate between true parenchymal and pre-renal azotaemia in clinical practice is still lacking. In the last decade, many papers on the use of new urinary and serum biomarkers for the diagnosis and prognostication of AKI have been published. Thus, the question arises which biomarker is a reliable differential diagnostic tool under which circumstances.

**Methods.** We searched Medline from inception to April 2012 using medical subject heading and text words for AKI and biomarkers [neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), Cystatin C, interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), N-acetyl-glucosaminidase (NAG), glutathione transferases (GST) and liver fatty acid binding protein (LFABP)] to identify relevant papers in five different settings (paediatrics, cardiac surgery, emergency department, critically ill and contrast-induced nephropathy).

**Results.** We included 87 relevant papers, reporting on 74 studies. Depending upon the setting, 7–27 different definitions of AKI were used. Reported diagnostic performance of the different biomarkers was variable from poor to excellent, and no consistent generalizable conclusions can be drawn on their diagnostic value.

**Conclusions.** Early diagnosing of AKI in clinical conditions by using new serum and urinary biomarkers remains cumbersome, especially in those settings where timing and aetiology of AKI are not well defined. Putting too much emphasis on markers that have not convincingly proven reliability might lead to incorrect interpretation of clinical trials. Further research in this field is warranted before biomarkers can be introduced in clinical practice.

Vanmassenhove, NDT 2012
<table>
<thead>
<tr>
<th>Author</th>
<th>PY</th>
<th>Biomarker</th>
<th>U/S/P</th>
<th>Outcome</th>
<th>AKI def/outcome def</th>
<th>Patients/events</th>
<th>AUROC</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tr>
<td>Parikh [67]</td>
<td>2011</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>Doubling of Screra</td>
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<td>Xin [68]</td>
<td>2008</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>AKIN both</td>
<td>33/9</td>
<td>0.88</td>
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<td>91</td>
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<td>Wagener [69]</td>
<td>2007</td>
<td>NGAL</td>
<td>U</td>
<td>AD</td>
<td>Screra*1.5</td>
<td>81/6</td>
<td>0.8</td>
<td>4</td>
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<td>Wagener [46]</td>
<td>2008</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>AKIN crea</td>
<td>426/85</td>
<td>0.61</td>
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<td>Haase-Fielitz [50]</td>
<td>2009</td>
<td>NGAL</td>
<td>P</td>
<td>AKI</td>
<td>Screra*1.5 within 5 days postoperatively</td>
<td>100/23</td>
<td>0.80/0.87 (ICU arr/24 h post)</td>
<td>52/53</td>
<td>93/97</td>
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<td>Haase-Fielitz [19]</td>
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<td>AKI</td>
<td>Screra*1.25 within 48 h</td>
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<td>Tuladhar [70]</td>
<td>2009</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>↑Screa 0.5 mg/dL within 48 h</td>
<td>50/9</td>
<td>0.96</td>
<td>47</td>
<td>97</td>
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<td></td>
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<td>NGAL</td>
<td>P</td>
<td>AKI</td>
<td>Screra*1.5 within 4 days</td>
<td>879/75</td>
<td>0.64</td>
<td>16</td>
<td>93</td>
</tr>
<tr>
<td>Prabhu [71]</td>
<td>2010</td>
<td>NGAL</td>
<td>P</td>
<td>AKI</td>
<td>RIFLE crea</td>
<td>30/8</td>
<td>0.98</td>
<td>79</td>
<td>100</td>
</tr>
<tr>
<td>McIlroy [51]</td>
<td>2010</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>AKIN crea</td>
<td>426/85</td>
<td>0.98</td>
<td>79</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koyner [20]</td>
<td>2008</td>
<td>NGAL</td>
<td>P</td>
<td>AKI</td>
<td>Screra*1.25 or RRT need within 72 h</td>
<td>72/34</td>
<td>0.54</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>U</td>
<td>AKI</td>
<td></td>
<td>72/34</td>
<td>0.54</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Haase [72]</td>
<td>2009</td>
<td>NGAL</td>
<td>P</td>
<td>AKI</td>
<td>AKIN both</td>
<td>100/46</td>
<td>0.77</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>Koyner [73]</td>
<td>2012</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>AKI progression</td>
<td>380/45</td>
<td>NA</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>
Initial search: 5035 articles

Potentially relevant: 263 articles

Study | Area Under the ROC Curve (95% CI)
--- | ---
Wagner, 2008 | 0.81 (0.54 - 0.69)
Liangos, 2009 | 0.50 (0.33 - 0.68)
Han, 2009 |
Koyner, 2010 |
Hobst, 2011 |
Eke, 2012 |
Matsui, 2012 |
Sargeant, 2012 |
Liepke, 2013 |
Liu, 2013 |
Mehiri, 2013 |
Pasemann, 2013 |
Park, 2013 |
Meier, 2014 |
Gages, 2015 |
Provene, 2015 |
Composite: a-NGAL |
Liangos, 2009 |
Han, 2009 |
Kestigri, 2012 |
Matsui, 2012 |
Composite: a-NAG |
Liangos, 2009 |
Han, 2009 |
Koyner, 2010 |
Liangos, 2010 |
Pasemann, 2013 |
Park, 2013 |
Composite: a-KIM-1 |
Haasar, 2008 |
Liangos, 2009 |
Liang, 2010 |
Ejaz, 2012 |
Park, 2013 |
Composite: a-IL-13 |
Kestigri, 2012 |
Liu, 2013 |
Matsui, 2012 |
Pasemann, 2013 |
Park, 2013 |
Provene, 2015 |
Composite: a-L-FABP |
Koyner, 2010 |
Sanehi, 2013 |
Provene, 2015 |
Composite: a-alpha-GST |
Koyner, 2010 |
Sanehi, 2013 |
Provene, 2015 |
Composite: a-pl-GST |

by exclusion of studies sampling after 6 hours.

**DISCUSSION**

Our meta-analysis of biomarkers in the early detection of AKI following cardiac surgery has 2 important findings. First, we found that current biomarkers have generally poor and at best moderate discrimination for AKI when measured within the first 24 hours after cardiac surgery in adults. Second, at present, there are comparatively few data for the discrimination of these biomarkers in the intraoperative period, a time of potential active management to mitigate kidney injury. Only u-NGAL has been studied more than once, but its intraoperative diagnostic performance was limited. Our findings highlight the need for further investigation into the early detection of cardiac surgery-associated AKI, particularly given the need for early prevention and treatment of this prescheduled ischemia-reperfusion injury event.

Several other published systematic reviews have
studies were conducted in critically ill children. Only one study in the paediatric setting [6] explored the use of bio-
markers for early prediction of need for RRT [19]. Patients, 4 events, area under the receiver operating
characteristic curve (AURoC) 0.86, PPV and NPV not
available. All other studies considered the predictive
value for AKI, which was defined according to seven
different definitions. The number of patients varied from
23 to 374, and the number of events varied from 6 to 121.
AURoCs for the prediction of AKI varied from 0.44 to
1.00. PPVs and NPVs ranged from 27 to 100% and from
10 to 100%, respectively.

In adult cardiac surgery, 26 papers reporting on 22
studies were included. Twenty-seven different de-
finitions for AKI were used. Patient number varied from 30 to
1219 and event number varied from 1 to 85. The
AURoCs varied from 0.27 to 0.98. PPVs and NPVs
ranged from 4 to 100% and from 61 to 100%, respect-
ively. One study [19] reported on the use of biomarkers
for the prediction of need for RRT (100 patients, 4
events, AURoC 0.83, PPV 100%, NPV 99%), although
another study [20] also defined AKI as a 25% increase in
serum creatinine (Screa) or RRT need with AURoCs
between 0.54 and 0.73 and PPV 64–72%, NPV 67–73%.

In the emergency department setting, four studies were
included [21–24]. The patient number varied from 616 to
1635 and the event number from 24 to 130. Three differ-
ent definitions of AKI were used. AURoCs varied from
0.59 to 0.95. PPVs and NPVs varied from 4 to 90% and
from 84 to 99.5%, respectively.

In critically ill patients, 33 papers reporting on 29
studies, of which 1 was a meta-analysis, were included.
Twenty-one different definitions were used to define AKI.
The patient number varied from 26 to 1345 and the event
number varied from 4 to 209. AURoCs for the prediction
of AKI varied from 0.35 to 0.99 and PPVs and NPVs
ranged from 1 to 100% and from 50 to 100%, respect-
ively. Fifteen papers reported on the adverse clinical out-
comes of AKI (failure of recovery, RRT or the composite
outcome of RRT and mortality). AURoCs for the predic-
tion of adverse clinical outcomes varied from 0.51 to 0.92
(PPV 5–75% and NPV 86–99.5%).

Eight studies exploring the use of biomarkers in CIN
were included. Seven different definitions of CIN were
used. The patient number ranged from 30 to 410 and
event number from 2 to 34. AURoCs varied from 0.73 to
0.93. PPVs and NPVs ranged from 20 to 68% and from
96 to 100%, respectively.

Discussion

This paper evaluated the state of the art on the diagnostic
usefulness of biomarkers in AKI. Most striking was the
wide array of definitions used for AKI. With regard to the
diagnostic usefulness of biomarkers, a variety of results
were reported. A summary of these results is provided in
Table 4.

### Table 4. Emergency department

<table>
<thead>
<tr>
<th>Author</th>
<th>PY</th>
<th>Biomarker</th>
<th>U/S/P</th>
<th>Outcome</th>
<th>AKI def/outcome def</th>
<th>Patients/events</th>
<th>AURoC</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickolas et al.</td>
<td>2008</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>RIFLE crea</td>
<td>635/30</td>
<td>0.95</td>
<td>90</td>
<td>99.5</td>
</tr>
<tr>
<td>Shapiro et al.</td>
<td>2010</td>
<td>NGAL</td>
<td>P</td>
<td>AKI</td>
<td>†0.5 mg/dL or RRT need within 72 h ≥RIFLE R Screa*1.5</td>
<td>661/24</td>
<td>0.82</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>Nickolas et al.</td>
<td>2012</td>
<td>NGAL</td>
<td></td>
<td></td>
<td>T0 creatinine &gt; 1.4</td>
<td>1635/96</td>
<td>0.81</td>
<td>23</td>
<td>97</td>
</tr>
<tr>
<td>Nickolas et al.</td>
<td>2008</td>
<td>NAG</td>
<td>U</td>
<td>AKI</td>
<td>RIFLE crea</td>
<td>635/30</td>
<td>0.71</td>
<td>9</td>
<td>98.5</td>
</tr>
<tr>
<td>Shapiro et al.</td>
<td>2010</td>
<td>Creatinine</td>
<td>P</td>
<td>AKI</td>
<td>≥RIFLE I Screa*1.5</td>
<td>661/27</td>
<td>NA</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>Soto et al.</td>
<td>2010</td>
<td>Cystatin C</td>
<td>S</td>
<td>AKI</td>
<td>AKIN crea</td>
<td>616</td>
<td>0.87</td>
<td>48</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>U</td>
<td>AKI</td>
<td>AKIN crea</td>
<td></td>
<td>0.59</td>
<td>32</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S</td>
<td>AKI</td>
<td>AKIN crea</td>
<td></td>
<td>0.62</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

6 studies

ROC Range: 0.62-0.95

Limited data / 3 groups
Table 5. Critically ill patients at ICU

<table>
<thead>
<tr>
<th>Author</th>
<th>PY</th>
<th>Biomarker</th>
<th>U/S/P</th>
<th>Outcome</th>
<th>AKI def/outcome def</th>
<th>Patients/events</th>
<th>AUROC (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahlström [83]</td>
<td>2004</td>
<td>Cystatin C</td>
<td>S</td>
<td>ARF</td>
<td>RIFLE F both</td>
<td>202/54</td>
<td>0.89</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Herget-Rosenthal [84]</td>
<td>2004</td>
<td>Cystatin C</td>
<td>U</td>
<td>RRT</td>
<td>Patients with non-oliguric ATN</td>
<td>73/26</td>
<td>0.92</td>
<td>75/95</td>
<td>95/95</td>
</tr>
<tr>
<td>Herget-Rosenthal [85]</td>
<td>2004</td>
<td>Cystatin C</td>
<td>S</td>
<td>ARF</td>
<td>RIFLE crea</td>
<td>85/44</td>
<td>Rday-2/-1: 0.82/0.97</td>
<td>92/95</td>
<td>66/83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rday-2/-1: 0.92/0.98</td>
<td>100/100</td>
<td>63/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fday-2/-1: 1.97/0.99</td>
<td>100/100</td>
<td>76/93</td>
</tr>
<tr>
<td>Mazul-Sunko [86]</td>
<td>2004</td>
<td>Cystatin C</td>
<td>P</td>
<td>ARF</td>
<td>Screa ≥ 267 µmol/L or diuresis &lt;30 mL/h in patients without CKD</td>
<td>29/10</td>
<td>0.65</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hei [87]</td>
<td>2008</td>
<td>Cystatin</td>
<td>S</td>
<td>ARF</td>
<td>†Screa to 132 µmol/L or †BUN to</td>
<td>60/10</td>
<td>0.83</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Perianayagam [58]</td>
<td>2009</td>
<td>Cystatin C</td>
<td></td>
<td>ARF</td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Portal [88]</td>
<td>2010</td>
<td>Cystatin C</td>
<td>P</td>
<td>AKI</td>
<td>AKIN crea</td>
<td>51/73 (no AKI on entry)</td>
<td>0.77</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nejat [89]</td>
<td>2010</td>
<td>Cystatin</td>
<td>U</td>
<td>AKI 48 h</td>
<td>AKIN crea</td>
<td>51/73 (no AKI on entry)</td>
<td>0.54</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine</td>
<td>U</td>
<td>AKI 48 h</td>
<td></td>
<td></td>
<td>51/? (sepsis, no AKI on entry)</td>
<td>0.71</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cystatin</td>
<td>P</td>
<td>AKI 48 h</td>
<td></td>
<td></td>
<td>268/? (no sepsis, no AKI on entry)</td>
<td>Not predictive</td>
<td>NA</td>
</tr>
<tr>
<td>Nejat [59]</td>
<td>2010</td>
<td>Cystatin C</td>
<td>S</td>
<td>AKI</td>
<td>AKIN both 2/16</td>
<td>20/9</td>
<td>0.67</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Metzger [63]</td>
<td>2010</td>
<td>Cystatin C</td>
<td>P</td>
<td>AKI</td>
<td></td>
<td></td>
<td>268/? (no sepsis, no AKI on entry)</td>
<td>0.45</td>
<td>NA</td>
</tr>
</tbody>
</table>

Continued
Eighty-seven papers reporting on 74 studies were included in the review. Sixty-eight papers were excluded for reasons outlined in Figure 1. All biomarkers and their abbreviations as used further in the text are summarized in Table 1.

Results of the data extraction of the 87 selected papers are presented in Tables 2–6. We organized papers according to the five different clinical settings [paediatrics, cardiac surgery, emergency department, critically ill patients at intensive care unit (ICU) and contrast-induced nephropathy (CIN)].

In the paediatric setting, 16 papers reporting on 11 studies were discussed. Eleven papers reporting on seven studies were conducted post-cardiac surgery [6–16], one studied CIN [17], one was conducted in the emergency department setting [18] and three papers reporting on two studies were

<table>
<thead>
<tr>
<th>Author</th>
<th>PY</th>
<th>Biomarker</th>
<th>U/S/P</th>
<th>Outcome</th>
<th>AKI def/outcome def</th>
<th>Patients/events</th>
<th>AURoC</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra et al.</td>
<td>2005</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>Screa*1.5</td>
<td>71/20</td>
<td>0.99</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Hirsch et al.</td>
<td>2007</td>
<td>NGAL</td>
<td>S</td>
<td>CIN</td>
<td>Screa*1.5</td>
<td>91/11</td>
<td>0.92</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Zappitelli [43]</td>
<td>2007</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>Persistent AKI lasting &gt;48 h</td>
<td>140/22</td>
<td>0.68</td>
<td>39</td>
<td>94</td>
</tr>
<tr>
<td>Dent et al. [8]</td>
<td>2007</td>
<td>NGAL</td>
<td>P</td>
<td>AKI</td>
<td>Screa*1.5</td>
<td>120/45</td>
<td>0.96</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td>Bennett et al. [6]</td>
<td>2008</td>
<td>NGAL</td>
<td>U</td>
<td>AKI</td>
<td>Screa*1.5</td>
<td>196/99</td>
<td>0.95</td>
<td>89</td>
<td>83</td>
</tr>
<tr>
<td>Wheeler et al. [42]</td>
<td>2008</td>
<td>NGAL</td>
<td>S</td>
<td>AKI</td>
<td>BUN &gt; 100 mg/dL, Screa &gt;2 mg/dL</td>
<td>143/22</td>
<td>0.68</td>
<td>39</td>
<td>94</td>
</tr>
<tr>
<td>Krawczeski et al. [10]</td>
<td>2011</td>
<td>NGAL</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portilla et al. [14]</td>
<td>2008</td>
<td>NGAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Du et al. [18]</td>
<td>2011</td>
<td>NGAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parikh et al. [13]</td>
<td>2011</td>
<td>IL-18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parikh et al. [16]</td>
<td>2006</td>
<td>IL-18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Du et al. [18]</td>
<td>2011</td>
<td>IL-18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washburn [41]</td>
<td>2008</td>
<td>IL-18</td>
<td>U</td>
<td>RIFLE-I</td>
<td></td>
<td>137/103</td>
<td>0.54</td>
<td>27</td>
<td>85</td>
</tr>
<tr>
<td>Portilla et al. [14]</td>
<td>2008</td>
<td>LFABP</td>
<td>U</td>
<td>AKI</td>
<td>Screa*1.5</td>
<td>40/21</td>
<td>0.81</td>
<td>71</td>
<td>68</td>
</tr>
<tr>
<td>Dennen et al. [7]</td>
<td>2010</td>
<td>IL-6</td>
<td>U</td>
<td>AKI</td>
<td>Screa*1.5</td>
<td>23/10</td>
<td>NA</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Liu et al. [11]</td>
<td>2009</td>
<td>IL-6</td>
<td>S</td>
<td>AKI</td>
<td>Screa*1.5 within 3 days</td>
<td>39/18</td>
<td>0.76</td>
<td>69</td>
<td>87</td>
</tr>
<tr>
<td>Zappitelli et al. [15]</td>
<td>2011</td>
<td>Clinical model (CM)</td>
<td>S</td>
<td>AKI</td>
<td>Screa*1.5</td>
<td>288/121</td>
<td>0.77</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Krawczeski et al. [9]</td>
<td>2010</td>
<td>KIM-1</td>
<td>U</td>
<td>AKI</td>
<td>Screa*1.5 within 48 h</td>
<td>374/119</td>
<td>0.81</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>Du et al. [18]</td>
<td>2011</td>
<td>KIM-1</td>
<td>U</td>
<td>AKI</td>
<td>RIFLE-I</td>
<td>252/18</td>
<td>0.61</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β2-MG</td>
<td>U</td>
<td></td>
<td></td>
<td></td>
<td>0.59</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KIM-1</td>
<td>U</td>
<td></td>
<td></td>
<td></td>
<td>0.73</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β2-MG</td>
<td>U</td>
<td></td>
<td></td>
<td></td>
<td>0.80</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 2. Paediatric setting

Majority are CPB patients!
Validation of Cell-Cycle Arrest Biomarkers for Acute Kidney Injury Using Clinical Adjudication


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A complete list of Sapphire Investigators is provided in the online appendix.

ABSTRACT

Background. Acute kidney injury (AKI) is a leading cause of mortality and morbidity. Kidney function is often measured using the Acute Kidney Injury Network (AKIN) criteria. However, these criteria have been shown to be inaccurate, and the need for a more accurate biomarker for AKI remains.

Objectives. The primary goal of this study was to validate two novel biomarkers, the markers of the cell cycle arrest (G0/G1). The secondary goal was to compare these biomarkers with the AKIN criteria.

Methods. Preclinical and clinical studies were conducted to determine the sensitivity and specificity of the markers. A retrospective cohort study was conducted to compare the AKIN criteria with the markers in patients with AKI.

Results. The markers were able to predict AKI with a sensitivity of 80% and a specificity of 90%. The AKIN criteria had a sensitivity of 50% and a specificity of 70%.

Conclusions. The markers of cell cycle arrest have the potential to be a more accurate biomarker for AKI than the AKIN criteria.

Keywords: acute kidney injury; biomarker; cell cycle arrest; kidney injury; diagnostic accuracy

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392 American Journal of Respiratory and Critical Care Medicine Volume 189 Number 8 | April 2014
agenda

- Troponin, The Cherry Picking Biomarker
- AKI Biomarkers, Finally Usable?
- Risk stratification and Renal Angina
- Risk Assessment and Moving the Needle
Mortality after prognostic scores

GM Chertow1, SH Soroko for the Program to Improve Care

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To adjust adequately for comorbidity quality improvement efforts on the risk of death after acute renal failure (ARF) have focused on scoring models. Most of these models have been developed in multicenter trials, and their performance in individual centers has been examined at single time points. Therefore, it is not known whether these scoring systems may be widely applicable.

Design: Prospective clinical investigation.

Setting: Intensive care units.

Patients: One thousand, seven hundred and forty-two intensive care unit patients with acute renal failure who were either treated with renal replacement therapy or fulfilled predefined criteria.

Interventions: Demographic and clinical information and outcomes were measured. Measurements and Main Results: Scores for four acute renal failure scoring systems and two general scoring systems (Simplified Acute Physiology Score II and Sequential Organ Failure Assessment) were calculated, and their discrimination and calibration were tested with receiver operating characteristic curves.

Conclusions: None of the scoring systems tested had a high level of discrimination or calibration to predict mortality in patients with acute renal failure when tested in a broad cohort of patients from multiple countries. A large, multicenter database might be needed to improve the discrimination and calibration of acute renal failure scoring systems.

Key Words: acute renal failure; critical illness; severity score; renal replacement therapy; hemodialysis; hemofiltration

Refining Predictive Models in Critical Acute Renal Failure

RAVINDRA L. MEHTA*, MARIA T. PAS SHUNPING ZHUANG* GLENN M. CHEI

*Division of Nephrology, University of California, San Francisco, and 1Division of Nephrology, University of California, San Francisco, California; and 2Project 1 Group includes the University of California, San Diego Medical Center, San Francisco, California, and Indiana University, Indianapolis, Indiana.

Abstract: Mortality rates in acute renal failure remain extremely high, and risk-adjustment tools are needed for quality improvement initiatives and design (implementation) of randomized clinical trials. A total of 605 patients with acute renal failure in the intensive care unit during 1989-1995 were evaluated, and demographic, clinical, laboratory, and physiologic variables were associated with in-hospital death rates using multivariable logistic regression. Thirty-three and fourteen (9.1%) patients died in hospital. The following variables were significantly associated with in-hospital death: age (odds ratio OR 1.04), blood pressure (OR 1.35), respiratory (OR 2.62), liver (OR 2.53), and acute renal failure (ARF) (P < 0.001). Despite improvements in intensive care and dialysis technology, particularly with continuous renal replacement therapies, we have not observed meaningful improvements in patient survival over the past three decades (1-5). In most series, more than 50% of patients with hospital-acquired ARF die before hospital discharge, of those who survive, between 10 and 33% require long-term dialysis (9-11). Over the past decade, several clinical trials have been conducted, aimed at reducing ARF-associated mortality (12-14). Most of these studies have unfortunately proved unsuccessful, including relatively large, well-designed trials using pharmacologic agents with strong preclinical data (e.g., natriuretic peptide [APD]). Among the difficulties in design and analysis of clinical trials in ARF are the lack of a standardized definition of ARF, the heterogeneity of ARF, morbidity, and severity of illness directly influencing the process in the design of clinical trials.

Despite continuing progress in medical treatment, acute renal failure (ARF) in critical illness carries a hospital mortality rate of >50% (1-3). Several randomized controlled trials have been unsuccessful in demonstrating that specific interventions reduce this mortality rate. We have attempted to conduct clinical trials with continuous clinical trials to confirm successful randomization. However, the accuracy of these systems for ARF has been questioned (9, 10), because only a small fraction of subjects with ARF were involved in the original database. Thus, ARF-specific severity scoring systems have been generated to overcome this issue (11-14). These scoring systems also have been validated (15, 16). However, most of both development and validation of these scoring systems were conducted in a single center or a small number of centers. It is unclear whether such studies would lead to findings that are reproducible and generally applicable.

The ending and Beginning Supportive Therapy for the Kidney (B.E.S.T. Kidney) study is a multicenter, multinational, prospective, epidemiologic study with the aim of understanding multiple aspects of ARF at an international level. This study included >1,700 patients in 34 centers in 23 countries. Such a large database was among other goals, collected for the purpose of validating proposed ARF-specific illness severity scores.

External validation of severity scoring systems for acute renal failure using a multinational database

Shigehiko Uchino, MD; Rinaldo Bellomo, MD; Hiroshi Morimatsu, MD; Stanislav Morgera, MD; Miet Schetz, MD, PhD; Ian Tan, MD; Catherine Bouman, MD; Etienne Macedo, MD; Noel Gibney, MD; Ashita Tolwani, MD; Gordon S. Doig, PhD; Heleen Oudemans van Straaten, MD; Claudio Ronco, MD; John A. Kellum, MD for the Ending and Beginning Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

Objective: Several different severity scoring systems specific to acute renal failure have been proposed. However, most validation studies have been conducted in a single center or in a small number of centers, often the same ones used for their development. Therefore, it is not known whether these severity scoring systems may be widely applied.

Design: Prospective clinical investigation.

Setting: Intensive care units.

Patients: One thousand and seventy-five intensive care unit patients with acute renal failure who were either treated with renal replacement therapy or fulfilled predefined criteria.

Interventions: Demographic and clinical information and outcomes were measured. Measurements and Main Results: Scores for four acute renal failure scoring systems and two general scoring systems (Simplified Acute Physiology Score II and Sequential Organ Failure Assessment) were calculated, and their discrimination and calibration were tested with receiver operating characteristic curves.

Conclusions: None of the scoring systems tested had a high level of discrimination or calibration to predict mortality in patients with acute renal failure when tested in a broad cohort of patients from multiple countries. A large, multicenter database might be needed to improve the discrimination and calibration of acute renal failure scoring systems.

Key Words: acute renal failure; critical illness; severity score; renal replacement therapy; hemodialysis; hemofiltration

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Mehta’s score (11):

Log odds of death = 0.0170 \cdot \text{age} + 0.8605 \cdot \text{male} + 0.0144 \cdot \text{BUN} - 0.3398 \cdot \text{Cr} + 1.2242 \cdot \text{hematologic failure} + 1.1183 \cdot \text{liver failure} + 0.9637 \cdot \text{respiratory failure} + 0.0119 \cdot \text{heart rate} - 0.4432 \cdot \log (\text{urine output}) - 0.7207

[1]

Liano’s score (12):

Probability of death

= 0.032 \cdot \text{age decades} - 0.086 \cdot \text{male} - 0.109 \cdot \text{nephrotoxic} + 0.109 \cdot \text{oliguria} + 0.116 \cdot \text{hypotension} + 0.122 \cdot \text{jaundice} + 0.150 \cdot \text{coma} - 0.154 \cdot \text{consciousness} + 0.182 \cdot \text{assisted respiration} + 0.210

[2]

Chertow’s score (13):

Log hazard ratio of death

= 0.6991 \cdot \text{male} + 0.8128 \cdot \text{oliguria} + 0.0557 \cdot \text{total bilirubin} + 0.6215 \cdot \text{ventilation} + 1.1245 \cdot \text{stroke or seizure} + 1.1432 \cdot \text{acute myocardial infarction} + 0.8643 \cdot \text{immunosuppression} - 0.0555 \cdot \text{bicarbonate} - 0.3139 \cdot \text{albumin} \ [3]

Paganini’s score (14):

Variable—Score Used

Male—2
Intubation/mechanical ventilation—3
Platelets <50,000/mm³, leukocytes <2,500/mm³, or bleeding diathesis—3
Bilirubin >2.0 mg/dL—3
Absence of surgery—1
Number of organ failures: 1—0
2 to 3—2
4 to 7—3
Change in blood urea nitrogen 0–50 mg/dL—1
Table 4  Log odds of death or probability of death given acute renal failure (ARF) in kidney-specific severity scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Log odds of death = sum of variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullock (Log)</td>
<td>-1.765-0.687 (CP1+.037)+0.822 (CP2+0.1)+1.053 ([pulmonary complications]-.087)+0.05 (age 61.1)+0.7</td>
</tr>
<tr>
<td></td>
<td>([jaundice]+.143)+0.608 ([CV complications]-.247)+0.365 ([hypercatabolism]+.0303)</td>
</tr>
<tr>
<td>Liano (Prob)</td>
<td>0.32 (age in decades) - 0.086 (male) - 0.109 (nephrotoxic)+0.109 (oliguric)+0.116 (hypotensive)+0.122</td>
</tr>
<tr>
<td></td>
<td>(jaundice)+0.15 (coma) -0.154 (conscious)+0.182 (assisted ventilation)+0.210</td>
</tr>
<tr>
<td>Mehta</td>
<td>0.17 (age)+0.8605 (male)+0.0144 (BUN) −0.3398 (creatinine)+1.2242 (hematologic failure)+1.1183</td>
</tr>
<tr>
<td></td>
<td>(liver failure)+0.9637 (respiratory failure)+.0119 (heart rate) −0.4432 (log[UOP]) −0.7207</td>
</tr>
<tr>
<td>SHARF-II_o</td>
<td>3 (age in decades)+2.6 (albumin category)+1.3 (prothrombin category)+16.8 (mechanical ventilation)+3.9</td>
</tr>
<tr>
<td></td>
<td>(heart failure)+2.8 (bilirubin)+27 (sepsis)+21 (hypotension) −17</td>
</tr>
<tr>
<td>PICARD</td>
<td>0.1241 (age in decades) −.2063 (log UOP)+.69 (serum creatinine&lt;2)+0.0828 (BUN per 10)+0.4811</td>
</tr>
<tr>
<td></td>
<td>(liver failure)+0.58 (ARDS)+0.5074 (platelet count&lt;150)+0.4803 (sepsis) −1.2563</td>
</tr>
</tbody>
</table>

SHARF Stuivenberg Hospital Acute Renal Failure, PICARD Program to Improve Care in Acute Renal Disease, Anuria CP1=0, CP2=1, Nonoliguria CP1=1, CP2=0, CV cardiovascular, BUN blood urea nitrogen, UOP urine output, ARDS acute respiratory distress syndrome

Can it be simpler?
More AKI focused?
<table>
<thead>
<tr>
<th>Proposed Step</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk assessment</td>
<td>Several risk factors are already established</td>
</tr>
<tr>
<td>Identify patients at risk for AKI</td>
<td></td>
</tr>
<tr>
<td>Develop preventive strategies</td>
<td>Effective preventive strategies can be tested</td>
</tr>
<tr>
<td>Early detection</td>
<td></td>
</tr>
<tr>
<td>Identification of subclinical prodromes</td>
<td>More frequent monitoring of renal function is possible</td>
</tr>
<tr>
<td>Monitoring of renal function injury biomarkers</td>
<td>Point-of-care testing for biomarkers is available</td>
</tr>
</tbody>
</table>
The Importance of Context
### Renal Angina?

**Table 1. Risk factors for developing AKI**

<table>
<thead>
<tr>
<th>Demographic and Clinical</th>
<th>Biochemical Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
</tr>
<tr>
<td>age &gt; 65 years</td>
<td>Elevated IL-6</td>
</tr>
<tr>
<td>diabetes</td>
<td>Elevated soluble TNF-α receptor</td>
</tr>
<tr>
<td>cirrhosis/hepatic failure</td>
<td>PAI-1</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td></td>
</tr>
<tr>
<td>volume depletion</td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td></td>
</tr>
<tr>
<td>cardiopulmonary bypass</td>
<td></td>
</tr>
<tr>
<td>exposure to</td>
<td></td>
</tr>
<tr>
<td>nephrotoxins</td>
<td></td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
</tr>
<tr>
<td>invasive mechanical ventilation</td>
<td>IL-6 (10)</td>
</tr>
<tr>
<td>vasoactive medications</td>
<td>IL-8</td>
</tr>
<tr>
<td>nephrotoxic medications</td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td></td>
</tr>
<tr>
<td>multiorgan failure</td>
<td></td>
</tr>
<tr>
<td>volume depletion</td>
<td></td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>hypoxemia</td>
<td></td>
</tr>
<tr>
<td>neurologic dysfunction</td>
<td></td>
</tr>
<tr>
<td>stem cell transplantation</td>
<td></td>
</tr>
</tbody>
</table>

---

**Renal Angina Threshold**

- **Hazard Tranche 1**
  - Very High Risk Patients
  - Estimated creatinine clearance decrease of 25%

- **Hazard Tranche 2**
  - High Risk Patients
  - Increase in 0.3 mg/dl over baseline OR
  - eGFR decrease of 25-50% OR
  - ICU fluid overload 10%

- **Hazard Tranche 3**
  - Moderate Risk Patients
  - eGFR decrease >50% OR
  - ICU fluid overload > 15%

---

Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children

Rajit K. Basu\textsuperscript{1,2}, Michael Zappitelli\textsuperscript{3}, Lori Brunner\textsuperscript{1}, Yu Wang\textsuperscript{4}, Hector R. Wong\textsuperscript{2}, Lakhmir S. Chawla\textsuperscript{5}, Derek S. Wheeler\textsuperscript{1,2} and Stuart L. Goldstein\textsuperscript{1,6}

\begin{table}[h]
\centering
\begin{tabular}{lccc}
\hline
 & Day-3 AKI outcome & \\
 & UOP & Cr & Worse \\
\hline
\textit{RAI} & & & \\
$\Delta e\text{CCL}$ & 0.81 (0.71-0.90) & 0.73 (0.59-0.88) & 0.78 (0.69-0.87) \\
FO & 0.57 (0.44-0.71) & 0.63 (0.49-0.76) & 0.60 (0.49-0.71) \\
Worse & 0.78 (0.68-0.88) & 0.75 (0.62-0.89) & 0.77 (0.68-0.86) \\
\hline
\textit{Illness score} & & & \\
PRISM-II & 0.65 (0.52-0.79) & 0.61 (0.45-0.79) & 0.66 (0.54-0.79) \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{lccccc}
\hline
 & N & Sensitivity & Specificity & PPV & NPV & Youden's index \\
\hline
KDIGO 1 & 25 & 21 (8-41) & 84 (76-90) & 24 (9-45) & 82 (73-88) & 5 \\
KDIGO 2-3 & 24 & 46 (28-66) & 91 (84-95) & 54 (33-74) & 87 (80-93) & 37 \\
ANG(+) & 52 & 75 (55-89) & 73 (64-81) & 40 (27-55) & 92 (85-97) & 48 \\
\hline
\end{tabular}
\end{table}
Incorporation of Biomarkers with the Renal Angina Index for Prediction of Severe AKI in Critically Ill Children

Rajit K. Basu,*‡§ Yu Wang,† Hector R. Wong,‡ Lakhmir S. Chawla,‖ Derek S. Wheeler,*‡ and Stuart L. Goldstein*‡†

Table 6. Inclusion of biomarkers increases the predictive performance of the RAI

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC</th>
<th>Increase in AUC (95% Confidence Interval)</th>
<th>P Value</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAI</td>
<td>0.80</td>
<td></td>
<td></td>
<td>135.39</td>
</tr>
<tr>
<td>RAI+NGAL</td>
<td>0.85</td>
<td>0.05 (0.01 to 0.09)</td>
<td>0.01</td>
<td>132.77</td>
</tr>
<tr>
<td>RAI+MMP-8</td>
<td>0.84</td>
<td>0.04 (0.001 to 0.07)</td>
<td>0.04</td>
<td>133.23</td>
</tr>
<tr>
<td>RAI+Ela-2</td>
<td>0.87</td>
<td>0.06 (0.01 to 0.12)</td>
<td>0.03</td>
<td>125.14</td>
</tr>
<tr>
<td>RAI+NGAL+MMP-8</td>
<td>0.86</td>
<td>0.06 (0.01 to 0.11)</td>
<td>0.03</td>
<td>128.97</td>
</tr>
<tr>
<td>RAI+NGAL+Ela-2</td>
<td>0.88</td>
<td>0.07 (0.01 to 0.14)</td>
<td>0.02</td>
<td>123.45</td>
</tr>
<tr>
<td>RAI+MMP-8+Ela-2</td>
<td>0.87</td>
<td>0.06 (0.01 to 0.12)</td>
<td>0.03</td>
<td>126.93</td>
</tr>
</tbody>
</table>
**AKI Risk Tranche**

**Table 3. Multivariate regression for Day₃ AKI**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Odds ratio</th>
<th>All Day₀ patients</th>
<th>Patients with Day₃ data</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM-III</td>
<td>1.12 (1.05, 1.19)</td>
<td>1.09 (1.04, 1.16)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>7.1 (2.26, 22.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant history</td>
<td>8.62 (2.69, 27.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal angina</td>
<td>10.1 (2.71, 37.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Discrimination for Day₃-AKI by the RAI in combination with urinary biomarkers

<table>
<thead>
<tr>
<th>Terms</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>+LR</th>
<th>ORᵃ (95% CI)</th>
<th>AUC-ROC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day₀ RAI</td>
<td>80 (52–97)</td>
<td>72 (64–78)</td>
<td>20 (11–32)</td>
<td>98 (93–100)</td>
<td>2.8 (2.0–4.0)</td>
<td>n/a</td>
<td>0.80 (0.58, 1.00)</td>
</tr>
<tr>
<td>Day₀ RAI+ NGAL</td>
<td>86 (42–99)</td>
<td>85 (77–90)</td>
<td>23 (9–44)</td>
<td>99 (95–100)</td>
<td>5.6 (3.4–9.2)</td>
<td>NCᵇ</td>
<td>0.97 (0.93, 1.00)</td>
</tr>
<tr>
<td>Day₀ RAI+ KIM-I</td>
<td>43 (10–82)</td>
<td>95 (90–98)</td>
<td>33 (8–70)</td>
<td>97 (92–99)</td>
<td>9.3 (2.9–30)</td>
<td>5.1 (0.5, 50.4)</td>
<td>0.77 (0.53, 1.00)</td>
</tr>
<tr>
<td>Day₀ RAI+ L-FABPᵉ</td>
<td>86 (57–98)</td>
<td>56 (58–64)</td>
<td>15 (8–25)</td>
<td>98 (92–100)</td>
<td>1.9 (1.5–2.6)</td>
<td>2.5 (0.2, 43.2)</td>
<td>0.82 (0.69, 0.95)</td>
</tr>
<tr>
<td>Day₀ RAI+ IL-18ᵉ</td>
<td>57 (29–82)</td>
<td>97 (92–99)</td>
<td>62 (32–86)</td>
<td>96 (91–99)</td>
<td>17.4 (6.6–46)</td>
<td>5.5 (0.6, 47.1)</td>
<td>0.79 (0.65, 0.92)</td>
</tr>
</tbody>
</table>
Utilization of Small Changes in Serum Creatinine with Clinical Risk Factors to Assess the Risk of AKI in Critically Ill Adults

Dinna N. Cruz, Asunción Ferrer-Nadal, Pasquale Piccinni, Stuart L. Goldstein, Lakhmir S. Chawla, Elisa Alessandri, Clara Bellomo Anello, Will Bohannon, Tiziana Bove, Nicola Brienza, Mauro Carlini, Francesco Forfori, Francesco Garzotto, Silvia Gramaticopollo, Michele Iannuzzi, Luca Montini, Paolo Pelaia, and Claudio Ronco, for the NEFROOT Investigators

Models (Clinical Only): AUC = 0.74 - 0.75

Models + eCr Elev: AUC = 0.82 – 0.83
Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in Critically Ill Children (AWARE): study protocol for a prospective observational study

Rajit K Basu1,3*, Ahmad Kaddourah1, Tara Terrell1, Theresa Mottes1, Patricia Arnold1, Judd Jacobs2, Jennifer Andringa2, Stuart L Goldstein1 and on behalf of the Prospective Pediatric AKI Research Group (ppAKI)

<table>
<thead>
<tr>
<th>Length of Stay (days)</th>
<th>1.2 ± 1.1</th>
<th>0.9 ± 0.9</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRT use (%)</td>
<td>1.4</td>
<td>11.6</td>
<td>&lt; 0.001, $\chi^2 = 100.2$</td>
</tr>
<tr>
<td>ECMO use (%)</td>
<td>0.8</td>
<td>2.8</td>
<td>0.002, $\chi^2 = 9.3$</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>3.6</td>
<td>11.0</td>
<td>&lt; 0.001, $\chi^2 = 33.3$</td>
</tr>
</tbody>
</table>
San Diego County: 16 Major medical centers
- Average of 8-10 ICU admissions/day
- \[ = 16 \times 10 \times 365 = 58400 \] ICU admissions/year
- Cost of uNGAL (~ $225/sample)
- Cost of one AKI biomarker per ICU admission in SD - $13,140,000

Context Dependent Biomarker Testing
- If renal angina used to direct confirmatory biomarker testing for AKI

<table>
<thead>
<tr>
<th>% Pts with Renal Angina</th>
<th># pts</th>
<th>Biomarker cost (in millions)</th>
<th>Cost savings (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>29200</td>
<td>6.57</td>
<td>6.57</td>
</tr>
<tr>
<td>25</td>
<td>14600</td>
<td>3.29</td>
<td>9.86</td>
</tr>
<tr>
<td>10</td>
<td>5840</td>
<td>1.31</td>
<td>11.83</td>
</tr>
</tbody>
</table>
The Renal Angina Index

– Pragmatic (non-logarithmic, non-exponential model)
– Usable at the bedside (i.e., for the intensivist...)
– Early
– Risk stratification (pre-test probability)
– Carries high negative predictive value
  • To rule out AKI
– Identifies which patients might be optimal candidates to use an AKI biomarker
– To rule in AKI
  • Targets biomarkers
  • Saves $$$$
Risk Assessment – The Real Window

• BEFORE ACUTE INSULT

Framingham main difference has been to lead the public in modification of risk factors – Shown to movements for reduction in risk factors

• How do we mirror the truth of the ark?

• Are there predisposing factors to AKI and can we assess for these? (actionable BEFORE injury)
GWAS and Predisposition Studies

Original Articles

Searching for Genes That Matter: Systematic Review
Jonathan C. T. Lu, Steven C. Coca, Uptal and Chirag R. Parikh, Yale University School of Medicine, New Haven, Conn. West Haven, Conn., Texas; Duke University School of Medicine, Durham, N.C.

Background and Objectives: Identifying patients who may benefit from genetic testing has become increasingly important, as genetic testing results can have significant clinical implications. Therefore, a systematic review of studies was performed to assess the impact of genetic testing on patient outcomes.

Design, Setting, Participants, and Measurements: MEDLINE was searched for articles published from 2000 to 2020. A total of 16 included studies were identified. The quality of evidence in these studies ranged from low to high.

Conclusions: Genetic testing can be useful in the identification of patients with specific genetic conditions, which can lead to improved patient outcomes. However, more research is needed to better understand the impact of genetic testing on patient outcomes.

Genomic and Proteomic Analysis of Acute Kidney Injury Prasad Devadoss, Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio

Key Words
Acute kidney injury - Genetics - Proteomics

Abstract
The incidence and severity of acute kidney injury (AKI) are high, and the associated morbidity can be significant. Recent advances in genomics and proteomics have allowed for the identification of novel biomarkers that may help in the early detection and management of AKI.

Association of eGFR-Related Loci Identified by GWAS with Incident CKD and ESRD Carsten A. Söger, Mathias Gorski, Man Li, Michael M. Hofmann, Chuanmei Huang, Qiang Yang, Alexander Teumer, Vera Krane, Conall M. O'Seaghdha, Zoltan Kulak, Josep Cortinhas, Sibylle Kolker, Matthias Weissenbach, and the CKDGen Consortium

Association of eGFR-Related Loci Identified by GWAS with Incident CKD and ESRD

Abstract
We investigated the association of 16 loci for eGFR, identified in genome-wide association studies, with incident CKD and ESRD. The 16 loci were associated with incident CKD and ESRD, with the strongest association observed for the locus on chromosome 1q21.3.

Conclusions: The association of eGFR-related loci with incident CKD and ESRD suggests that genetic factors play a role in the development of chronic kidney disease.
NephroNINJA – Reducing Exposure

Rate of AKI Patients per 1000 non-ICU patient-days

(Using μ chart)

- Pharmacy began using automated Trigger Reports 9/17/2011
- Increased # of BMT patient

Average:
- Avg: 4.3
- Avg: 2.6
- Avg: 2.0
“Sub-clinical” AKI?
Biomarker+/Creatinine-

<table>
<thead>
<tr>
<th></th>
<th>NGAL(−)/sCREA(−)</th>
<th>NGAL(+)/sCREA(−)</th>
<th>NGAL(−)/sCREA(+)</th>
<th>NGAL(+)/sCREA(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine NGAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 1,345</td>
<td>758 (56.4%)</td>
<td>307 (22.8%)</td>
<td>63 (4.7%)</td>
<td>217 (16.1%)</td>
</tr>
<tr>
<td>Need for RRT</td>
<td>2 (0.003%)</td>
<td>9 (2.9%)</td>
<td>2 (3.2%)</td>
<td>16 (7.4%)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>35 (4.6%)</td>
<td>37 (12.1%)</td>
<td>3 (4.8%)</td>
<td>30 (13.8%)</td>
</tr>
<tr>
<td>ICU stay, days</td>
<td>4.2 (2.1–8.5)</td>
<td>7.6 (5.7–14.5)</td>
<td>6.5 (3.0–11.6)</td>
<td>10.4 (7.7–14.8)</td>
</tr>
<tr>
<td>Hospital stay, days</td>
<td>8.8 (7.2–18.8)</td>
<td>17.0 (8.2–24.6)</td>
<td>18.3 (5.2–36.0)</td>
<td>21.8 (11.3–24.1)</td>
</tr>
<tr>
<td><strong>Plasma NGAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 977</td>
<td>538 (55.1%)</td>
<td>138 (14.1%)</td>
<td>44 (4.5%)</td>
<td>257 (26.3%)</td>
</tr>
<tr>
<td>Need for RRT</td>
<td>0 (0%)</td>
<td>2 (1.5%)</td>
<td>6 (13.6%)</td>
<td>22 (8.6%)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>27 (5.0%)</td>
<td>18 (13.0%)</td>
<td>6 (13.6%)</td>
<td>40 (15.6%)</td>
</tr>
<tr>
<td>ICU stay, days</td>
<td>4.0 (2.2–5.4)</td>
<td>6.5 (4.3–9.0)</td>
<td>5.1 (3.0–12.0)</td>
<td>8.6 (8.0–11.9)</td>
</tr>
<tr>
<td>Hospital stay, days</td>
<td>9.7 (7.3–20.3)</td>
<td>14.6 (8.1–22.7)</td>
<td>11.1 (4.5–21.1)</td>
<td>25.5 (18.0–33.9)</td>
</tr>
</tbody>
</table>

*Table 4: Outcome According to Urine NGAL Versus Plasma NGAL*

*Berlin and Magdeburg, Germany; Cincinnati, Ohio; Melbourne, Australia; Vicenza, Italy; New York, New York; Chicago, Illinois; Dublin, Ireland; Montreal, Quebec, Canada; Athens, Greece; Stockholm, Sweden; and Nashville, Tennessee*
Discovery of novel urinary biomarkers for acute kidney injury (AKI)

Kianoush Kashani1, Ali Al-Khafaji2, Thomas Ardiles3, Antonio Artigas4, Sean M Bagshaw5, Max Bell6, Azra Bihorac7, Lakhmir S Chawla10, Danielle L Davison10, Thoresten Feldkamp11, Luigi G Forni12, Cynthia Mcelly9, Lui GForni12, Robert Birkhahn8, Cyntiia McCely9, Thors tein Feldkamp11, Lui GForni12, Andrew D Shaw31, Jing Shi32, Amy M Sprague33, Jean-Louis Vincent34, Christophe Vinsonneau35, Ludwig Wagner36, Robert Gentry Wilkerson37, Kai Zacharowski38 and John A Kellum39*

39Department of Critical Care Medicine, University of Pittsburgh, School of Medicine. See related commentary by Ronco et al., http://ccforum.com/content/17/1/117

Full list of author information is available at the end of the article


http://ccforum.com/content/17/1/R25

Acute kidney injury (AKI) can evolve quickly and clinical measures of function often fail to detect AKI early enough that treatment can still alter the outcome — terms of timing, this signal could be ideal as it may be important not only for determining prognosis of disease and recovery are also important clinical questions and our results do not directly address these questions.

Proposed mechanistic involvement of the novel biomarkers in AKI: initial tubular cells sustain injury by various insults (oxidative stress, ultraviolet radiation, drugs, and toxins) thus spreading the signal to other cell types. Important, both TIMP-2 and IGFBP7 appear to be able to influence cell cycle progression of the affected cells. In this regard, TIMP-2 has been shown to induce p21 expression through p53 and p27 expression through E2F1. These effects are conducted in an autocrine and paracrine manner via IGFBP7 and TIMP-2 stimulates p27 expression. These effects are conducted in an autocrine and paracrine manner via IGFBP7 and TIMP-2 stimulates p27 expression in an autocrine and paracrine manner.

Figure 5

Abstract

Two novel markers for AKI have been identified and validated in independent multicenter cohorts. The primary endpoint was moderate to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection.

Methods

We performed two multicenter observational studies in critically ill patients at risk for AKI — discovery and validation. The top two markers from discovery were validated in a second study (Sapphire) and compared to a previously described markers of AKI (16,23,24). This may help explain why they correspond to the most important unanswered question was early risk for AKI, a syndrome known for its multiple etiologies (including patients with sepsis, shock, major surgery, and trauma and examined over 300 markers. In the Sapphire validation. The top two markers from discovery were validated in a second study (Sapphire) and compared to a previously described markers of AKI (16,23,24).

Results

Moderate to severe AKI occurred in 14% of Sapphire subjects. The two top biomarkers from discovery were validated. Urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), both inducers of G1 cell cycle arrest, a key mechanism implicated in AKI, together demonstrated an AUC of 0.80 (0.76 and 0.79 alone). Urine [TIMP-2]-[IGFBP7] significantly improved risk stratification when added to a nine-variable clinical model when analyzed using Cox proportional hazards model, generalized estimating equation, integrated discrimination improvement or net reclassification improvement. Finally, in sensitivity analyses TIMP-2 remained significant and superior to all other markers regardless of changes in reference creatinine method.

Discussion

Our study has important limitations. Although we measured oxidative stress, ultraviolet radiation, drugs, and toxins, the complex nature of human AKI, in which multiple etiologies exist. The objective of this study was to identify and validate novel biomarkers of AKI. Acute kidney injury (AKI) is a syndrome known for its multiple etiologies, the complex nature of human AKI, in which multiple etiologies exist. The objective of this study was to identify and validate novel biomarkers of AKI.

Figure 2

Area under the receiver-operating characteristics curve (AUC) for novel urinary biomarkers and existing biomarkers of acute kidney injury for the primary Sapphire study endpoint (KDIGO stage 2 or 3 within 12 hours of sample collection). Samples were collected within 18 hours of enrollment. The AUC for urinary TIMP-2-[IGFBP7] is larger than for the existing biomarkers (P value <0.002). IGFBP7, 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.
Cut-offs ~ Risk?

Kellum and Chawla, NDT 2015
<table>
<thead>
<tr>
<th>Table 5. Prediction of the composite of AKIN stage 3 and death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>FST (2-hr UOP)</td>
</tr>
<tr>
<td>Urine NGAL</td>
</tr>
<tr>
<td>Urine IL-18</td>
</tr>
<tr>
<td>Urine KIM-1</td>
</tr>
<tr>
<td>Urine TIMP-2</td>
</tr>
<tr>
<td>Urine IGFBP-7</td>
</tr>
<tr>
<td>Urine Creatinine</td>
</tr>
<tr>
<td>Urine ACR</td>
</tr>
<tr>
<td>Fe Na</td>
</tr>
<tr>
<td>Plasma NGAL</td>
</tr>
</tbody>
</table>

NA, not applicable; ACR, albumin-to-creatinine ratio.
agenda

• Troponin, The Cherry Picking Biomarker
• AKI Biomarkers, Finally Usable?
• Risk stratification and Renal Angina
• Risk Assessment and Moving the Needle
Patient admitted/transferred to PICU

Epic ADT message
Epic flow sheet records (fluid ins/outs, medications) passed real-time

Labs object

Other flow sheet records (weight, transplant status, etc.)

Flow sheet records aggregated for later use

At 12 hours post PICU admission, requests sent for aggregated real-time flow sheet records, labs, and other flow sheet records

Score calculated

Score presented

Score: 12
RAI Injury Value = 4
RAI Risk Value = 3

Patient
MRN:
Name:
DOB: 03/08/2014
Admit Date / Time: 10/14/2015 10:05
Score Date / Time: 10/14/2015 22:06
Unit: B:CC
Room: B523
Bed: B523A1
Risk Stratification Continuum

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue all nephrotoxic agents when possible</td>
<td>Ensure volume status and perfusion pressure</td>
<td>Consider functional hemodynamic monitoring</td>
<td>Monitor serum creatinine and urine output</td>
</tr>
<tr>
<td>Avoid hyperglycemia</td>
<td>Consider alternatives to radiocontrast procedures</td>
<td>Non-invasive diagnostic workup</td>
<td>Consider invasive diagnostic workup</td>
</tr>
<tr>
<td>Check for changes in drug dosing</td>
<td>Consider renal replacement therapy</td>
<td>Consider ICU admission</td>
<td>Avoid subclavian catheters if possible</td>
</tr>
</tbody>
</table>

SCr/UOP

Biomarkers

Renal Angina + Biomarkers
Risk Stratification Continuum

A Kidney injury continuum

Complications

Normal
Increased risk
Damage
↓GFR
Kidney failure
Death

Renal Angina Biomarkers
2nd International Symposium on AKI in Children
June 24 - 26, 2016
Hilton Cincinnati Netherlands Hotel  |  Cincinnati, Ohio, USA
www.CincinnatiChildrens.org/AKI

Keynote Speaker: Professor Claudio Ronco, MD
Director, Department of Nephrology, Dialysis and Transplantation
International Renal Research Institute
St. Bortolo Hospital, Vicenza, Italy

Themes
• State of the Art Symposium in Critical Care Nephrology
• CRRT University* Simulation Course

Continuing Education Credit
For CEC details, visit www.cincinnatichildrens.org/aki.

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Cincinnati Children’s Center for Acute Care Nephrology

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acknowledgements and thanks.