Application of Novel Biomarkers in Peri-Operative AKI

Chirag R. Parikh, MD, PhD
Director, Program of Translational Research
Associate Professor of Medicine
Yale University and VA Medical Center

Disclosures

– Co-inventor on IL-18 patent issued to University of Colorado (no commercial value)

– NIH grants on Biomarker Discovery & Validation

Outline of the Talk

• Why do we need biomarkers in peri-operative acute kidney injury (AKI)?

• Biomarkers of AKI
  – Biomarker Results from Multicenter studies
  – The future: Application of New Biomarkers
Failure with Therapeutic Development in Kidney Diseases

• Dependence on serum creatinine

  – As enrollment criteria for treatment trials of AKI
    • Miss the “window of opportunity” due to the delayed rise in serum creatinine
    • Cannot differentiate “pre-renal azotemia” from “true kidney injury” and thus the true effect size of the drug is underestimated

  – As an outcome criteria for prevention trials of AKI
    • Not sensitive to small improvements in kidney function
    • “Noise” in the endpoint requiring larger sample size

Biomarkers in Relation to Site of Injury in Nephron
HOW CAN KIDNEY INJURY BIOMARKERS HELP?

• Early detection of AKI
• Predicting outcomes in hospital: Severity of AKI, dialysis, mortality, resource utilization
• Differential diagnosis of AKI
  – Pre-renal, ATN, AIN
• Ascertaining site and etiology of renal injury
• Monitoring effects of an intervention
  – Nephrotoxicity

PHASES OF BIOMARKER DEVELOPMENT

<table>
<thead>
<tr>
<th>Preclinical Exploratory</th>
<th>Phase 1</th>
<th>Promising directions identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Assay and Validation</td>
<td>Phase 2</td>
<td>Clinical assay detects established disease</td>
</tr>
<tr>
<td>Retrospective Longitudinal</td>
<td>Phase 3</td>
<td>Biomarker detects disease early before it becomes clinically obvious Determine sensitivity/specificity</td>
</tr>
<tr>
<td>Prospective Screening</td>
<td>Phase 4</td>
<td>Use biomarker to screen population “False referral” rate are identified</td>
</tr>
<tr>
<td>Disease Control</td>
<td>Phase 5</td>
<td>Impact of screening on reducing the burden of disease</td>
</tr>
</tbody>
</table>

Pepe MS et al. Journal of National Cancer Institute, 2001

TRIBE-AKI Consortium

TRANSLATIONAL RESEARCH INVESTIGATING BIOMARKER ENDPOINTS- ACUTE KIDNEY INJURY

• Created in 2005
• www.yale.edu/tribeaki
Eligible Patients:
CABG +/- Valve Surgery patients at risk for developing Acute Kidney Injury (AKI)

One pre-op blood sample (10mL)
One pre-op urine sample (10mL)

Post-OP Blood Collection
Day 1: 10mL sample
Day 2: 10mL sample
Day 3: 10mL sample
Day 4: 10mL sample
Day 5: 10mL sample

Post-OP Urine Collection
Day 1: 10mL samples X 4
Day 2: 1 10mL sample
Day 3: 1 10mL sample
Day 4: 1 10mL sample
Day 5: 1 10mL sample

Data Collection

Baseline serum creatinine > 2 mg/dL
Ejection fraction < 35%
Age > 65 years
Diabetes mellitus
Concomitant CABG & valve surgery
Repeat revascularization surgery

Surgical Biomarkers
- NGAL
- IL-18
- KIM-1
- L-FABP
- Albumin

Patient outcomes

<table>
<thead>
<tr>
<th></th>
<th>N=1219</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe AKI, n (%)</td>
<td>60 (5%)</td>
</tr>
<tr>
<td>First Day of AKI, median (IQR)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Dialysis, n (%)</td>
<td>18 (1.5%)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>20 (1.6%)</td>
</tr>
<tr>
<td>Length of stay, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>In ICU</td>
<td>3.4 (8)</td>
</tr>
<tr>
<td>In hospital</td>
<td>8.5 (10)</td>
</tr>
</tbody>
</table>

Opportunities of Assessing Risk of AKI in Cardiac Surgery

1. Plasma Cystatin C
2. Plasma BNP
3. Urine Albumin

Koyner J, Parikh CR: CJASN 2013
Biomarker results

- Peaked within 6 hours after surgery
- Significantly different between cases and controls
- Declined after peak

Urine IL-18

Urine NGAL and Plasma NGAL
- Peaked 6 hours after surgery
- Plasma NGAL remains elevated after peak

Parikh CR et al, JASN 2011
Peaked 2 days after surgery

Significantly different between cases and controls except 1 day after surgery

Urine KIM-1

Urine L-FABP and Urine Cystatin C

Simplified Framework for Biomarker Analysis & Interpretation

New Biomarker and Outcome

ROC Analysis

AUC<90%

Not a Good Classifier

AUC>90%

Good Classifier

Multivariate Association (OR/RR)

Clinically and Statistically Significant

Yes

Check incremental value on existing clinical models

Biomarker Not Helpful

NRVI/DI

Change in AUC/C-Index

Parikh CR et al: CJASN 2013
1-Specificity

Sensitivity

Urine IL-18 0.74 (0.04)
Urine KIM-1 0.71 (0.04)
Plasma NGAL 0.70 (0.04)
2-way combo 0.76 (0.04)
3-way combo 0.78 (0.04)

Moderate Classifiers

Biological Gradient (Dose Response)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC (SE) Mild AKI</th>
<th>AUC (SE) Severe AKI</th>
<th>AUC (SE) Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine IL-18</td>
<td>0.65</td>
<td>0.74</td>
<td>0.79</td>
</tr>
<tr>
<td>Urine NGAL</td>
<td>0.61</td>
<td>0.67</td>
<td>0.78</td>
</tr>
<tr>
<td>Plasma NGAL</td>
<td>0.67</td>
<td>0.7</td>
<td>0.82</td>
</tr>
<tr>
<td>Urine KIM-1</td>
<td>0.64</td>
<td>0.71</td>
<td>0.75</td>
</tr>
<tr>
<td>Urine L-FABP</td>
<td>0.60</td>
<td>0.61</td>
<td>0.66</td>
</tr>
<tr>
<td>Urine Cystatin C</td>
<td>0.67</td>
<td>0.72</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Prerenal Azotemia Attenuates the Performance of AKI Biomarkers

Parikh CR, Han G: AJKD 2013 (in press)
First post-operative sample and risk of AKI

Significant association between biomarkers and AKI

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine IL-18</td>
<td>10.3 (3.3, 46)</td>
<td>6.0 (1.8, 24.3)</td>
</tr>
<tr>
<td>Urine NGAL</td>
<td>4.7 (1.9, 11.7)</td>
<td>2.5 (0.8, 8.0)</td>
</tr>
<tr>
<td>Plasma NGAL</td>
<td>7.8 (2.7, 22.6)</td>
<td>5.0 (1.4, 18.3)</td>
</tr>
<tr>
<td>Urine KIM-1</td>
<td>6.2 (2.1, 18.7)</td>
<td>4.8 (1.6, 14.6)</td>
</tr>
<tr>
<td>Urine L-FABP</td>
<td>2.8 (1.2, 6.1)</td>
<td>1.8 (0.7, 4.9)</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, race, CPB time, non-elective surgery, pre-op eGFR, diabetes, and hypertension

Biomarkers (like AKI) are associated with length of stay
Opportunities of Assessing Risk of AKI in Cardiac Surgery

- Pre-operative Assessment
- Immediately after Surgery
- At AKI Diagnosis

1. Plasma Cystatin C
2. Plasma BNP
3. Urine Albumin

Koyner J, Parikh CR: CJASN 2013

Using Biomarkers To Predict Prognosis on day of AKI

AKI progression was defined as worsening in AKIN Stage (n=45, 11.8%)
Association of Biomarkers with AKI Progression

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Albumin to Creatinine Ratio</td>
<td>4.8 (1.9, 11.9)</td>
<td>4.0 (1.5, 10.4)</td>
</tr>
<tr>
<td>Urine NGAL</td>
<td>2.3 (1.1, 4.8)</td>
<td>2.1 (0.9, 4.7)</td>
</tr>
<tr>
<td>Urine IL-18</td>
<td>3.6 (1.6, 8.0)</td>
<td>3.2 (1.4, 7.6)</td>
</tr>
<tr>
<td>Plasma NGAL</td>
<td>11.7 (4.5, 30.3)</td>
<td>9.7 (3.4, 27.5)</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, white race, CPB time > 120 minutes, non-elective surgery, pre-op eGFR (<30, 30-60, >60), diabetes, hypertension, and percent change in post-operative serum creatinine from baseline at the time of AKI diagnosis.


Further multicenter validation

Confirming the predictive value of IL-18

IL-18 was the best predictor of the primary outcome of worsening AKI to AKIN stage 2/3 or death (AUC=0.74) and the secondary outcome of AKIN stage 3 or death (AUC=0.89).


HOW CAN KIDNEY INJURY BIOMARKERS HELP?

- Early detection of AKI
- Predicting outcomes in hospital: Severity of AKI, dialysis, mortality, resource utilization
- Differential diagnosis of AKI
  - Pre-renal, ATN, AIN
- Ascertaining site and etiology of renal injury
- Monitoring effects of an intervention
  - Nephrotoxicity
Adjudication of AKI:
The TRIBE AKI Experience

How we did it

• 67 consecutive cases of mild AKI were adjudicated
• Panel of 3 experienced nephrologists
• Independent review of the Case Report Form
  • No biomarker data
• Completed a AKI Checklist (next slide)
  • ATN, Pre-renal, Indeterminate
• Met in person to finalize in the setting of disagreement

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-renal Anemia</td>
<td>Pattern and kinetics of blood creatinine's rise and fall during AKI episode.</td>
</tr>
<tr>
<td></td>
<td>Negative fluid balance</td>
</tr>
<tr>
<td></td>
<td>Other: Please print a description</td>
</tr>
<tr>
<td>Acute Tubular Necrosis (ATN)</td>
<td>Pattern and kinetics of blood creatinine's rise and fall during AKI episode.</td>
</tr>
<tr>
<td></td>
<td>Hypotension and its management around the time of the AKI episode.</td>
</tr>
<tr>
<td></td>
<td>RRT time</td>
</tr>
<tr>
<td></td>
<td>Other: Please print a description</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Please provide reasoning</td>
</tr>
</tbody>
</table>
Breakdown of the Diagnoses

<table>
<thead>
<tr>
<th>Panelists Adjudications</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATN</td>
<td>11 (16.4)</td>
</tr>
<tr>
<td>PRA</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0</td>
</tr>
<tr>
<td>2 ATN, 1 PRA</td>
<td>17 (25.3)</td>
</tr>
<tr>
<td>2 ATN, 1 Indeterminate</td>
<td>10 (14.9)</td>
</tr>
<tr>
<td>2 PRA, 1 ATN</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>2 PRA, 1 Indeterminate</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>2 Indeterminate, 1 ATN</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>2 Indeterminate, 1 PRA</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>1 ATN, 1 PRA, 1 Indeterminate</td>
<td>10 (14.9)</td>
</tr>
</tbody>
</table>

ATN in 41 (~60%)

PRA in 13 (~20%)

Indeterm. in 13 (~15%)

Adjudication Experience

- ATN is cause of AKI 60% of the time
- All 3 Adjudicators only agreed 20% of the time
- No urinary biomarker predicted ATN
- Peri-operative AKI is a heterogenous disease where functional and structural injury may coexist
Use Biomarkers to Improve Clinical Trial Design

Biomarkers in AKI trials

1. Biomarkers as entry criteria
   - High risk trial defined by biomarker risk score
2. Biomarkers as surrogate outcomes
   - Acute kidney injury defined by biomarkers

Entry Criteria

- Low biomarkers: No enrollment
- High biomarkers: Randomize to Intervention or Standard of Care
Biomarkers as Surrogates

Randomize

Standard of Care

Cardiac Surgery

Intervention

Measure Biomarkers 0-6 Hours

AKI > 0.3mg/dL

AKI > 100% or dialysis

Day 1

In-Hospital Stay

Summary

• Urine and Plasma biomarkers of AKI are elevated before serum creatinine
• Biomarkers by themselves had only modest classification potential for diagnosis of AKI
• First post-operative values of urine IL-18, urine KIM-1 and Plasma NGAL are independently associated with severe AKI in adults and predict other in-hospital outcomes
• Biomarkers also predict progression of AKI at the time of clinical AKI

Challenges for AKI biomarkers

• Gold standard is serum creatinine
• Cannot separate ATN from prerenal azotemia within AKI participants
  – Peri-operative AKI may be a heterogenous state with co-existence of functional and structural injury
• Need to power studies looking at hard endpoints (long term outcomes)
• Need to use biomarkers in clinical trials of AKI
The TRIBE Team

Co-Investigators
- Dr. Steven Coca
- Dr. Prasad Devarajan
- Dr. Amit Garg
- Dr. Jay Koyner
- Dr. Catherine Krawczeski
- Dr. Simon Li
- Dr. Cary Passik
- Dr. Uptal Patel
- Dr. Michael Shlipak
- Dr. Michael Zappitelli

Statisticians
- Heather Thiessen-Philbrick

Coordinators
- Isabel Butryniewcz
- Rowena Kemp

New Horizon or False Dawn?
Further explorations are needed?

Questions??
HOW CAN KIDNEY INJURY BIOMARKERS HELP?

- Early detection of AKI
- Predicting outcomes in hospital: Severity of AKI, dialysis, mortality, resource utilization
- Differential diagnosis of AKI
  - Pre-renal, ATN, AIN
- Ascertaining site and etiology of renal injury
- Monitoring effects of an intervention
  - Nephrotoxicity