Clinical use of Biomarkers in Acute Kidney Injury

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Division of Nephrology, Department of Medicine, Chulalongkorn University & King Chulalongkorn Memorial Hospital
SEA-AKI study group

Thailand
20 centers
5038 cases

Laos PDR
5 centers
500 cases

Philippines
1 center
200 cases
Zamboanga City Medical Center, Zamboanga city, Philippines

SEA-AKI cohort

Luang Prabang, Laos PDR
2,334 patients

1,264 AKI (54.2%)
- 212 KDIGO1 (9.1%)
- 403 KDIGO2 (17.3%)
- 649 KDIGO3 (27.8%)

1,070 No AKI (45.8%)

Mortality rate
- 1,264 AKI: 25.6%
- 1,070 No AKI: 15.5%

AKI related Mortality 42.8%
Scope

• Overview and type of AKI biomarkers
• Dimension and phases of clinical trials in AKI biomarkers
• Clinical implication of AKI biomarkers
Traditional biomarkers using filtration markers: sCr and UOP


RIFLE
Creatinine has a lag time effect

- Half life 4 hours
- 50% reduction in GFR = 8 hours
- Require 3–5 half life

Before reach a new steady state

24–40 hours
Analytical problems with serum creatinine

- False high
  - Cephalosporins
  - Rhabdomyolysis
  - Calibration
  - Non-steady state
  - Extra-renal clearance

- False low
  - Liver cirrhosis
  - Hyperbilirubinemia
  - Overhydration
3 problems with conventional markers

• Not specific
• Not sensitive
• and Delayed
Dimension of AKI biomarkers research

Biology of biomarkers
- NGAL
- KIM-1
- Cystatin C
- L-FABP
- IL-18
- Etc.

Clinical trials
- Discovery phase
- Validation phase
- Implication

Aim
- For early diagnosis of AKI
- For prediction severity, RRT, death
- For prediction renal recovery

Timing of testing
- Before rising creatinine
- After rising creatinine
- At ICU admission
- When start RRT

- Differential dx
- Surrogate outcome
- Directed starting intervention
- Directed stopping treatment
Where does urinary biomarker come from?

1. Filtrate Plasma protein

2. Diminished Tubular Reabsorption

3. Tubular proteins
   - Tubular protein upregulated by injury: KIM-1, IL-18, NGAL, clusterin
   - Tubular proteins released due to cell damage (preformed): NAG, GST
   - Markers released by recruited inflammatory cells: IL-18, NGAL
<table>
<thead>
<tr>
<th>Type</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtered Aprotinin</td>
<td></td>
</tr>
<tr>
<td>Filtered-impaired tubular Reabsorption</td>
<td>Albumin, Cystatin C, B2 MG, L-FABP</td>
</tr>
<tr>
<td>Up-regulation</td>
<td>NGAL, KIM-1, Clusterin, IL-18, Netrin-1</td>
</tr>
<tr>
<td>Down-regulation</td>
<td>Trefoil factor 3 (TFF3)</td>
</tr>
<tr>
<td>Preformed</td>
<td>ALP, GGT, GST, NAG, L-FABP</td>
</tr>
</tbody>
</table>
Marker of proximal tubular injury
- L-FABP
- γ-GGT
- NAG
- KIM-1
- Clusterin
- IL-18
- TFF3

Marker of TAL, distal tubular injury
- NGAL
- GST
CLINICAL TRIALS OF BIOMARKERS
Dimension of AKI biomarkers research

Biology of biomarkers
- NGAL
- KIM-1
- Cystatin C
- L-FABP
- IL-18
- Etc.

Clinical trials
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Timing of testing
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- At ICU admission
- When start RRT

- Differential dx
- Surrogate outcome
- Directed starting intervention
- Directed stopping treatment
# Phases of clinical trials

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>NGAL (n=35)</td>
<td>NGAL (n=19)</td>
<td>NGAL (n=22)</td>
<td>NGAL (n=1)</td>
<td>none</td>
</tr>
<tr>
<td>Cystatin C (n=22)</td>
<td>Cystatin C (n=12)</td>
<td>Cystatin C (n=11)</td>
<td>GGT/ALP (n=1)</td>
<td></td>
</tr>
<tr>
<td>IL-18 (n=17)</td>
<td>IL-18 (n=9)</td>
<td>IL-18 (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIM-1 (n=14)</td>
<td>KIM-1 (n=4)</td>
<td>KIM-1 (n=14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST (n=9)</td>
<td>GST (n=3)</td>
<td>GST (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-FABP (n=7)</td>
<td>L-FABP (n=1)</td>
<td>L-FABP (n=3)</td>
<td></td>
<td></td>
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<tr>
<td>IL-6 (n=6)</td>
<td>IL-6 (n=4)</td>
<td>IL-6 (n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netrin (n=2)</td>
<td>Netrin (n=2)</td>
<td>Netrin (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT/ALP (n=4)</td>
<td>GGT/ALP (n=3)</td>
<td>GGT/ALP (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAG (n=15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Potential role of biomarkers **BEFORE** developed AKI

- Increased Risk
- Stressor
- Damage
- Decrease GFR/AKI
- Kidney failure/RRT
- Death

Predict AKI early, outcome, severity, RRT
Potential role of biomarkers AFTER developed AKI

- Increase Risk
- Stressor
- Damage
- Decrease GFR/AKI
- Kidney failure/ RRT

Predict AKI early, outcome, severity, RRT

Predict renal recovery, outcome
AUC-ROC > 0.8
Phase 3: Increment to known clinical predictor

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine at enrollment</td>
<td>0.60 (0.52 to 0.68)</td>
</tr>
<tr>
<td>Urine output(^b)</td>
<td>0.65 (0.57 to 0.73)</td>
</tr>
<tr>
<td>Urinary KIM-1 level</td>
<td>0.61 (0.53 to 0.69)</td>
</tr>
<tr>
<td>Urinary NAG activity</td>
<td>0.71 (0.63 to 0.78)</td>
</tr>
<tr>
<td>Urinary KIM-1 level and NAG activity</td>
<td>0.71 (0.63 to 0.78)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>0.78 (0.71 to 0.84)(^c)</td>
</tr>
<tr>
<td>APACHE II score and urinary NAG activity</td>
<td>0.79 (0.73 to 0.85)(^c)</td>
</tr>
<tr>
<td>APACHE II score and urinary KIM-1 level</td>
<td>0.80 (0.74 to 0.86)(^c)</td>
</tr>
<tr>
<td>APACHE II score, urinary KIM-1 level, and NAG activity</td>
<td>0.83 (0.77 to 0.88)(^c)</td>
</tr>
<tr>
<td>Cirrhosis, sepsis, oliguria, mechanical ventilation, and urinary NAG activity</td>
<td>0.78 (0.71 to 0.84)(^c)</td>
</tr>
<tr>
<td>Cirrhosis, sepsis, oliguria, mechanical ventilation, and urinary KIM-1 level</td>
<td>0.78 (0.71 to 0.84)(^c)</td>
</tr>
<tr>
<td>Cirrhosis, sepsis, oliguria, mechanical ventilation, urinary KIM-1 level, and NAG activity</td>
<td>0.80 (0.73 to 0.86)(^c)</td>
</tr>
</tbody>
</table>

\(^a\)AUC, area under the ROC curve; ROC, receiver operating characteristic.

\(^b\)The negative value of the urine output was used for the analysis.

\(^c\)Statistically significant difference compared with serum creatinine at enrollment.

NGAL

Hepcidin

Schematic overview of renal iron metabolism

The NGAL reporter mouse

- Specific cells of the distal nephron were the source of uNGAL
  - Nat Med 2011; 17:216–222
- PMN mainly release the dimeric form, and some of monomeric form
- Tubular cells mainly produce the monomeric form and to some extent NGAL conjugated with MMP-9 (heterodimeric NGAL).
Summary studies using NGAL to predict AKI

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Cardiac surgery</th>
<th>Mixed ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagener, 2006 [28]</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Wagener, 2008 [29]</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Xin, 2008 [30]</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Liangos, 2009 [31]</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Koyner, 2010 [24]</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Che, 2010 [32]</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Parikh, 2011 [33]</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Heise, 2011 [34]</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Makris, 2009 [35]</td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Siew, 2009 [36]</td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Martensson, 2010 [37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Geus, 2011 [25]</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Metzger, 2010 [38]</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Endre, 2011 [39]</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Endre, 2011 [39]</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>de Geus, 2013 [40]</td>
<td></td>
<td>0.75</td>
</tr>
</tbody>
</table>

Blood Purif 2014;37:304–310
NGAL: meta-analysis

- N = 19 studies
- 2,538 patients
- 487 with AKI (19.2%)
- AUC for predict AKI = 0.82
- AUC for predict RRT = 0.78
- AUC for predict death = 0.71

Cell cycle arrest biomarkers

SAPPHIRE study

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


See related commentary by Ronco et al., http://ccforum.com/content/17/1/117
Novel prognostic test: FST

Development and Standardization of a Furosemide Stress Test to Predict the Severity of Acute Kidney Injury


Table 2 Furosemide stress test effect on urine flow

<table>
<thead>
<tr>
<th>Measurement time point</th>
<th>Combined n = 77</th>
<th>Non-progressors n = 52</th>
<th>Progressed to AKIN III n = 25</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour 1</td>
<td>251 (35.2)</td>
<td>329 (46.0)</td>
<td>89 (33.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hour 2</td>
<td>296 (35.8)</td>
<td>392 (42.2)</td>
<td>96 (46.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hour 3</td>
<td>246 (26.6)</td>
<td>311 (31.7)</td>
<td>109 (35.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hour 4</td>
<td>207 (24.1)</td>
<td>265 (31.1)</td>
<td>88 (23.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hour 5</td>
<td>175 (18.6)</td>
<td>219 (22.8)</td>
<td>83 (23.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hour 6</td>
<td>155 (17.4)</td>
<td>194 (22.3)</td>
<td>75 (17.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Urine volume in ml is shown as mean (standard error). AKIN, Acute Kidney Injury Network; n, number of patients.
Role of biomarkers in prediction renal recovery
Mechanism of renal recovery

Tubular epithelial cell injury

Renal progenitor cell proliferation

A variety of growth factors probably contribute to the restoration of a normal tubular epithelium.

BM mesenchymal stem cell proliferation & differentiation

EME: Epithelial Mesenchymal Epithelial cycling

EMT: Epithelial Mesenchymal Transition
Plasma neutrophil gelatinase-associated lipocalcin predicts recovery from acute kidney injury following community-acquired pneumonia

Nattachai Srisawat¹,², Raghavan Murugan¹, Minjae Lee¹,³, Lan Kong¹,³, Melinda Carter¹, Derek C. Angus¹ and John A. Kellum¹, on behalf of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study Investigators

¹The CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; ²Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand and ³Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, USA
Table 3 | Plasma NGAL concentration at various cutoff values to predict failure to recover renal function

<table>
<thead>
<tr>
<th>pNGAL cutoff (ng/ml)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>0.91</td>
<td>0.33</td>
<td>0.58</td>
<td>0.77</td>
</tr>
<tr>
<td>257</td>
<td>0.68</td>
<td>0.75</td>
<td>0.73</td>
<td>0.70</td>
</tr>
<tr>
<td>393</td>
<td>0.47</td>
<td>0.90</td>
<td>0.83</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Abbreviations: NPV, negative predictive value; pNGAL, plasma neutrophil gelatinase-associated lipocalin; PPV, positive predictive value.
Urinary Biomarkers and Renal Recovery in Critically Ill Patients with Renal Support


The NEW ENGLAND JOURNAL of MEDICINE

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network®
AUC-ROC = 0.94
Dimension of AKI biomarkers research

Biology of biomarkers
- NGAL
- KIM-1
- Cystatin C
- L-FABP
- IL-18
- Etc.

Clinical trials
- Discovery phase
- Validation phase
- Implication phase

Aim
- For early diagnosis of AKI
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Timing of testing
- Before rising creatinine
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- Directed severity
- Directed Differential dx
- Directed surrogate outcome
- Directed starting intervention
- Directed stopping treatment
Routine using AKI biomarkers
Point of care test

High cost 25-30 $ per test

Parikh C, Kidney Int 2009; 76:8-10
Cut the price from 25 $ to 1$ per test

Figure 3. Scatter plot of plasma NGAL concentrations measured using ELISA and the slide-based platform.

DOI: 10.3109/1354750X.2013.773084

y = 0.9894x - 4.0735
R² = 0.99742

Lab service for AKI biomarkers at Excellence Center for Critical Care Nephrology, Thai Red Cross

Urine NGAL and Plasma NGAL

Open in April 2014

- Use the request form of the Renal unit laboratory, which will be sent with the laboratory request. The template will indicate the lab tests that will be performed. The lab tests are listed in the form.

Request form
Number of NGAL tests at KCMH

April 2016 = 120 tests/month
Phase 4: Clinical implication

- For directed severity of AKI
- For directed differential diagnosis
- For directed surrogate outcome
- For directed starting intervention: RRT, fenoldopam, dobutamine, ANP, EPO, furosemide
- For directed stopping intervention
Biomarkers directed severity of AKI

Biomarkers differentiate Pre-renal from ATN

Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes

Eugenia Singer¹,²,⁴, Antje Elger¹,², Saban Elitok², Ralph Kettritz¹,², Thomas L. Nickolas³, Jonathan Barasch³, Friedrich C. Luft¹,² and Kai M. Schmidt-Ott¹,²

¹Experimental and Clinical Research Center, a joint institution of the Charité Medical Faculty and the Max-Delbrück Center for Molecular Medicine, Berlin, Germany; ²Department of Nephrology and Hypertension, Franz-Volhard Clinic, Helios Clinics Berlin, Berlin, Germany and ³Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA

Pre-renal criteria: creatinine improve to baseline in 72 hours

Singer E et al, Kidney Int 2011;80:405-411
Case example

- 71 year old Thai man who admitted for elective TURP, complicated by massive blood loss and AKI after operation
- No significant hypotension perioperation
- Hgb drop from 15 mg/dl to 10 mg/dl
- Ultrasound KUB: no hydrenephrosis
- Renal consult on Day 3

<table>
<thead>
<tr>
<th>Case</th>
<th>Serum creatinine mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>sCr</td>
<td>1.0</td>
</tr>
<tr>
<td>UOP</td>
<td>3000 ml</td>
</tr>
</tbody>
</table>

Urine NGAL < 116 ng/ml
Giving PRC 2 unit
Biomarker directed surrogate outcome

Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: A pilot double-blind, randomized controlled trial

Michael Haase, MD; Anja Haase-Fielitz, BPharm; Rinaldo Bellomo, MD, FRACP; Prasad Devarajan, MD; David Story, MD, FANZCA; George Matalanis, FRACS; Michael C. Reade, MD, PhD, FANZCA; Sean M. Bagshaw, MD, MSc, FRCCP; Narelle Seevanayagam, RN; Siven Seevanayagam, FRACS; Laurie Doolan, MD, FANZCA; Brian Buxton, FRACS; Duska Dragun, MD

# First 5 cases in KCMH using pNGAL as POCT: marker of severity

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>NGAL level</th>
<th>Serum Cr (on the same day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic severe PAD, TENS, septic AKI</td>
<td>&gt; 1300 ng/ml</td>
<td>1.3</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Advance CA Colon, septic AKI</td>
<td>&gt; 1300 ng/ml</td>
<td>1.08 (0.6)</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>Perianal abscess, CKD, Septic AKI</td>
<td>&gt; 1300 ng/ml</td>
<td>3.46 (2.44)</td>
<td>Survive</td>
</tr>
<tr>
<td>4</td>
<td>CA esophagus, S/P esophagectomy, AKI</td>
<td>839 ng/ml</td>
<td>1.29 (0.8)</td>
<td>Survive</td>
</tr>
<tr>
<td>5</td>
<td>Advance CA Colon, s/p total pelvic colostomy, ischemic</td>
<td>336 ng/ml</td>
<td>1.24 (0.8)</td>
<td>Survive</td>
</tr>
</tbody>
</table>
Biomarkers directed intervention

Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial)

Zoltán H. Endre¹, Robert J. Walker², John W. Pickering¹, Geoffrey M. Shaw¹,³, Christopher M. Frampton¹, Seton J. Henderson¹,³, Robyn Hutchison², Jan E. Mehrtens¹,³, Jillian M. Robinson¹, John B.W. Schollum²,⁶, Justin Westhuyzen¹, Leo A. Celi², Robert J. McGinley⁴, Isaac J. Campbell¹ and Peter M. George⁵

¹Christchurch Kidney Research Group, Department of Medicine, University of Otago, Christchurch, New Zealand; ²Department of Medicine and Surgery, University of Otago, Dunedin, New Zealand; ³Intensive Care, Christchurch Hospital, Christchurch, New Zealand; ⁴Deakin University Medical School, Geelong, Australia; ⁵Canterbury Health Laboratories, Christchurch, New Zealand and ⁶Dunedin Hospital, Department of Nephrology, Dunedin, New Zealand

- Biomarkers: GGT and ALP
- N = 162
- IV EPO 500 u/kg x 2 dose VS placebo
- 1st outcome: RAVC
<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Placebo</th>
<th>EPO</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>(n=78)</td>
<td>(n=84)</td>
<td>0.40</td>
</tr>
<tr>
<td>RAVC</td>
<td>17 ± 44</td>
<td>23 ± 49</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>9.0 (−9.4–33.6)</td>
<td>10.7 (−1.8–32.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>PP population</td>
<td>(n=63)</td>
<td>(n=70)</td>
<td>0.20</td>
</tr>
<tr>
<td>RAVC</td>
<td>12 ± 38</td>
<td>22 ± 46</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>8.2 (−11–30)</td>
<td>11 (−1.9–29)</td>
<td>0.91</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>(n=78)</td>
<td>(n=84)</td>
<td>0.69</td>
</tr>
<tr>
<td>Length of ICU Stay (h)</td>
<td>84 (43–80)</td>
<td>86 (45–163)</td>
<td>0.91</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>27 (14–48)</td>
<td>22 (14–45)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

RAVC: relative average value of creatinine
Biomarkers directed starting RRT
Case example

47 year-old male
Developed severe ARDS from pneumonia, admitted to ICU
On admission; BP drop to 79/38 mmHg and a rise in Body Temperature 39 c
Septic work up was done, start ABX

Treatment
- Central line, A-line, Norepinephrine at 0.4 mcg/kg/min
- Fluid: Normal saline 4 litre

Lab: WBC 24,000 (N 90%)
- Baseline BUN and Cr were 20/1.0
- Now serum creatinine 1.4 mg/dl
- No acidosis, no hyperkalemia
- UOP 15 ml/hr for 6 hours

- Shall we start RRT?

No absolute indication

If urine NGAL 5680 ng/mL
Timing: Indication to start RRT

Changing paradigm of AKI

Absolute indication (life threatening)
- Refractory acidosis
- Refractory hyperkalemia
- Refractory volume overload
- Uremic symptom

Renal support
- Better control fluid balance
- Better control acid-base and electrolyte disorder
- Probable remove some inflammatory mediators, DAMP, PAMP
Potential Role of Neutrophil Gelatinase-Associated Lipocalin in Identifying Critically Ill Patients With Acute Kidney Injury Stage 2–3 Who Subsequently Require Renal Replacement Therapy

Khajohn Tiranathanagul, Sukgasem Amornsuntorn, Yingyos Avihingsanon, Nattachai Srisawat, Paweena Susantitaphong, Keerkit Praditpornsilpa, Kriang Tungsang, and Somchai Eiam-Ong

1Division of Nephrology, Department of Medicine, 2Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Thai Red Cross Society and Faculty of Medicine, Chulalongkorn University, Bangkok, and 3Department of Medicine, Prachuap Khiri Khan Hospital, Prachuap Khiri Khan, Thailand

pNGAL > 1000 ng/ml
uNGAL > 2000 ng/ml
Propose cut point for NGAL

<table>
<thead>
<tr>
<th></th>
<th>Dx AKI</th>
<th>DX severe AKI</th>
<th>Consideration RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine NGAL</strong></td>
<td>100-150</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>(ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plasma NGAL</strong></td>
<td>100-150</td>
<td>400</td>
<td>1000</td>
</tr>
<tr>
<td>(ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tiranathanagul K et al. Ther Apher Dial 2013; 17(3):332–338
Biomarkers directed starting RRT

Biomarker + Clinical prediction model

AKI

High risk

Low risk

No need RRT

Delay RRT

Early RRT
AKI Biomarkers and Tropical infection causing AKI
Clinical applications of novel biomarkers for leptospirosis-AKI

- Triage patient: refer to the tertiary center
- Early intervention: EGDT
- Stop nephrotoxic agent
- Predict prognosis
10 participant hospitals

- KCMH
- Prapokkloa hospital
- Kraburi hospital
- Maharaj Nakhon Si Thammarat hospital
- Tungsong hospital
- Uttaradit hospital
- Nan hospital
- Krasang hospital
- Roiet hospital
- Mahasarakam hospital
RESEARCH ARTICLE

Neutrophil Gelatinase Associated Lipocalin (NGAL) in Leptospirosis Acute Kidney Injury: A Multicenter Study in Thailand

Nattachai Srisawat1,2*, Keerati Praditpornsilpa1, Kanitha Patarakul3, Malee Techapornrungruang4, Tinnapop Daraswang5, Theerapon Sukmark6, Kamol Khositranonsil5, Apinya Fakthongyoo6, Petchdee Oranrigsupak6, Laksamon Praderm10, Ummarit Suwattanasilpa11, Sadudee Peeraponratana1, Passiss Loahaveeravat1, Nattachai Suwachittanont1, Thaksa-on Wirotwan1, Chayanat Phonork8, Sarinya Kumpunya1, Khajo John Tiranathanagul1, Chintana Chirathaworn3, Somchai Eiam-ong1, Kriang Tungsang1, Visith Sitprija1,12, John A. Kellum2, Natavudh Townamchai1, Thai Lepto-AKI study group11

1 Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, and King Chulalongkorn Memorial Hospital, Bangkok, Thailand, 2 Center for Critical Care Nephrology, The CRISMA Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, 3 Department of Microbiology and Immunology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, 4 Prapokklao hospital, Chantaburi, Thailand, 5 Krasang hospital, Buriram, Thailand, 6 Tungsong hospital, Nakhon Si Thammarat, Thailand, 7 Maharaj Nakhon Si Thammarat hospital, Nakhon Si Thammarat, Thailand, 8 Uttaradit hospital, Uttaradit, Thailand, 9 Nan hospital, Nan, Thailand, 10 Roet hospital, Roet, Thailand, 11 Mahasarakham hospital, Mahasarakham, Thailand, 12 Queen Saovabha Memorial Institute, Thai Red Cross, Bangkok, Thailand

† Membership of the Thai Lepto-AKI study group is provided in the Acknowledgments.
* dmattachai@yahoo.com

OPEN ACCESS

Leptospirosis suspected cases
n = 221

10 unavailable urine samples and 5 can not diag AKI samples

Leptospirosis suspected cases
n = 206

Leptospirosis
n = 113

AKI
n = 42

Recovery
n = 38

Non-AKI
n = 71

Non-recovery
n = 4

Non-leptospirosis
n = 93

AKI
n = 13

Recovery
n = 7

Non-recovery
n = 6

Non-AKI
n = 80

Recovery
n = 7
Fig 2. Urine and plasma neutrophil gelatinase-associated lipocalin (NGAL) concentration stratified by AKI status.
PLoS One. 2015 Dec 2;10(12):e0143367

**All cases (n=206)**

- uNGAL 0.94
- pNGAL 0.90

**Leptospirosis cases (n=113)**

- uNGAL 0.92
- pNGAL 0.87

**Non-Leptospirosis cases (n=93)**

- uNGAL 0.96
- pNGAL 0.90
SURVEY OF AKI PRACTICE IN THAILAND

Data from National survey of AKI and RRT practice in Thailand
Monkey survey
N = 130 (nephrologist, intensivist, internist, anesthesiologist)

Patita Sitticharoenchai
Nattaya Sinthavichai
Nattachai Srisawat

Data unpublished
Are AKI biomarkers useful?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>93.54%</td>
<td>6.45%</td>
</tr>
</tbody>
</table>

Data from national survey
What is the benefit from AKI biomarkers?

<table>
<thead>
<tr>
<th>Diagnosis AKI</th>
<th>Prediction prognosis</th>
<th>Guiding RRT initiation</th>
<th>Triage patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>81.4%</td>
<td>55.8%</td>
<td>44.2%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>

Data from national survey
<table>
<thead>
<tr>
<th>Name of AKI biomarkers</th>
<th>NGAL</th>
<th>IL-18</th>
<th>KIM-1</th>
<th>Cystatin C</th>
</tr>
</thead>
<tbody>
<tr>
<td>91.5%</td>
<td>67.4%</td>
<td>72.9%</td>
<td>80.6%</td>
<td></td>
</tr>
</tbody>
</table>

Data from national survey
FDA allows marketing of the first test to assess risk of developing acute kidney injury

For Immediate Release

September 5, 2014

Today the U.S. Food and Drug Administration allowed marketing of the NephroCheck test, a first-of-a-kind laboratory test to help determine if certain critically ill hospitalized patients are at risk of developing moderate to severe acute kidney injury (AKI) in the 12 hours following the administration of the test. Early knowledge that a patient is likely to develop AKI may prompt closer patient monitoring and help prevent permanent kidney damage or death.
2000 - Present

Future ?

2004 - Present

Time Course of Cardiac Enzyme Elevations

- CK
- AST
- LDH

Days after onset of chest pain

GFR Criteria

<table>
<thead>
<tr>
<th>Risk</th>
<th>Increased creatinine × 1.5 or GFR decrease &gt; 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury</td>
<td>Increased creatinine × 2 or GFR decrease &gt; 50%</td>
</tr>
<tr>
<td>Failure</td>
<td>Increase creatinine × 3 or GFR decrease &gt; 75% or creatinine ≥ 4 mg/dl (Acute rise of ≥ 0.5 mg/dl)</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent ARF - complete loss of renal function &gt; 4 weeks</td>
</tr>
</tbody>
</table>

Urine Output Criteria

- UO < 0.5 ml/kg/h × 6 h
- UO < 0.5 ml/kg/h × 12 h
- UO < 0.3 ml/kg/h × 24 h or Anuria × 12 h

ESRD

End-stage renal disease

Roche CARDIAC T Quantitative Troponin T
Conclusions

• Currently, we still do not have the perfect biomarkers to diagnosis, or predict renal recovery in AKI
• Still need “Renal troponin”
• Always interpret result with clinical scenario
• Future trials will focus on clinical implication and cost-effectiveness