Recovery from Acute Kidney Injury

…from basics to the latest advances

Wen, Xiaoyan MD, MS
Research Associate
The CRISMA Laboratory
Department of Critical Care Medicine
School of Medicine
University of Pittsburgh

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### Table 3. Primary and Secondary Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Strategy (N = 563)</th>
<th>Less-Intensive Strategy (N = 561)</th>
<th>Odds Ratio or Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause by day 60 — no. (%)</td>
<td>302 (53.6)</td>
<td>289 (51.5)</td>
<td>0.99 (0.86 to 1.40)</td>
<td>0.47</td>
</tr>
<tr>
<td>In-hospital death — no. (%)</td>
<td>288 (51.2)</td>
<td>269 (48.0)</td>
<td>1.15 (0.90 to 1.47)</td>
<td>0.27</td>
</tr>
<tr>
<td>Discharged to home, off dialysis, by day 60 — no./no. with data (%)</td>
<td>88/560 (15.7)</td>
<td>92/561 (16.4)</td>
<td>0.54 (0.68 to 1.32)</td>
<td>0.75</td>
</tr>
<tr>
<td>Recovery of kidney function by day 28 — no./no. with data (%)</td>
<td></td>
<td></td>
<td>0.03 (0.02 to 0.07)</td>
<td>0.24</td>
</tr>
<tr>
<td>Complete</td>
<td>85/553 (15.4)</td>
<td>102/555 (18.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>49/553 (8.9)</td>
<td>50/555 (9.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>419/553 (75.8)</td>
<td>403/555 (72.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRT-free days through day 28</td>
<td>6.0±0.4</td>
<td>7.0±0.4</td>
<td>−0.9 (−1.9 to 0.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital-free days through day 60</td>
<td>11.0±0.7</td>
<td>13.0±0.7</td>
<td>−1.9 (−3.9 to 0.0)</td>
<td>0.053</td>
</tr>
<tr>
<td>ICU-free days through day 60</td>
<td>18.7±0.9</td>
<td>20.1±0.9</td>
<td>−1.5 (−4.0 to 1.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Organ-failure–free days through day 14, according to SOFA organ-system score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>7.4±0.2</td>
<td>7.4±0.2</td>
<td>0.0 (−0.6 to 0.5)</td>
<td>0.94</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7.1±0.2</td>
<td>7.2±0.2</td>
<td>−0.1 (−0.8 to 0.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>Liver</td>
<td>8.8±0.2</td>
<td>8.7±0.2</td>
<td>0.0 (−0.6 to 0.7)</td>
<td>0.91</td>
</tr>
<tr>
<td>Coagulation</td>
<td>9.0±0.2</td>
<td>9.1±0.2</td>
<td>0.0 (−0.6 to 0.6)</td>
<td>0.95</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>7.1±0.2</td>
<td>7.2±0.2</td>
<td>−0.1 (−0.7 to 0.6)</td>
<td>0.89</td>
</tr>
</tbody>
</table>
Long-term renal outcome of AKI

Biomarker

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Cerdá J et al. CJASN 2008;3:881-886
Inflammatory reaction

IL-1β, IL-6, IL-8, IL-10, IL-18, TNF-α, HMGB1, MIF

Tubular cell injury
KIM-1, NAG, NGAL, GSTA1

Cell apoptosis

Bcl-2, Cytochrome C

Extracellular matrix exposure
Type IV collagen alpha excretion, Haluronan acid (HA)

Kidney function
Cystatin C, α1-microglobulin

Oxidative stress
iNOS, NO, intracellular reduced glutathion

Repair
BMP7

Fibrosis
TGFβ1

Cell transdifferentiation

TGFβ1, HGF

Cellular hypoxia
Adenosine, ATP, Lactate

Inflammatory reaction

IL1β, IL6, IL8, IL10, IL18, TNFα, HMGGB1, MIF

Coagulation disorders

TAT, D-dimers, fibrinopeptides, Antithrombin, Protein C, Tissue factor

Cell transdifferentiation

MSCs & progenitor cells

recovery

migration

proliferation

repair

Atrophy

Cell cycle arrest

Schmitt R et al. Am J Physiol Renal Physiol 2008; F1265-F1272
AKI Incidence and Survival in ICU CAP patients

AKI 631 (34 %)

Risk 307 (49%)

Injury 135 (21%)

Failure 189 (30 %)

Non-recovery n= 88

Recovery n= 93

Murugan et al. Kidney Int Mar 2010
Clinical predictors included
• age,
• serum creatinine,
• pneumonia severity index, and
• maximum nonrenal Sequential Organ Failure Assessment (SOFA) score

60% sepsis
80% vented
Apache II score 26 (predicted mortality 55%)
BUN at initiation of RRT 65
Roughly half in the MICU and half in the SICU
Randomized to:
- **Standard RRT (563)** [Thrice weekly HD or CRRT @ 20ml/kg/hr]
- **Intensive RRT (561)** [Daily HD or CRRT @ 35ml/kg/hr]
Plasma BioMaRK study

ATN Study (1124 subjects)

Excluded of ATN specimen bank (304 subjects)

BioMaRK study (820 subjects)
With sample collections at day 1 and 8.

Intensive Monitor cohort (109 subjects)

AKI with RRT

Day 60 endpoint

<table>
<thead>
<tr>
<th>Recovery</th>
<th>Non-recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=298</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>N=217 (26.46%)</td>
</tr>
<tr>
<td>Partial recovery</td>
<td>N=81 (9.88%)</td>
</tr>
<tr>
<td>Dialysis dependent</td>
<td>N=107 (13.1%)</td>
</tr>
<tr>
<td>Death on dialysis</td>
<td>N=327 (39.88%)</td>
</tr>
<tr>
<td>Death without dialysis</td>
<td>N=87 (10.61%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>N=1 (0.12%)</td>
</tr>
</tbody>
</table>

Excluded of ATN specimen bank (304 subjects)

Plasma BioMaRK study
Day 1 Plasma markers associated with outcomes

### Odds Ratio of Non-Recovery

<table>
<thead>
<tr>
<th>Marker</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR5</td>
<td>1.17 (0.93-1.47)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0.99 (0.86-1.13)</td>
</tr>
<tr>
<td>IL6</td>
<td>1.23 (1.13-1.35)</td>
</tr>
<tr>
<td>IL8</td>
<td>1.36 (1.22-1.52)</td>
</tr>
<tr>
<td>IL10</td>
<td>1.19 (1.07-1.33)</td>
</tr>
<tr>
<td>IL18</td>
<td>1.24 (1.10-1.39)</td>
</tr>
<tr>
<td>IL1β</td>
<td>1.12 (0.92-1.35)</td>
</tr>
<tr>
<td>MIF</td>
<td>1.16 (1.06-1.28)</td>
</tr>
<tr>
<td>TNFRI</td>
<td>2.18 (1.60-2.97)</td>
</tr>
<tr>
<td>TNFRII</td>
<td></td>
</tr>
<tr>
<td>TNFα</td>
<td>0.92 (0.78-1.09)</td>
</tr>
</tbody>
</table>

### Odds Ratio of Death

<table>
<thead>
<tr>
<th>Marker</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR5</td>
<td>1.35 (1.07-1.70)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>1.09 (0.96-1.25)</td>
</tr>
<tr>
<td>IL6</td>
<td>1.32 (1.21-1.45)</td>
</tr>
<tr>
<td>IL8</td>
<td>1.48 (1.33-1.64)</td>
</tr>
<tr>
<td>IL10</td>
<td>1.30 (1.17-1.44)</td>
</tr>
<tr>
<td>IL18</td>
<td>1.35 (1.19-1.52)</td>
</tr>
<tr>
<td>IL1β</td>
<td>1.21 (1.01-1.45)</td>
</tr>
<tr>
<td>MIF</td>
<td>1.33 (1.21-1.46)</td>
</tr>
<tr>
<td>TNFRI</td>
<td>2.02 (1.49-2.72)</td>
</tr>
<tr>
<td>TNFRII</td>
<td></td>
</tr>
<tr>
<td>TNFα</td>
<td>0.94 (0.80-1.12)</td>
</tr>
</tbody>
</table>

Note: Odds ratios are calculated for one unit increase in natural log transformed marker concentration.
Acute Renal Failure Trial Network study cohort (n=1,124)

Biological Markers of Recovery for the Kidney (BioMaRK): Intensive monitoring cohort (n=109)

Study cohort (n=76)

Recovery (n=38)
- Complete recovery (n=26)
- Partial recovery (n=12)
- Death (n=25)
- Alive with dialysis dependence (n=13)

Non-recovery (n=38)

5 incomplete data
28 unavailable urine sample
Biomarker Panel: uCystatin C, uNGAL, uIL-18, uHGF

Day 1

The clinical risk prediction model included:
• Age
• Charlson comorbidity index.

Day 14


the Clinical Research, Investigation, and Systems Modeling of Acute illness
Novel Markers for Recovery from AKI – Hyaluronic Acid (HA) …a Damage Associated Molecular Pattern (DAMP)

HA: components of the extracellular matrix

Exposure of matrix HA

Stimulates the expression of inflammatory genes by a variety of immune cells at the injury site

Fragmented HA accumulates during tissue injury and impaired clearance of HA leads to persistent inflammation.
Urinary Hyaluronic Acid

ΔHA/Creatinine relative (%) (urine)

Day 7/Day1  Day 14/Day1  Day 14/Day7
R  NR  R  NR  R  NR

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AKI-Recovery – The First “Real” Marker?

Within first 14d of RRT, marker can predict need for RRT after 60 days

AREA UNDER ROC CURVE:
Area under fitted curve = 0.9686
Estimated std. error = 0.0518
Trapezoidal (Wilcoxon) area = 0.9692
Estimated std. error = 0.0568

Exosomes

Collaboration with John Arthur, MD


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Conclusions

- NGAL appears to have potential as a marker of “non-recovery” from AKI
- HA appears to be extremely sensitive and specific for renal non-recovery
- Other markers may also be useful alone or in panel combined with clinical variables in prediction.