 ASN BOARD REVIEW 2014  
AKI Pathogenesis, Diagnosis, Biomarkers and Risk Assessment  

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Outline  
• Pathogenesis of Acute Kidney Injury and Repair  
  • Prerenal and Ischemic AKI  
  • Sepsis  
  • Toxin  
• Pathogenesis of AKI in the Elderly  
  • Definition, Incidence  
  • Diagnosis, Biomarkers  
  • Clinical Risk Assessment of AKI  

Pathogenesis of AKI  

<table>
<thead>
<tr>
<th>Vascularure</th>
<th>Tubules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Mitochondrial dysfunction</td>
</tr>
<tr>
<td>Plugging</td>
<td>Back-leak</td>
</tr>
<tr>
<td>No Reflow</td>
<td>Detachment</td>
</tr>
<tr>
<td>Intermittent flow</td>
<td>Obstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microenvironment</th>
<th>Systemic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate immunity</td>
<td>Proinflammatory cytokines</td>
</tr>
<tr>
<td>Adaptive immunity</td>
<td>Antiinflammatory cytokines</td>
</tr>
<tr>
<td>Paracrine factors</td>
<td></td>
</tr>
<tr>
<td>Autocrine factors</td>
<td></td>
</tr>
</tbody>
</table>

Pathogenesis of AKI  

<table>
<thead>
<tr>
<th>Biophysical Basis of Decreased GFR</th>
</tr>
</thead>
</table>

PreRenal AKI

Hepatorenal Syndrome
Severe Vasconstriction

Intraabdominal Compartment Syndrome

Physiologic Sequelae

• Elevated intra-abdominal pressure causes:
  • Compression of renal veins and IVC
  • Reduced cardiac output to kidneys
  • Renal failure, oliguria/anuria

The Result:
• Reduced blood flow to kidney
• Renal congestion and edema
• Decreased glomerular filtration rate (GFR)
• Acute tubular necrosis (ATN)
Ischemia

- Microvascular Injury
- Vasoconstriction
- Leukocyte Adhesion
- Permeability
- Microvascular Congestion

Inflammation

- Innate Immunity
- DAMPS Immune Cells
- Cytokines

Acute Tubular Injury

- Apoptosis
- Necrosis

Tubular Obstruction

Backleak

Continued Ischemia

DECREASED GFR

Endothelium

Microvascular endothelial injury and dysfunction during IRI

- Endothelial Cell activation, Dysfunction, Injury and/or Detachment
- Impaired Vasodilation
- Coagulation
- Leukocyte Adhesion

Inflammation

- Capillary Obstruction and Continued Ischemia

Extension of ARF

Early Pathogenic Mechanisms of AKI

Endothelial, Epithelial, Immune Cells and Interstitium

Blood Flow velocity (µm/sec)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline treated</td>
<td>253.36±95.01</td>
</tr>
<tr>
<td>sTM treated</td>
<td>798.75 ± 280.75 *</td>
</tr>
</tbody>
</table>

Injury and Repair in Ischemic Acute Kidney Injury

- Backleak
- NonReplacement Site

Human Acute Kidney Injury

Regenerating Cell

NonReplacement Site

Adapted from Bonventre and Weinberg JASN 14:2199-2210, 2003

Microvascular Blood Flow at 24h Post Ischemia Effect of sTM


TS Olsen, HS Olsen, HE Hansen Vichows Arch 1985, 406:75
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Sepsis Related AKI

Mechanisms
- Pro-inflammatory State
- Systemic Vasodilation
- Impaired Microcirculation
- Cytokine mediated cell injury

Hyperdynamic Circulation in Experimental Septic AKI: Systemic Parameters

Hyperdynamic Circulation in Experimental Septic AKI: Renal Parameters

Hyperemic AKI: Loss of glomerular filtration pressure

- Septic AKI may represent a unique form of AKI: hyperemic AKI.
- GFR is determined by glomerular filtration pressure.
- If afferent arteriole dilates and the efferent arteriole dilates even more, RBF will markedly increase, yet pressure within the glomerulus will fall. GFR will also decrease.
Sepsis is a Disorder of the Microcirculation

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Aminoglycosides

- ↓GFR is not apparent until 7-10 days after initiating therapy.
- Occurs in setting of hypotension, prerenal azotemia other nephrotoxins
  - $U_{\text{Na}} > 20$ meq/L, $F_{\text{ENa}} > 2$
  - Usually reversible
- Risk factors: prolonged treatment, volume depletion, preexisting renal disease, hypokalemia, old age, other nephrotoxins
- Monitor drug levels and creatinine every 2-3 days

Aminoglycoside Nephrotoxicity

- Aminoglycoside binds to the anionic phospholipid of the PTC, it is transferred to the transmembrane protein megalin and endocytosed
- Megalin-expressed in the renal proximal tubules, podocytes and ciliary and inner ear epithelium
- After endocytosis, endosomes accumulate in organelles such as the mitochondria and the nucleus disrupting in mitochondrial function

Site Specificity of Common Nephrotoxins

Aminoglycoside Nephrotoxicity

- $\text{TGF} \to \text{TO} \to \text{VC and MC}$
**Structure of Contrast Media**

Sodium Diatrizoate-ionic monomer (1500-1800 mosm/kg)

Iohexol-nonionic monomer (780 mosm/kg)

Iodixanol-nonionic dimer (290 mosm/kg)

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**Contrast Media-Nephrotoxicity**

Contrast Media → PGE2 → Endothelin → ANP → Vasopressin → Blood Flow → Oxygen Delivery → Blood viscosity → Systemic Hypoxemia

→ Oxygen Consumption → Osmotic Load → Direct Cellular Toxicity → Renal Medullary Hypoxia

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**Pathogenesis of CIAKI**

- Decreased oxygen diffusion from peritubular capillaries to tubular and interstitial cells
- Stagnation of peritubular capillary blood flow
- Decreased peritubular capillary blood flow as a result of imbalance of vasoactive substances
- Decreased peritubular capillary blood flow as a result of imbalance of vasoactive substances induced by oxidative stress
- Decreased oxygen delivery as a result of anemia
- Increased metabolic demands of tubular cells

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**Progression of AKI to CKD/ESRD**

- Stage of full recovery
- Stage of AKI
- Stage of chronic kidney disease
- Stage of end-stage renal disease

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**Loss of Peritubular Capillaries Lead to Chronic Hypoxia**

- Decreased oxygen delivery to tubular and interstitial cells
- Decreased oxygen diffusion from peritubular capillaries to tubular and interstitial cells
- Stagnation of peritubular capillary blood flow
- Decreased peritubular capillary blood flow as a result of imbalance of vasoactive substances
- Decreased peritubular capillary blood flow as a result of imbalance of vasoactive substances induced by oxidative stress
- Decreased oxygen delivery as a result of anemia
- Increased metabolic demands of tubular cells

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**MSCs Repair Kidney**

MSCs differentiate into renal cells and improve kidney function by secreting factors that stimulate renal cell proliferation and differentiation.

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MSCs Repair Kidney

Florian E. Tögel & Christof Westenfelder Nature Reviews Nephrology 6, 179-183 (March 2010)
What is the origin of myofibroblasts in the kidney?

Molecular Mechanisms of Fibrosis
Cell Cycle and Epigenetic Modification

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Population incidence of dialysis-requiring AKI in the United States by age groups from 2000 to 2009

AKI Susceptibility in Elderly

Prevention of AKI in elderly depends on awareness of reduced GFR
• Age dependent decline in GFR; worse with clinical risk factors
• CKD is risk factor for AKI
• Prevention depends on awareness of reduced GFR in elderly despite normal creatinine
Pathogenesis of AKI

Key Points

- Ischemic, septic or toxin induced AKI often occur concomitantly
- Ischemic AKI results is a summation of events that involve capillary endothelium, tubular epithelial cells, and inflammatory cells and humoral mediators (cytokines and chemokines).
- Nephrotoxins-site specificity
- Sepsis models of AKI
  - Pro-inflammatory cytokines due to host response.
  - Disorder of microcirculation
- AKI in aging
  - Due to comorbid factors (heart failure, diabetes) and
  - Due to noncomorbid factors that relate to age related changes in kidney function.
  - Due in part to decrease in renal reserve
- Chronic medullary hypoxia and activation of myofibroblasts are thought to contribute to mechanisms by which AKI leads to CKD.

Pathogenesis of AKI: Update

- Role of mesenchymal stem cells –
  - i) Immediate effects ameliorate injury (paracrine)
  - ii) late effects in recovery (“homing”)
- Single episode of kidney injury triggers long-term changes to structure & function.
- Epithelial regeneration leads to repair and fibroblast/pericyte proliferation leads to fibrosis.

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Over 30 definitions of AKI/ARF exist in the literature

1. Creat \( \Delta \geq 0.1 \text{ mg/dL} \)
2. Creat increase \( >0.5 \text{ mg/dL} \)
3. Creat\( =\) 0.5 mg/dL
4. Creat \( \geq 1.7 \text{ mg/dL} \)
5. Creat \( \geq 1.5 \text{ mg/dL} \)
6. Creat \( \geq 2 \text{ mg/dL} \)
7. Creat\( =\) 2.1 mg/dL and \( \times 2 \)
8. Creat\( >\) 3.3 mg/dL
9. Creat\( =\) 2.7 mg/dL (1.98 mmol/L)
10. Creat\( >\) 2.9 mg/dL or \( \times 2 \)
11. Creat\( =\) 1.5 mg/dL
12. Creat\( >\) 1.8 mg/dL or \( \times 2 \)
13. Creat\( >\) 2.5 mg/dL
14. Creat\( >\) 2.7 mg/dL
15. Creat\( >\) 2.9 mg/dL
16. Creat\( =\) 1.5 mg/dL
17. Creat\( >\) 1.8 mg/dL or \( \times 2 \)
18. Creat\( >\) 2.5 mg/dL
19. Creat\( >\) 2.7 mg/dL
20. Creat\( >\) 2.9 mg/dL
21. Cockcroft-Gault Cr Cl < 30 mL/min
22. Cockcroft-Gault Cr Cl 30–60 mL/min
23. Cockcroft-Gault Cr Cl \( > 60 \text{ mL/min} \)
24. U\( \geq\) 300 g/d
25. U\( \geq\) 250 g/d
26. U\( \geq\) 200 g/d
27. MDRD: 50% change in Cr
28. UO <100 ml q 8hr
29. U\( \alpha\)-microglobulin
30. U\( \beta\)-microglobulin
31. U N-acetyl-\( \beta\)-D-glucosaminidase
32. U glutathion transferase-\( \pi\)
33. U glutathion transferase-\( \alpha\)
34. NGAL
35. RRT

Mortality Risk in Hospitalized Patients

KDIGO Definition of AKI

- Increase in Scr by \( \geq 0.3 \text{ mg/dL} \) within 48 hours; or
- Increase in Scr to \( \geq 1.5 \times \) baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume \(< 0.5 \text{ ml/kg/hour} \) for 6 hours.

Examples

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 7</th>
<th>RIFLE</th>
<th>AKIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0.5</td>
<td>0.7</td>
<td>0.4</td>
<td>1.0</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>1.0</td>
<td>1.1</td>
<td>1.3</td>
<td>1.2</td>
<td>1.0</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>
5 Problems (at least) with Serum Creatinine

RIFLE/AKIN/KDIGO-Creatinine based

1. Not sensitive: There is lot of cellular injury that does not affect (GFR)/creatinine
2. Not Specific: Creatinine can increase without kidney injury (pre-renal state)
3. Delayed: The rise in serum creatinine is delayed by 2-3 days
4. Fluid therapy may dilute serum creatinine delaying diagnosis
5. Inter-laboratory variation in measuring creatinine, and bilirubin and other compounds interfere with the colorimetric modified Jaffe assay hence affect serum creatinine levels.

Definition and Incidence:

Summary

- RIFLE or AKIN Definitions
  - Increase in stage associated with increase in mortality
  - Both have important limitations
- KDIGO Definition
  - Consensus definition- Combines RIFLE and AKIN into a single definition
  - Limitations-number of limitations
  - Need to integrate biomarkers of injury

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Primary and Secondary Prevention

Risk Profiling and Biomarkers

Outline

- What Can An Ideal AKI Biomarker Teach Us?
  - Predict and diagnose AKI early (before increase in serum creatinine)
  - Identify the primary location of injury (proximal tubule, distal tubule, interstitium)
  - Pinpoint the type (pre-renal, AKI, CKD), duration and severity of kidney injury
  - Identify the etiology of AKI (ischemic, septic, toxic, combination)
  - Predict clinical outcomes (dialysis, death, length of stay)
  - Monitor response to intervention and treatment
  - Expedite the drug development process (safety)
**Biomarkers after AKI**

**Early Detection**

<table>
<thead>
<tr>
<th>SCr</th>
<th>Kim-1</th>
<th>IL-18</th>
<th>NGAL</th>
<th>L-FABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idealized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Value of Damage Biomarkers**

**Differential Diagnosis of AKI**

- **Urinary NGAL**
- **Serum Creatinine**

(505 patients admitted to the hospital with AKI, prerenal azotemia, CKD, or normal kidney function.

- RIFLE criteria for AKI used.
- At a cutoff value of 130 μg/g creatinine, sensitivity and specificity of NGAL for detecting acute injury were 0.900 (95% CI, 0.73 to 0.98) and 0.995 (CI, 0.990 to 1.00).

**Combined use of damage biomarkers and functional biomarkers Predicts clinical events**

Clinical events (initiation of dialysis or inhospital mortality)

**Diagnosis of AKI: Combination of Functional and Damage Markers**

**RenaStick**

**Point of Care Testing for AKI**

**Timing in Secondary Prevention**

**EarlyARF Study**

- Double-blind placebo-controlled trial: early treatment with erythropoietin (E) could prevent the development of AKI in ICU setting.
- Urinary levels of two biomarkers, γ-GT and AP (46.3) triggered randomization to either placebo or two doses of E.
- Primary outcome of relative average plasma creatinine increase from baseline over 4 to 7 days.
- Of 529 patients, 162 were randomized within an 3.5 h of a positive sample.
- Early intervention with high-dose erythropoietin did not alter the outcome.


**Zh Endre et al Contrib Nephrol. 2013;182:30-44**


**Zh Endre et al Kidney Int. (2010) 77, 1020–1030**

**Steps in the EarlyARF study**

- Double-blind placebo-controlled trial: early treatment with erythropoietin (E) could prevent the development of AKI in ICU setting.
- Urinary levels of two biomarkers, γ-GT and AP (46.3) triggered randomization to either placebo or two doses of E.
- Primary outcome of relative average plasma creatinine increase from baseline over 4 to 7 days.
- Of 529 patients, 162 were randomized within an 3.5 h of a positive sample.
- Early intervention with high-dose erythropoietin did not alter the outcome.
Thresholds for Detection of AKI
Caveats?

<table>
<thead>
<tr>
<th>Healthy Adult</th>
<th>Adult with CKD??</th>
<th>Pediatric</th>
<th>Elderly Adult??</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>AKI</td>
<td>AKI</td>
<td>AKI</td>
</tr>
<tr>
<td>No AKI</td>
<td>No AKI</td>
<td>No AKI</td>
<td>No AKI</td>
</tr>
</tbody>
</table>

What are the cut points for: L-FABP, KIM-1, and IL-18
Surgery, contrast-induced AKI, sepsis and critical illness.

Biomarkers: Summary

Biomarkers – General
- Transition from discovery to validation to clinical use: IL-18; Cystatin C; KIM-1; NAG
- Combination of “functional” and “damage” biomarkers
- Optimal “context specific” cut-points for the diagnosis of AKI need to be developed for L-FABP, KIM-1, and IL-18 and other

Biomarkers - Older patients
- The use of serum creatinine is the current gold standard but its use necessitates a clear understanding of its limitations especially the older population
- Validation of lead biomarkers need testing in the older population
- L-FABP, KIM-1, and IL-18 and others
- Cut-points need to be identified in the older population

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Pre-Exposure Risk Factors

Shared Susceptibility Factors
- Hypertension
- Diabetes
- Advanced age
- Female gender
- Black race
- Previous MI

Chronic Comorbidities
- Nephrotic syndrome
- Chronic kidney disease
- Coronary artery disease
- Chronic obstructive pulmonary disease
- Multimorbidity

Medications
- NSAIDs
- ACEI/ARBs
- Statins

Pre-Exposure Risk Factors

Adapted from KDIGO; appendix C, Kidney Int. 2012
Risk Prediction for RCIN

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5</td>
</tr>
<tr>
<td>IABP</td>
<td>5</td>
</tr>
<tr>
<td>CHF</td>
<td>4</td>
</tr>
<tr>
<td>Age&gt;75</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Contrast volume</td>
<td></td>
</tr>
<tr>
<td>Cr&gt;1.5 mg/dl</td>
<td>4</td>
</tr>
<tr>
<td>eGFR&lt;60 ml/min/1.73 m²</td>
<td>1 for each 100ml</td>
</tr>
<tr>
<td>2 for 40-60</td>
<td></td>
</tr>
<tr>
<td>4 for 20-40</td>
<td></td>
</tr>
<tr>
<td>≥2 for &lt;20</td>
<td></td>
</tr>
</tbody>
</table>

Risk of Score | Risk of RCIN | Risk of Dialysis |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>7.5%</td>
<td>0.04%</td>
</tr>
<tr>
<td>6-10</td>
<td>14%</td>
<td>0.12%</td>
</tr>
<tr>
<td>11-16</td>
<td>26.1%</td>
<td>1.09%</td>
</tr>
<tr>
<td>≥16</td>
<td>57.3%</td>
<td>≤12.6%</td>
</tr>
</tbody>
</table>

Risk Factors for AKI: Importance of CKD

Kaiser Permanente Northern California

1,746 hospitalized AKI-D and 800,820 hospitalized with no AKI

Documented Proteinuria
Diagnosed Hypertension
Diabetes Mellitus
Baseline GFR
<15
15-29
30-44
≥45-59

Unadjusted Odds ratio
0 20 40 60 80 100 120


<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;35%</td>
<td>1</td>
</tr>
<tr>
<td>Preoperative use of IABP</td>
<td>2</td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
</tr>
<tr>
<td>Insulin-requiring diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>1</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>2</td>
</tr>
<tr>
<td>Valve surgery only (reference to CABG)</td>
<td>1</td>
</tr>
<tr>
<td>CABG + valve (reference to CABG)</td>
<td>2</td>
</tr>
<tr>
<td>Other cardiac surgeries</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative creatinine 1.3 to &lt;2.1 mg/dl (reference to 1.3)</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative creatinine ≥2.1 mg/dl (reference to 1.3)</td>
<td>2</td>
</tr>
</tbody>
</table>

Minimum score: 0
Maximum score: 17

Hyperglycemia increases AKI Risk

Unadjusted Odds ratio
1.746 hospitalized AKI-D and 600,820 hospitalized with no AKI

Hyperglycemia increases AKI Risk

Unadjusted Odds ratio
1.746 hospitalized AKI-D and 600,820 hospitalized with no AKI

Proteinuria increases AKI Risk

Unadjusted Odds ratio
1.746 hospitalized AKI-D and 600,820 hospitalized with no AKI

Obesity and Risk of Acute Kidney Injury Following Cardiac Surgery

• Examined body mass relationship between BMI and AKI in 445 patients undergoing cardiac surgery
• Higher BMI independently associated with increased odds of AKI
• 26.2% increase per 5 kg/m² (95% CI: 13.4-39.0; P<0.001)
• Baseline and intraop F2-isoprostane, and intraop PAI-1 independently predicted AKI
• Obesity independently predicts AKI after cardiac surgery in part through oxidative stress.
Predictive and intraoperative Risk Assessment

Non Dialysis AKI Associates with Increased Long Term Mortality

Clinical Risk Assessment: Summary

Cirrhotic Cardiomyopathy

• 50 ys ago Kowalski and Abel described hyperdynamic circulation in cirrhotic patients
• Gould 1969 demonstrated cardiac contractile response was depressed in alcoholic cirrhosis, confirmed in several other studies (alcoholic cirrhosis)….alcohol cardiomyopathy?
• Depressed cardiac function due to cirrhosis
  - β-blocker receptors density of lymphocytes of patients
  - Animal studies confirmed
  - Nonalcoholic cirrhosis with blunted cardiac inotropic and chronotropic response to exercise, drugs, hemorrhage, surgery and stress.
  - Conduction abnormalities

AKI Transition of Care: A Potential Opportunity to Detect and Prevent CKD

Summary
The incidence rate of AKI is increasing across the spectrum of hospitalized children and adults. Given the increased morbidity and mortality associated with AKI, significant research effort has been appropriately focused on better understanding the etiology, pharmacology, pathogenesis, and pharmacotherapeutics of AKI. In addition, a growing body of evidence demonstrates that AKI is a risk factor for the future development of cardiovascular outcomes and, for this reason, AKI should be a clinical consideration in the evaluation and management of patients hospitalized for a variety of other reasons. In this review, we briefly summarize the current literature on AKI and the potential impact of AKI on the long-term outcomes of hospitalized patients and the role of systemic therapies in the prevention and management of AKI. We also discuss the potential role of AKI in the development and progression of cardiovascular disease and the importance of early detection and intervention in patients with AKI. Finally, we provide a research agenda for future studies on the prevention, diagnosis, and treatment of AKI in hospitalized patients.