Role of Uric Acid in Acute Kidney Injury?

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Outline

• The crystal-dependent role of uric acid-related diseases

• The crystal-independent role of uric acid-related diseases

• Acute kidney injury
  • Experimental studies
  • Clinical studies

AKI = acute kidney injury; SUA = serum uric acid
Scarcity of Vitamin C

Natural selection favored human individuals who could repair arteries with a layer of lipid

Survival benefit?

Subsequent million years:

Mutation of L-gulonolactone Oxidase: **Loss of ability to synthesize Vit C in humans**
Humans can not synthesize Vitamin C, nor degrade uric acid

The loss of the ability to synthesize ascorbic acid parallels the loss of the ability to degrade uric acid due to mutation of the gene encoding for uricase / urate oxidase.
Uric acid is a protective mechanism against oxidative stress

In 1981, Ames proposed that one of these protective systems is plasma uric acid. Soluble uric acid may act as an antioxidant that can react with a variety of oxidants including superoxide anion and peroxynitrite.

Plasma uric acid levels have increased during primate evolution.

Lengthening of life-span improved protective mechanisms against oxygen radicals.

In 1981, Ames proposed that one of these protective systems is plasma uric acid.

Soluble uric acid may act as an antioxidant that can react with a variety of oxidants including superoxide anion and peroxynitrite.
Uric acid is a powerful antioxidant and scavenger of reactive oxygen radicals.

Uric acid is the major antioxidant in humans.

Plasma uric acid concentrations are higher than Vit C.

Total antioxidant capacity correlates with increase in plasma uric acid.
A changing role for uric acid in disease states

Crystal dependent mechanism

Gouty arthritis

Urate nephropathy
Nephron 1975; 14:88
Mol Med 2000;6:837

Known for centuries that the biological significance of uric acid was that it crystallizes in joints to cause gouty arthritis, and in the urinary tract to cause kidney stones.

Acute crystallization of uric acid within the kidney during TLS was considered the cause of nephropathy.

Nephrolithiasis

Howard, Childhood Leukemia
Uric acid crystals can induce inflammatory response via activation of inflammatory cells

- **via complement activation**
  - Arthritis Rheum 1975;18:765
  - Curr Opinion Rheumatol 1993;5:510

- **Stimulate neutrophil chemotaxis, phagocytosis, respiratory burst**

- **Produce IL-1 and IL-1Ra**
  - J Immunol 1994; 152:5485

- **Releases leukotrienes, kinins, IL-8, PAF**
  - Arthritis Rheum 1975;18:765
  - Curr Opinion Rheumatol 1993;5:510
  - Prostaglandins 1984; 27:563

- **Stimulation of IL-8 thru activation of MAPK and NFκB**
  - Arthritis Rheum 2000; 43:1145

- **Induce production of TNF-α, MCP-1, MIP-2, IL-6**
  - J Clin Invest 1991; 87:1375
  - Arthritis Rheum 2003; 48:2931; 1898; 32:1443

- **Mo release IL-1B that induce an inflammatory response via IL-1β receptor and MyD88 signaling pathway**

- **Activates T, B and dendritic cells**
  - Nature 2003; 425:516
  - Blood 111:1472
Linking uric acid crystals to the evolution of Chronic Kidney Disease

• In 1975, Bluestone et al demonstrated the link between chronic hyperuricemia and chronic kidney disease.

• Bluestone et al induced and sustained moderately severe hyperuricemia and hyperuricosuria in rats for up to 52 weeks.

• Performed periodic renal biopsies (4, 36 and 52 weeks) to investigate the evolution of urate nephropathy.
At 4 weeks – the acute phase

Massive intratubular urate deposition

Dilated tubules

Peritubular acute inflammatory response

Atrophied and ruptured tubules

Tophi

At 52 weeks – the chronic phase

Chronic hyperuricemia leads to progression to chronic kidney disease via a Crystal-Dependent mechanism

Fibrosis

Mononuclear cell infiltrates
Johnson et al demonstrated that mild hyperuricemia, in concentrations that do not cause crystal precipitation, can cause chronic tubulo-interstitial damage.

Absence of intrarenal urate crystal deposition

Mild hyperuricemia was associated with severe arteriolar hyalinosis and tubulointerstitial damage

Mild hyperuricemia can cause chronic kidney disease via Crystal-independent mechanisms
### Clinical conditions associated with uric acid

<table>
<thead>
<tr>
<th>Crystal dependent</th>
<th>Soluble uric acid / crystal independent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gouty arthritis</strong></td>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td>MRFIT (Krishnan, 2006)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Urate nephropathy</strong></th>
<th><strong>Stroke</strong></th>
<th><strong>Diabetes</strong></th>
<th><strong>Chronic Kidney Injury</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soluble uric acid / crystal independent</strong></td>
<td><strong>Atherosclerosis 2006;187:401</strong></td>
<td><strong>Diabetes Care 2010</strong></td>
<td><strong>Am J Physiol 2007; 292:F116</strong></td>
</tr>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td><strong>NDT 2009</strong></td>
<td><strong>Kidney Blood Pressure 2012</strong></td>
<td><strong>Am J Nephrol 2015;</strong></td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong></td>
<td><strong>CJASN 2010</strong></td>
<td><strong>AJKD 2006</strong></td>
<td><strong>PLoSOne 2015</strong></td>
</tr>
<tr>
<td>Condition</td>
<td>OR</td>
<td>(95% C.I.)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.60</td>
<td>(2.15-3.14)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>3.12</td>
<td>(2.43-4.01)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.63</td>
<td>(1.13-2.34)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.74</td>
<td>(1.16-2.59)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.45</td>
<td>(1.12-1.88)</td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2.52</td>
<td>(1.58-4.04)</td>
<td></td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>2.33</td>
<td>(1.94-2.80)</td>
<td></td>
</tr>
</tbody>
</table>

NKHES, N=5707
### Relationship of allopurinol with improved endothelial function

<table>
<thead>
<tr>
<th>Study population</th>
<th>Relative improvement</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>58%</td>
<td>Doehner, 2002</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>50%</td>
<td>Farquharson, 2002</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>30%</td>
<td>George, 2006</td>
</tr>
<tr>
<td>Normotensive type 2 diabetes</td>
<td>50%</td>
<td>Dogan, 2010</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>30%</td>
<td>El Solh, 2006</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>50%</td>
<td>Yiginer, 2008</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>30%</td>
<td>Butler, 2000</td>
</tr>
<tr>
<td>Asymptomatic hyperuricemia</td>
<td>20%</td>
<td>Kanbay, 2011</td>
</tr>
<tr>
<td>Asymptomatic hyperuricemia</td>
<td>30%</td>
<td>Mercuro, 2011</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>100%</td>
<td>Yelken, 2012</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>25%</td>
<td>Kao, 2011</td>
</tr>
</tbody>
</table>

#### ClinicalTrials.gov

1. NCT0158911: Uric Acid and Long-term Outcomes in Chronic Kidney Disease
2. NCT00978653: The Effect of Uric Acid Decrement on Endothelial Function in Patients With Chronic Renal Failure
3. NCT00978653: The Effect of Uric Acid Decrement on Endothelial Function in Patients With Chronic Renal Failure
4. NCT01226903: Uric Acid and the Endothelium in CKD
5. NCT01350388: Effects of Febuxostat on Adipokines and Kidney Disease in Diabetic Chronic Kidney Disease
6. NCT00860366: Efficacy Study of Combined Treatment With Uric Acid and rHAm in Acute Ischemic Stroke
8. NCT02344602: The Effect of Uric Acid Lowering on Type 1 Diabetes
9. NCT00793855: A Controlled Study of Uric Acid on the Progression of IgA Nephropathy
10. NCT0087415: Using Allopurinol to Relieve Symptoms in Patients With Heart Failure and High Uric Acid Levels
11. NCT01082640: Effect of Febuxostat on Renal Function in Patients With Gout and Moderate to Severe Renal Impairment
12. NCT00477789: Effects of Allopurinol on Diastolic Function in Chronic Heart Failure Patients
Serum uric acid is associated with many chronic diseases via both crystal-dependent and crystal-independent mechanisms.
Crystal-dependent AKI associated with Tumor Lysis Syndrome

Tumor cell death

Rapid release

Nucleic acid → purines → uric acid → uric acid crystals

Phosphorus → calcium phosphate crystals

Volume depletion

Metabolic acidosis → uric acid crystals precipitation

Potassium → hyperkalemia

Arrhythmias

Uremia

Oliguria/anuria

Fluid overload
Pulmonary edema
Respiratory failure
## Estimating the role of uric acid in AKI

<table>
<thead>
<tr>
<th>N</th>
<th>All Causes of AKI</th>
<th>Uric Acid Crystal Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>6.2 ± 3.1</td>
<td>4.8 ± 3.4</td>
</tr>
<tr>
<td>Serum Uric acid (mg/dL)</td>
<td>13.8 ± 5.6</td>
<td>21 ± 20</td>
</tr>
<tr>
<td>Urine uric acid to urine creatinine ratio</td>
<td>0.43 ± 0.19 (range 0.12-0.9)</td>
<td>1.68 ± 0.63 (range 1.00-2.60)</td>
</tr>
</tbody>
</table>

Kelton Arch Intern Med. 1978:138:612
Intraluminal precipitation of uric acid crystals associated with alterations in renal function in experimental urate nephropathy

2.5%UA + 5%OA + Chow

7 days

Micropuncture Clearance

Uric acid crystals

50% decrease in Glomerular Filtration Rate

GFR (mL/min/kg body wt)

Control

Hyperuricemia

50% decrease in renal blood flow

Renal Blood Flow (mL/min/kg body wt)

Control

Hyperuricemia

Spencer Kidney Int 1976: 9:489
Soluble uric acid causes renal vasoconstriction via crystal-independent mechanisms

- Normal
- Mild hyperuricemia (OA, 750 mg/kg)
- Mild hyperuricemia (OA) + Allopurinol

Model: Experimental
Strain: SD
N= 8, 9, 7
T= 5wks
Technique: Micropuncture

Glomerular filtration rate

\[ r = -0.47 \]
\[ P = 0.03 \]

~50% decrease in SNGFR

Vasoconstriction

\[ r = 0.54 \]
\[ P = 0.01 \]

40-60% decrease in renal blood flow

i.e. uric acid in concentrations that do not cause intratubular crystal precipitation was also shown to decrease GFR and renal blood flow, suggesting a crystal independent pathway
The adverse events associated with uric acid are mediated by endothelial dysfunction and pathologic vascular remodeling.
Uric acid has proliferative effect on vascular smooth muscle cells. inhibitory effect on vascular endothelial cells

**Human Vascular Smooth Muscle Cells**
- Stimulates proliferation
- migration

**Human Umbilical Vein Endothelial Cells**
- Antiangiogenic
- inhibits proliferation, migration
- Stimulates apoptosis

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![Graphs showing proliferation and migration](image-url)

*Kang/Johnson  JASN 2005;16:3553*
Uric acid stimulates proinflammatory chemokine (MCP-1) production in vascular smooth muscle cells

Proinflammatory / Prooxidative

MCP-1 is an inflammatory response

Probenecid blocks MCP-1 synthesis

Kanellis/Johnson Hypertension 2003; 41:1287

Kang AJN 2005;25:425-433
Uric acid stimulates CRP production in HVSMC and HUVEC

Proinflammatory / Prooxidative

CRP expression in both VSMC and VEC

CRP is an inflammatory protein associated with the secretion of various cytokines, including IL-6, TNF-α, and IL-1

CRP is associated with atherothrombosis

CRP is responsible for uric acid mediated vascular remodeling
Uric acid decreases bioavailability of nitric oxide

**HUVEC**
Uric acid inhibits NO production

NO inhibiting effect of uric acid blocked by probenecid anti-CRP antibody
Inverse relationship between plasma uric acid and nitric oxide

- N=217. M108, F109; 48±10.6yrs
- Hypertensive patients
- Untreated
- Endothelial function evaluated by vasodilatory response to intra-arterial infusion of ACh
- Forearm blood flow and arterial pressure measured

**Result**
Uric acid reduces brachial artery flow mediated vasodilation
Hyperuricemia induces thickening of vascular wall

Control

Hyperuricemia

PAS stain + alpha-actin SM antibody (100X)
Summary of the renal effects of uric acid

Vasoconstriction
- decreases renal blood flow ~40-60%
  - ↑ RAS activation
  - ↓ NO bioavailability
  - ↑ Oxidants
  - ↑ inflammatory mediators
  - ↑ vascular responsiveness

Impaired autoregulation
- ↑ VSMC proliferation & migration
- ↓ VEC proliferation & migration
- ↑ preglomerular arteriolar thickening

Glomerulus
- ↓ Glomerular filtration rate
  ~40-50%
  Sanchez-Lozada AJP 2002
  Sanchez-Lozada KID 2015

Proximal Tubules
Oxidative stress

Inflammation
- ↑ MCP-1, ICAM-1
  - KHK dependent
  Griffin AJP 2009

Innate and adaptive immunity
- ↑ complement, TLR activation
  Bunne Tawney AJP 2000
  Tubbi AJP 2000

Inhibition of PTC proliferation
- ↑ MAPK, NFκB
  Seelin AJP 2007

Mitochondrial dysfunction

RAS: renin angiotensin system; VSMC: vascular smooth muscle cells; VEC: vascular endothelial cells; KHK: keto-hexokinase; PTC: proximal tubular cells;
Renal vasoconstriction: potential initiator of ischemic AKI

Diagram showing the progression of GFR over days, with phases labeled as Prerenal, Inflation, Extention, and Recovery.
**Hypothesis of the mechanism of ischemic AKI**

Reduction in outer medullary oxygen tension

- Impaired Autoregulation
  - Vasoconstrictors: Ang II, Catechol, ET-1, ROS, Cytokines
  - Vasodilators: NO, PGI₂, Bradykinin, EDHF
- iATP
- Impaired Autoregulation
  - hCa++
  - Calpain
  - Cytoskeletal changes
  - Tight junction / Apical-basolater / Microfilament polarity
- Hemodynamic changes / tubular injury

↓RBF  ↓PO₂

↑Calpain
↑NOS
↑NO
↑OONO⁻

↑PL

Membrane PL hydrolysis
**TG Feedback**

AA vasoconstriction
A1 – AR

↓
↓P_{GC}

↓
↓GFR

+  –

Vasoconstriction

Impaired autoregulation

EA vasodilatation
A2a – AR

↓ ATP

↓ NO

↓ RBF

↓ PO_{2}

TG Feedback activation vasodilates the efferent arteriole by an adenosine-dependent mechanism.
**The Inflammatory cascade**

- **Neutrophil Sequestration**
- **OM vasa recta congestion**
- **Entrapment of leukocytes, Platelets, T, others**
- **Enhanced EC-Leukocyte adhesion**
- **↑ ROS, cytokines, chemokines, complements**
- **Ischemia-reperfusion injury**
  - **VASCULAR INJURY**
  - **TUBULAR INJURY**
- **↓ Nitric Oxide**
- **↑ Renin-Angiotensin**
- **↓ RBF**
- **↓ PO₂**
- **Microvessels dropout**
  - **↓ Tubulointerstitial fibrosis**
  - **↓ Concentration capacity**

**JASN 2006; 17:1503**
Mechanism of acute kidney injury

Intact tubular epithelium

Loss of polarity, tight junction integrity, cell-substrate adhesion, simplification of brush border

Toxic injury

Cell death

Necrosis

Apoptosis

Sloughing of viable and nonviable cells with intraluminal cell-cell adhesion

Cytoskeleton

Extracellular matrix

Na+/K+/ATPase

β1 Integrin

RGD peptide

Cast formation and tubular obstruction

Epithelial cell cast

Mixed cellular & granular cast

Coarse granular cast

Fine granular cast

Waxy cast
Interval Summary

- Serum uric acid associated with many disease conditions via crystal-independent mechanisms
- SUA causes renal vasoconstriction
- SUA is proinflammatory and anti-angiogenic
- SUA causes thickening of preglomerular arteriolar thickening
- SUA appears to affect many of the hypothetical mechanisms of acute kidney injury
Effect of elevated serum uric acid on cisplatin-induced acute renal failure

Carlos A. Roncal,1* Wei Mu,1* Byron Croker,2 Sirirat Reungjui,1 Xiaosen Ouyang,1 Isabelle Tabah-Fisch,3 Richard J. Johnson,1 and A. Ahsan Ejaz1

Hypothesis: hyperuricemia might exacerbates AKI in CP-induced AKI

Control (C)
(0.25% methyl cellulose gavage x 5 days)

Cisplatin (CP)
(5 mg/kg, NS x 1 dose)

Cisplatin-Hyperuricemia (OA/CP)

1 wk

Day 5 Sacrifice

Cisplatin-Hyperuricemia-Rasburicase
(OA/CP/Rasburicase)
(+ 25 mg/kg IP x 5 days)

S-D rats
N=6 each group
Tissue injury scores were highest in the hyperuricemia /cisplatin group

Loss of brush border
Karyolysis
Tubular swelling
Nuclear condensation

Lowering uric acid reduced tissue injury

Roncal/Ejaz AJP 2007: 292:F116
Hyperuricemic rats with CP injury displayed significantly more monocytes and macrophages in the cortex and inner stripe. MCP-1 mRNA and protein was significantly increased hyperuricemic rats that received CP.
Results of inflammatory cytokines

MCP-1 mRNA and protein was significantly increased hyperuricemic rats that received CP.
Could Uric Acid Have a Role in Acute Renal Failure?

A. Ahsan Ejaz,* Wei Mu,* Duk-Hee Kang,† Carlos Roncal,* Yuri Y. Sautin,* George Henderson,* Isabelle Tabah-Fisch,‡ Birgit Keller,§ Thomas M. Beaver,‖ Takahiko Nakagawa,* and Richard J. Johnson*

Preoperative uric acid increases the risk for AKI in cardiac surgery

GUARDIAN/EXPEDITION Trials

SUA > 5.5mg/dL: 2 - 3 x risk for AKI
SUA > 7.5mg/dL: 3 - 4 x risk for AKI

GUARDIAN / EXPLORER
NHE inhibitors (cariporide) to prevent reperfusion injury during cardiac surgery

865 and 2832 patients who were in the placebo arm qualified for the study
SUA is a novel, independent predictor of postoperative AKI in CV surgery.

Preoperative serum uric acid >6.1 mg/dL confers a 4-fold increased risk for AKI.

Hyperuricemia is associated with increased risk for AKI, longer hospital stay, and more severe decrease in postoperative GFR.

SUA >6.1 mg/dL increases the risk of AKI by 4-fold.
Epidemiological evidence

Investigated the potential influence of preoperative serum uric acid (SUA) on acute kidney injury in patients undergoing cardiovascular
Results

Baseline SUA was divided into deciles

The higher the SUA, the higher the incidences of AKI

Plotted incidence of AKI against all the available values of SUA at increments of 0.5mg/dL

U-shaped curve emerged
Univariate analysis: Risk for AKI by threshold SUA levels

<table>
<thead>
<tr>
<th>SUA ≥5.5mg/dL</th>
<th>SUA ≥6mg/dL</th>
<th>SUA ≥6.5mg/dL</th>
<th>SUA ≥7mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI 95%: 2.4-8.2</td>
<td>CI 95%: 3.2-11.3</td>
<td>CI 95%: 3.9-15.8</td>
<td>CI 95%: 11.6-131.8</td>
</tr>
<tr>
<td>N=112</td>
<td>N=91</td>
<td>N=76</td>
<td>N=63</td>
</tr>
</tbody>
</table>

Unadjusted Odds Ratio CI 95%
Multivariate analysis: Substitution of SUA $>$ 7mg/dL with other SUA values

<table>
<thead>
<tr>
<th>SUA $\geq$ 5.5mg/dL:</th>
<th>OR for AKI:</th>
<th>3.83</th>
<th>CI$_{95%}$ 1.93-7.63</th>
<th>$p$&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUA $\geq$ 6mg/dL:</td>
<td>OR for AKI</td>
<td>5.15</td>
<td>CI$_{95%}$ 2.56-10.35</td>
<td>$p$&lt;0.001</td>
</tr>
<tr>
<td>SUA $\geq$ 6.5mg/dL:</td>
<td>OR for AKI</td>
<td>6.79</td>
<td>CI$_{95%}$ 3.23-14.23</td>
<td>$p$&lt;0.001</td>
</tr>
</tbody>
</table>

For reference

| SUA $\geq$ 7mg/dL: | OR for AKI | 39.68 | CI$_{95\%}$ 11.1-141.9 | $p$<0.001 |
Multivariate analysis in subgroups at high risk for AKI

- **Thoracic aortic aneurysm (N=63)**
- **Cardiac valves (N=54)**
- **CABG (N=73)**
- **GFR <60mL/min (N=84)**
- **LVEF <45% (N=41)**
- **Males (N=118)**

* = significant p-value
Preoperative elevated uric acid (≥6.5 mg/dL) was associated independently with AKI after CV surgery OR 1.46; 95%CI 1.04–2.06, p = 0.030).
Investigation of the relationship between post-op serum uric acid and AKI and comparison with conventional and novel biomarkers of AKI.

SUA has a graded relationship with AKI, therefore we divided SUA into tertiles:

1st tertile SUA < 4.53 mg/dL
2nd tertile SUA > 4.53 mg/dL and < 5.77 mg/dL
3rd tertile SUA > 5.77 mg/dL.

The 1st, 2nd, and 3rd SUA tertiles were associated with 15.1%, 11.7%, and 54.5% incidence of AKI, respectively.

Ejaz, J Nephrology 2012; 25:497
The 3rd SUA tertile: OR 8.38, CI95% 2.13-33.05, p=0.002) risk for AKI.

Compared to referent 1st tertile

3rd tertile vs. referent 1st SUA tertile:

- AKI on day 2: adjusted OR 7.94, CI95% 1.50-42.08, p=0.015
- AKI during hospital stay: adjusted OR 4.83, CI95% 1.21-19.20, p=0.025

Since the prooxidant effect of SUA manifests at levels ≥5.5mg/dL, we also calculated that the incidence of AKI for

- SUA<5.5mg/dL 13.1% vs.
- SUA≥5.5mg/dL 48.7%, p<0.001.

Ejaz, J Nephrology 2012; 25:497
**Important finding:** was that SUA had comparable predictive values as the conventional preoperative biomarker SCr and novel biomarkers at 24 hours from start of surgery, and was superior to preoperative GFR.

The observations that pre- and postoperative SUA are associated with AKI offers the potential to predict AKI at any perioperative time-point.
Prediction of TLS and institution of prophylactic and therapeutic options are paramount to the favorable clinical outcomes for patients undergoing cancer treatment.

The current prediction models of laboratory TLS (LTLS) in acute myeloid leukemia (AML) are based on white blood cell count (WBC), with or without lactate dehydrogenase (LDH), and specific cytogenetic abnormalities and karyotype complexity.

None of the prediction models include SUA.

We have demonstrated that SUA is an independent predictor of acute kidney injury (AKI).

Given our findings, we wanted to investigate the discrimination ability of baseline SUA to predict TLS and also to compare it to common laboratory variables, cytogenetic profiles, tumor markers and prediction models in acute myeloid leukemia patients.
Retrospective study of 183 AML patients between 2000-2012

- **Cairo-Bishop definition** of LTLS
  - Uric acid ≥8 mg/dL or 25% increase from baseline
  - Potassium ≥6 mEq/L or 25% increase from baseline
  - Phosphorus ≥6.5 mg/dL (children) or ≥4.5 mg/dL (adults) or 25% increase from baseline
  - Calcium ≤7 mg/dL or 25% decrease from baseline

**Cairo prediction model**
- **Low:** WBC <25x10^9/L and LDH <2x ULN
- **Intermediate:** WBC 25x10^9/L and LDH ≥2x ULN
- **High:** WBC ≥100x10^9/L

**SUA prediction model**
- **Low:** SUA <5.5mg/dL
- **Intermediate:** SUA >5.5mg/dL and <7mg/dL
- **High:** SUA > 7mg/dL

**NHS prediction model**
- **Low:** WBC <10x10^9/L
- **Intermediate:** WBC 10-50x10^9/L
- **High:** WBC >50x10^9/L
  
  *Does not include LDH*

**CALGB prediction model**
- Favorable
- Intermediate
- **Adverse groups** based on remission outcomes for specific cytogenetic abnormalities and karyotype complexity.
<table>
<thead>
<tr>
<th>Cytogenetic risk group</th>
<th>Induction success</th>
<th>Cumulative incidence of relapse</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable</strong></td>
<td>t(8;21)</td>
<td>t(8;21)</td>
<td>t(8;21)</td>
</tr>
<tr>
<td></td>
<td>inv(16) or t(16;16)</td>
<td>inv(16) or t(16;16)</td>
<td>inv(16) or t(16;16)</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>Normal karyotype</td>
<td>Normal karyotype</td>
<td>Normal karyotype</td>
</tr>
<tr>
<td></td>
<td>−Y</td>
<td>−Y</td>
<td>−Y</td>
</tr>
<tr>
<td></td>
<td>del(5q)</td>
<td>t(9;11)</td>
<td>del(5q)</td>
</tr>
<tr>
<td></td>
<td>t(6;9)</td>
<td>del(9q)</td>
<td>Loss of 7q</td>
</tr>
<tr>
<td></td>
<td>t(6;11)</td>
<td>+8 sole</td>
<td>t(9;11)</td>
</tr>
<tr>
<td></td>
<td>−7</td>
<td>+8 with 1 other abnormality</td>
<td>+11</td>
</tr>
<tr>
<td></td>
<td>Loss of 7q</td>
<td></td>
<td>+13</td>
</tr>
<tr>
<td></td>
<td>+8 sole</td>
<td>+8 with 1 other abnormality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+8 with 1 other abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>del(9q)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(9;11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>del(11q)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(11;19)(q23;p13.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>del(20q)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+21</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse</strong></td>
<td>Complex karyotype (≥ 3 abnormalities)</td>
<td>Complex karyotype (≥ 3 abnormalities)</td>
<td>Complex karyotype (≥ 3 abnormalities)</td>
</tr>
<tr>
<td></td>
<td>inv(3) or t(3;3)</td>
<td>−7</td>
<td>inv(3) or t(3;3)</td>
</tr>
<tr>
<td></td>
<td>abn(12p)</td>
<td>+21</td>
<td>t(6;9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t(6;11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+8 sole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+8 with 1 other abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t(11;19)(q23;p13.1)</td>
</tr>
</tbody>
</table>
Univariate analysis of risk factor for LTLS in AML

<table>
<thead>
<tr>
<th>Variables</th>
<th>LTLS</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pretreatment laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (full cohort), N=183</td>
<td>1.00</td>
<td>0.9-1.0</td>
<td>0.390</td>
</tr>
<tr>
<td>WBC &lt;10x10⁹/L, N=95</td>
<td>0.94</td>
<td>0.7-1.2</td>
<td>0.603</td>
</tr>
<tr>
<td>WBC 10-50x10⁹/L, N=43</td>
<td>0.98</td>
<td>0.9-1.0</td>
<td>0.477</td>
</tr>
<tr>
<td>WBC &gt;50x10⁹/L, N=15</td>
<td>1.00</td>
<td>0.9-1.0</td>
<td>0.449</td>
</tr>
<tr>
<td>WBC &gt;100x10⁹/L, N=6</td>
<td>0.99</td>
<td>0.9-1.0</td>
<td>0.943</td>
</tr>
<tr>
<td>SUA (full cohort), N=183</td>
<td>1.12</td>
<td>1.0-1.2</td>
<td>0.042</td>
</tr>
<tr>
<td>SUA low risk, N=113</td>
<td>0.33</td>
<td>0.2-0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUA intermediate risk, N=38</td>
<td>1.22</td>
<td>0.5-3.1</td>
<td>0.663</td>
</tr>
<tr>
<td>SUA high risk, N=32</td>
<td>7.26</td>
<td>3.2-16.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDH, N=145</td>
<td>1.00</td>
<td>1.0-1.0</td>
<td>0.930</td>
</tr>
<tr>
<td>LDH, 2xULN, N=65</td>
<td>1.00</td>
<td>1.0-1.0</td>
<td>0.486</td>
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<tr>
<td><strong>Tumor markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD34, N=99</td>
<td>0.32</td>
<td>0.1-0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB (full cohort)=169</td>
<td>1.83</td>
<td>1.1-3.2</td>
<td>0.031</td>
</tr>
<tr>
<td>CALGB adverse, N=48</td>
<td>0.56</td>
<td>0.2-1.3</td>
<td>0.169</td>
</tr>
<tr>
<td>CALGB intermediate, N=96</td>
<td>0.89</td>
<td>0.4-1.8</td>
<td>0.755</td>
</tr>
<tr>
<td>CALGB favorable, N=25</td>
<td>2.62</td>
<td>1.1-6.3</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>Gene mutations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPM1, N=33</td>
<td>1.00</td>
<td>0.1-5.1</td>
<td>1.000</td>
</tr>
<tr>
<td>FLT3, N=35</td>
<td>0.87</td>
<td>0.2-3.4</td>
<td>0.322</td>
</tr>
</tbody>
</table>

**Adjusted model**

- **CALGB favorable**: OR 2.7, CI95% 1.1-6.5, p=0.031
- **baseline SUA**: OR 1.12, CI95% 1.0-1.3, p=0.048
- **SUA high-risk**: OR 6.6, CI95% 2.4-17.9, p<0.001
- **LTLS modified baseline SUA**: OR 2.8, CI95% 1.1-7.1, p=0.033
Uric acid: a Novel Risk Factor for Acute Kidney Injury in High-Risk Cardiac Surgery Patients?

Comparison of clinical parameters to predict LTLS

The discriminatory ability of SUA was superior to LDH, cytogenetic profile and tumor markers but not to WBC ($AUC_{WBC} 0.679$).

However in comparisons between high-risk SUA and high-risk WBC, SUA had superior distinguishing capability ($AUC_{SUA} 0.664$ vs. $AUC_{WBC} 0.520; p < 0.001$) to predict LTLS.
Major finding: SUA had comparable predictive value as conventional prediction models and the combined model.

SUA demonstrated better performance than the prediction models (AUC_{high-risk SUA} 0.695, p<0.001)

In direct comparison of high-risk groups of each prediction model, SUA again demonstrated superior performance than the prediction models (AUC_{high-risk SUA} 0.668, p=0.001) in predicting LTLS, approaching that of the combined model (AUC 0.685, p<0.001).
**Pilot Study**

**Inclusion**
1. Age > 18 years
2. CABG, Valves, TAA
3. Serum Uric Acid > 6.5mg/dL
4. MDRD GFR > 30 - < 60 ml/min

**Exclusion:**
1. Adverse reaction to Rasburicase
2. Study drug cannot be administered at least 2 hours prior to CPB
3. Organ transplant recipient
4. On IABP

---

**Effect of uric acid lowering therapy on the prevention of acute kidney injury in cardiovascular surgery**

A. Ahsan Ejaz · Bhagwan Dass · Vijaykumar Lingegowda · Michiko Shimada · Thomas M. Beaver · Noel I. Ejaz · Amer S. Abouhamze · Richard J. Johnson

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**Flowchart:**

- **Eligible patient**
- **Randomization**
- **Placebo control**
- **Rasburicase**

**Study Drug**
- **2-4 hours prior to CPB**

**SUA**
- **Post-operatively**
  - **Post-op 24hr**
  - **Post-op 48hr**
  - **Post-op 120hr**

**Outcomes:**
- **Post-op**
  - **<5mg/dL**
    - **No study drug**
  - **>5mg/dL**
    - **Study drug**

**Post-op 24hr**

**Post-op 48hr**

**Post-op 120hr**

**Dialysis + Death 28-day**
Uric acid: a Novel Risk Factor for Acute Kidney Injury in High-Risk Cardiac Surgery Patients?

Effect of rasburicase on S_Creat

**Perioperative serum uric acid levels**

**Change in serum creatinine (%)**

<table>
<thead>
<tr>
<th>Day</th>
<th>Rasburicase</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>4.90%</td>
<td>2.30%</td>
</tr>
<tr>
<td>Day 2</td>
<td>24.20%</td>
<td>19.20%</td>
</tr>
<tr>
<td>Day 3</td>
<td>16.90%</td>
<td>7.90%</td>
</tr>
<tr>
<td>Day 4</td>
<td>14%</td>
<td>5.40%</td>
</tr>
<tr>
<td>Day 5</td>
<td>6.70%</td>
<td>4.90%</td>
</tr>
<tr>
<td>Discharge</td>
<td>-6.60%</td>
<td>-2.90%</td>
</tr>
</tbody>
</table>

No benefits on S_Creat were observed
Lowering hyperuricemia resulted in less renal structural injury as measured by the AKI biomarker NGAL.
Effects of Serum Uric Acid on Estimated GFR in Cardiac Surgery Patients: A Pilot Study

A. Ahsan Ejaz\textsuperscript{a} Kawther F. Alquadan\textsuperscript{a} Bhagwan Dass\textsuperscript{a} Michiko Shimada\textsuperscript{b} Mehmet Kanbay\textsuperscript{c} Richard J. Johnson\textsuperscript{d}

The effect of SUA on GFR) in the non-steady state is uncertain, calculations of which have been hindered by the technical complexities and the lack of broad consensus on guidelines about estimating GFR.

Chen has recently retooled the fundamental creatinine clearance equation with the power and versatility to estimate renal function under non-steady conditions.

We therefore utilized this novel kinetic estimated GFR (KeGFR) method, along with traditional (serum creatinine, SCr) and non-traditional biomarkers (NGAL) to investigate the effects of SUA on renal function in patients undergoing cardiac surgery.
$T_{\text{max}}$ for NGAL, IL-18 and Screat following ischemia-reperfusion injury
Methods and Materials

N=37

Adjusted for dilution effect of intraoperative fluid administration on SCr adjusted according to the following equation (Macedo):

SCr adjustments were performed for postoperative SCr values. Daily cumulative fluid balance was calculated according to the following formula: (sum of daily fluid received (L) - total amount of fluid eliminated (L)/preoperative weight (kg) × 100).

KeGFR: kinetic estimated GFR

Since there is no broad consensus method to correct for dilution effect on SUA, we used the absolute value of SUA measured at 1hr (SUA1h) post aortic cross-clamp (ACC) release, the time of maximum dilution based on our previous studies.
Uric acid: a Novel Risk Factor for Acute Kidney Injury in High-Risk Cardiac Surgery Patients?

Early biomarkers as a function of SUA concentration.
Uric acid: a Novel Risk Factor for Acute Kidney Injury in High-Risk Cardiac Surgery Patients?

Conventional biomarkers as a function of SUA concentration.

**SUA and day1 serum creatinine**

- POD1 serum creatinine (mg/dL)
- Serum uric acid (mg/dL)
- $r = 0.49$
- $p = 0.002$

**SUA and day2 serum creatinine**

- POD2 serum creatinine (mg/dL)
- Serum uric acid (mg/dL)
- $r = 0.39$
- $p = 0.018$

**SUA and day3 serum creatinine**

- POD3 serum creatinine (mg/dL)
- Serum uric acid (mg/dL)
- $r = 0.42$
- $p = 0.009$

**SUA and day4 serum creatinine**

- POD4 serum creatinine (mg/dL)
- Serum uric acid (mg/dL)
- $r = 0.32$
- $p = 0.056$

POD: postoperative day
Kinetic eGFR as a function of SUA concentration.
Confirmation with Jeliffe creatinine clearance
Major findings

The major findings of the study were the demonstration of significant correlations of SUA$_{1h}$ with early biomarkers (NGAL) and traditional biomarkers (SCr) of kidney injury and inverse correlations with KeGFRs measured by two independent method developed especially for use in non-steady states.

Furthermore, the highest tertile of SUA$_{1h}$ was associated with more severe renal injury as measured by NGAL in comparison to that associated with the lowest SUA$_{1h}$ tertile.

The results provide further evidence that SUA$_{1h}$ is a predictor of acute kidney injury in the early, intermediate and late phases of injury and also that higher SUA$_{1h}$ concentrations are associated with lower KeGFRs.

These findings suggest that uric acid precedes and predicts acute changes in renal function and cannot be ascribed to a simple relationship in which a reduced GFR raises serum uric acid.
Conclusion

Provided experimental, epidemiological and interventional data of the role of uric acid in AKI

Uric acid contributes to acute kidney injury
  impairs renal blood flow autoregulation, causes severe cortical vasoconstriction and decreases renal flow and GFR, stimulates inflammatory response

Serum uric acid is an intriguing risk factor and target for treatment
Thank you

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Puneet Sood, Pittsburgh

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Abraham Hartzema
Daniel Pauly, Kansas City
Minakashi Devidas, Gainesville
Michiko Shimada, Hirosaki

Tomas D. Martin
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S. Abouhamze
W. Stratford May

Matthew Pfeiffer
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Michelle Armstrong
Susan Beltz, PharmD
Deborah Kahler, PharmD