Measuring Renal Function: Which Biomarkers?
Creatinine and Cystatin c

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Consultant Intensivist & Nephrologist
Acute Kidney Injury

- Diagnose AKI
- Determine Severity
- Determine Prognosis
- Direct treatment

Kidneys for Life: Stop Acute Kidney Injury

www.worldkidneyday.org
**CKD after AKI**

- Diagnose CKD
- Determine Severity
- Determine Prognosis
- Direct treatment
Creatinine Production

[Diagram showing the production of creatinine from the liver, kidneys, urine, and its chemical structure.]
Steady State: \( \text{In} = \text{Out} \)

\[
G = K \cdot Cr
\]

\[
K = \frac{G}{Cr}
\]

Double Creatinine = Half GFR
20yr Male GFR 120 to 35ml/min/1.73m²

Baseline
AKIN 1
RIFLE R
RIFLE I
RIFLE F

AKI Category
Creatinine µmol/L

Time hr

0 5 10 15 20 25 30 35 40

50 100 150 200 250 300
\[ \frac{dCr}{dt} \times V = G - K \times Cr \]
Reduced Production of Creatinine Limits Its Use as Marker of Kidney Injury in Sepsis

Creatinine generation is reduced in patients requiring continuous venovenous hemodialysis and independently predicts mortality.

Francis P. Wilson, Jessica M. Sheehan, Laura H. Mariani and Jeffrey S. Berns

**Fig. 2.** Box plot demonstrating measured versus predicted CGR in the cohort. Prediction equations appear in appendix [23–25].
20yr Male GFR 120 to 35ml/min/1.73m²

AKI Category

Creatinine even fluid balance
Creatinine modeled with +ve Fluid Balance 8L over 48hr
20yr Male GFR 120 to 35ml/min/1.73m²

**AKI Category**
- Baseline
- AKIN 1
- RIFLE R
- RIFLE I
- RIFLE F

**Creatinine µmol/L**
- Creatinine even FB
- Creatinine modeled with +ve FB 8L over 48hr
- Creatinine modeled with +ve FB 8L over 48hr and 20% fall in Generation Rate

**Time hr**
- 0  6  12  18  24  30  36  42  48
- 0  50  100  150  200  250  300
75yr Male GFR 82 to 25

**AKI Category**
- RIFLE F
- RIFLE I
- RIFLE R
- AKIN 1
- Baseline

**Creatinine even FB**

**Creatinine modeled with +ve FB 8L over 48hr**

**Creatinine modeled with +ve FB 8L over 48hr and 20% fall in G**

**Creatinine µmol/L**
- 0
- 50
- 100
- 150
- 200
- 250
- 300

**Time hr**
- 0
- 6
- 12
- 18
- 24
- 30
- 36
- 42
- 48
Critical illness: variable severity
75yr Male Baseline GFR 82

Time hr

AKI Category

Creatinine µmol/L

Baseline

RIFLE F

RIFLE I

RIFLE R

AKIN 1

GFR 25  G fall 20%

GFR 1  G fall 40%

GFR 1  G fall 20%
Long-term risk of mortality and acute kidney injury during hospitalization after major surgery

5544 patients admitted to critical care

781 Received RRT*

394 received RRT* and survived to hospital discharge

261 received RRT* for AKI 3 who were not previously known to the renal team

219 analysed

7 were discharged on RRT (2.5%)

8 were re-admitted to hospital within three months of discharge

22 Died within three months of discharge

5 transferred out of area to continue their rehabilitation and their outcomes are unknown

124 Had a creatinine measurement 4-6 months post discharge

104 Had a creatinine measurement at baseline and 4-6 months post discharge
104 RRT Survivors with Baseline and 6/12 eGFR

Median 49

Median 60
Serum Creatinine Changes Associated with Critical Illness and Detection of Persistent Renal Dysfunction after AKI

John R. Prowle,*†‡ Ivana Kolic,* Jeremy Purdell-Lewis,* Rachelle Taylor,* Rupert M. Pearse,*† and Christopher J. Kirwan*†‡

Creatinine (mg/dl)

- No AKI
- AKI 1
- AKI 2
- AKI 3

**Versus Admission:**  
NS $p > 0.05$;  * $p < 0.05$;  ** $p < 0.01$
160 patients with Baseline Creatinine

**Creatinine (mg/dl)**

- Baseline
- Admission
- Peak
- Discharge

**Versus Baseline:** NS $p > 0.05$; * $p < 0.05$; ** $p < 0.01$
135% increase in potential CKD diagnoses
Comparison of different equations to assess glomerular filtration in critically ill patients
The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU

**Fig. 1** eGFR (gray boxes) and Ccr (white boxes) (in ml/min/1.73 m²) at ICU discharge for subgroups of a AKI patients and b no-AKI patients with ICU stay less than 8, 8–14, and longer than 14 days. *Boxes* show median and IQR, *whiskers* 10th and 90th percentile.
Creatinine Production AKI Patients

<table>
<thead>
<tr>
<th>ICU LOS</th>
<th>Measured</th>
<th>Predicted</th>
<th>1.7d</th>
<th>8-14d</th>
<th>&gt;14d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Median creatinine production (IQR)
- NS
- *
Acute kidney injury and mortality 1 year after major non-cardiac surgery

M. E. O’Connor¹,², R. W. Hewson¹,²,³, C. J. Kirwan¹,²,⁴, G. L. Ackland¹,³, R. M. Pearse¹,²,³ and J. R. Prowle¹,²,⁴

¹Critical Care and Perioperative Medicine Research Group, William Harvey Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, and ²Adult Critical Care Unit, ³Department of Anaesthesia and ⁴Department of Renal and Transplant Medicine, Royal London Hospital, Barts Health NHS Trust, London, UK

Correspondence to: Dr J. R. Prowle, Adult Critical Care Unit, Royal London Hospital, Whitechapel Road, London E1 1BB, UK
(e-mail: j.prowle@qmul.ac.uk)

Inclusion

• 1862 Major surgical patients
• 1770 with post discharge information
Trajectory of serum creatinine in 1225 patients with post-operative length of stay of 5 or more days who survived to hospital discharge and a subgroup of 91 with post-operative AKI in the first 5 days after surgery. Median and IQR.
## Creatinine at Discharge

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Baseline eGFR</th>
<th>Discharge eGFR</th>
<th>P</th>
<th>Median Difference Discharge-Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AKI</td>
<td>1662</td>
<td>90.7 (74.3-103.2)</td>
<td>97.3 (83.4-110.6)</td>
<td>&lt;0.001</td>
<td>5.9 (0-13.6)</td>
</tr>
<tr>
<td>AKI</td>
<td>108</td>
<td>74.6 (51.7-95.8)</td>
<td>76.4 (50.4-98.7)</td>
<td>0.40</td>
<td>0.0 (-11.9-9.4)</td>
</tr>
<tr>
<td>P No AKI vs. AKI:</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Discharge:Baseline eGFR Ratio

P<0.001
For linear trend
# Creatinine at Follow-up

<table>
<thead>
<tr>
<th></th>
<th>No. with bloods at 181-365 days</th>
<th>Baseline eGFR</th>
<th>Discharge eGFR</th>
<th>Latest eGFR 181-365 days</th>
<th>Median Difference Latest-Discharge</th>
<th>Median Difference Latest-Baseline</th>
<th>P (Baseline vs. Latest)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No AKI</strong></td>
<td>625</td>
<td><strong>88.6</strong> (72.4-102.1)</td>
<td><strong>95.8</strong> (80.5-110.0)</td>
<td><strong>89.5</strong> (72.1-105.4)</td>
<td>-5.8 (-14.6-1.1)</td>
<td>0.44 (-6.9-7.4)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>AKI</strong></td>
<td>34</td>
<td><strong>71.6</strong> (60.8-97.6)</td>
<td><strong>77.5</strong> (54.0-97.8)</td>
<td><strong>67.7</strong> (45.3-92.7)</td>
<td>-6.5 (-13.0-7.3)</td>
<td>-3.9 (-15.5-2.8)</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>P No AKI vs. AKI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Major routes of Cr metabolism in the mammalian body.

Markus Wyss, and Rima Kaddurah-Daouk
Physiol Rev 2000;80:1107-1213
Acute Skeletal Muscle Wasting in Critical Illness

Figure 2. Measurements of Muscle Wasting During Critical Illness

A Change in rectus femoris (RF) cross-sectional area (CSA) over 10 d

B Measures of muscle wasting in patients assessed by all 3 measures on both day 1 and day 7 (n = 28)

Summary data (dark circles) are expressed as medians and 95% confidence intervals.

\[ P = .002 \text{ for change from day 1 to day 7 by repeated measures 2-way analysis of variance.} \]

\[ P < .001 \text{ for change from day 1 to day 10.} \]
Traumatic patients visited the Emergency Department (N=7128)

Traumatic patients admitted in the ICU (N=871)

Total study cohort (N=830)

Sub-group for CT analysis (N=81)

Excluded by:
- Creatinine ≥ 354 µmol/L: 4 patients
- Survival less than 24 hours: 37 patients
### Baseline Characteristics of the subgroup and the cohort

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Sub-group (n=81)</th>
<th>Cohort (n=830)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 (16-54)</td>
<td>42 (27-57)</td>
</tr>
<tr>
<td>Male Sex (%)</td>
<td>83.0</td>
<td>81.4</td>
</tr>
<tr>
<td>NISS</td>
<td>38 (27-50)</td>
<td>34 (24-50)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>12 (9-16)</td>
<td>12 (8-16)</td>
</tr>
</tbody>
</table>
L3 cross sectional area (CSA) - Image J
% Decrease in L3 CSA (A) / Psoas (B) vs. days between scans (log scale)
Creatinine data

![Creatinine data graph]

- % Change in area from baseline
- Days from admission

Legend:
- L4 Psoas Area
- L3 Total Area
- Creatinine
Creatinine

Days

Median Creatinine
Cystatin C

• In humans, all cells with a nucleus (cell core containing the DNA) produce cystatin C as a chain of 120 amino acids.
• Cystatin C has a low molecular weight (13.3 kDa), and it is removed from the bloodstream by glomerular filtration.
• Normally catabolised in PCT and does not appear in the urine.
• Cystatin C levels are less dependent on age, sex, race and muscle mass compared to creatinine.
Cystatin C versus Creatinine in Determining Risk Based on Kidney Function


A Death from Any Cause

CONCLUSIONS
The use of cystatin C alone or in combination with creatinine strengthens the association between the eGFR and the risks of death and end-stage renal disease across diverse populations. (Funded by the National Kidney Foundation and others.)
Cystatin C versus Creatinine in Predicting Risk of Death in the Year after ICU Discharge

Bo Ravn\textsuperscript{1}, John Prowle\textsuperscript{2}, Max Bell\textsuperscript{1} et al

\textsuperscript{1}Karolinska Hospital, Stockholm
\textsuperscript{2}Queen Mary University of London
- 3077 ICU admissions of ≥1 day
- Survived to ≥3 days after ICU discharge
- Discharge Creatinine and Cystatin-c measurements
- Excluded ESRD
- Complete survival data
ICU Discharge Creatinine and Cystatin-c as Renal Functional Assessments?

<table>
<thead>
<tr>
<th>ICU Discharge:</th>
<th>Creatinine</th>
<th>Cystatin-c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute value</td>
<td>0.83 mg/dl (0.63-1.20)</td>
<td>1.1 mg/L (0.80-1.63)</td>
</tr>
<tr>
<td>CKDepi eGFR (ml/min/1.73m²)</td>
<td><strong>91.7 (58-112)</strong></td>
<td><strong>67.7 (39-105)</strong></td>
</tr>
</tbody>
</table>

Median and IQR shown

3077 Patients – full survival long-term data in community
eGFR ratio by ICU LOS
Relative change in Median Cystatin-c and Creatinine over the first 7 days in ICU (5016 patients)

Error bars represent a binomial estimate of the 95% CI of the median. Patients who received RRT in ICU are excluded. Values are only included if both Cys-c and Creatinine values are available on that day. All patients had d1 and either a d6 or d7 Cys-c.
ICU days

Median % change from Day 1 value

-40 -30 -20 -10 0 10 20 30 40 50

Day1 Day2 Day3 Day4 Day5 Day6 Day7 Discharge

Cystatin c
Creatinine
CRP
Cystatin C, a marker for successful aging and glomerular filtration rate, is not influenced by inflammation.
Comparison of serum creatinine and serum cystatin C as biomarkers to detect sepsis-induced acute kidney injury and to predict mortality in CD-1 mice

Marked discrepancy between Renal Filtration Markers

- Which is the better test?
- Difficult to look at CKD as this is defined by the tests we are examining
- Rates of ESRD in the year after ICU discharge (excluding patients discharged on RRT) was low - only 9 patients.
- Examine post-ICU survival as most informative outcome
Unadjusted Kaplan-Meier plots for post ICU survival by quartiles of ICU discharge Creatinine or Cystatin-c
<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Post-ICU Survival by Quartile of Cystatin-c or Creatinine</th>
<th>Adjusted HR 75th relative to 25th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td><strong>Cystatin-c</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values (mg/L)</td>
<td>0.20-0.80</td>
<td>0.80-1.10</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>2.4%</td>
<td>5.9%</td>
</tr>
<tr>
<td>365-day mortality</td>
<td>5.4%</td>
<td>10.8%</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values (µmol/L)</td>
<td>9-56</td>
<td>56-73</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>8.3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>365-day mortality</td>
<td>13.6%</td>
<td>12.6%</td>
</tr>
</tbody>
</table>

*Adjusted analysis stratified for Age and Comorbidity Index*
Age and Sex adjusted Hazard Ratios for survival in the year after ICU discharge fitted with penalized spline regression for ICU discharge Cystatin-c and Creatinine (Cox-Model)

- Values plotted from the 5\(^{th}\) to 95\(^{th}\) centiles of the predictor variable
- Reference is 25\(^{th}\) centile value set to HR=1
- 25\(^{th}\), 50\(^{th}\) & 75\(^{th}\) centiles are marked with vertical lines
- Distribution of values within this range is marked above the x-axis
Cystatin is better than creatinine at predicting eGFR$_{Cr}$ at follow-up!
Including Cystatin-c and Creatinine together in one Cox-Proportional Hazard model.
### Evaluating Muscle Mass by Using Markers of Kidney Function: Development of the Sarcopenia Index

**Kashani et al CCM 2016**

DOI: 10.1097/CCM.0000000000002013

<table>
<thead>
<tr>
<th></th>
<th>eGFR&lt;sub&gt;Scr&lt;/sub&gt;</th>
<th>eGFR&lt;sub&gt;CysC&lt;/sub&gt;</th>
<th>Index</th>
<th>Correlation (r)</th>
<th>Coefficient of Determination (r²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTMSA</td>
<td></td>
<td>CTMSA</td>
</tr>
<tr>
<td>MDRD</td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Cockcroft and Gault (14)</td>
<td></td>
<td></td>
<td></td>
<td>-0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td></td>
<td></td>
<td></td>
<td>-0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Jelliffe and Jelliffe (15)</td>
<td></td>
<td></td>
<td></td>
<td>-0.24</td>
<td>0.006</td>
</tr>
<tr>
<td>MDRD</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
<td>0.13</td>
</tr>
<tr>
<td>Cockcroft and Gault (14)</td>
<td></td>
<td></td>
<td></td>
<td>-0.36</td>
<td>0.02</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
<td>0.08</td>
</tr>
<tr>
<td>Jelliffe and Jelliffe (15)</td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
<td>0.04</td>
</tr>
<tr>
<td>Scr/cystatin C × 100</td>
<td></td>
<td></td>
<td></td>
<td>0.62</td>
<td>0.27</td>
</tr>
<tr>
<td>Scr</td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Note:**

- **MDRD** = Modification of Diet in Renal Disease
- **CKD-EPI** = Chronic Kidney Disease Epidemiology Collaboration
- **CTMSA** = CT muscle surface area
- **eGFR<sub>Scr</sub>** = Estimated glomerular filtration rate based on serum creatinine
- **eGFR<sub>CysC</sub>** = Estimated glomerular filtration rate based on cystatin C

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**Nutrition Risk in the Critically Ill score**

- 76.7 × (cystatin C [CysC])<sup>-0.19</sup>
- 127.7 × (CysC)<sup>-0.17</sup> × age<sup>-0.13</sup> × (0.91 if female) × (1.06 if black).
Prognostic Importance of Low Admission Serum Creatinine Concentration for Mortality in Hospitalized Patients

Charat Thongprayoon, MD, a Wisit Cheungpasitporn, MD, a Wonngarm Kittanamongkolchai, MD, a Andrew M. Harrison, PhD, b Kianoush Kashani, MD a,b

aDivision of Nephrology and Hypertension, bDivision of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minn; cMayo Medical School, Mayo Clinic College of Medicine, Rochester, Minn.
Cystatin c for AKI diagnosis?

- Lack of baseline value
- It makes no sense to compare to a creatinine-defined ‘gold standard’
- Greater sensitivity for mild AKI may lead to worse association of a positive result with adverse outcomes
- -ve predictive value and accurate categorization of risk
Cystatin C is correlated with mortality in patients with and without acute kidney injury

Max Bell¹, Fredrik Granath², Johan Mårtensson¹, Erland Löfberg³, Anders Ekbom² and Claes-Roland Martling of KING (Karolinska Intensive care Nephrology Group)
Use of Both Serum Cystatin C and Creatinine as Diagnostic Criteria for Contrast-Induced Acute Kidney Injury and Its Clinical Implications

Wei-feng Zhang, MD;* Tuo Zhang, MD;* Ding Ding, MD; Shi-qun Sun, MD, Xiao-lei Wang, MD; Shi-chun Chu, MD; Ling-hong Shen, MD, PhD; Ben He, MD, PhD, FACC, FESC

Table 6. Predictors of MAEs at 12 Months Follow-Up by Multivariable Logistic Regression Analysis Using Firth’s Penalized-Likelihood Estimation

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl-AKI detected by a single marker</td>
<td>2.25 (1.24–4.10)</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Cl-AKI detected by both markers</td>
<td>10.00 (3.13–31.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>0.54 (0.19–1.49)</td>
<td>0.234</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.94 (0.43–2.07)</td>
<td>0.887</td>
</tr>
<tr>
<td>Prior or new-onset MI</td>
<td>2.26 (1.37–3.73)</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA Grade III–IV</td>
<td>0.77 (0.16–3.11)</td>
<td>0.709</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>1.00 (0.99–1.01)</td>
<td>0.909</td>
</tr>
<tr>
<td>Mehran risk score</td>
<td>1.03 (0.88–1.20)</td>
<td>0.730</td>
</tr>
</tbody>
</table>
Conclusions

- Critical illness is associated with significant and sustained decrease in serum creatinine.
- AKI is associated with relatively higher creatinine at hospital discharge.
- These effects can offset, potentially masking significant renal dysfunction in survivors of critical illness complicated by AKI.
- Serum creatinine-based methods of estimated GFR may not be applicable to survivors of critical illness.
- Cystatin c may be a useful alternative in this population but needs validation to measured GFR.
- In combination with other measures of GFR creatinine is a useful biomarker of muscle mass.
- AKI diagnosis is uncertain.