
37th Vicenza Course
on
AKI & CRRT
May 28-30, 2019

# Young People have Frail Kidneys Too

## 37th Vicenza Course on CRRT & AKI
## May 29, 2019

Dana Fuhrman DO, MS
Assistant Professor
Children's Hospital of Pittsburgh of UPMC
Department of Critical Care Medicine
Department of Pediatrics, Division of Nephrology

CENTER FOR CRITICAL CARE NEPHROLOGY

# Outline

- Discuss renal functional reserve as it relates to children and young adults
- Review the evidence for the potential use of urine biomarkers to predict kidney frailty in children and young adults

AJKD
Original Investigation

# Long-term Risk of CKD in Children Surviving Episodes of Acute Kidney Injury in the Intensive Care Unit: A Prospective Cohort Study

*Cherry Mammen, MD, MHSc[1], Abdullah Al Abbas, MD,[1] Peter Skippen, MD,[2] Helen Nadel, MD,[3] Daniel Levine, MD,[3] J.P. Collet, MD, PhD,[4] and Douglas G. Matsell, MD[1]*

**Table 2.** Summary of Results

| Outcome Variables | AKIN Stage 1 | AKIN Stage 2 | AKIN Stage 3 | Total[a] | *P*[b] |
|---|---|---|---|---|---|
| Microalbuminuria or proteinuria[c] | 2 (4.5) | 5 (10.6) | 5 (14.3) | 12 (9.5) | 0.3 |
| GFR <60 mL/min/1.73 m$^2$[c] | 0 (0) | 0 (0) | 1 (2.9) | 1 (0.8) | 0.3 |
| GFR = 60-90 mL/min/1.73 m$^2$ | 24 (54.5) | 14 (29.8) | 10 (28.6) | 48 (38.1) | 0.02 |
| Hypertension | 0 (0) | 3 (6.4) | 1 (2.9) | 4 (3.2) | 0.2 |
| Hyperfiltration | 1 (2.3) | 6 (12.8) | 4 (11.4) | 11 (8.7) | 0.2 |

*Note:* Categorical variables given as number (percentage).

Abbreviations: AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; GFR, glomerular filtration rate.

[a]Number of patients identified with CKD, 13 of 126 (10.3%); number of patients at risk of CKD, 59 of 126 (46.8%).

[b]Comparing proportion of patients with the outcomes among the 3 AKIN stages.

[c]Constitute criteria for CKD (remaining criteria indicate those "at risk of CKD").

JAMA Pediatrics | Original Investigation

# Kidney Outcomes 5 Years After Pediatric Cardiac Surgery
# The TRIBE-AKI Study

Jason H. Greenberg, MD, MHS; Michael Zappitelli, MD, MSc; Prasad Devarajan, MD; Heather R. Thiessen-Philbrook, MMath; Catherine Krawczeski, MD; Simon Li, MD, MPH; Amit X. Garg, MD; Steve Coca, DO, MS; Chirag R. Parikh, MD, PhD; for the TRIBE-AKI Consortium

- Prospective multicenter cohort study including 131 children (median age [IQR]=7.7 [5.9-9.9] years)
- Determine if perioperative AKI is associated with worse long-term kidney outcomes 5 years later
- 44% had postoperative AKI
- CKD (18%) and hypertension (17%) were common
- Perioperative AKI was not associated with hypertension, microalbuminuria, and CKD??

Pediatr Nephrol (2007) 22:1903–1909
DOI 10.1007/s00467-007-0502-6

ORIGINAL ARTICLE

# Renal hemodynamic changes and renal functional reserve in children with type I diabetes mellitus

Ann Raes · Raymond Donckerwolcke · Margarita Craen · Maraina Che Hussein · Johan Vande Walle

**Table 3** The effect of low-dose dopamine on change (Δ) in glomerular filtration rate (GFR), renal plasma flow (RPF), and filtration factor (FF) in type 1 diabetes mellitus (DM) patients and the control population in absolute values and in percentage (%)

| | DM | Control |
|---|---|---|
| Δ GFR ml/min per 1.73 $m^2$ (RFR) | −0.77±23.2 | 21±8[a] |
| Δ GFR, % | 0.35±18.3 | 18±8[a] |
| Δ RPF, ml/min per 1.73 $m^2$ | 37.6±103.1 | 188±61[a] |
| Δ RPF, % | 10.0±22.2 | 33±12[a] |
| Δ FF | −2.9±5.8 | −2±1[a] |
| Δ FF, % | −7.6±16.9 | −11±5[a] |

[a] $p<0.05$: significance level for differences between control and diabetic population

Pediatr Nephrol (2004) 19:1132–1136
DOI 10.1007/s00467-004-1550-9

ORIGINAL ARTICLE

Stanley Hellerstein · Max Berenbom · Pat Erwin ·
Nancy Wilson · Sylvia DiMaggio

# Measurement of renal functional reserve in children

**Table 3** Changes in [Cr]s, GFR, and Cr-exc-rate following stimulation with a protein meal

| Group | Baseline [Cr]s (mg/dl) | Baseline GFR (ml/min per 1.73 $m^2$) | d [Cr]s (mg/dl) | d GFR (mg/min per 1.73 $m^2$) | % d GFR (%) | d Cr-exc-rate (mg/kg per 24 h) | % d Cr-exc-rate (%) |
|---|---|---|---|---|---|---|---|
| All $n$=89 | 1.16±0.52 | 72.6±21.6 | −0.04±0.06 | 16.3±14.0 | 21.4±16.6 | 3.02±2.61 | 17.3±13.8 |
| % d GFR ≥20% $n$=41 | 1.02±0.28 | 76.7±17.9 | −0.06±0.06 | 27.1±13.1 | 34.9±13.1 | 4.7±2.5 | 26.5±12.6 |
| % GFR 10–20% $n$=25 | 1.23±0.64 | 71.4±23.1 | −0.02±0.07 | 11.4±4.5 | 15.8±2.9 | 2.7±1.3 | 15.1±6.9 |
| % GFR ≤10% $n$=23 | 1.33±0.65 | 66.5±25.1 | −0.03±0.06 | 2.6±3.9 | 3.3±5.6 | 0.4±1.5 | 3.3±6.9 |

# The Assessment of Renal Function Reserve by Cystatin C

- Establish a valid, reliable, rapid, and easily replicated measure of renal function reserve in young adults

- Cystatin C
  - Freely filtered by the kidneys and produced at a relatively constant rate
  - Independent of muscle mass, sex, body composition, and inflammatory conditions
  - Short half life
  - Does not require timed urine collections

- Study objective: Determine if there is a significant change in cystatin C-based GFR measured before and after a protein load

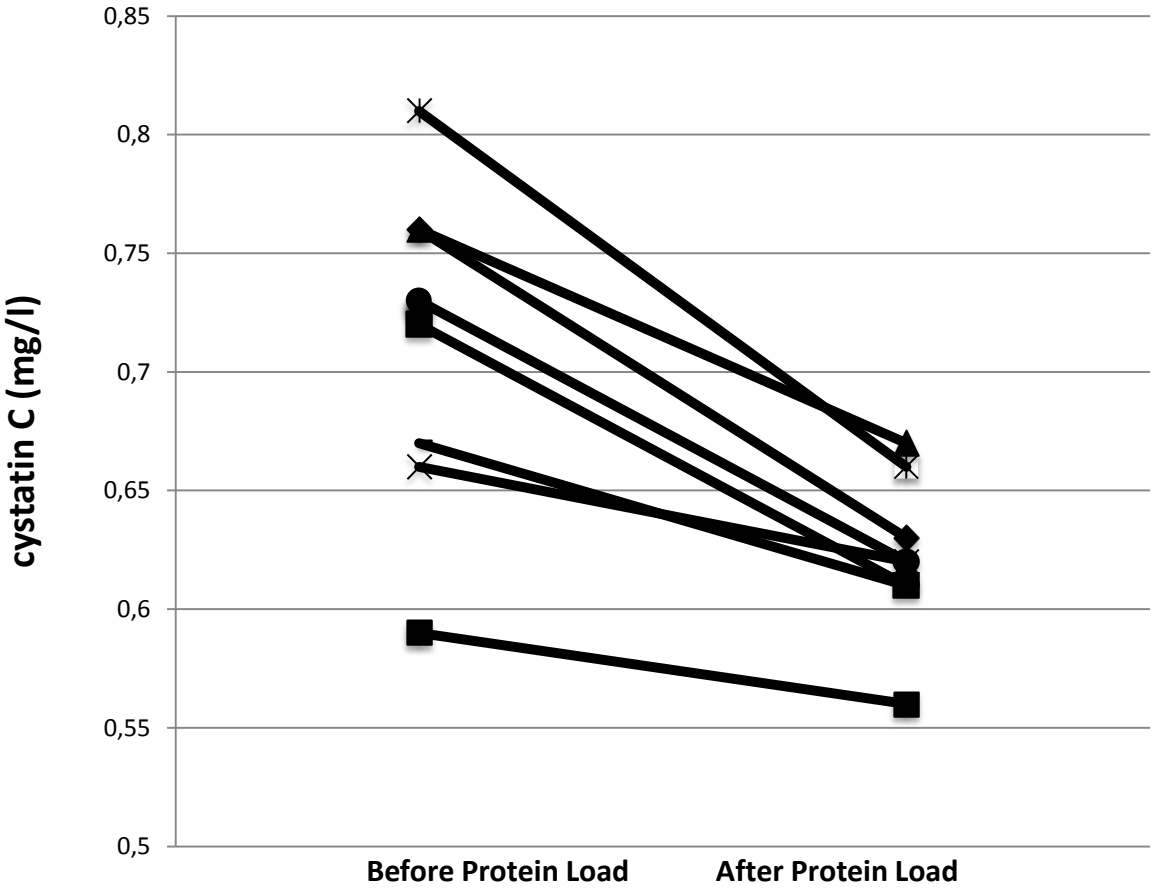
# The Assessment of Renal Functional Reserve by Cystatin C : Methods

- Eight subjects 19-25 years of age with no history of kidney disease, hypertension, or prematurity
- Iohexol levels were measured 120, 180, and 240 minutes after administration of iohexol
- Measured cystatin C at baseline and then 125-141 minutes after eating a beef burger containing 60 grams of protein

# The Assessment of Renal Functional Reserve by Cystatin C : Results

- The mean baseline iohexol based GFR of 100 +/- 10.8 ml/min/1.73m$^2$
- The mean baseline cystatin C-based GFR was 99.1 +/- 8.8 ml/min/1.73 m$^2$
- The mean change in cystatin C-based GFR was 12.0 +/- 4.9 ml/min/1.73 m$^2$

# Cystatin C Concentrations Before and After a Protein Load





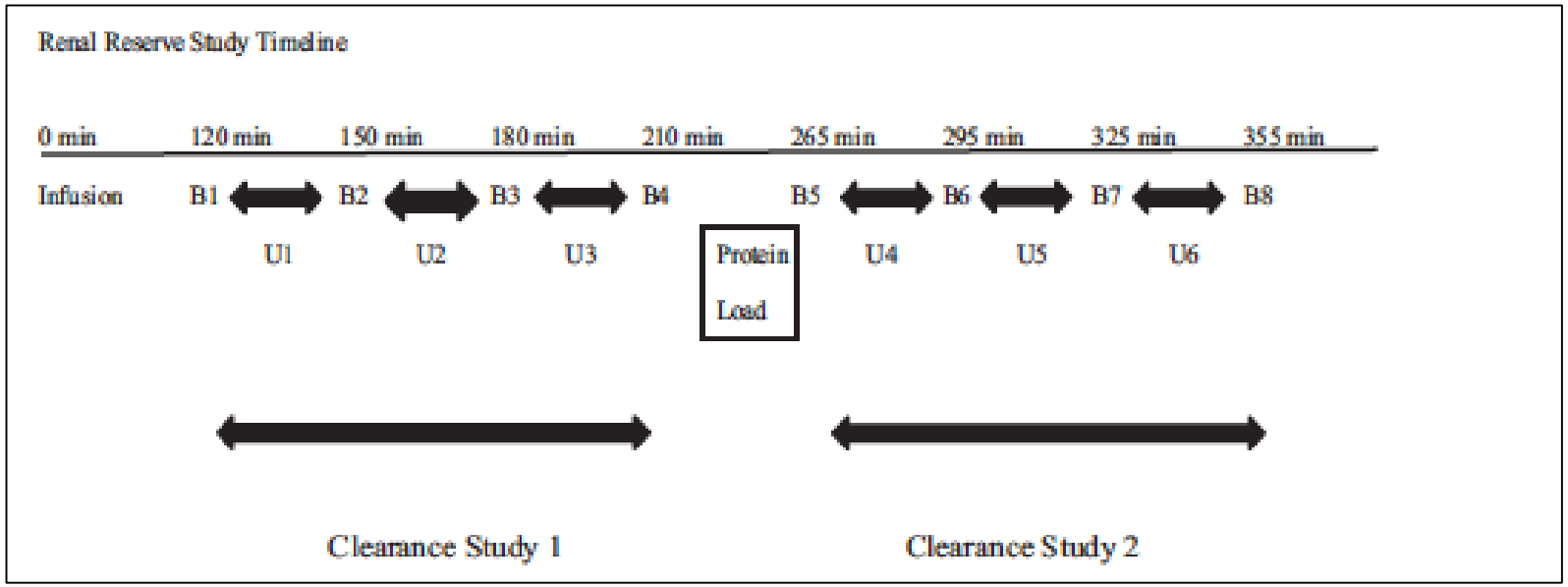

Fuhrman , et al. *ScandJClinLabInvest* 2013

# Subsequent Study

- Further discern if cystatin C estimated GFR before and after a protein load can be easily used in a clinical setting to measure renal functional reserve
- Determine if the type of protein load (animal vs liquid whey based) makes a difference
- Recruited an additional 16 subjects

# Methods for Measuring GFR

- Urinary clearance of creatinine within 48 hours of cimetidine pre-treatment
- Infusion clearance of iohexol
- Estimated GFR by cystatin C






Rodenbach, et al. *JRenNut* 2017

**Table 2.** GFR and Renal Reserve Values by Protein Type and GFR Method

| GFR Method | | | |
|---|---|---|---|
| Burger Group ($N = 8$) | Cimetidine-inhibited Cr Cl | Iohexol Infusion Cl | Cystatin-C eGFR |
| Mean preload | 106.9 ± 13.1 | 98.2 ± 6.8 | 117.7 ± 7.3 |
| Mean postload | 124.0 ± 13.1 | 105.4 ± 8.9 | 122.6 ± 9.2 |
| Mean RR* | 16.6 ± 12.3 | 7.2 ± 3.7 | 4.9 ± 2.6 |
| *P* value† | **.006** | **.0009** | **.001** |
| Mean peak RR | 29.4 ± 11.1 | 9.4 ± 4.6 | 10.3 ± 6.5 |
| *P* value† | **.0001** | **.0007** | **.003** |
| Shake Group ($N = 8$) | Cimetidine-inhibited Cr Cl | Iohexol infusion Cl | Cystatin-C eGFR |
| Mean preload | 99.1 ± 17.7 | 91.5 ± 7.9 | 116.4 ± 4.7 |
| Mean postload | 114.9 ± 21.2 | 101.6 ± 14.7 | 118.7 ± 5.3 |
| Mean RR* | 15.8 ± 5.8 | 10.1 ± 7.8 | 2.4 ± 2.9 |
| *P* value† | **.0001** | **.008** | **.05** |
| Mean peak RR | 26.0 ± 8.4 | 13.9 ± 8.8 | 4.5 ± 3.7 |
| *P* value† | **.0001** | **.003** | **.01** |

Cl, clearance; Cr, creatinine; eGFR, estimated GFR; GFR, glomerular filtration rate; RR = renal reserve.

*Renal reserve = post to pre GFR; preload, postload, and RR clearance values appear as mean ± standard deviation. All GFRs expressed as mL/minute/1.73 $m^2$.

†Statistically significant 2-tailed *P*-values for renal reserve for each method compared to zero at $P < .05$ level appear in bold.



Rodenbach, et al. *JRenNut* 2017

# Future Directions

- Determine if serum cystatin C adequately measures glomerular reserve in comparison to the kidney stress test used by Husain-Syed and colleagues

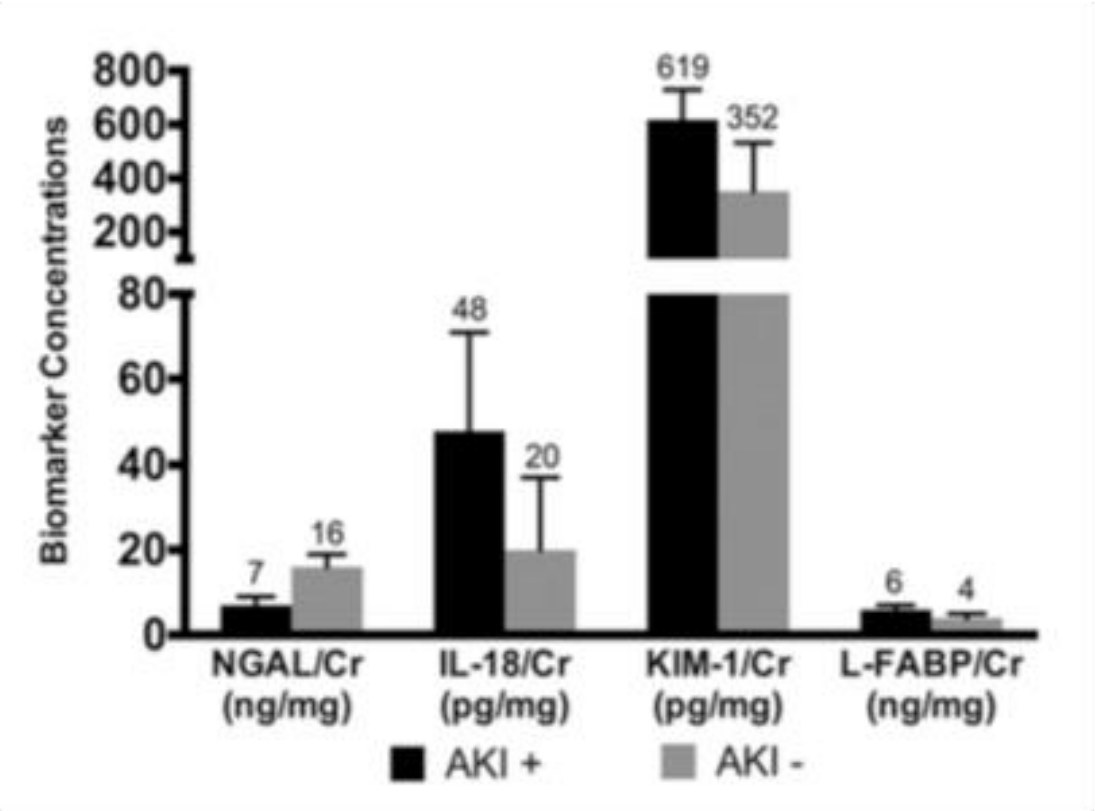
- Establish the association of renal functional reserve and AKI as well as the development of CKD in young adult patients with congenital heart disease

# Novel Urinary Biomarkers and Kidney Frailty

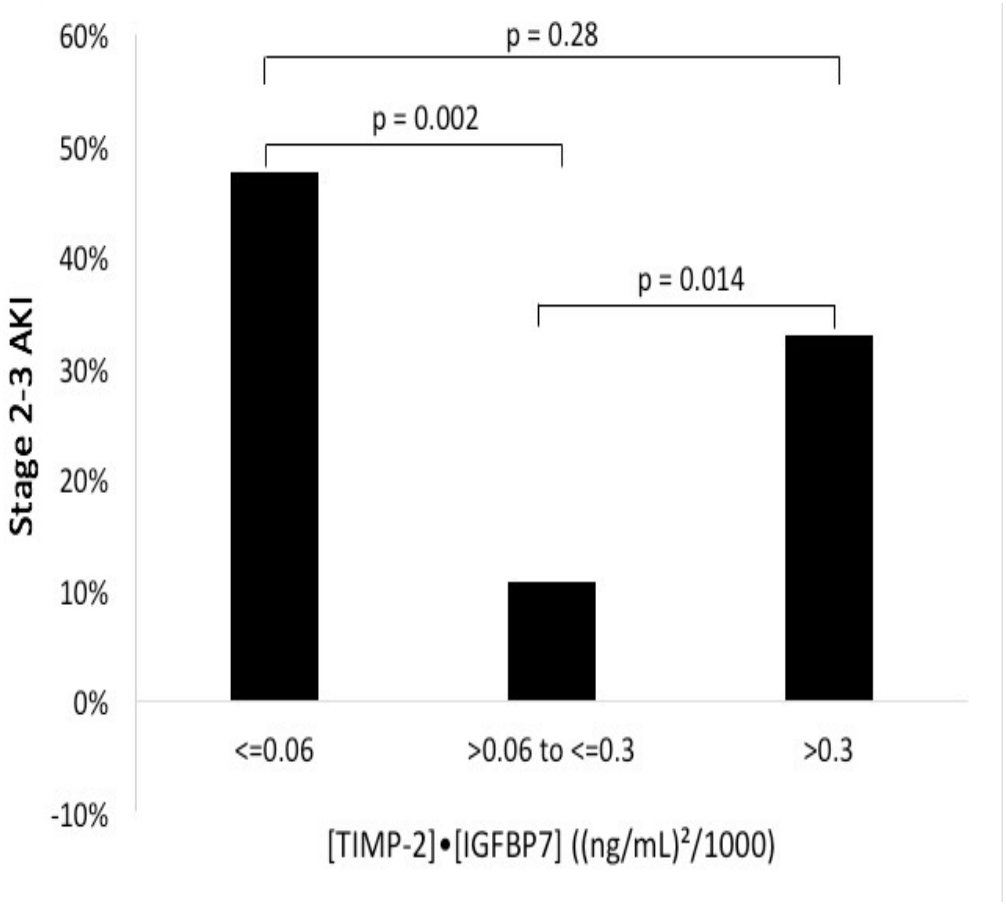
# Follow-Up Renal Assessment of Injury Long-Term After Acute Kidney Injury (FRAIL-AKI)

*David S. Cooper,[*†] Donna Claes,[†] Stuart L. Goldstein,[*†] Michael R. Bennett,[†] Qing Ma,[†] Prasad Devarajan,[†] and Catherine D. Krawczeski[*†]*

**Abstract**

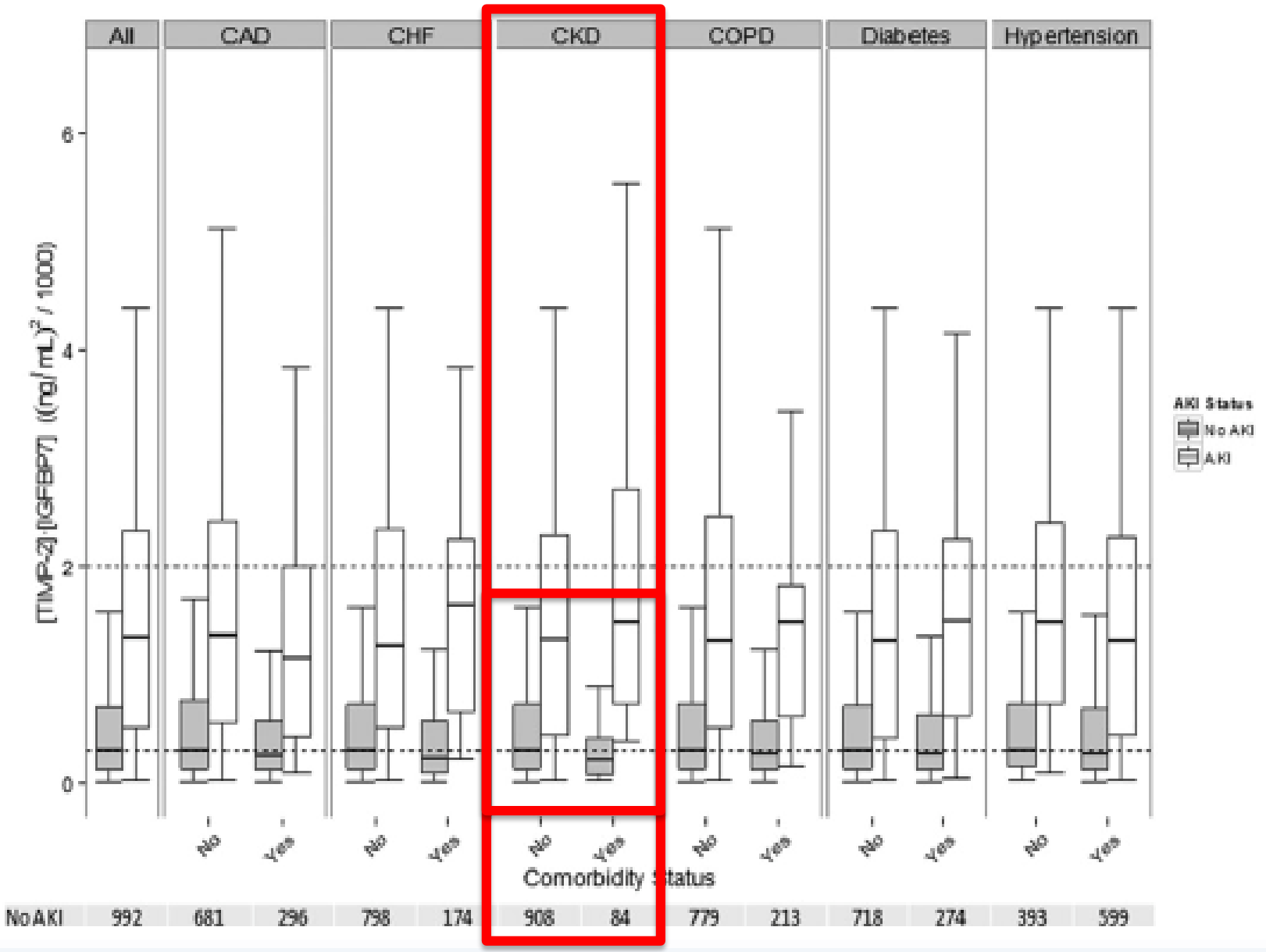


# Cell Arrest Biomarkers and Kidney Frailty






Zarbock, et al. *JAMA* 2015






Heung et al. *NDT* 2016

# Baseline Tubular Biomarkers in Young Adults with Congenital Heart Disease

- Controls:
  - Individuals 18-35 years of age from the University of Pittsburgh campus
  - Excluded if a history of heart or kidney disease
- Cases:
  - Patients 18-35 years of age presenting for follow-up to the Children's Hospital of Pittsburgh Adult Congenital Heart Disease Center
  - Excluded if:
    - Creatinine obtained in the past year was greater than 1.1 mg/dl in females and greater than 1.3 mg/dl in males
    - History of dialysis or kidney transplant
- Recruited 30 control and 30 case participants

# Results

**Table 1: Characteristics of Patients with CHD (n=30)**

| Characteristic | Median (inter-quartile range) or n (%) |
|---|---|
| Age (years) | 28 (26-31) |
| Male Sex | 20 (66.7) |
| Normal Blood Pressure* | 12 (40.0) |
| Elevated Blood Pressure* | 18 (60.0) |
| BMI ($kg/m^2$) | 20.2 (18.3-21.4) |
| Serum Creatinine (mg/dL) | 0.9 (0.8-1.0) |
| Ejection Fraction (%) | 56.7 (49.0-62.0) |

*Based on the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

# Results

**Table 2: Type of Congenital Heart Disease (n=30)**

| Diagnosis | n (%) |
|---|---|
| D-transposition of the great arteries | 7 (23.3) |
| Tetralolgy of Fallot | 4 (13.3) |
| Bicuspid aortic valve | 4 (13.3) |
| Pulmonary valve stenosis | 3 (10.0) |
| Coarctation of the aorta | 3 (10.0) |
| Double outlet left ventricle | 2 (6.7) |
| Aortic stenosis | 1 (3.3) |
| Complete atrioventricular septal defect | 1 (3.3) |
| Dilated aortic root | 1 (3.3) |
| Double outlet left ventricle | 1 (3.3) |
| Hypoplastic right ventricle | 1 (3.3) |
| Pulmonary Atresia | 1 (3.3) |
| Ventricular septal defect | 1 (3.3) |

# Results

**Table 4: Tubular Biomarkers when Comparing Subject Groups (n=60)**

| Tubular Biomarker | Healthy Young Adults[a] (n=30) | Young Adults with CHD[a] (n=30) | p-value |
|---|---|---|---|
| Alpha 1-microglobin/Cr (mg/g) | 11.49 (5.64-23.20) | 13.53 (6.93-21.93) | 0.80 |
| Beta 2- microglobin/Cr (ug/g) | 67.24 (44.33-148.03) | 74.77 (56.02-127.83) | 0.69 |
| KIM-1/Cr (pg/mg) | **332.77 (206.85-608.00)** | **576.50 (351.71-996.52)** | **0.01** |
| L-FABP/Cr (ng/mg) | 2.53 (1.44-4.81) | 2.49 (1.70-5.11) | 0.720 |
| N-acetyl-B-D-glucosaminidase/Cr (IU/g) | 9.54 (6.88-20.33) | 13.93 (8.70-23.03) | 0.16 |
| TIMP-2 (ng/mL) | **3.70 (2.85-5.23)** | **2.50 (2.00-3.94)** | **0.009** |
| IGFBP7 (ng/mL) | **69.75 (43.58-93.55)** | **33.50 (23.88-55.38)** | **0.001** |
| AKI Risk Score [(TIMP2 * IGFBP7)/1000] | **0.28 (0.14-0.44)** | **0.10 (0.05-0.19)** | **0.0004** |

[a] Median (inter-quartile range)

AKI, Acute Kidney Injury; Cr, Creatinine; IGFBP, Insulin-Like Growth Factor Binding Protein; KIM, Kidney Injury Molecule; L-FABP, Liver Fatty Acid-Binding Protein; TIMP, Tissue Injury Metalloproteinase

# Conclusions

- There is a need for an easily replicated standard method for quantifying renal functional reserve in children and young adults.
- There is a need for further investigation on the use of tubular biomarkers to prognosticate silent renal disease in high risk pediatric and young adult groups.

# Acknowledgments


**Mentors**

- John Kellum, MD
- Carlton Bates, MD
- Douglas Landsittel, PhD
- George Schwartz, MD

**Center for Critical Care Nephrology & The CRISMA Lab**

- Faye Cotton
- Michele Elder
- Vanessa Jackson
- Priyanka Priyanka, MPH
- Ali Smith

**CHP Adult Center for Congenital Heart Disease**

- Lan Nguyen, MD
- Morgan Hindes