Diagnosis Of Acute Kidney Injury

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Introduction

- AKI incidence varies from 1 to 7% of all hospitalized patients to 30–50% of intensive care unit (ICU) patients, with a high AKI mortality rate (50%).
- Significant proportion of surviving AKI patients (20–50%) later develop chronic kidney disease (CKD), end-stage renal disease (5%).
- Early identification is crucial for its prompt treatment and a better prognosis.

Acute Kidney Injury Definition

- The **KDIGO guidelines** define AKI as follows :
- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours, or
- Increase in serum creatinine **to ≥1.5 times baseline**, which is known or presumed to have occurred within the prior seven days, or
- Urine volume <**0.5 mL/kg/hour** for six hours

Source of Creatinine Error in GFR Estimation

- **Generation** :Race/ ethnicity, Muscle mass, Body size ,

Diet and nutritional status, High protein diet, supplements,

Muscle wasting diseases , Ingestion of cooked meat

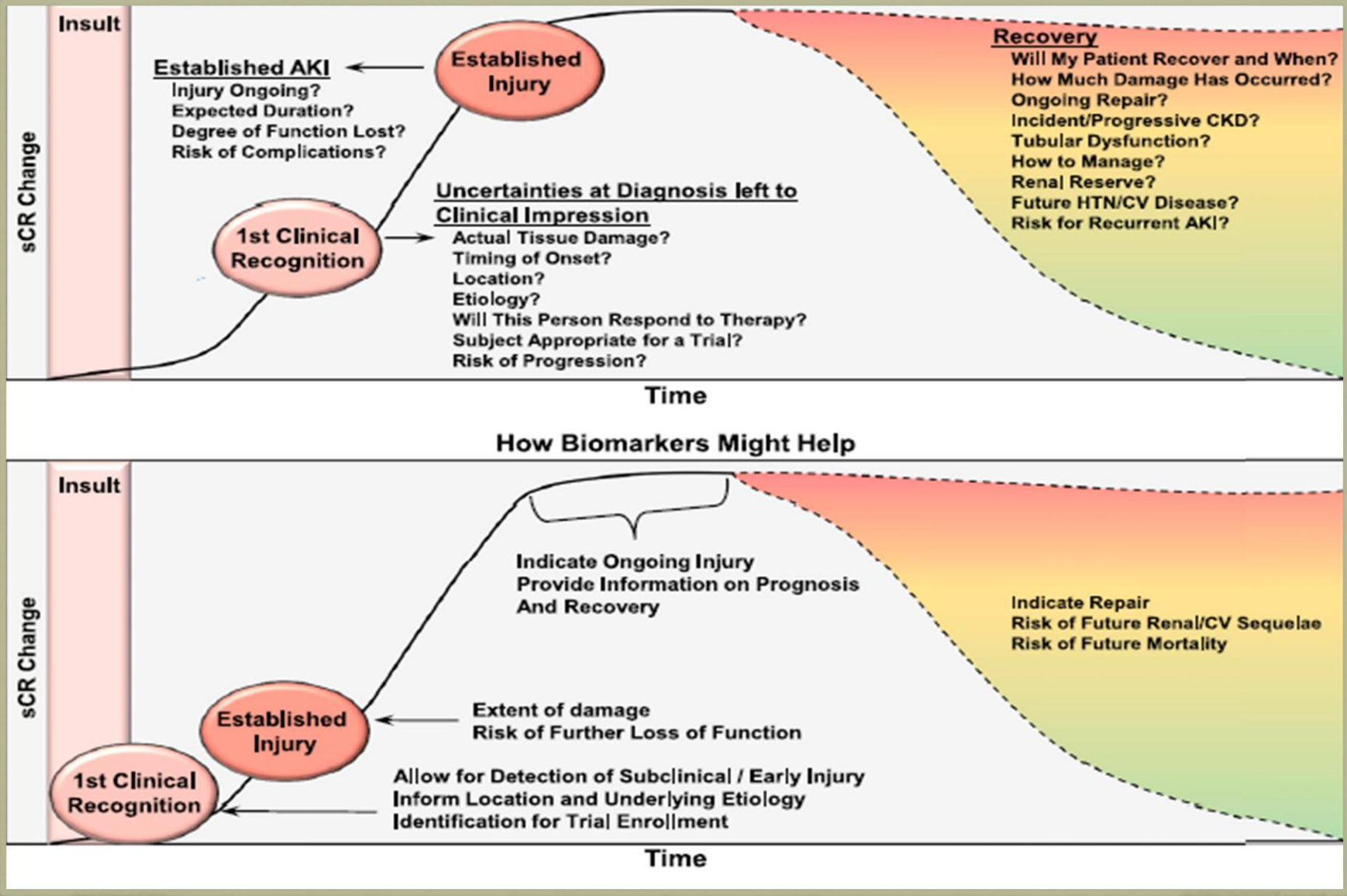
- **Tubular secretion** :Trimethoprim, Cimetidine

,Fenofibrate

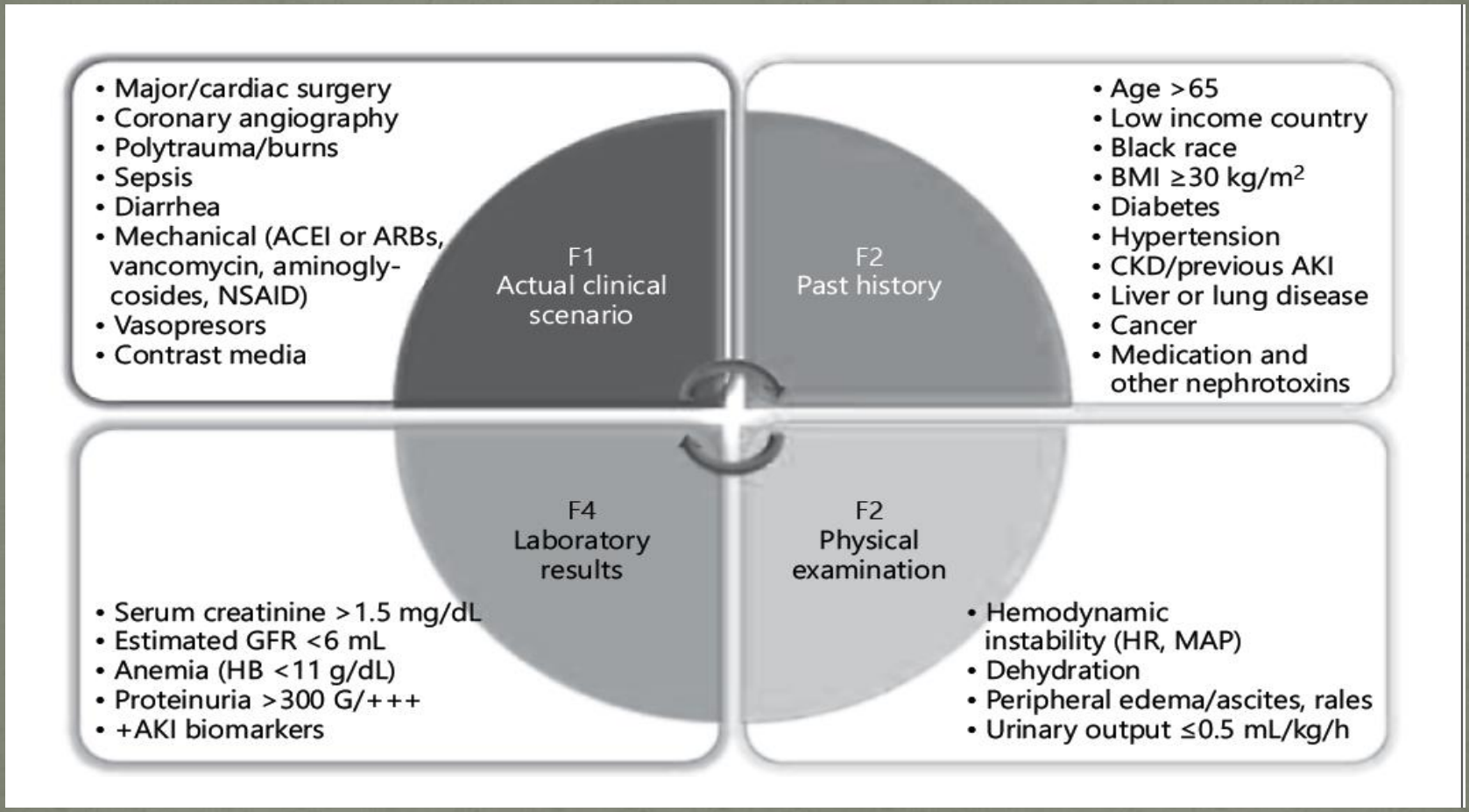
- **Extra renal elimination** :Bacterial overgrowth and

advanced kidney failure

Current Paradigm For AKI Evaluation & Knowledge Gaps

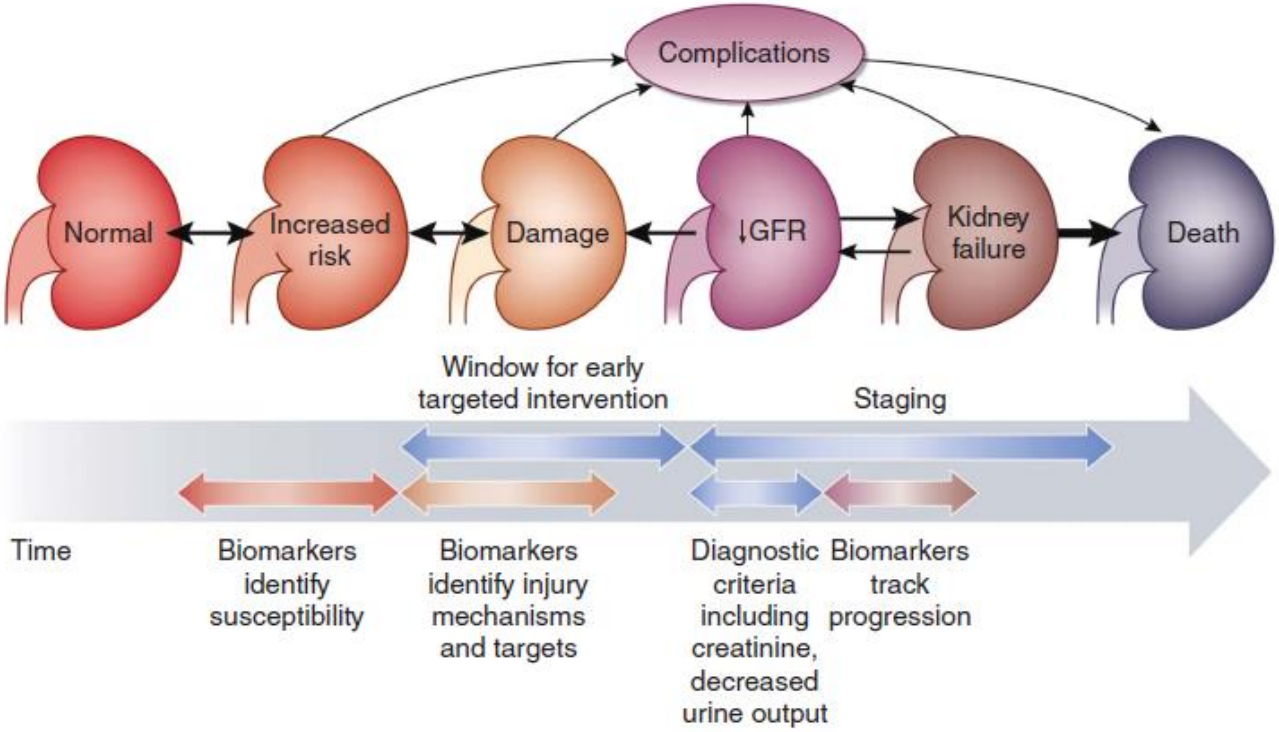


Composition Of The Acute Kidney Injury Risk Assessment

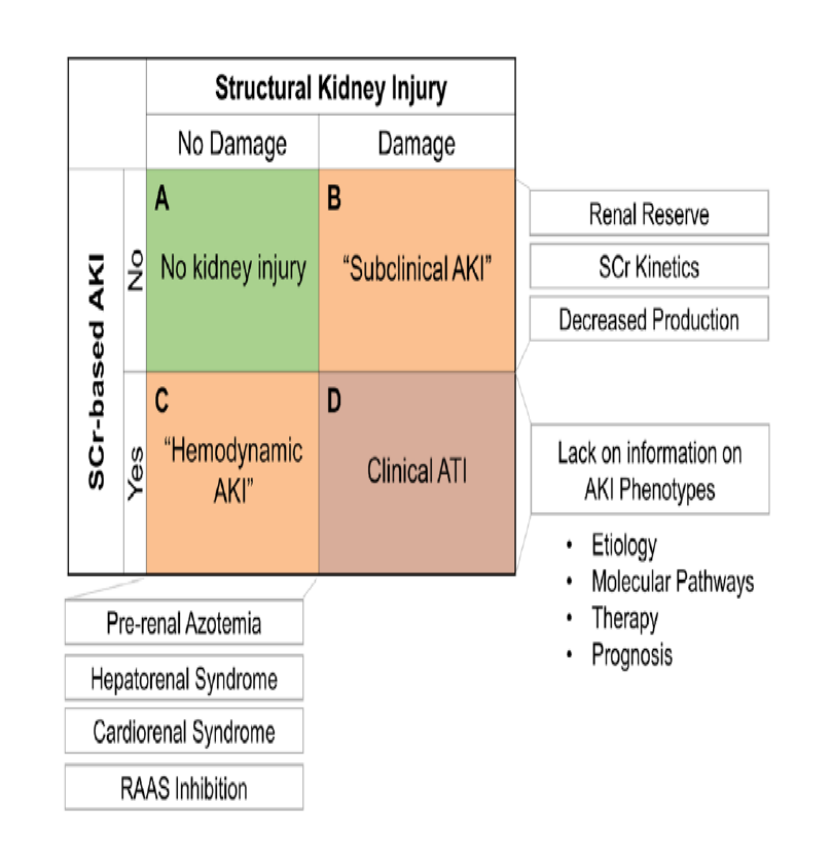


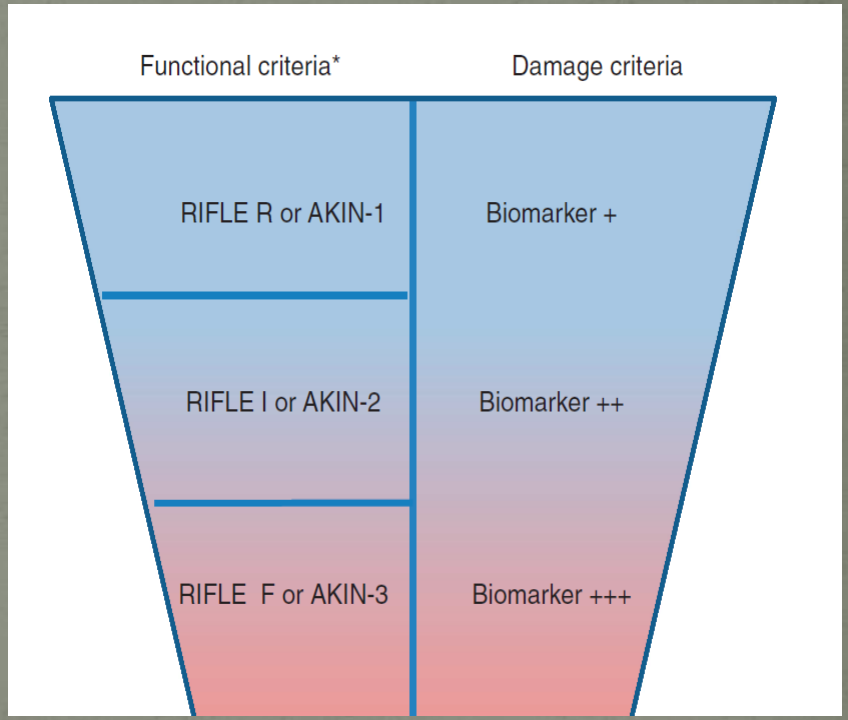
Jiang et al , 2018 Basic Research and Clinical Practice

Potential Utilization Of Biomarkers For Acute Kidney Injury (AKI)



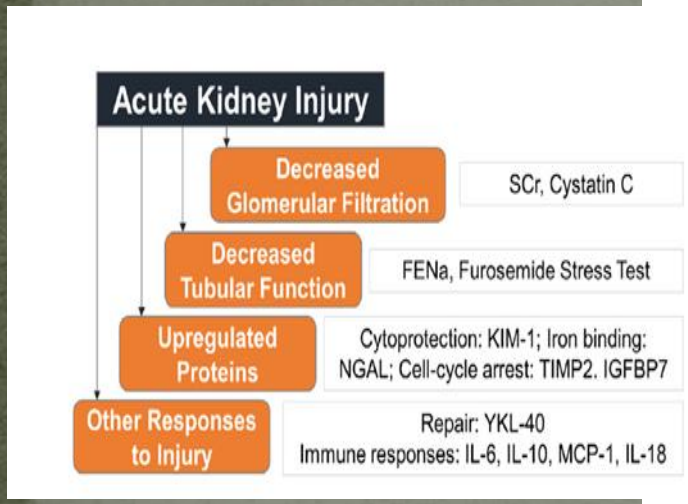
Proposed framework and criteria for acute kidney injury

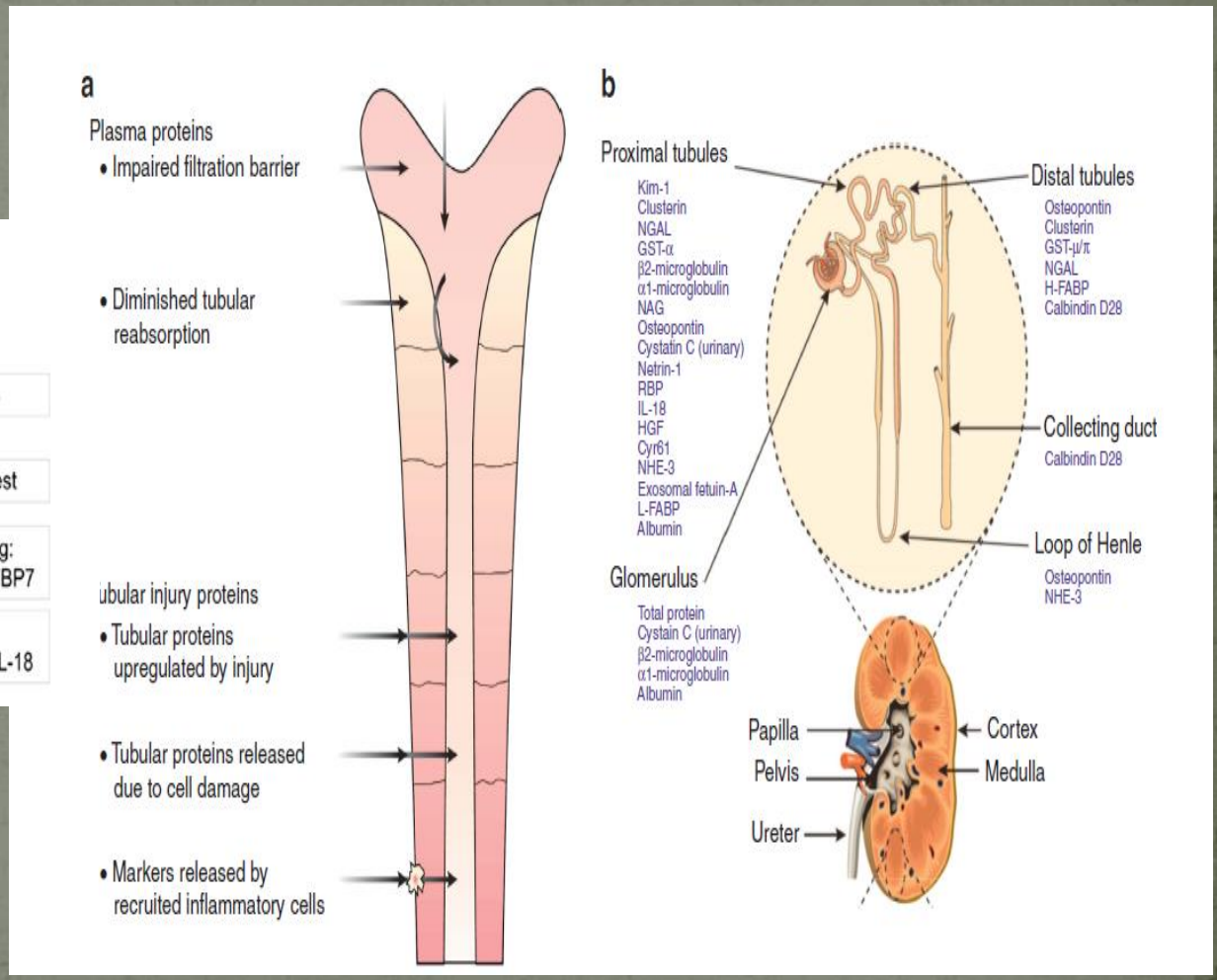




Murray et al kidney international 2014
Melodina et al seminar Nephrology 2017

Potential Mechanisms And Specificity Of Urinary Biomarkers Of Kidney Damage





Cystatin C

- Low-molecular-weight protein that is a member of the cystatin superfamily of cysteine protease inhibitors.
- Cystatin C is filtered at the glomerulus and not reabsorbed but metabolized in the tubules
- Increase in Cystatin C levels : male gender, greater height and weight, higher lean body mass fat mass, diabetes, markers of inflammation (eg, C-reactive protein), and hyper- and hypothyroidism , age
- Variation in Cystatin C assay

Neutrophil Gelatinase –Associated Lipocalcin (NGAL)

- 25KD family of lipocalcins .Normaly bind iron-siderophore complex and has bacteriostatic effect.
- It is upregulated in kidney after ischemic, toxic and septic insults
- Primary sites in kidney are thick ascending limb loop of Henle and intercalated cells .
- NGAL increase 3 hrs after injury and peak level after 6-12 hrs .
- Serum and urine NGAL increase based on severity of acute insult

Author	Year	AUCs AKI prediction	Settings (sample collections)
Singer et al	KI ,2011	0.87	All hospitalized patients
Nickolas et al	J Am Coll Cardiol, 2012	0.81	Emergency department
Nickolas et al	Ann Intern Med 2008	0.95	Emergency department
Dent et al	Critical Care 2007	0.96	Pediatric cardiac surgery
HO j et al	AJKD 2015	0.72	Cardiac surgery in adults
De Geus et	Am J crit care Med 2011	0.80	ICU
Moyake	J Am Coll Cardiol, 2006	0.61	**Preeclamptic women**

There is no cut – off value for diagnosis yet.

Kidney Injury Molecule (KIM-1)

- 38.7 –kDA type 1 transmemrane glycoprotein with an extracellular immunoglobin –like domain topping on a long mucin like domain .
- A marker of proliferation and regeneration in proximal tubules, mediates phagocytosis of apoptic cells .
- FDA approved AKI biomarker for preclinical drug development and can be assessed in 15 minutes.

Kidney Int. 2014 February ; 85(2): 431–438. doi:10.1038/ki.2013.333.

Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery

John M. Arthur, MD, PhD[1,2], Elizabeth G. Hill, PhD[3], Joseph L. Alge[2], Evelyn C. Lewis, MD[2],

- They measured the concentration of 32 candidate biomarkers in the urine of 95 patients with AKIN stage 1 after cardiac surgery.
- The combination of IL-18 and KIM-1 had a very good predictive value with an AUC of 0.93 to predict AKIN 3 or death.
- Thus, combination of IL-18 and KIM-1 would result in improved identification of high risk patients.

Interleukin 18

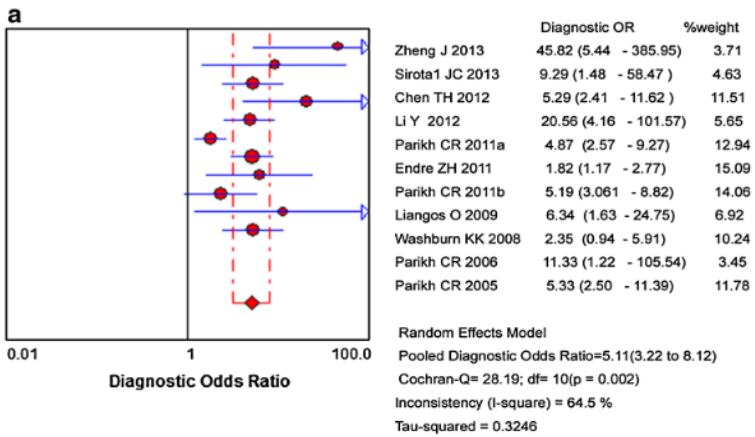
- IL-18 24 KD cytokine from IL-1 family of cytokines.
- In kidney synthesized by proximal tubular epithelial cells, intercalated cells of collecting ducts
- Proinflammatory effect by signal transduction through IL-18 Rec
- Level rises 6 hours after injury ,24-48 hours before AKI and peaks at 12 hours later

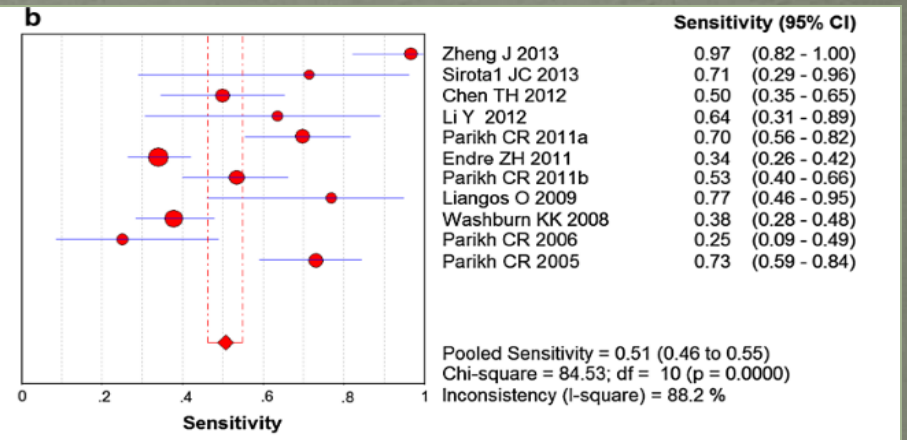
J Nephrol (2015) 28:7–16
DOI 10.1007/s40620-014-0113-9

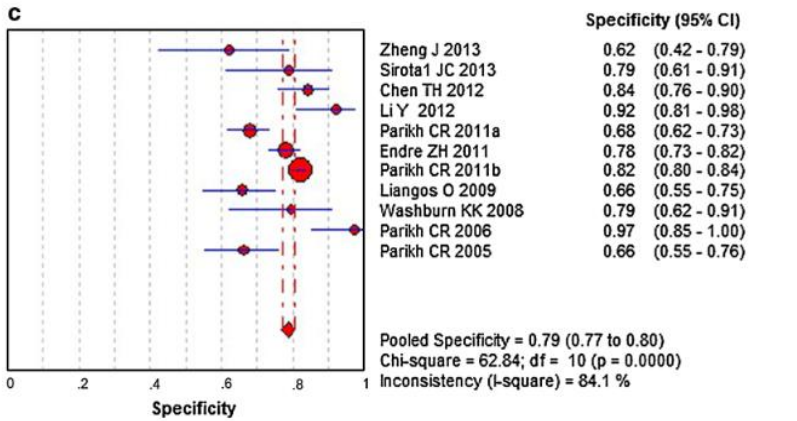
REVIEW

Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis

Xin Lin · Jing Yuan · Yingting Zhao · Yan Zha



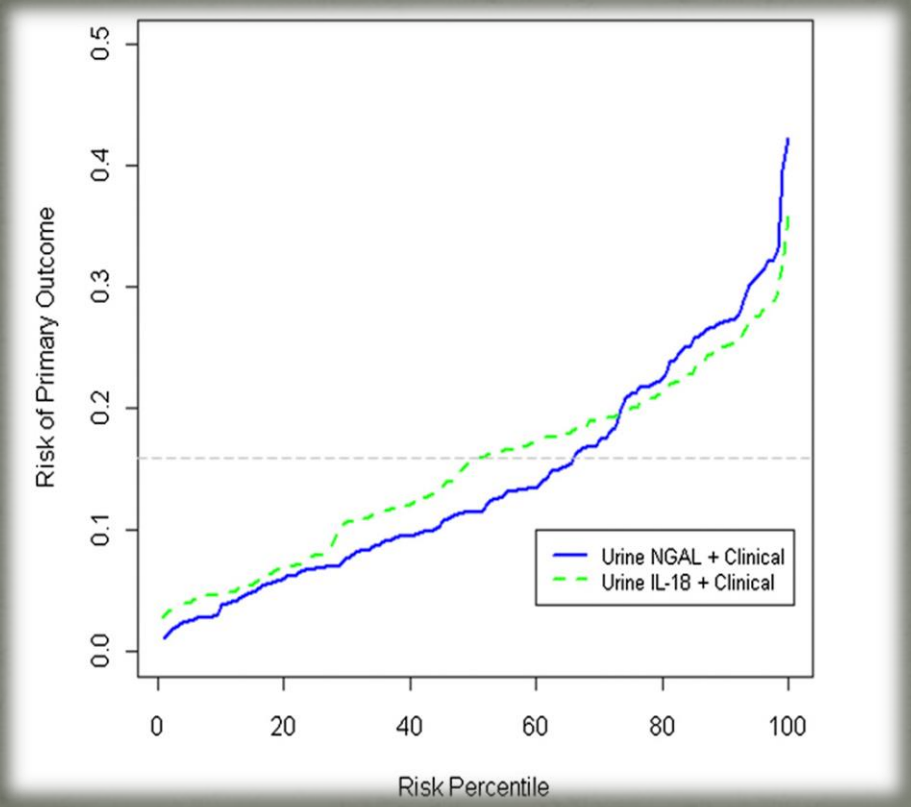


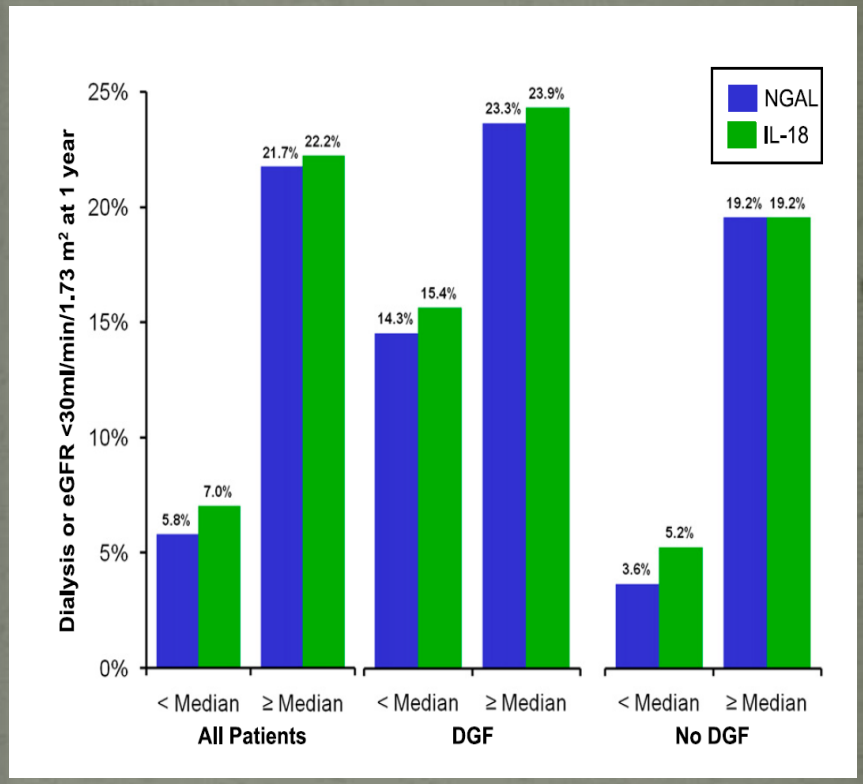


11 studies of 3 countries covering 2,796 patients

Conclusion: Urine IL-18 holds promise as a biomarker in the prediction of AKI but has only moderate diagnostic value.

Association between Peritransplant Kidney Injury Biomarkers and 1-Year Allograft Outcomes





Predictor Levels	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Urine NGAL		
first POD (continuous; per log unit increase)	1.52 (1.05–2.20)	1.61 (1.04–2.50)
first POD > median (422 ng/ml)	4.5 (1.4–14.4)	6.0 (1.5–24.0)
Urine IL-18		
first POD (continuous; per log unit increase)	1.24 (0.98–2.28)	1.26 (0.74–2.14)
first POD > median (137 pg/ml)	3.8 (1.3–10.9)	5.5 (1.4–21.5)

Hall et al CJASN 2012

Liver-Type fatty acid – binding protein

- L- FABP is 14 Kda protein from lipid binding proteins and is carrier of fatty acid .
- They transport fatty acid to mitochondria and have a cell protective role by mitigating H_2O_2 induced oxidative stress .
- In kidney they are located in proximal tubule and excreted in lumen.
- UL-FABP a promising biomarker for diagnosis and prediction of AKI

nephron Clinical Practice

Clinical Practice: Original Paper

Nephron
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Received
Accepted
Published

Modest Impact of Serial Measurements of Acute Kidney Injury Biomarkers in an Adult Intensive Care Unit

Rei Isshiki[a] Toshifumi Asada[b] Maki Sumida[a] Yoshifumi Hamasaki[a]

- 272 patients, 33 were determined to show newly developed AKI after ICU admission, 58 showed worsening of AKI, 57 recovered from AKI, and 38 died in the hospital.
- This study indicates that serial measurements of biomarkers (NGAL, L-FABP, and NAG) may provide additive information for predicting AKI outcomes even in a heterogeneous cohort of adult mixed ICU patients

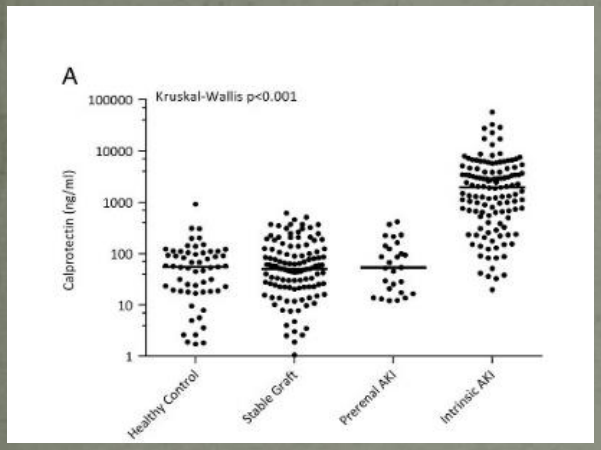
Calprotectin

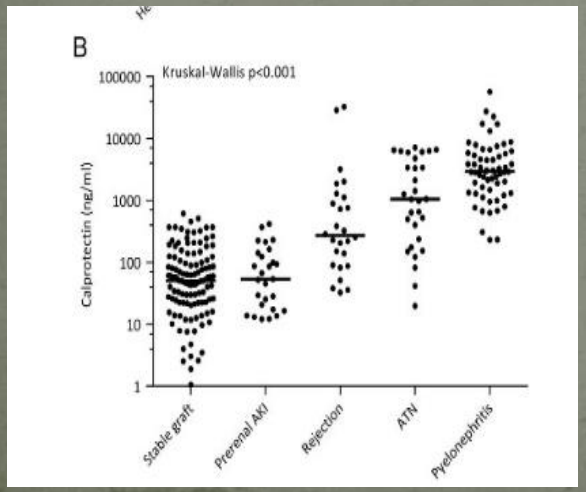
- A 24-Kda heterodimer composed of two monomers .
- Active monomers of calprotectin are endogenous activators of Toll –like receptor (S100A8 and S100A9)
- Renal tubular cells can produce calprotectin but the main source are monocytes and neutrophils. So elevated levels in pyuria and inflammatory diseases need to cautiously interpreted.
- It increases **2 hours** after ischemia and maximizes in **48 hours** after surgery.

Original Clinical Science—General

Urinary Calprotectin Differentiates Between Prerenal and Intrinsic Acute Renal Allograft Failure

Felix S. Seibert, MD,[1,2] Christian Rosenberger, MD,[3] Susanne Mathia, MD,[3] Robert Arndt, MD,[2] Wolfgang Arns, MD,[4] Huppertz Andrea, MD,[4] Nikolaos Pagonas, MD,[1,2] Frederic Bauer, MD,[1,2] Walter Zidek, MD,[2] and Timm H. Westhoff, MD[1,2]





Urinary calprotectin was assessed by enzyme-linked immunosorbent assay in 328 subjects including 125 cases of intrinsic acute allograft failure, 27 prerenal graft failures, 118 patients with stable graft function, and 58 healthy controls.

A cutoff level of 134.5 ng/mL provided a sensitivity of 90 .4% and a specificity of 74.1%.

Conclusions :Urinary calprotectin is a promising biomarker for the differentiation of prerenal and intrinsic acute renal allograft failure.

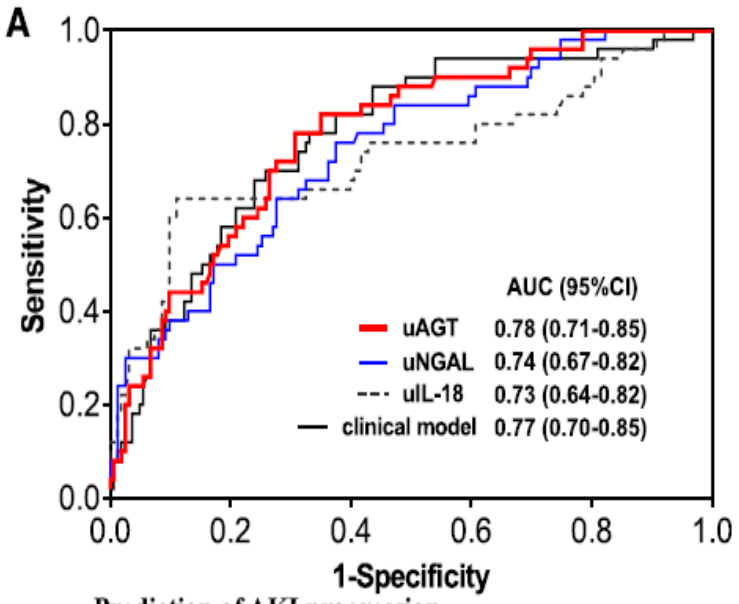
Transplant journal, 2017

Urine angiotensinogen (Uagt)

- 453 amino acid with 10 N-terminal amino acids that are cleavable by renin, which form angiotensin I.
- Among the renal injury biomarkers, uAGT:146.4 mg/g Cr at the time of AKI diagnosis conveyed a 10.8-fold risk of AKI progression compared with patients in the lowest
- It also increases the risk of death

Urinary Biomarkers at the Time of AKI Diagnosis as Predictors of Progression of AKI among Patients with Acute Cardiorenal Syndrome

Chunbo Chen,[*†] *Xiaobing Yang,*[*] *Ying Lei,*[*] *Yan Zha,*[‡] *Huafeng Liu,*[§] *Changsheng Ma,*[‖] *Jianwei Tian,*[*] *Pingyan Chen,*[*] *Tiecheng Yang,*[¶] *and Fan Fan Hou*[*]



Prediction of AKI progression

Marker	Best cutoff	Sensitivity	Specificity
uAGT, μg/g Cr	90.5	0.78	0.69
uNGAL, μg/g Cr	84.0	0.76	0.63
uIL-18, ng/g Cr	649.7	0.64	0.89

Prospective, Multicenter Study, 732 Adults ,With Acute Heart Failure From 2011- 2014

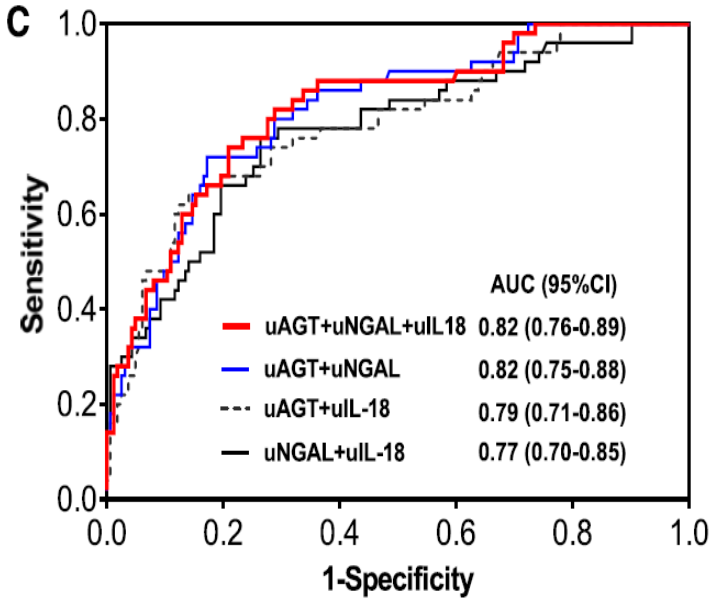
Six Renal Injury Biomarkers,including Urinary Angiotensinogen (Uagt), Ungal, Plasma Ngal,uil-18, Ukim-1, And Urinary Albumin-to-creatinine Ratio

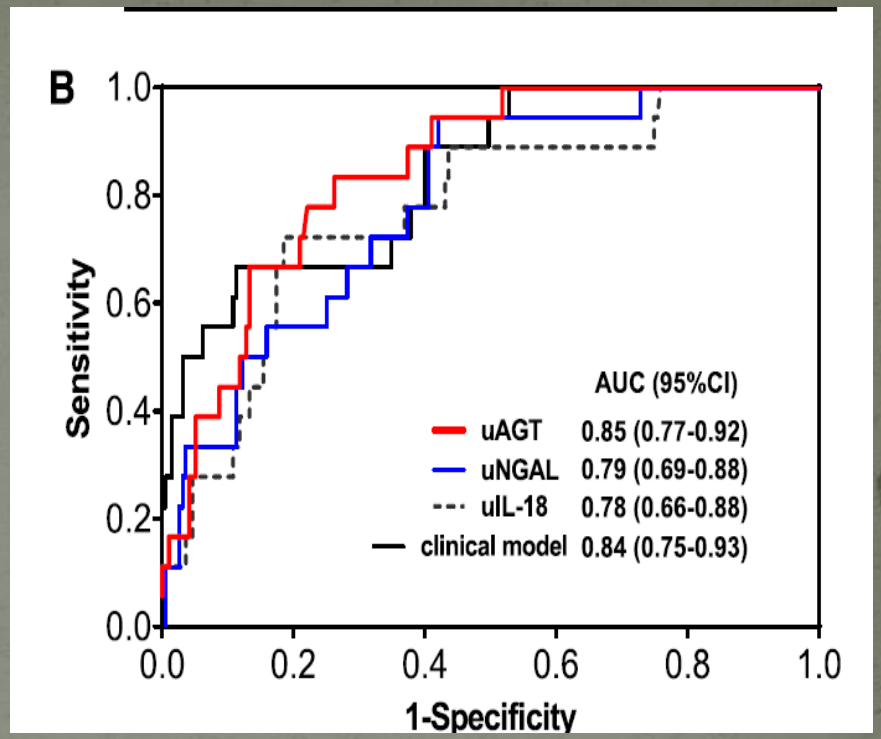
Conlusion :Uagt, Ungal, And Uil-18 Measured At Time Of AKI Diagnosis Improved Risk Stratification And Identified CRS Patients At Highest Risk Of Adverse Outcomes.

CJASN 2017

Prediction of AKI progression with death

Marker	Best cutoff	Sensitivity	Specificity
uAGT, µg/g Cr	162.9	0.83	0.74
uNGAL, µg/g Cr	90.7	0.89	0.59
uIL-18, ng/g Cr	724.9	0.66	0.83





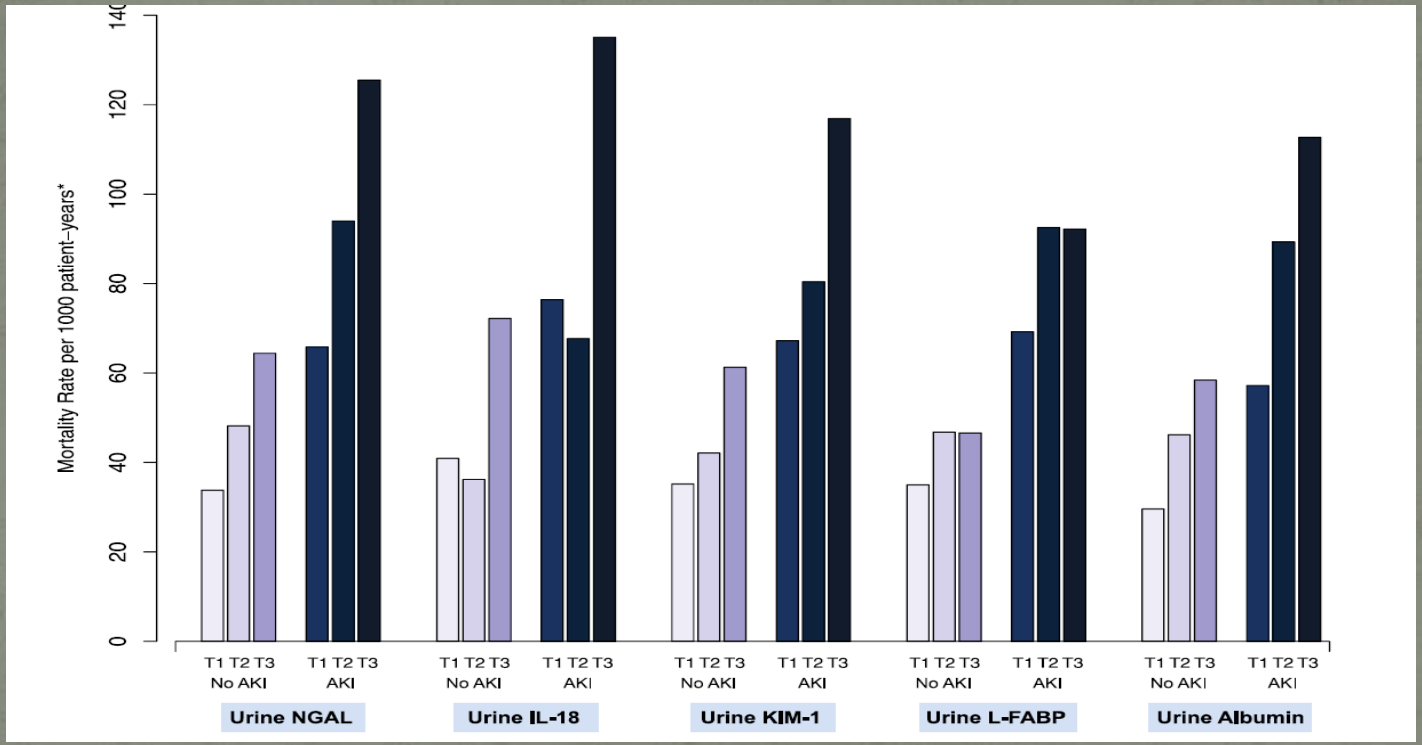
uAGT, uNGAL, and uIL-18 measurement at the time of AKI diagnosis predicted AKI progression and worsening of AKI with death in acute decompensated heart failure.

uAGT was the best predictor for both outcomes.

CLINICAL EPIDEMIOLOGY www.jasn.org

Urinary Biomarkers of AKI and Mortality 3 Years after Cardiac Surgery

Steven G. Coca,* Amit X. Garg,† Heather Thiessen-Philbrook,† Jay L. Koyner,‡ Uptal D. Patel,§



2014

Meisner *et al. Biomarker Research* (2018) 6:3
DOI 10.1186/s40364-018-0117-z

Biomarker Research

RESEARCH Open Access

Development of biomarker combinations for postoperative acute kidney injury via Bayesian model selection in a multicenter cohort study

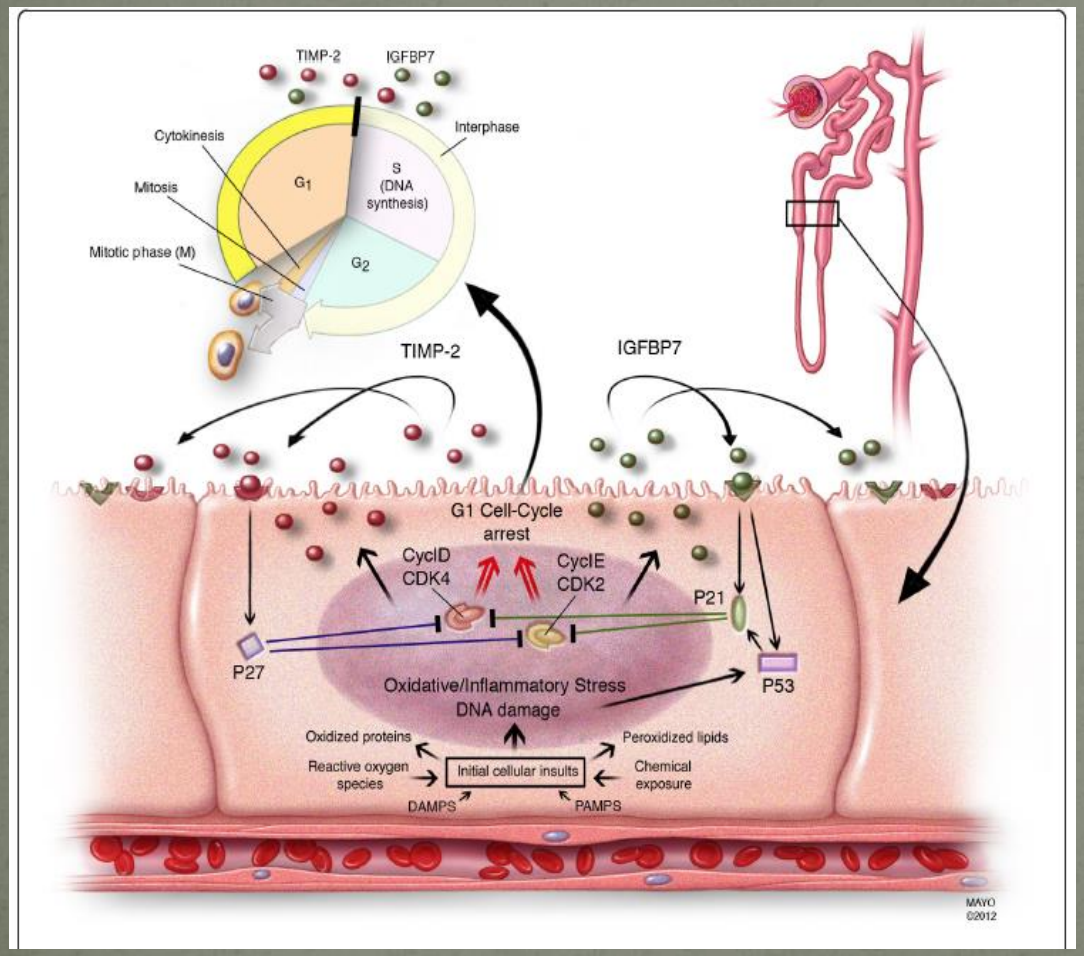
Allison Meisner[1], Kathleen F. Kerr[1], Heather Thiessen-Philbrook[2], Francis Perry Wilson[2,3], Amit X. Garg[4,5], Michael G. Shlipak[6], Peter Kavsak[7], Richard P. Whitlock[8], Steven G. Coca[9] and Chirag R. Parikh[2,3,10*]

- Data were from a cohort of 1219 adults undergoing cardiac surgery at 6 medical centers; among these, 117 developed sustained mild AKI and 60 developed severe AKI.
- They considered cardiopulmonary bypass time and 22 biomarkers as candidate predictors.
- The three novel biomarkers included in the combinations identified in our analysis were plasma NT-proBNP, plasma IL-6, and plasma h-FABP, all of which were positively associated with sustained mild AKI in our data.

Insulin Like Growth Factor Protein 7 & Tissue Inhibitor Of Metalloproteinase 2

- TIMP-2 a 21 KDa protein,is a member of TIMP family and endogenous inhibitor of metalloproteinase activity .
- IGFBP7, a 29 –KDa secreted protein , bind and inhibit insulin- like growth factor 1 receptors.
- Not significant different between men and women, small reverse correlation to age.
- Predictive in moderate to high risk patients

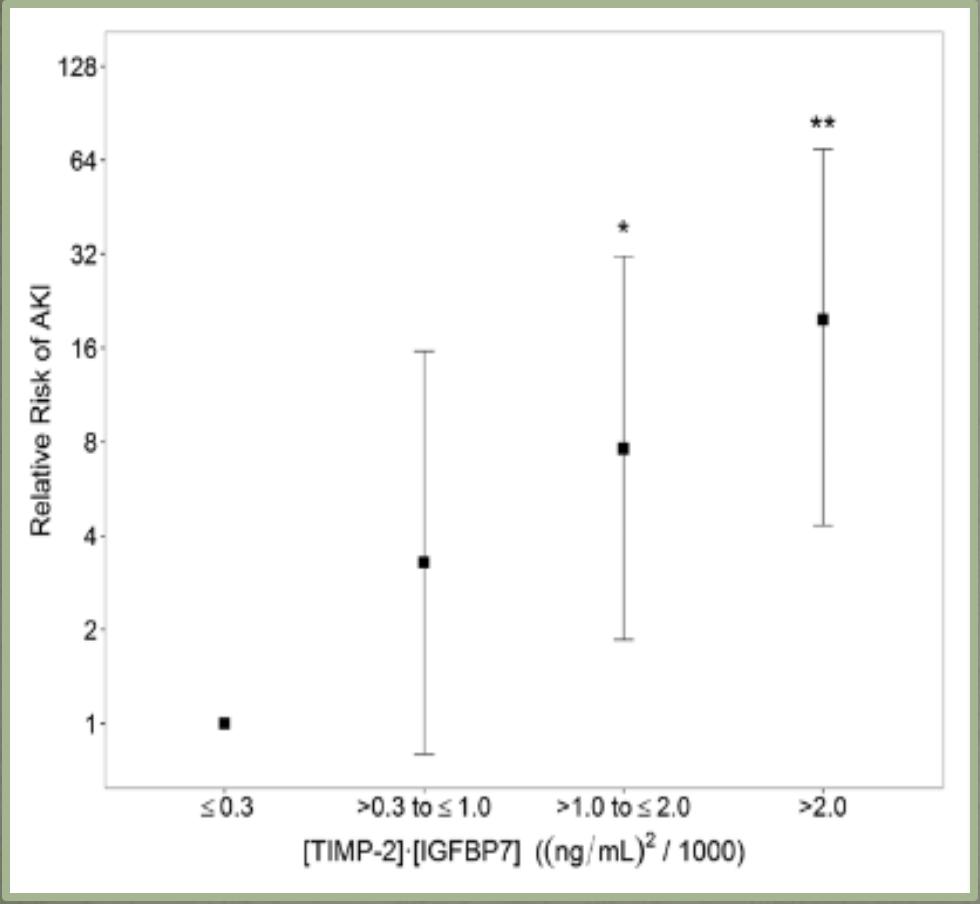
Proposed Mechanistic Involvement Of Biomarkers In AKI



IGFBP7 and TIMP-2 are both involved with the phenomenon of G1 cell cycle arrest during the very early phases of cell injury.

This prevents cells from dividing when the DNA may be damaged and protects cell from demise or senescence

Urinary Tissue Inhibitor Of Metalloproteinase-2 And Insulin-like Growth Factor-binding Protein 7 For Risk Stratification Of Acute Kidney Injury In Patients With Sepsis



Two trials including 39 ICUs across Europe and North America. The primary endpoint was moderate- severe acute kidney injury .

Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 accurately predicts acute kidney injury in septic patients with or without other organ failures

Honore et al , 2016,Crictical care Medcine

Kashani *et al. Critical Care* 2013, **17**:R25
http://ccforum.com/content/17/1/R25

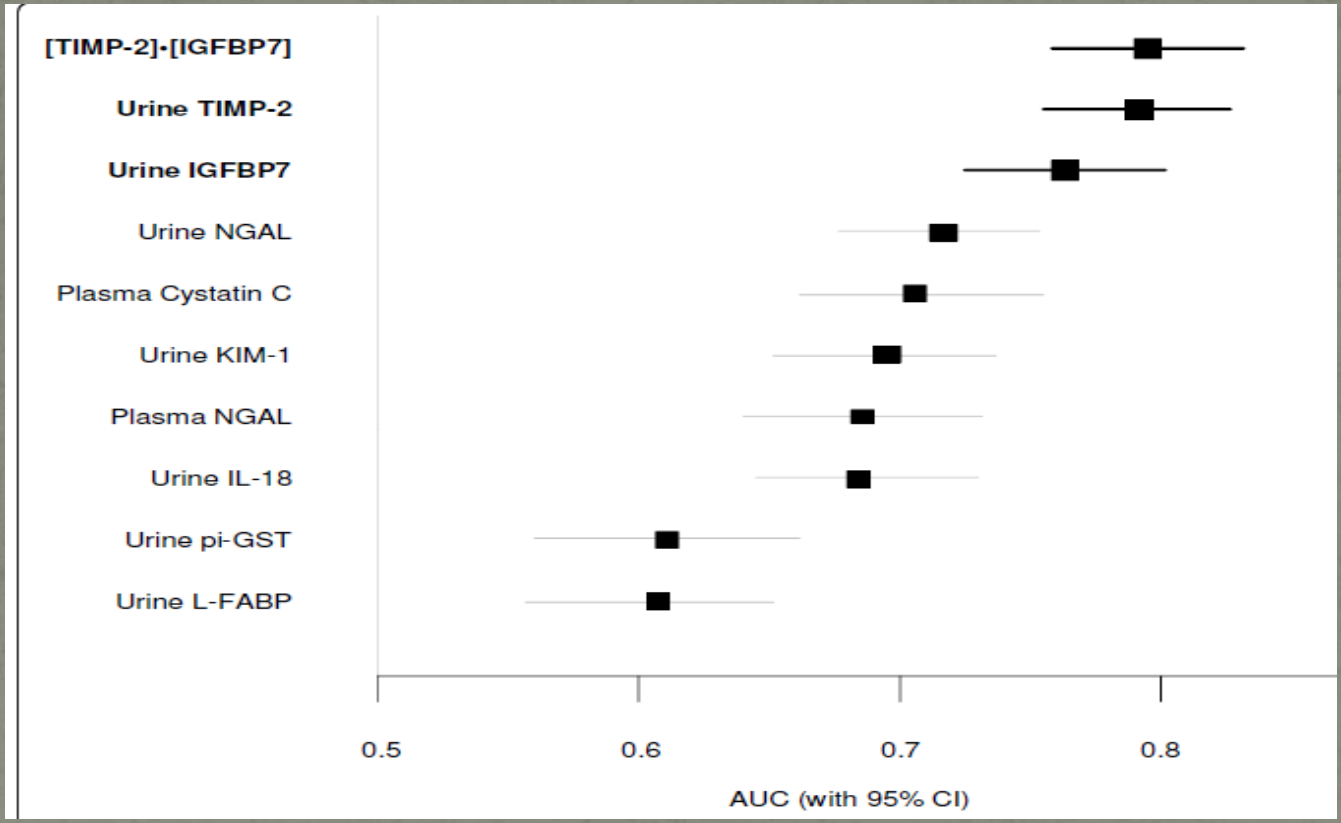
RESEARCH Open Access

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

Kianoush Kashani[1], Ali Al-Khafaji[2], Thomas Ardiles[3], Antonio Artigas[4], Sean M Bagshaw[5], Max Bell[6], Azra Bihorac[7],

- Two multicenter observational studies in critically ill patients at risk for AKI.
- They enrolled 522 adults in three distinct cohorts including patients with sepsis, shock, major surgery, and trauma and examined over 300 markers.
- Primary endpoint was moderate to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection.

AUC For Urinary Biomarkes For Primary End Point Of Sapphire Study



The AUC for urinary [TIMP-2]·[IGFBP7] is larger than for the existing biomarkers (P value <0.002)

Identification of a microRNA signature of renal ischemia reperfusion injury

Jonathan G. Godwin[a], Xupeng Ge[b], Kristin Stephan[a], Anke Jurisch[b], Stefan G. Tullius[b,1], and John Iacomini[a,1]

- MicroRNA endogenous and noncoding RNA molecules containing 18-22 nucleotides.
- Examined expression profiles of miRNAs following renal IRI.
- In vitro studies revealed that miR-21 is expressed in proliferating tubular epithelial cells.
- A molecular fingerprint of renal injury and suggest miR-21 may play a role in protecting TEC from death.

PNAS 2010

DOI: 10.4149/BLL_2017_120

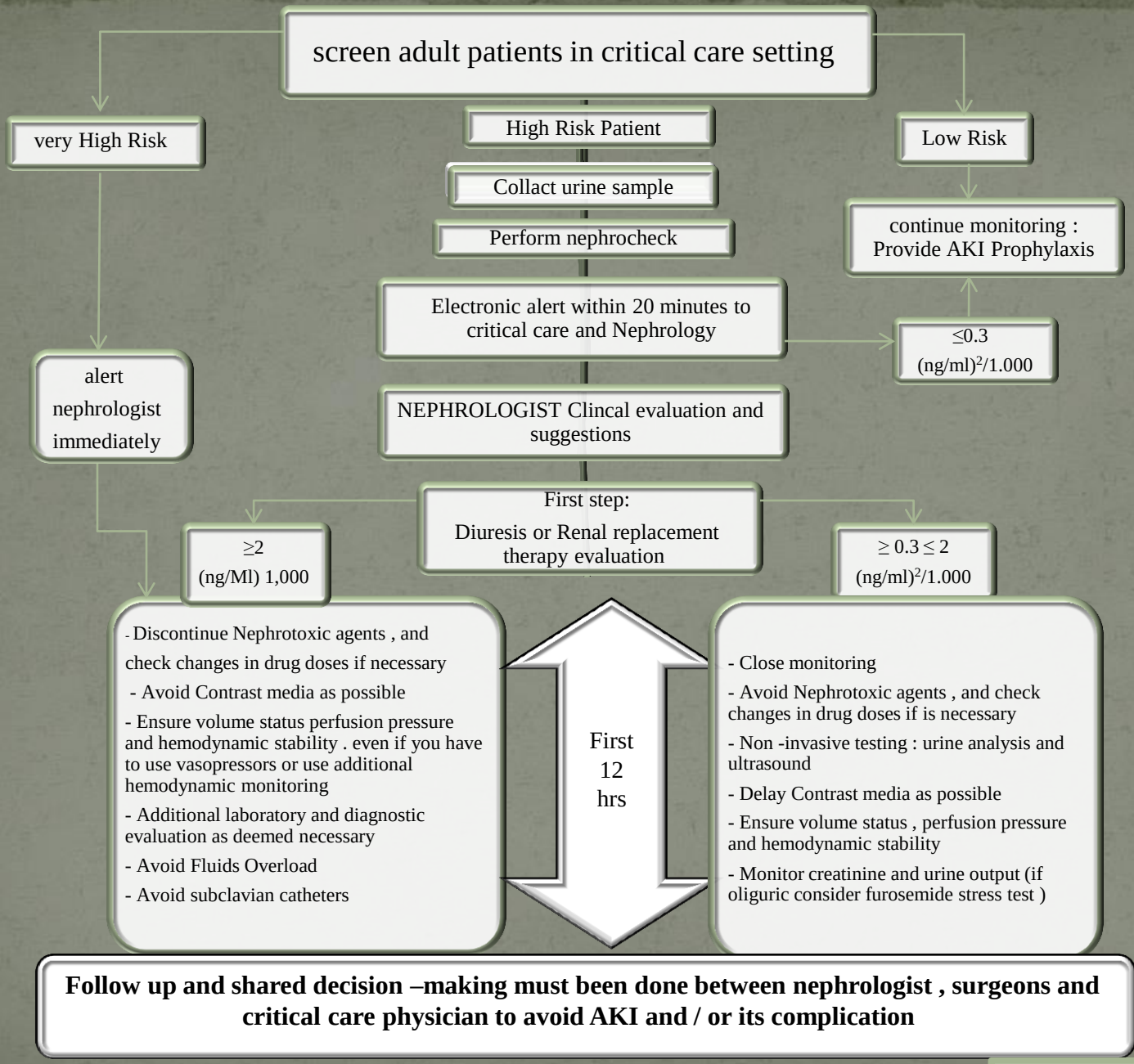
Bratisl Med J 2017; 118 (10)
626–631

CLINICAL STUDY

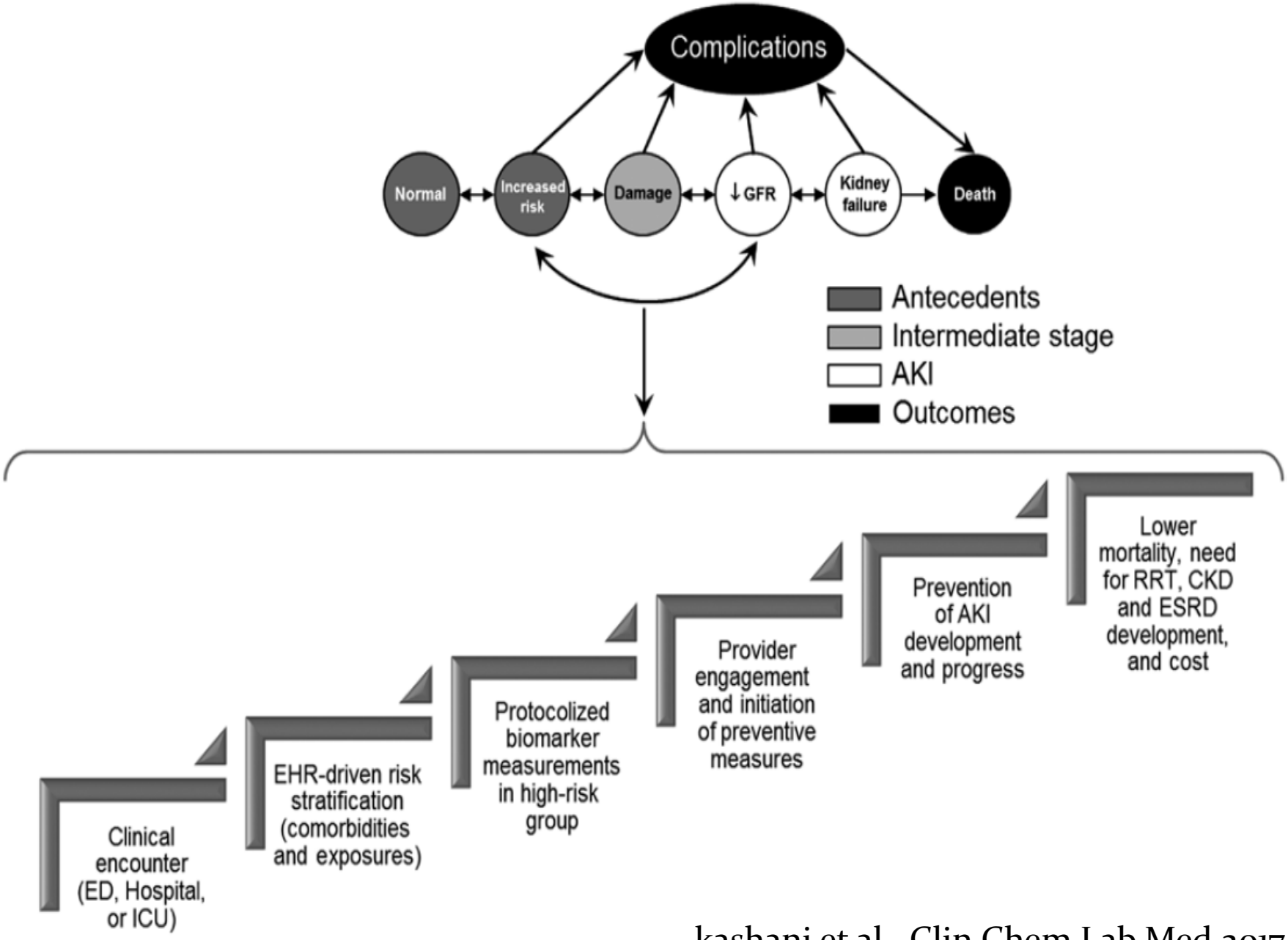
Early detection of cardiac surgery-associated acute kidney injury by microRNA-21

Arvin P[1], Samimagham HR[2], Montazerghaem H[3], Khayatian M[4], Mahboobi H[5], Ghadiri Soufi F[6]

- A total of 103 patients scheduled to undergo cardiac surgery.
- Serum and urinary miR-21 were measured prior to, and 6, 12 and 24 h after surgery.
- Both postoperative serum and urinary miR-21 levels can predict AKI development, urinary miR-21 especially 6 h after surgery is a more reliable marker than serum miR-21 for detection of established CSA-AKI.



Ronco et al ,NDT 2017



kashani et al , Clin Chem Lab Med 2017

Figure 1: Clinical implementation of EHR, biomarkers, and AKI teams within the conceptual model of AKI.