MARKERS OF ACUTE KIDNEY INJURY

Applying theory to practice

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- CASES
- REVIEWING OUR KNOWLEDGE
- CHANGING CONCEPTS
- UNDERSTANDING ABOUT BIOMARKERS
- MOVING FORWARD

FROM BEDSIDE TO BENCH...

Demonstrative ED cases

	AGE	COMORB	CKD	CVD	DM	CAUSE of ADM	no-RENAL DIAGNOSTIC
1	66	6	1	1	1	HIPOGLICEMIA	MM
2	73	4	1	1	0	ANGOR INST	EAM
3	65	1	0	0	0	RECTORRAGIA	HDA VARIZES ESOF
4	68	3	0	1	1	INFEC RESP	FMO SEPSIS
5	33	3	1	0	0	EAP HTA	CRISE HTA x COCAINA - GNC HVC
6	79	1	0	1	0	DIARREIA	EAM
7	72	3	1	0	1	HIPOGLICEMIA	RABDOMIOLISE - DM DESCOMP

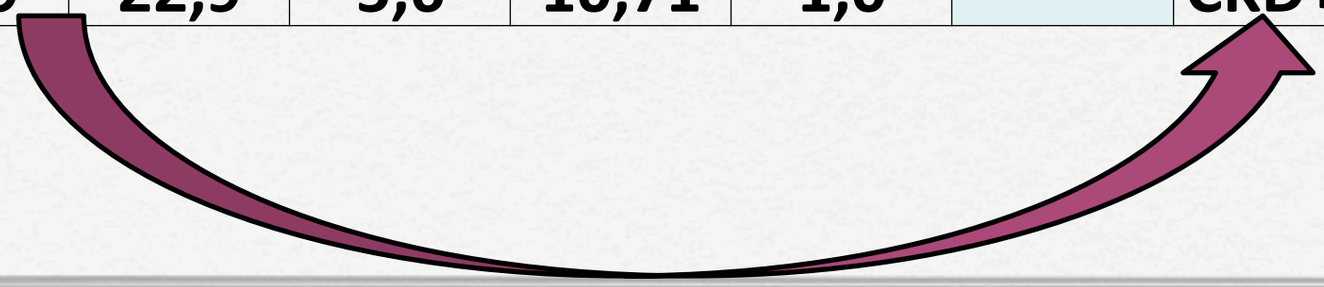
Cases: past history and outcome

Baseline ⇩ admission

	B_SCr	B_ eGFR	SUSCEPTIBILITY	SCr_S1	CyC_S1	AKI/TAz	DIALYSIS	ICU	ALL SEPSIS	DEAD1	DIAG
1	1,5	49,85	4	2,5	2,65	1	0	0	0	0	
2	1,8	35,53	4	2	1,73	1	0	1	0	0	
3	0,7	120,49	1	1,5	1,28	1	0	0	0	0	
4	1	79,11	2	1,6	1,38	1	1	1	1	1	FMO
5	1,8	46,49	3	2,7	1,89	1	0	0	0	0	
6	1	76,74	2	1,1	0,85	2	0	1	0	0	
7	1,8	39,68	3	3,1	2,46	1	1	0	1	1	SEPSIS

Cases: long term outcome

	SCr D	GFR_D	1FU Scr	1FU GFR	FU month	death FU	CKD + AKI	Last SCr	Last GFR	FU y
1	2,7	25,3	3,2	20,79	12,7	0	CKD 5	5,50	11,00	3,0
2	3,1	19,0	5	10,93	26,0	2	CKD5 HD			2,5
3	1,6	46,4	6	10,10	2,4	1	CKD+AKI HD			
4	7,4	7,9			0,3		AKI			
5	2,1	38,9	7,9	8,44	10,3	0	CKD5 HD			3,0
6	1	76,7	10,3	5,20	1,0	1	CKD+AKI HD			
7	2,9	22,9	5,6	10,71	1,0		CKD+AKI HD			



Changing concepts

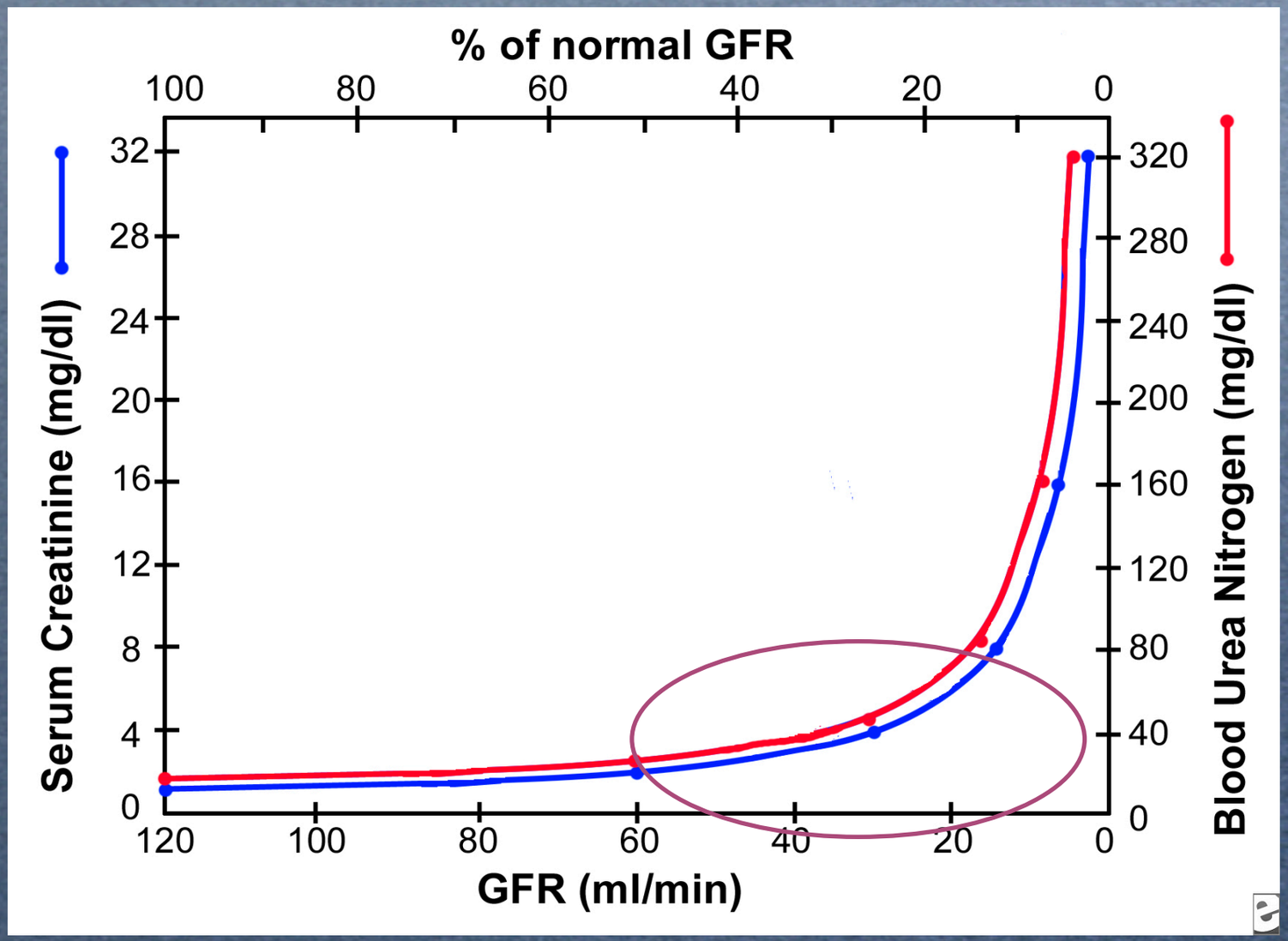
Grades of susceptibility	
1	0 eGFR > 90ml/ min/ 1.73 m^2
2	Previous CKD 2
3	Previous CKD 3
4	Previous CKD 2/3 +
	-DM with microalbuminuria
	-Dehydration
	-MM
	-HF
	-Decompensate cirrhosis

Adaptado de Mehta R et al; Acute Renal Failure Definitions and Classification: Time for Change? *JASN* 14: 2003

Biomarkers for AKI diagnosis

Reviewing

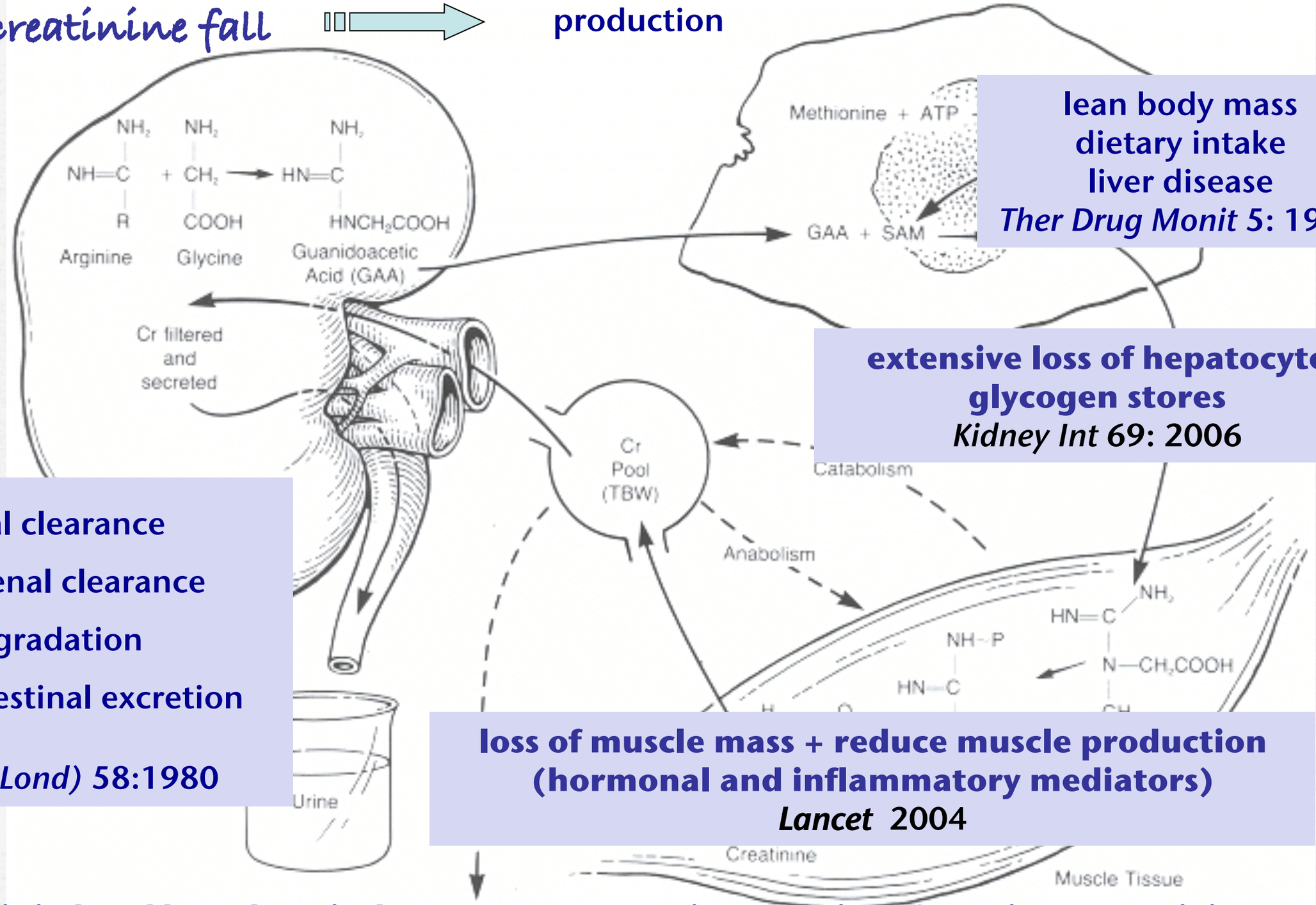
Limitations of SCr



Dennen P, Douglas I, Anderson R,: Acute Kidney Injury in the Intensive Care Unit: An update and primer for the Intensivist. *Critical Care Medicine* 2010; 38:261-275.

Serum creatinine fall

production



lean body mass
dietary intake
liver disease
***Ther Drug Monit* 5: 1983**

extensive loss of hepatocyte glycogen stores
***Kidney Int* 69: 2006**

Renal clearance

Extra-renal clearance

Degradation

Gastrointestinal excretion

***Clin Sci (Lond)* 58:1980**

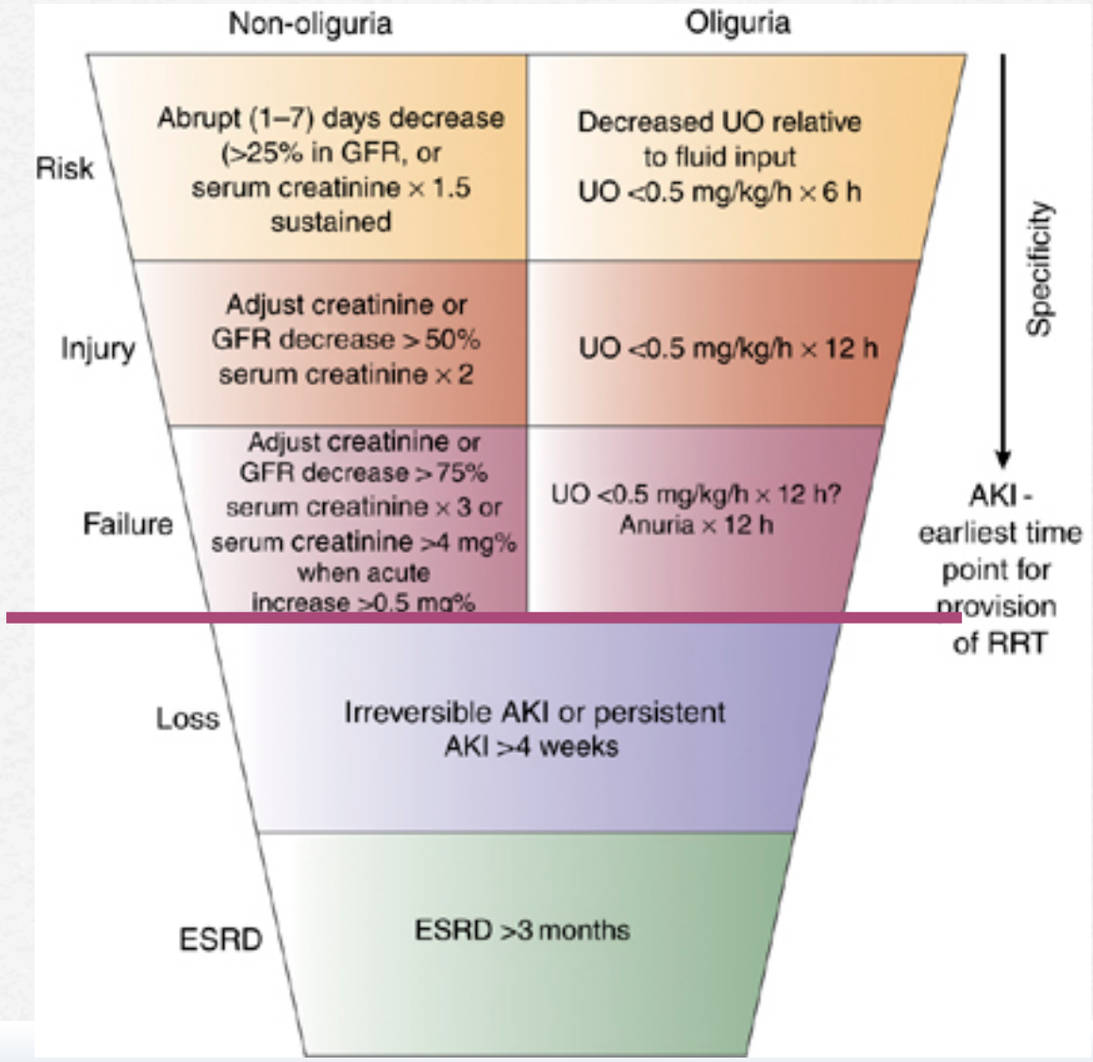
loss of muscle mass + reduce muscle production (hormonal and inflammatory mediators)
***Lancet* 2004**

Sepsis-induced hypothermia decrease nonenzymatic conversion of creatine to creatinine
***Infect Immun* 67: 6603–6610, 1999**

Changing concepts

RIFLE criteria for diagnosing AKI

SCr



UO

Bellomo, R. et al. Crit. Care 8, R204–R212 (2004)

Changing concepts

AKIN staging system for AKI

AKIN stage	Serum Creatinine Criteria	Urinary Output Criteria	Time
1	↑ Cr ≥ 0.3 mg/dL or ↑ ≥ 150-200% from baseline	< 0.5 mL/kg/hr	> 6 hrs
2	↑ Cr to > 200-300% from baseline	< 0.5 mL/kg/hr	> 12 hrs
3	↑ Cr to > 300% from baseline or Cr ≥ 4mg/dL with an acute rise of at least 0.5 mg/dL	< 0.5 mL/kg/hr or anuria	X 24 hrs X 12 hrs

***Patients needing RRT are classified stage 3 despite the stage they were before starting RRT**

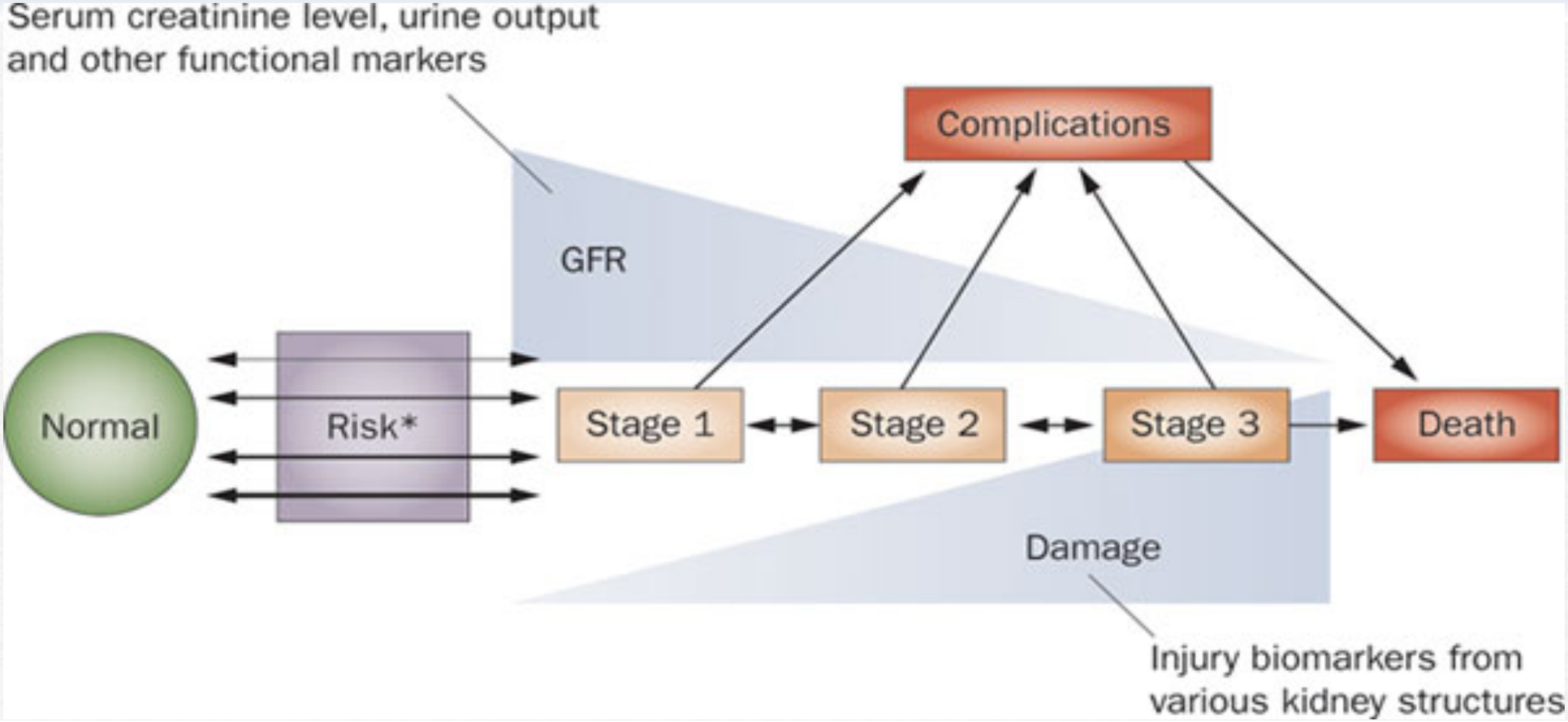
Mehta, R. L. et al. Crit. Care. **11**, R31 (2007)

Cases: AKI diagnosis

	RIFLE									
s	0 H	6H	12H	24H	48H	1W	DISCH	AKIN	death FU	CKD + AKI
4	R	R	R	R	R	R	R	1	0	CKD 5
4	0	R	R	R	R	R	R	1	2Y	CKD5 HD
1	I	I	I	R	I	0	I	2	1Y	CKD+AKI HD
2	R	0	R	R	R	F	F	3	INT	AKI
3	R	R	R	R	R	0	R	1	0	CKD5 HD
2	0	0	R	R	0	0	0	0	1Y	CKD+AKI HD
3	R	R	R	R	R	0	0	1	INT	CKD+AKI HD

About Biomarkers

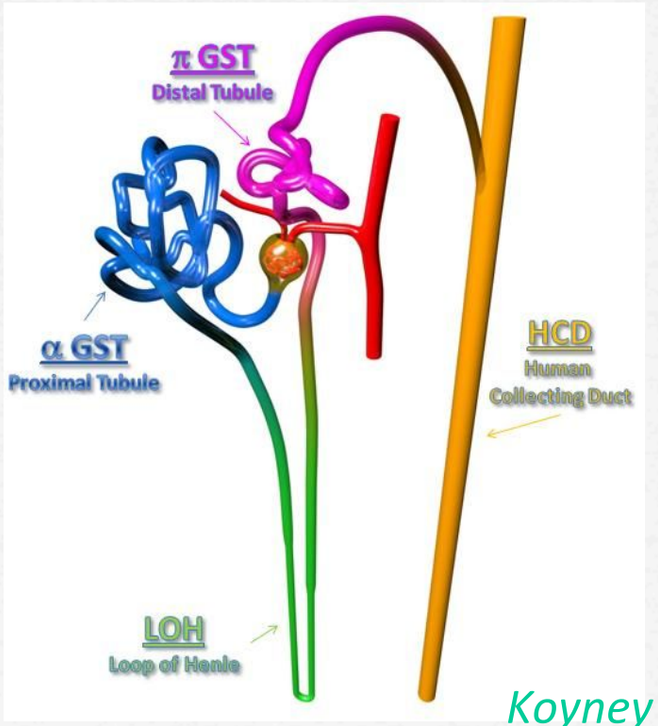
Conceptual model of AKI



Murugan, R. & Kellum, J. A. (2011) Acute kidney injury: what's the prognosis?
Nat. Rev. Nephrol. doi:10.1038/nrneph.2011.13

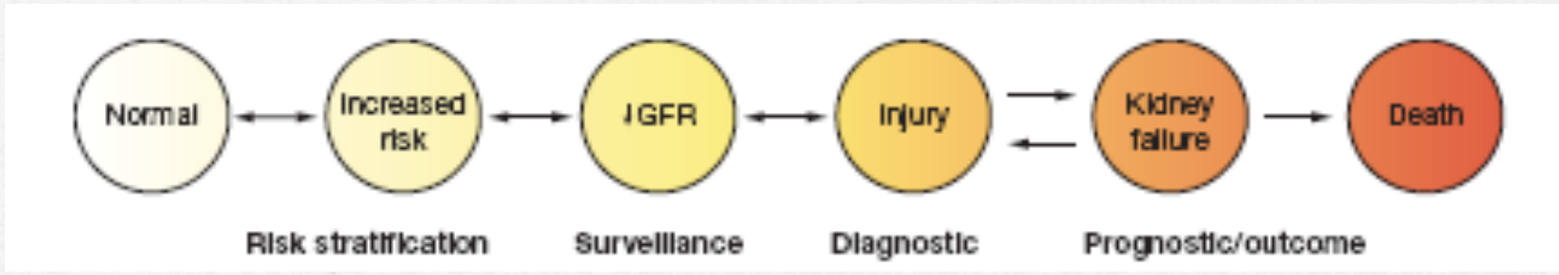
About Biomarkers

- Early prediction and diagnosis of AKI (before SCr)
- Identify the primary location of injury
- Discriminate PreRenal, CKD and AKI
- Predicttion of severity
- Identify the etiology: ischemic, toxic, septic, combination



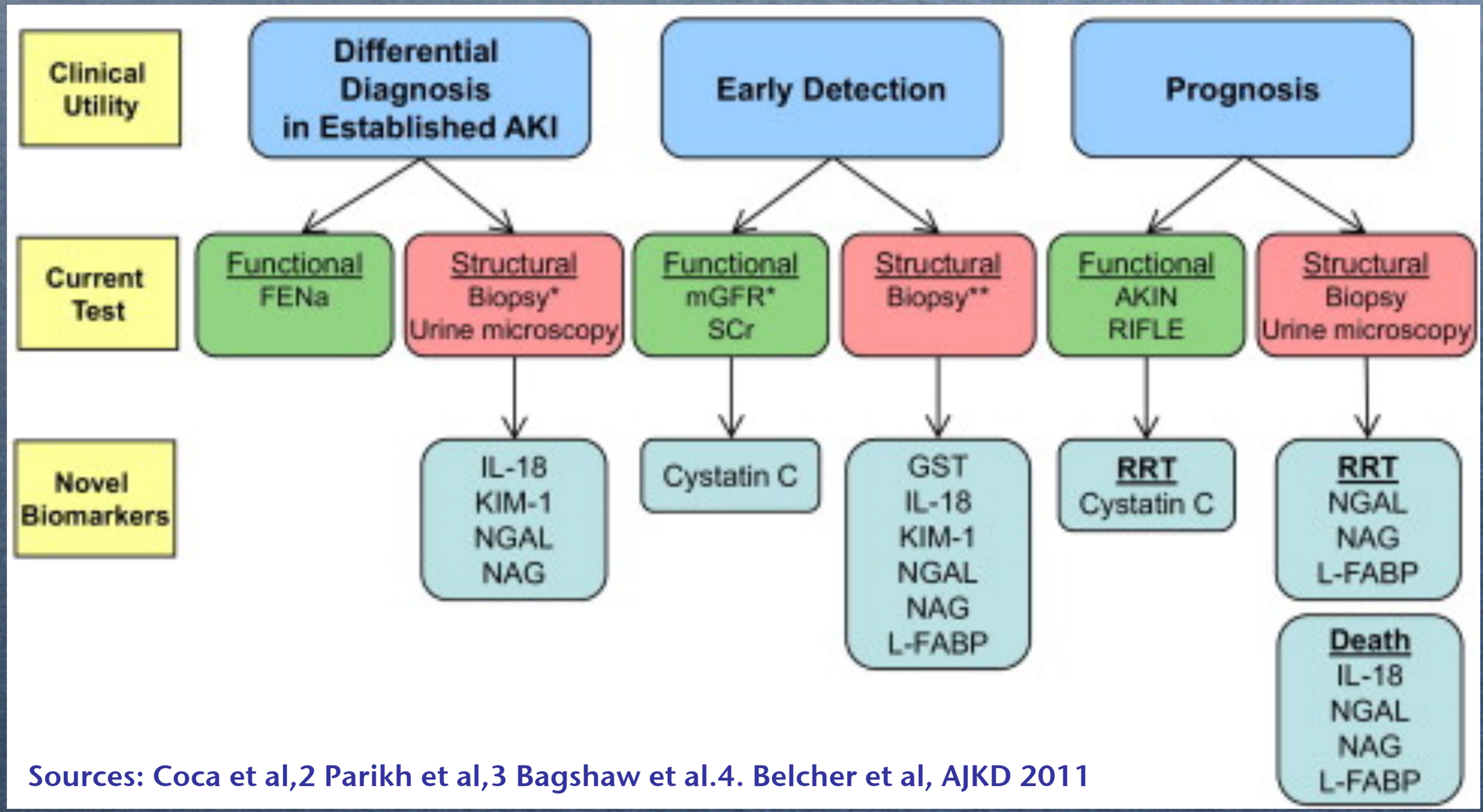
Koyney and Murray, Argutus Medical

Devarajan P, Sem Nephrol 2007 – Contrib Nephrol 2008



Mehta RL et al. (2007) Crit Care **11:** R31

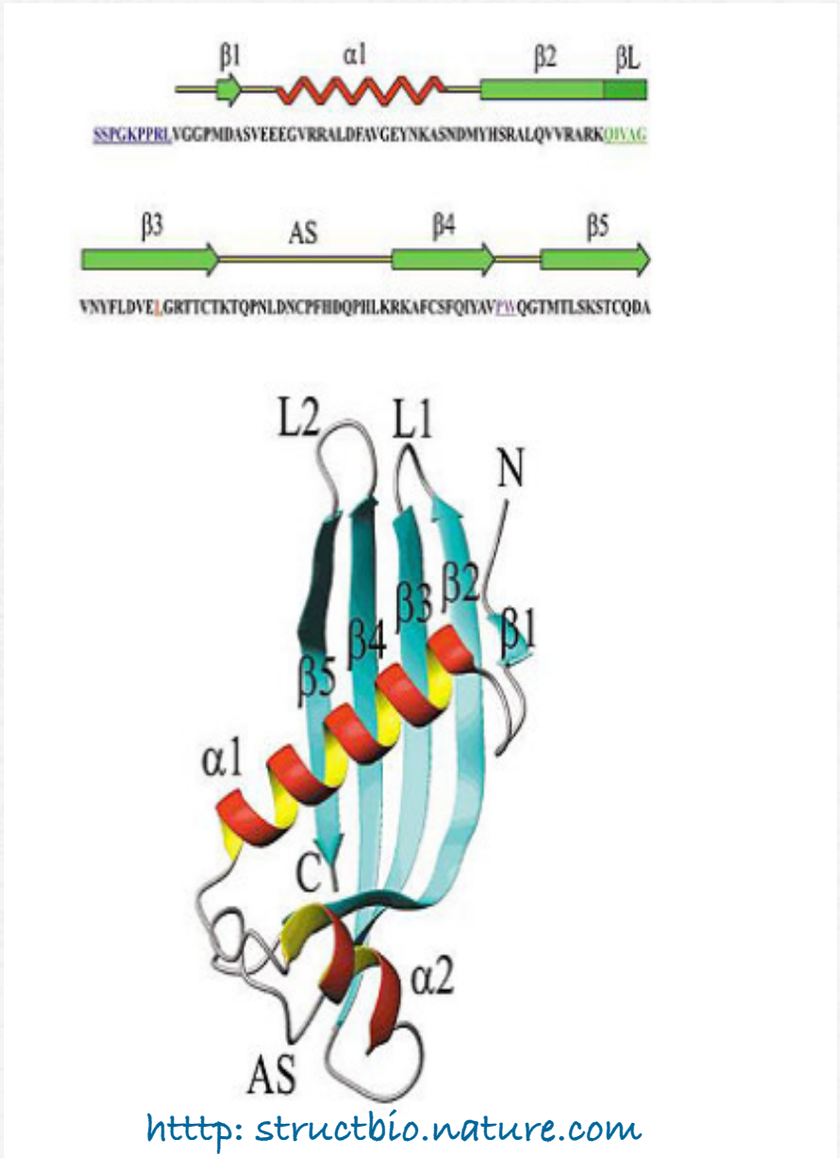
About Biomarkers for AKI diagnosis



Sources: Coca et al,2 Parikh et al,3 Bagshaw et al.4. Belcher et al, AJKD 2011

Biomarker	Origin in AKI cases	Significance of rise	Studied clinical settings
NGAL serum and urinary	Urine: synthesis in distal nephron and secreted into urine Circulating: synthesized systemically, filtered, and uptaken by proximal tubular cells with a little amount secreted in the urine	Tubular injury (ischemia and nephrotoxins)	i) Early detection of AKI after cardiac surgery, ICU, ED, and after nephrotoxins (ii) Risk stratification (iii) Prognostic marker after kidney transplantation (iv) Monitoring interventional trials in AKI (v) Prognosis of RRT and mortality
CysC serum and urinary	Produced at a constant rate by nucleated cells, filtered, and almost completely reabsorbed in the proximal tubules	Change in GFR (proximal tubule injury)	(i) Early detection of AKI after cardiac surgery, ICU , ED and after nephrotoxins (ii) Prognosis of RRT and mortality
KIM-1 urinary	Type 1 transmembrane protein, highly expressed in dedifferentiated proximal tubule epithelial cells after ischemic or toxic injury and is not detectable in normal tissue	Tubular injury (ischemia and nephrotoxins)	(i) Early detection of AKI after cardiac surgery and after nephrotoxins (ii) Prognosis of RRT and mortality
IL-18 urinary	Proinflammatory cytokine originates from tubular epithelial cells	Tubular injury (ischemia and nephrotoxins)	(i) Early detection of AKI after cardiac surgery, in ICU (ii) Prognostic marker after kidney transplantation (iii) Prognosis of mortality

CYSTATIN C

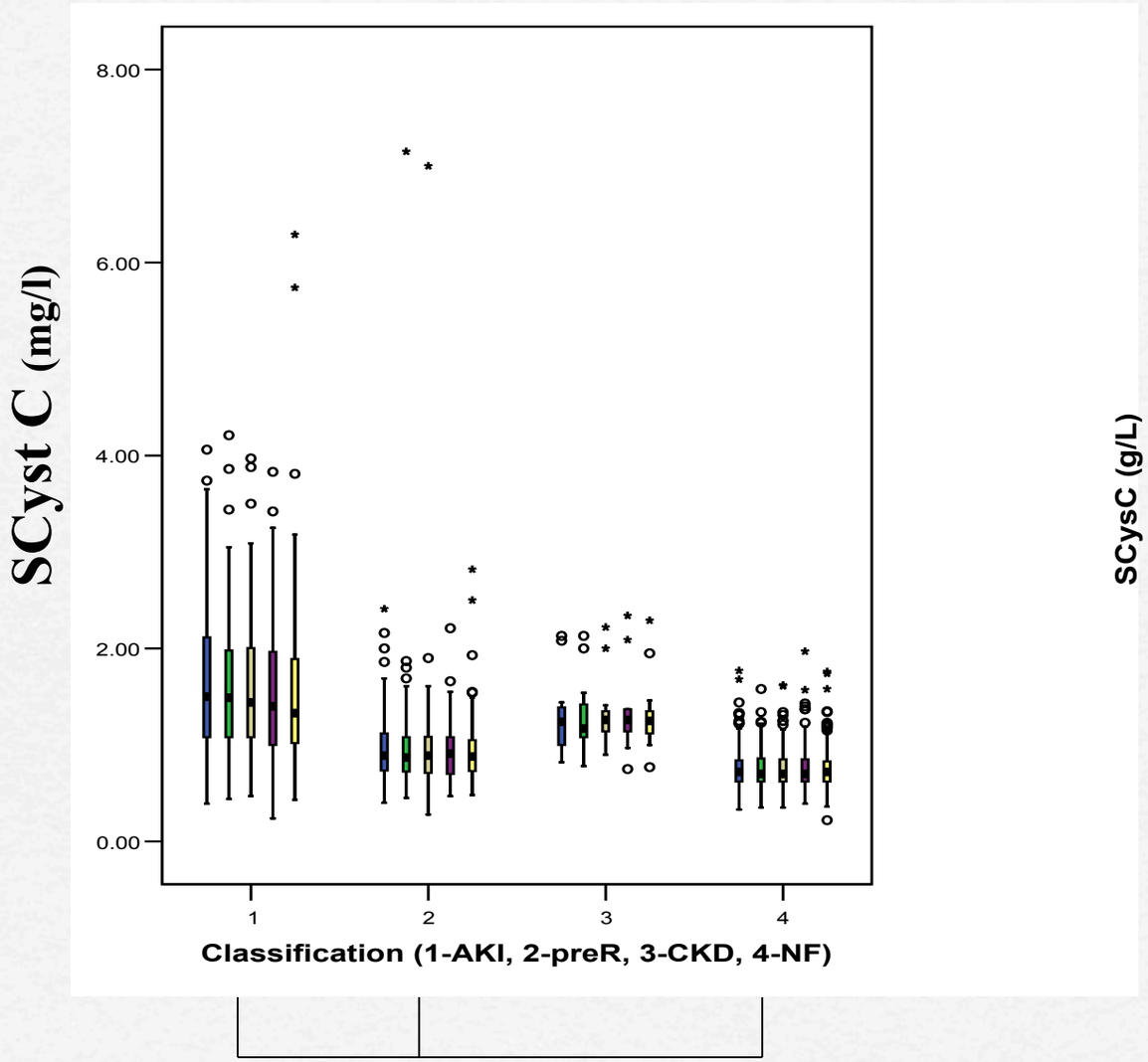


http: structbio.nature.com

- Cystatin C production is independent from muscle mass, constitution of the body, or nutrition
- It is independent or from gender and age
- Probably it is influenced by inflammation and malignancy
- It is influenced by very large doses of glucocorticoids and thyroid dysfunction

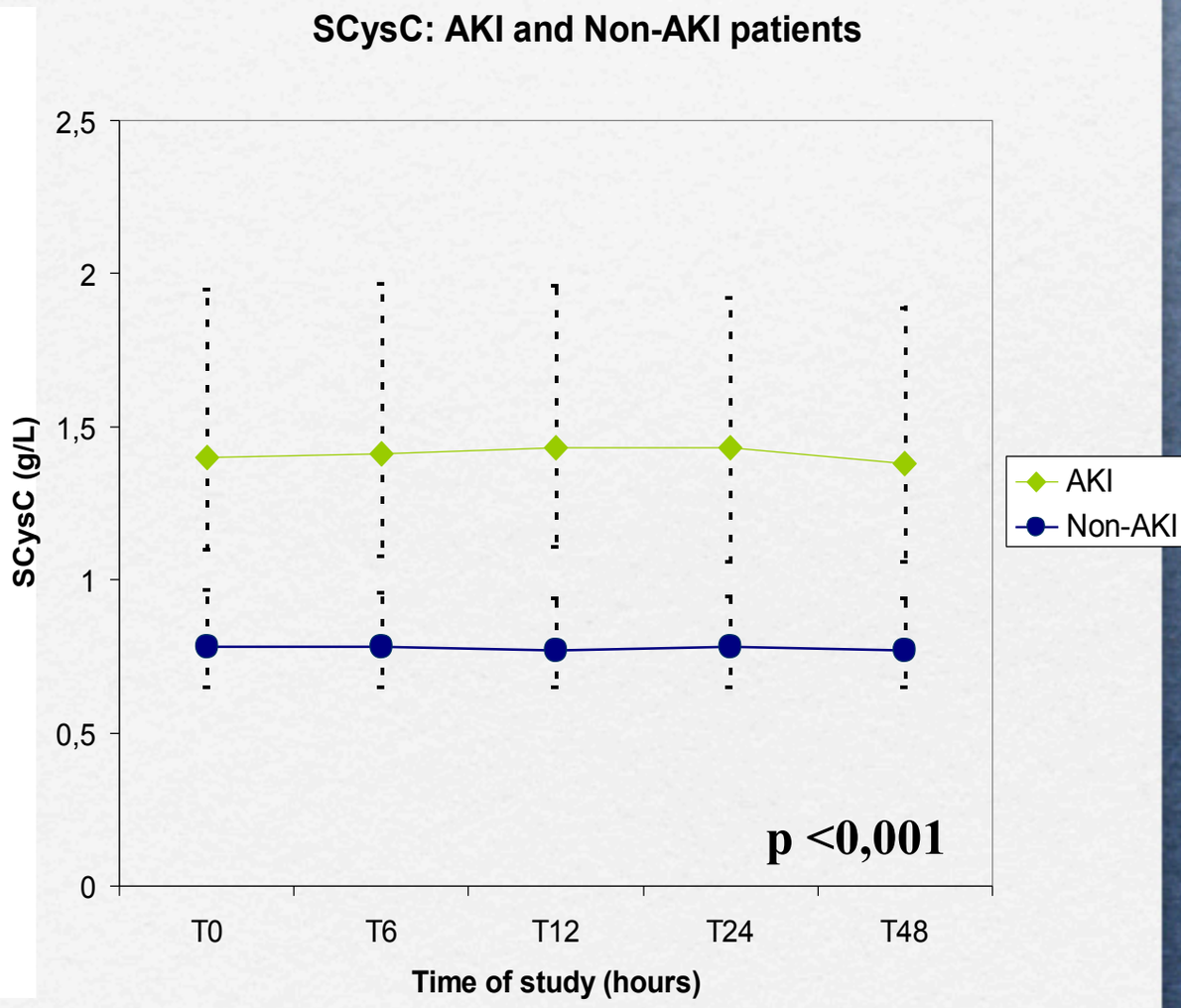
✓free renal filtration
✓no tubular secretion
✓no re-entry into circulation
✓tubular reabsorption followed by degradation

Cystatin C for differential diagnosis



AKI Pre-R CKD NF

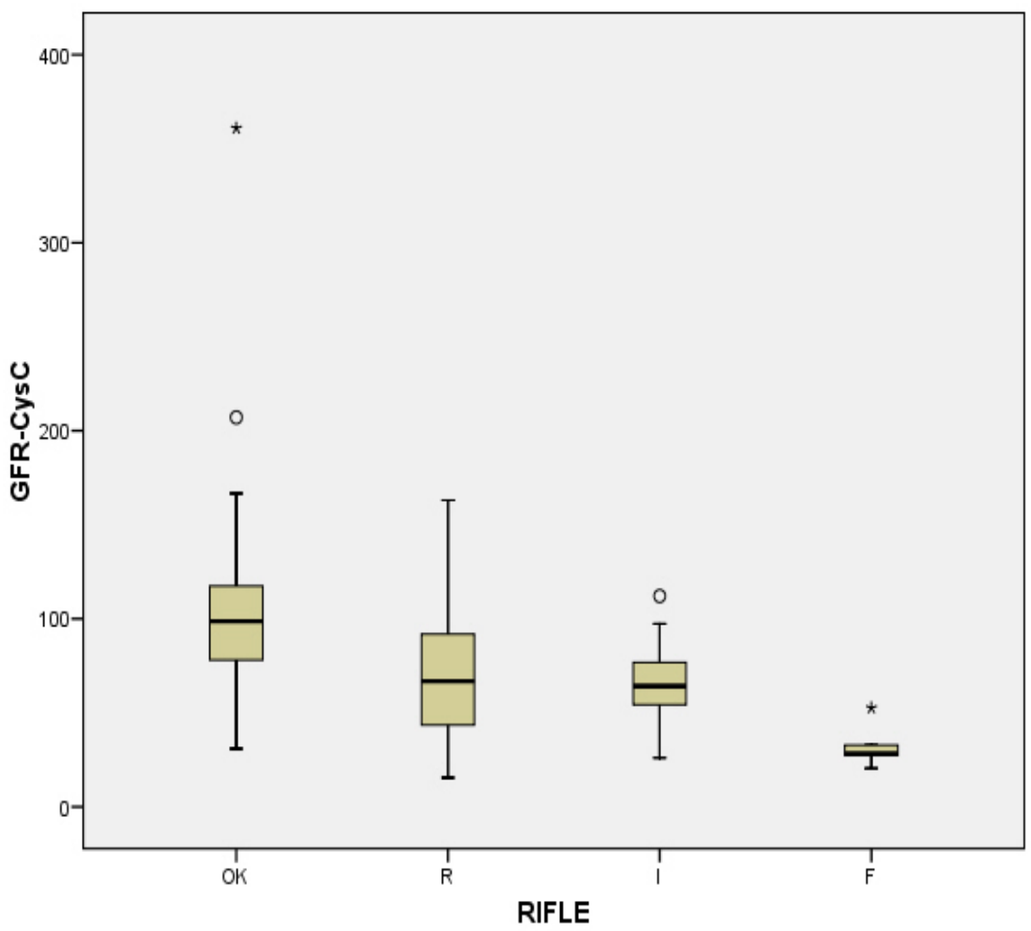
p <0,001



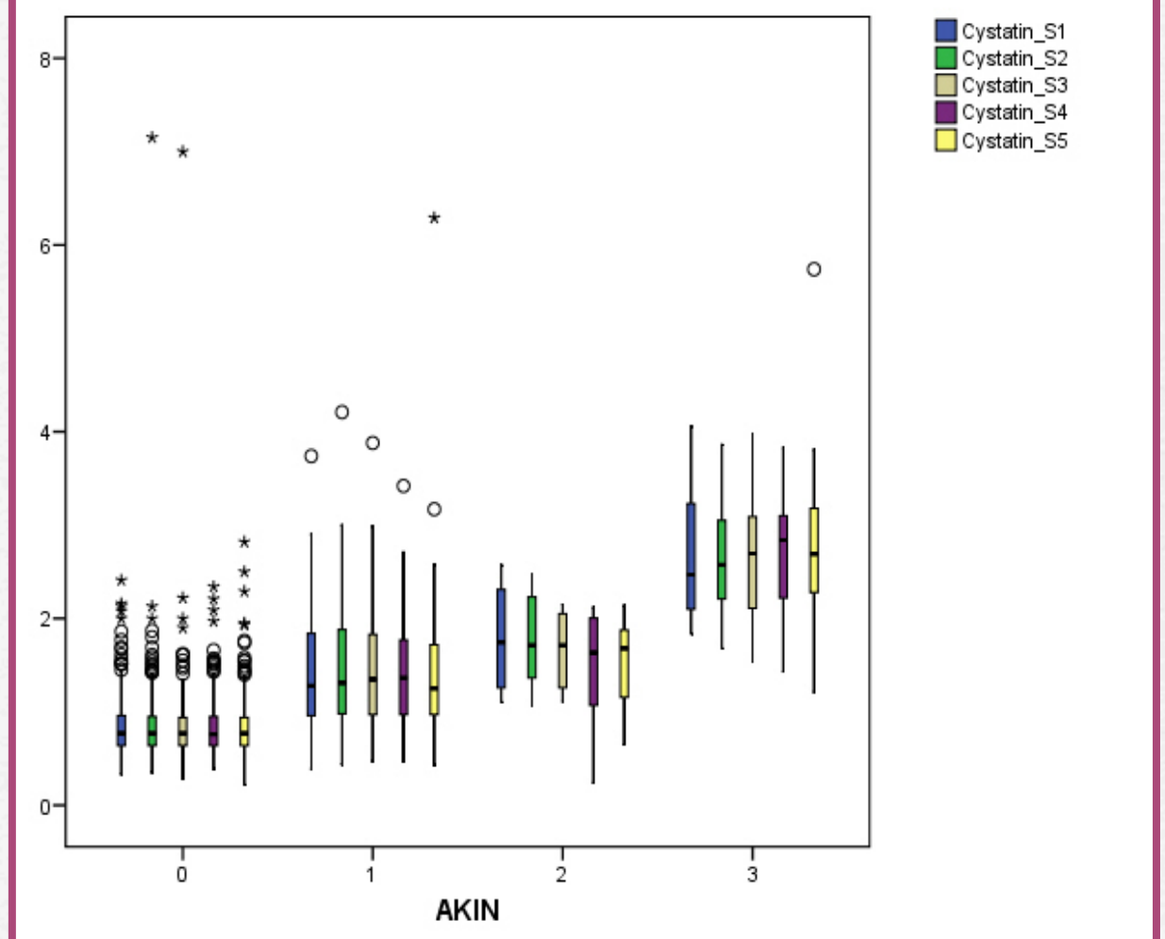
Soto K et al. CJASN 2010

Cystatin C as marker of severity

RIFLE and GFR based on SCysC



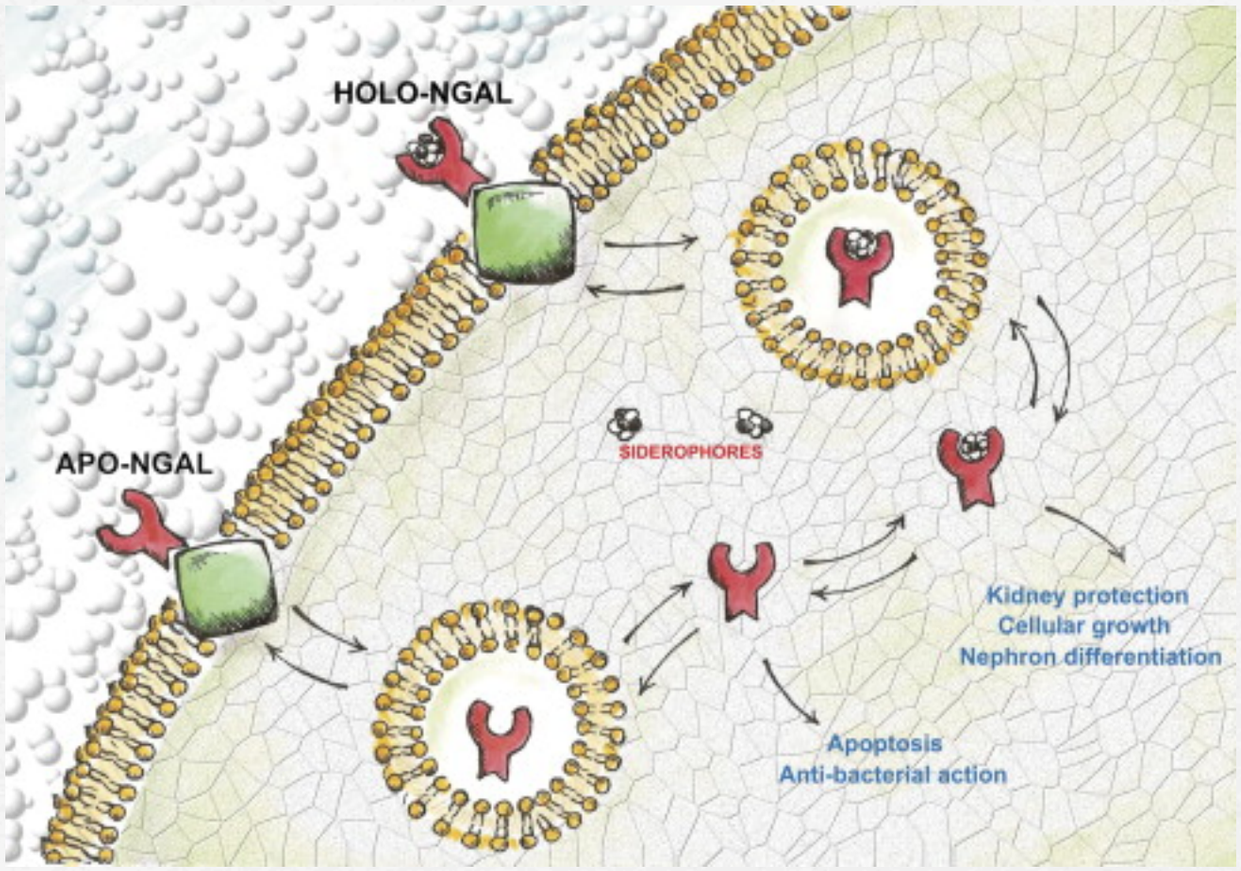
AKIN and levels of SCysC



Soto K et al. CJASN 2010

NGAL

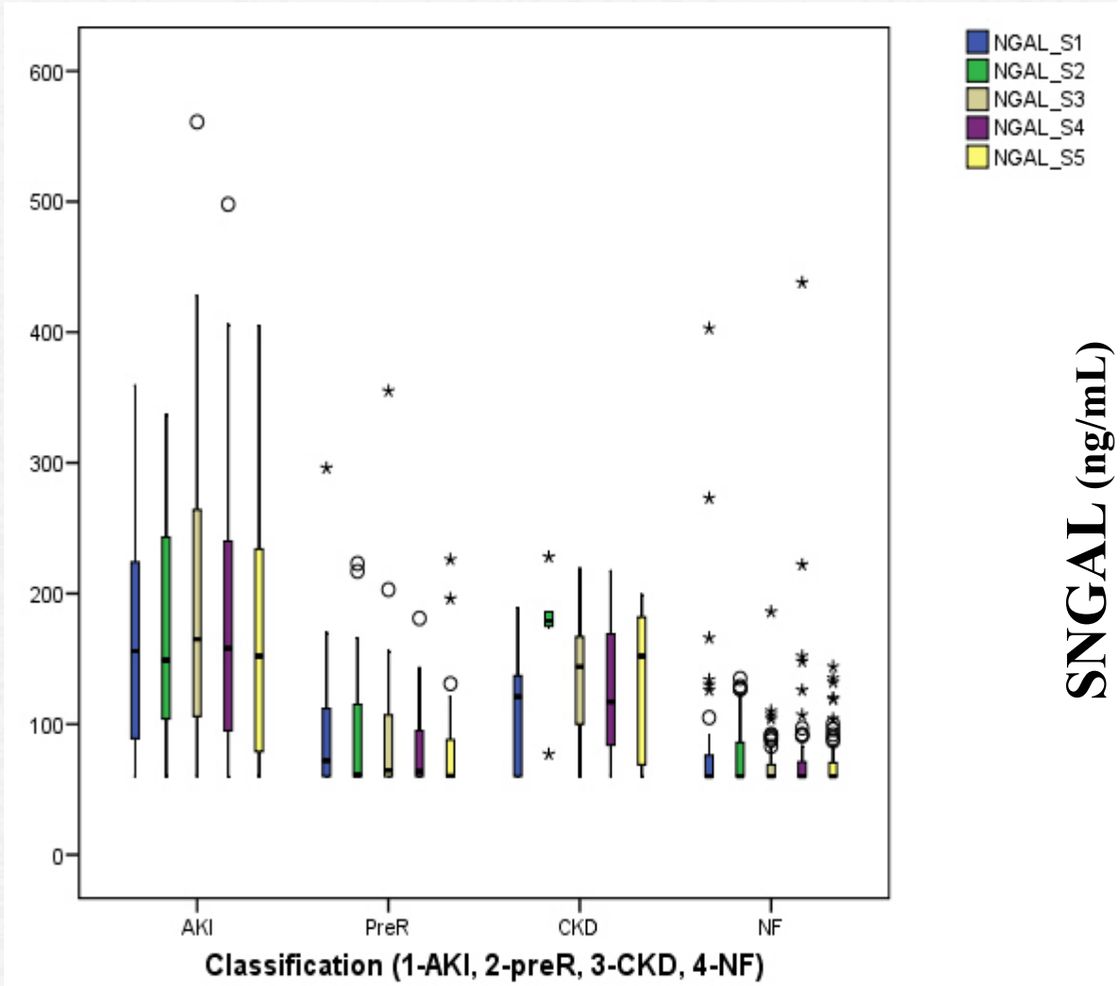
Neutrophil gelatinase-associated lipocalin

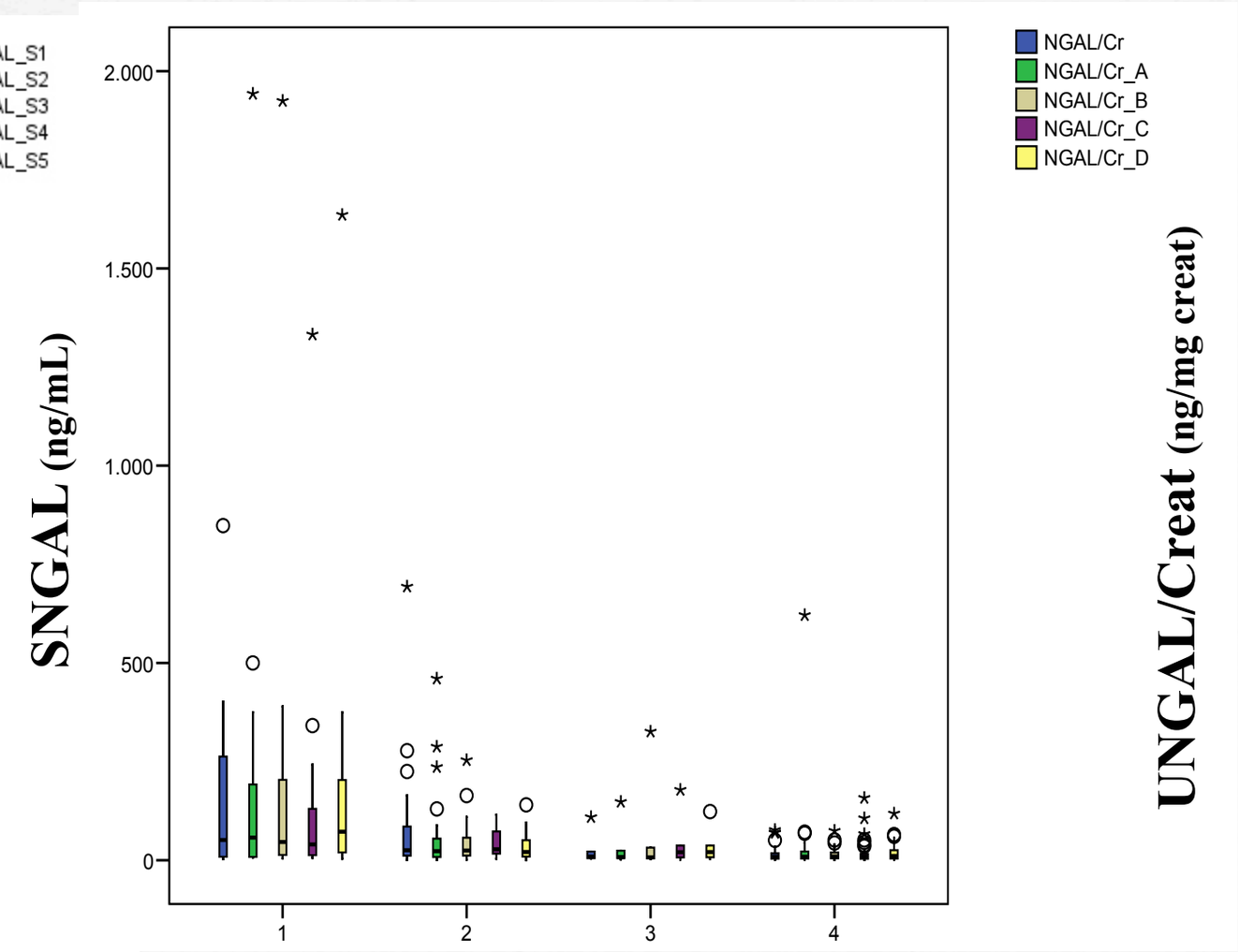


- First identified as a neutrophil granule protein
- Expressed at very low levels on several tissues
- Normally very small amounts in kidney tubules
- Induced in injured epithelial cells
- The most upregulated gene in the kidney, very early after ischemic or nephrotoxic AKI in animals

Reviewed by P Devarajan . Nephrology **15** (2010) 419–428 and Biomark Med. 2010 April; 4(2): 265–280.

NGAL for AKI diagnosis





AKI Pre-R CKD NF

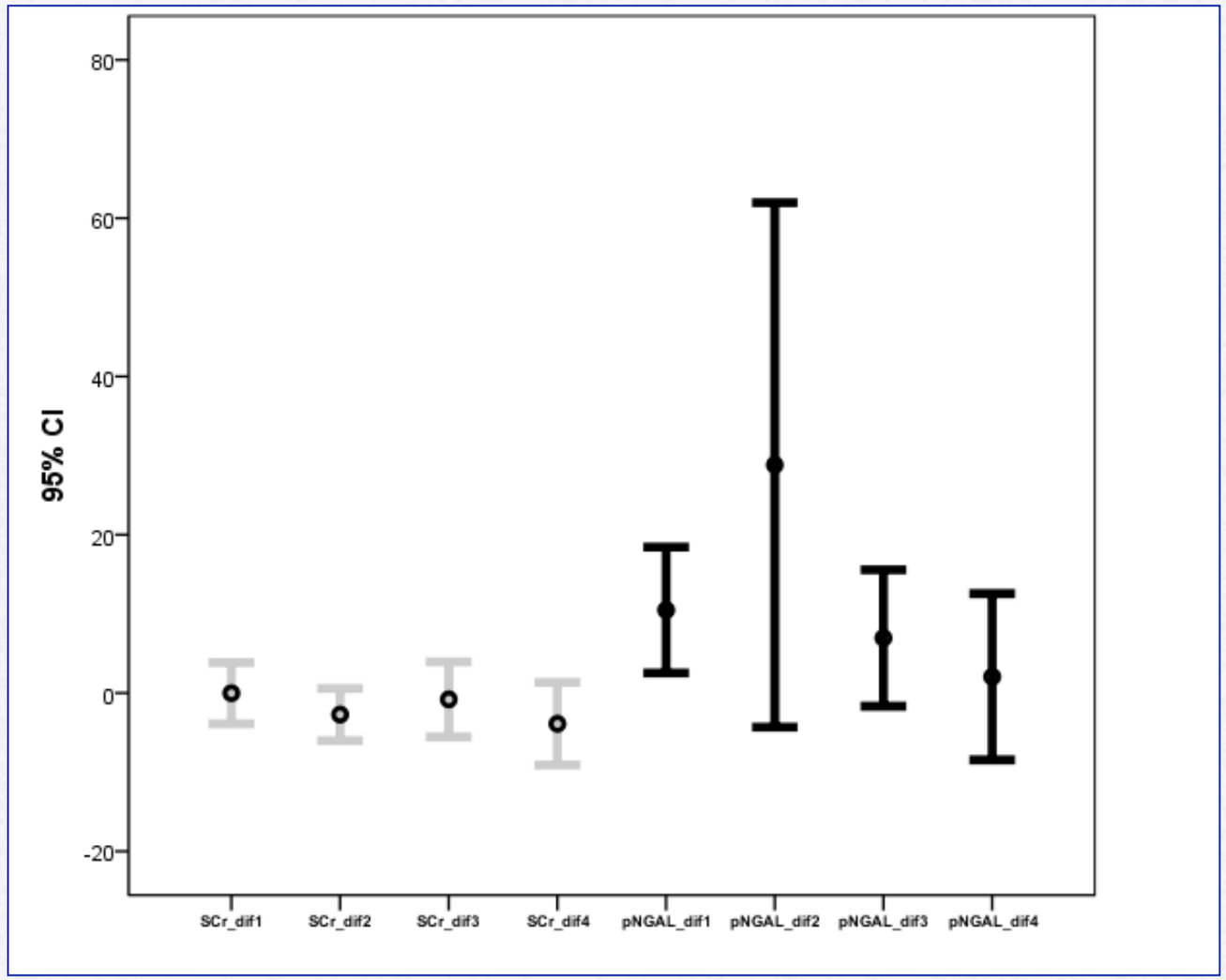
p <0,001

AKI Pre-R CKD NF

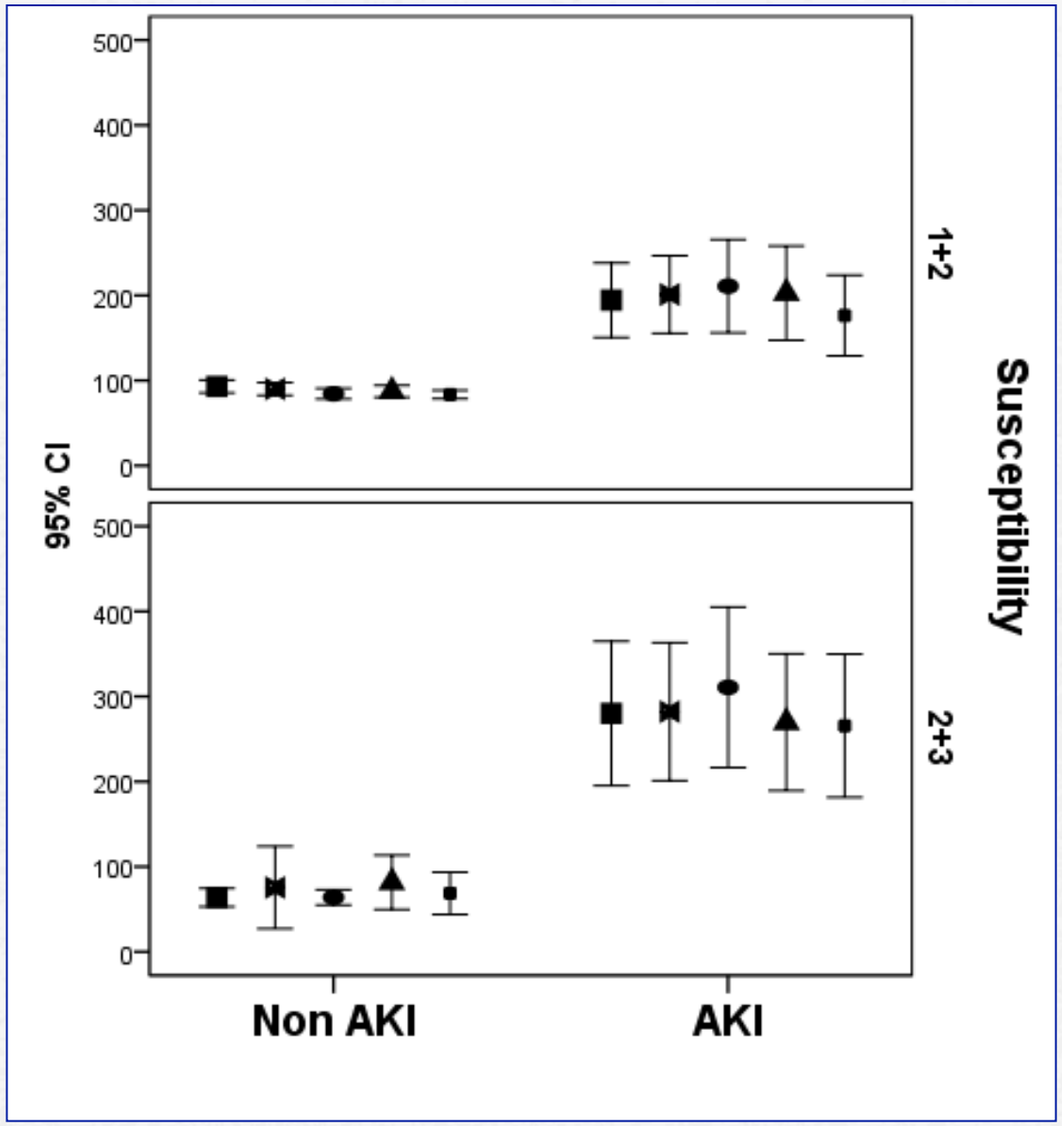
p <0,001

Soto K et al. 2009

NGAL and accurance



Comparison with Scr

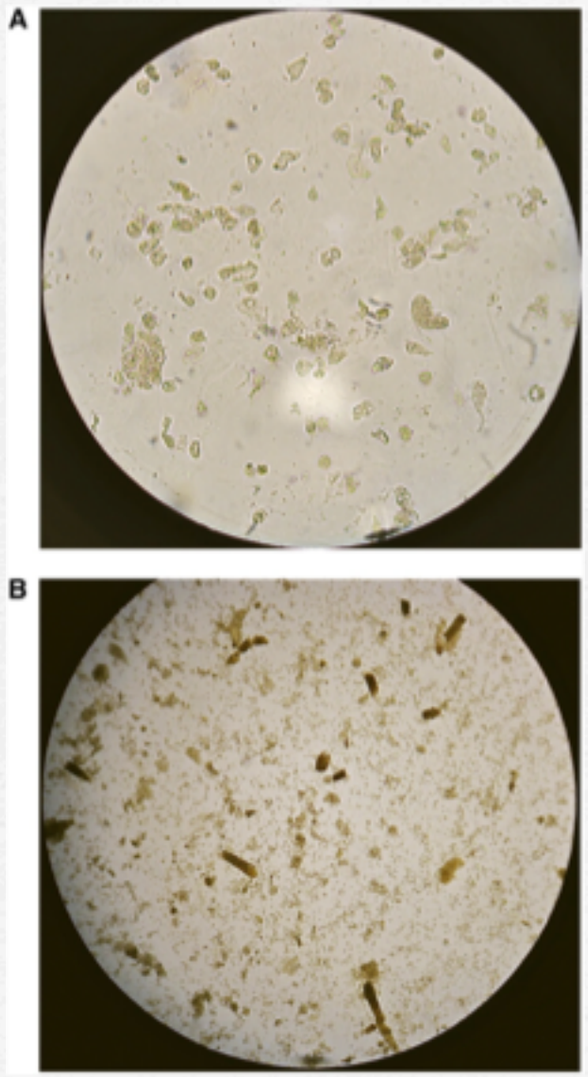


Marker of AKI on CKD

Changing concepts

Urine sediment score to quantitatively evaluate AKI

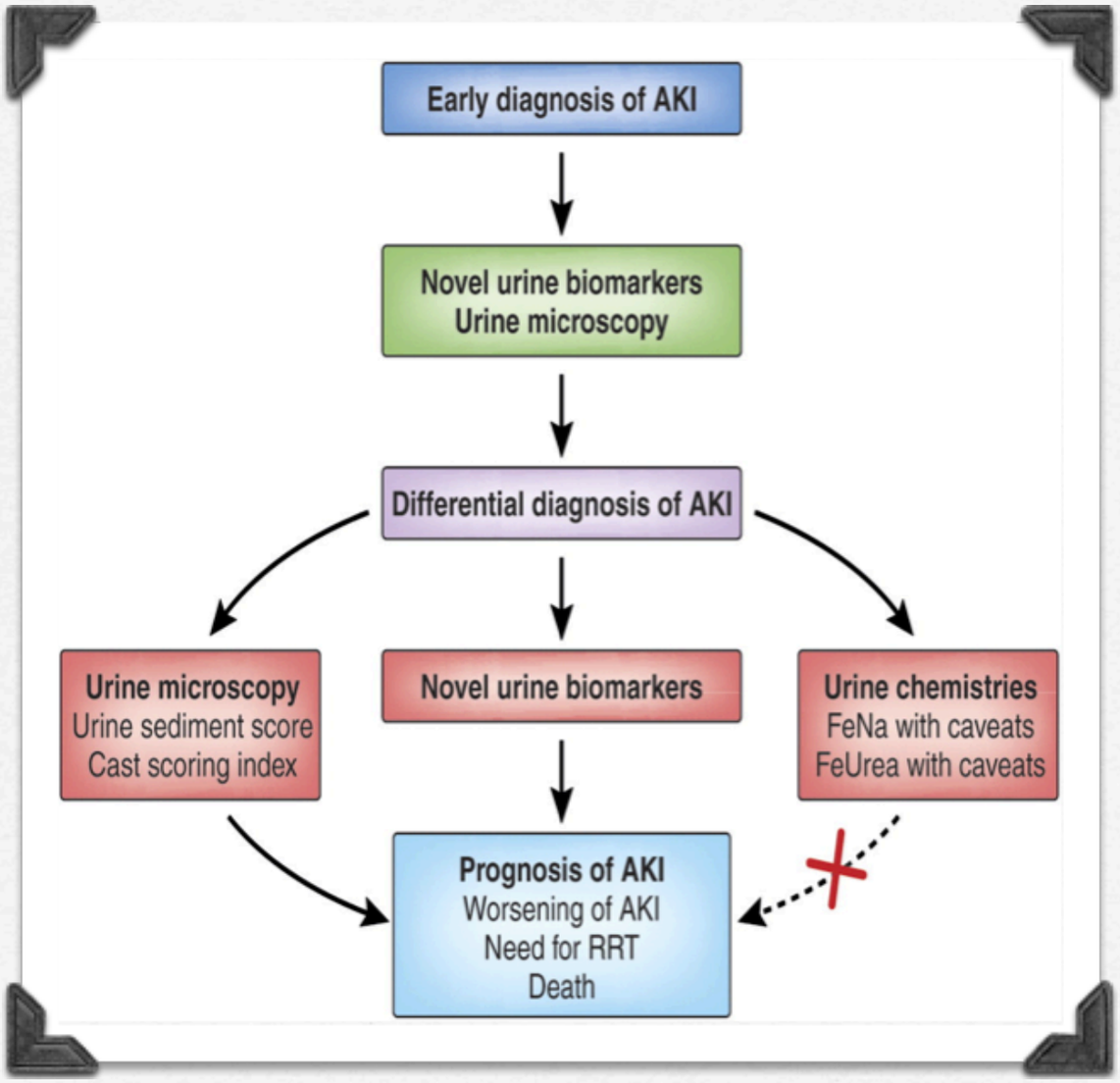
Score	Description
1	RTE cells 0 and granular casts 0
2	RTE cells 0 and granular casts 1 to 5 or RTE cells 1 to 5 and granular casts 0
3	RTE cells 1 to 5 and granular casts 1 to 5 or RTE cells 0 and granular casts 6 to 10 or RTE cells 6 to 20 and granular casts 0



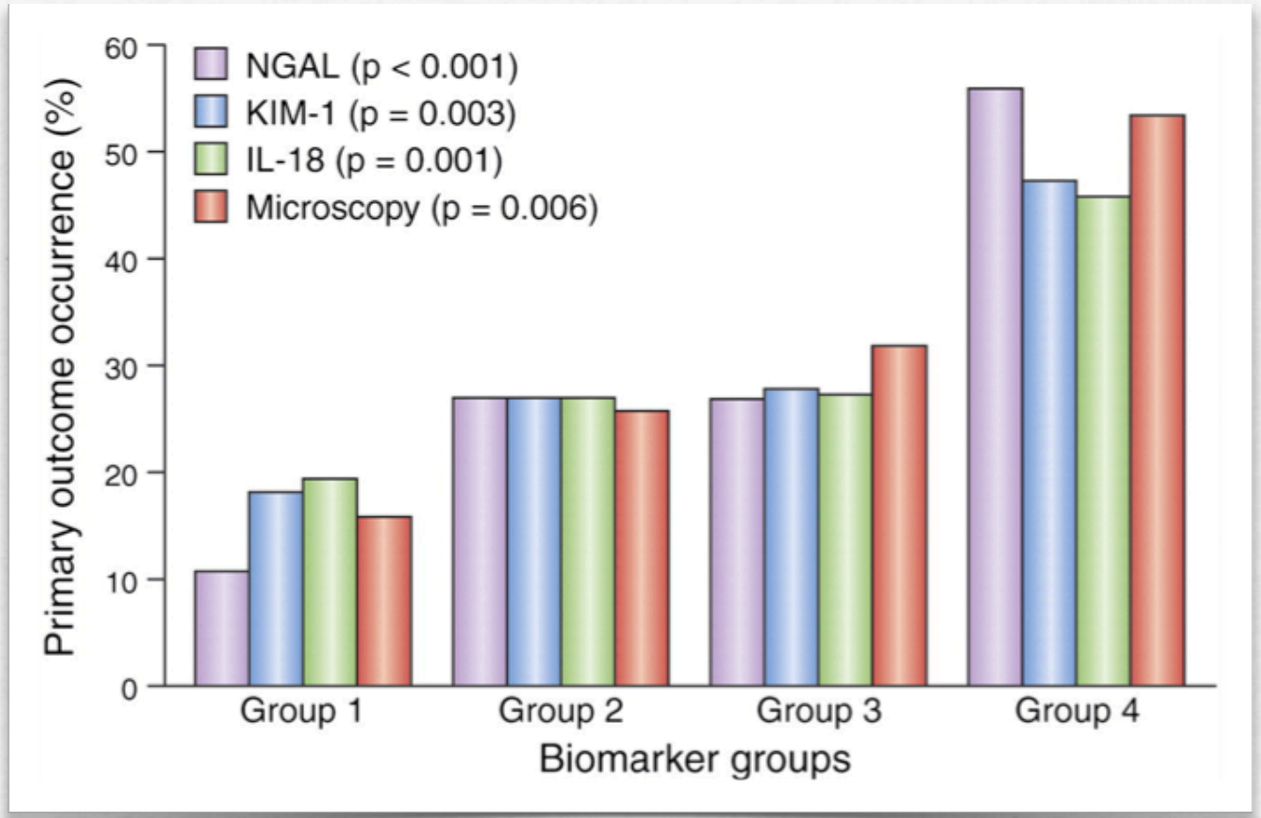
Perazella M A , G. Coca S CJASN 2012;7:167-174

- Urine profile in ATN: * renal tubular epithelial cells
  * coarse granular, muddy brown
  or mixed cellular casts

Biomarkers not only for accurate diagnosis



Primary outcome occurrence: worsened AKI or in-hospital death



Urine biomarker groups (NGAL, IL-18, KIM-1 in quartiles and urine microscopy score of 0, 1, 2, ≥3

Perazella M A , G. Coca S CJASN 2012;7:167-174

BIOMARKERS

EVALUATION

Ana Luisa Papoila, Faculdade de Ciências Médicas da UNL, CEAUL, Portugal

Understanding

BIOMARKERS

"biological characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes or pharmacologic response to therapeutic interventions".

Classification and prediction

Understanding

Classification and prediction

- **Diagnostic markers**

Used in people with signs or symptoms, to aid in assessing whether they have the condition under study

- **Screening markers**

Used in asymptomatic people, to detect a disease or condition at an early stage

- **Prognostic markers**

Used in subjects diagnosed with a condition, to predict subsequent outcomes, such as disease relapse or progression

Understanding

- Model ‘the risk of disease” (disease outcome) with, for instance, logistic (or Cox) regression. A marker is considered useful if it has a strong effect on risk.
- Evaluate classification performance – Receiver Operating Characteristic Curve (ROC)

Discretization procedure

Sensitivity, specificity, predictive values and likelihood ratios

Understanding

however

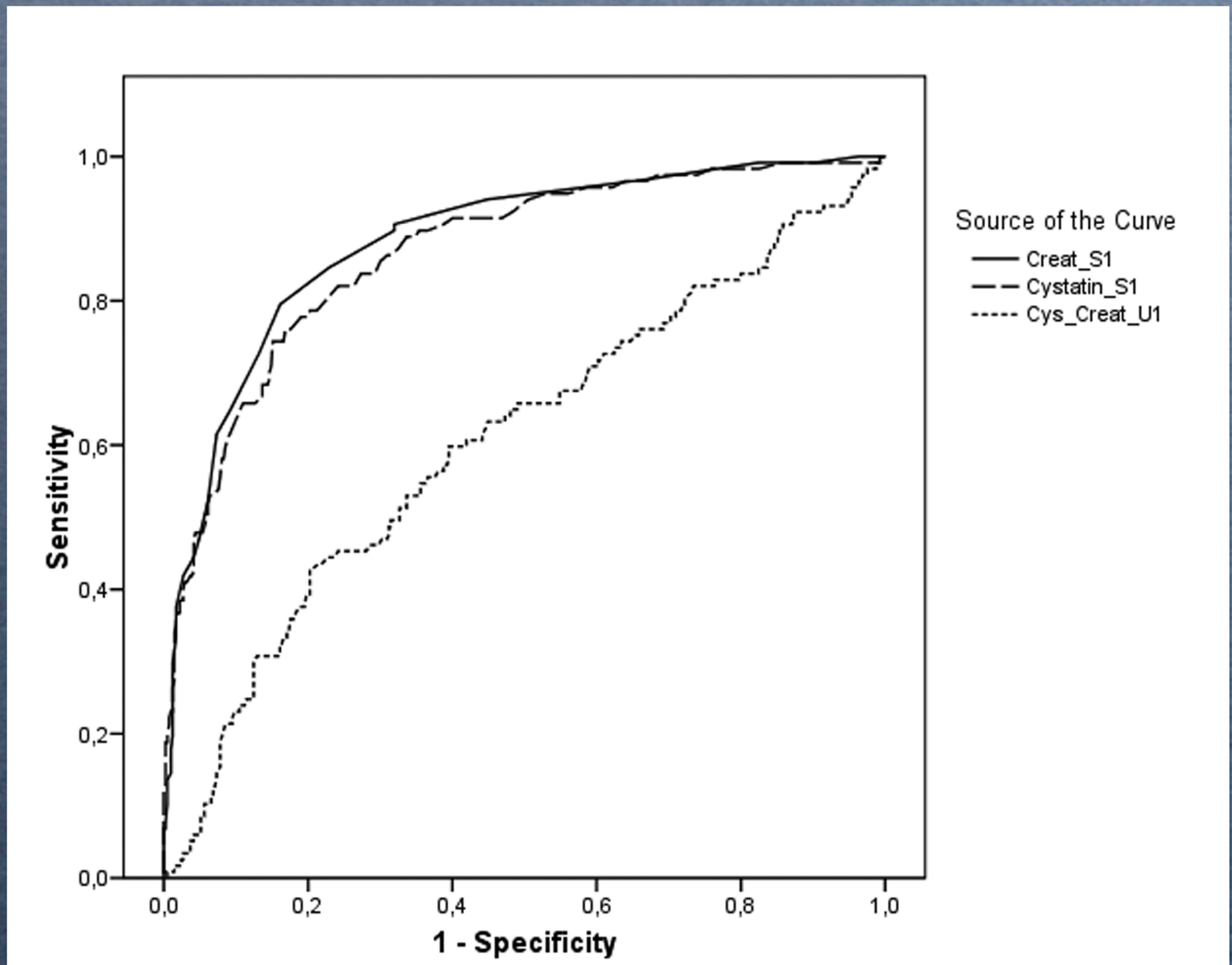
Results from these two evaluations may be apparently contradictory: A marker that is a strong predictor of risk may have a poor discriminative performance

Predictiveness curves

Ying Huang et al. 2007. Evaluating the predictiveness of a continuous marker. *Biometrics* **63**,

Understanding

Risk prediction



S Creatinine

AUC=0.88

95% CI: 0.85-0.92

S Cystatin C

AUC=0.87

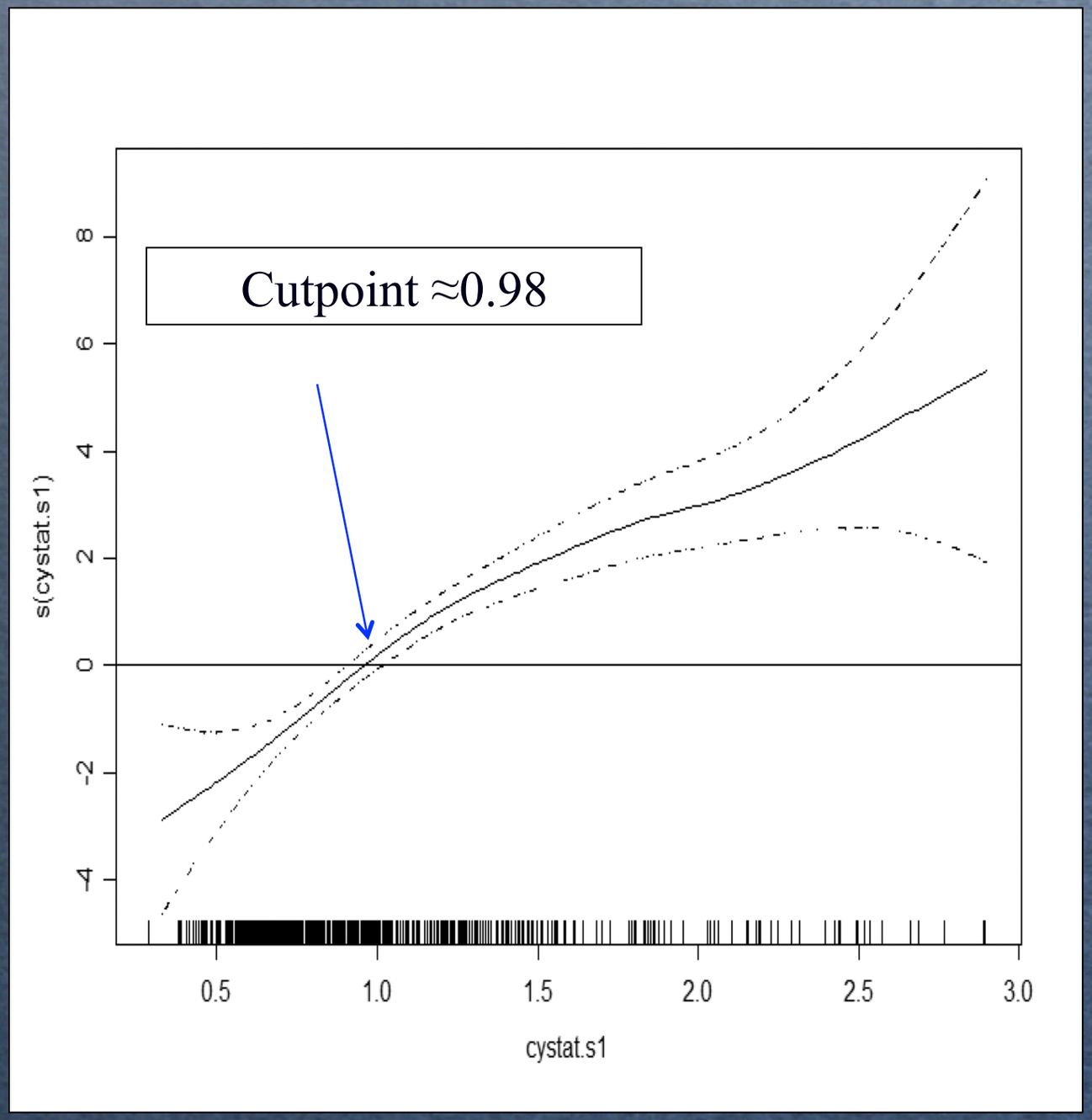
95% CI: 0.83-0.90

U CysC

AUC=0.61

95% CI: 0.55-0.67

Understanding



SCysC: Cupoint= 0.98

Sensitivity: 81.40%

Specificity: 76.70%

PPV: 48.20%

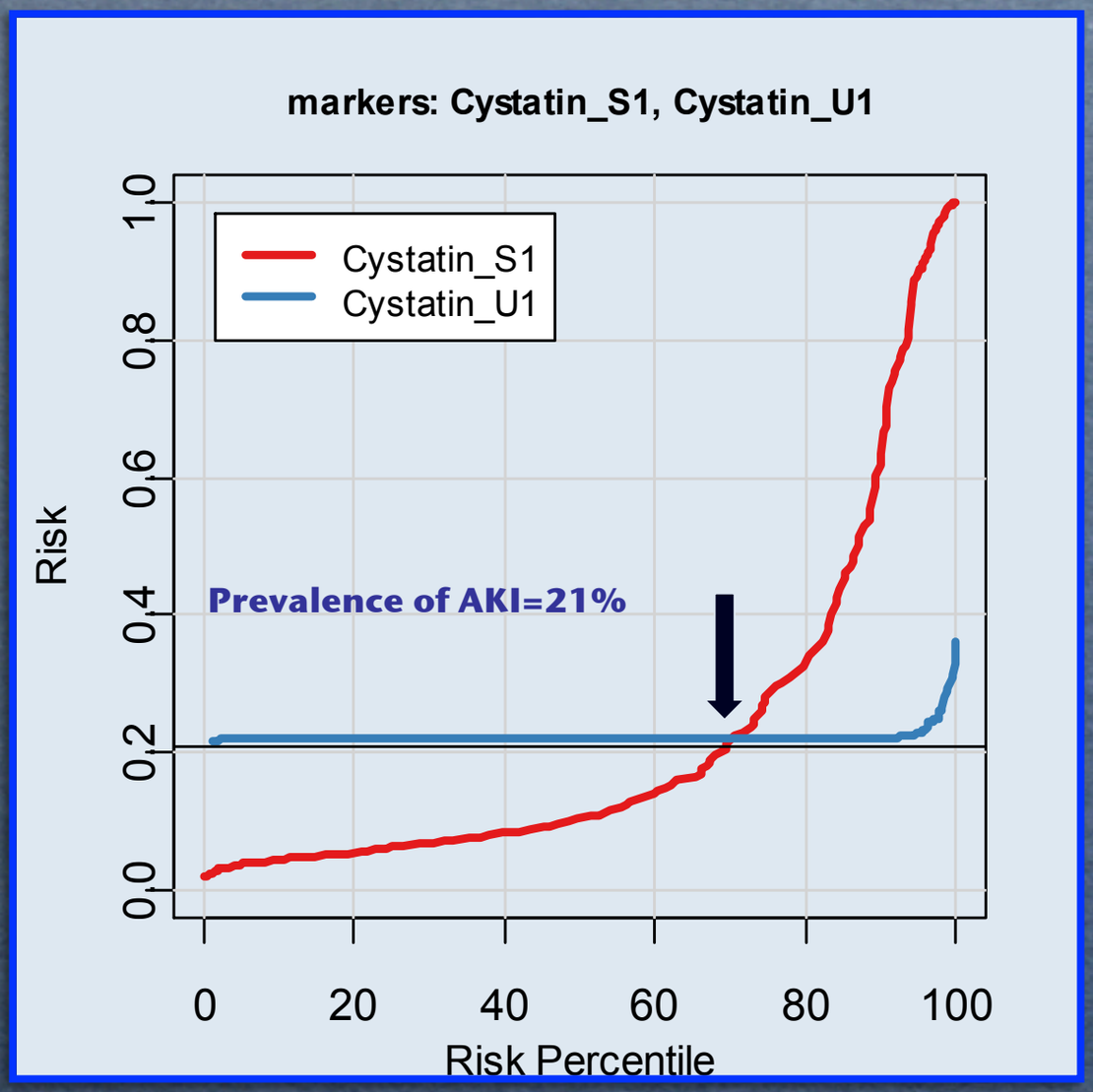
NPV: 93.90%

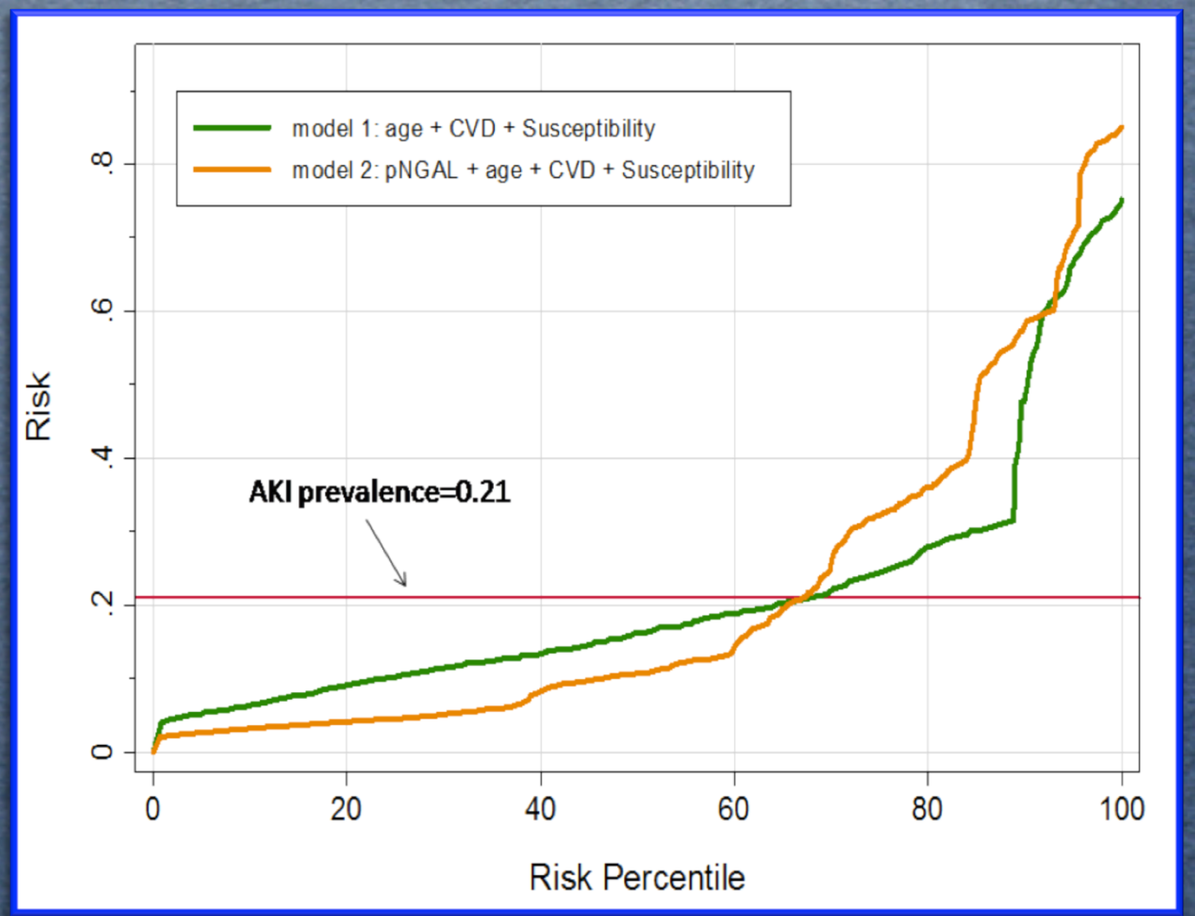
LR (+): 3.49

LR (-): 0.24

Understanding

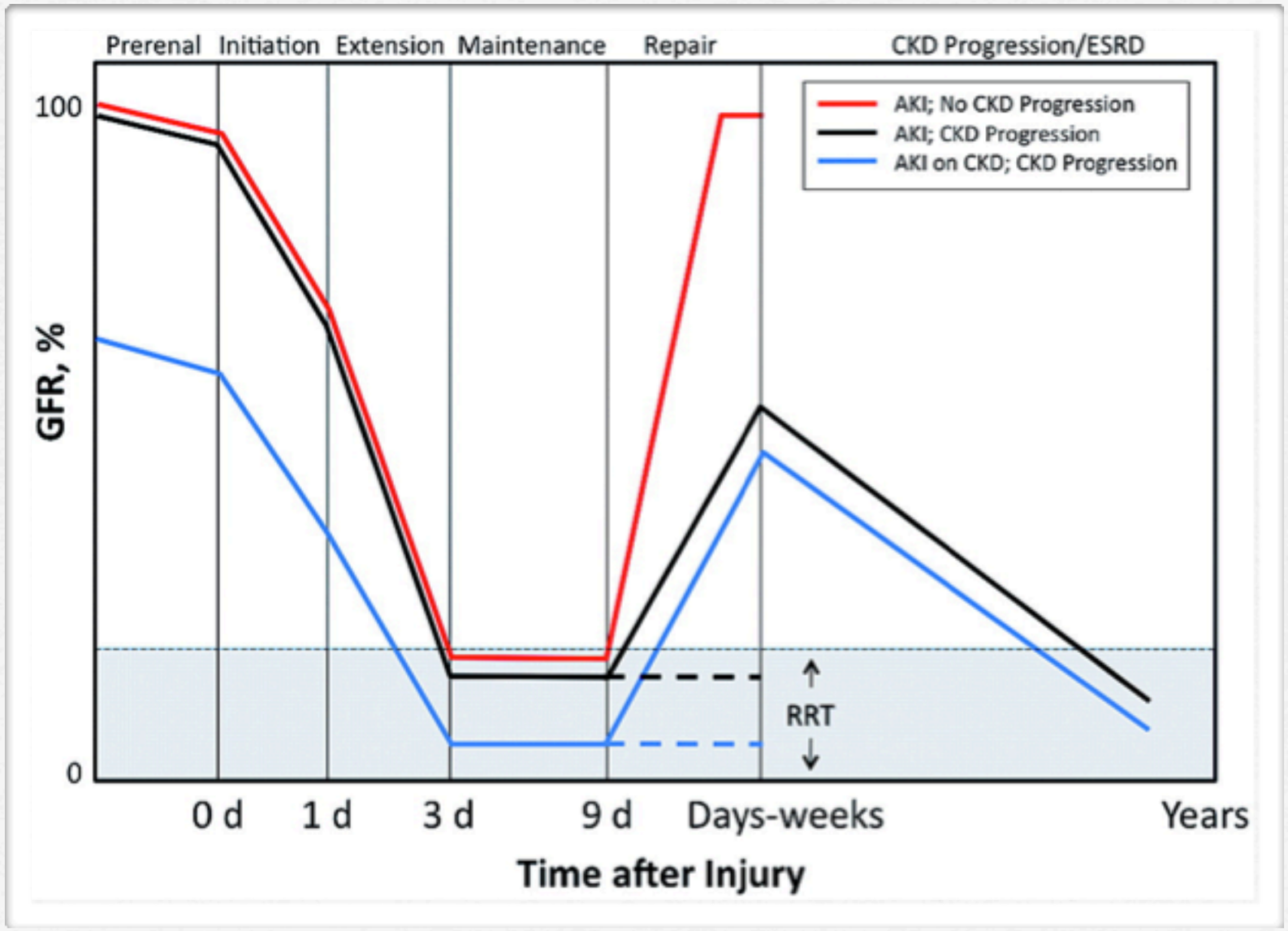
Application to risk prediction for AKI markers





Changing concepts

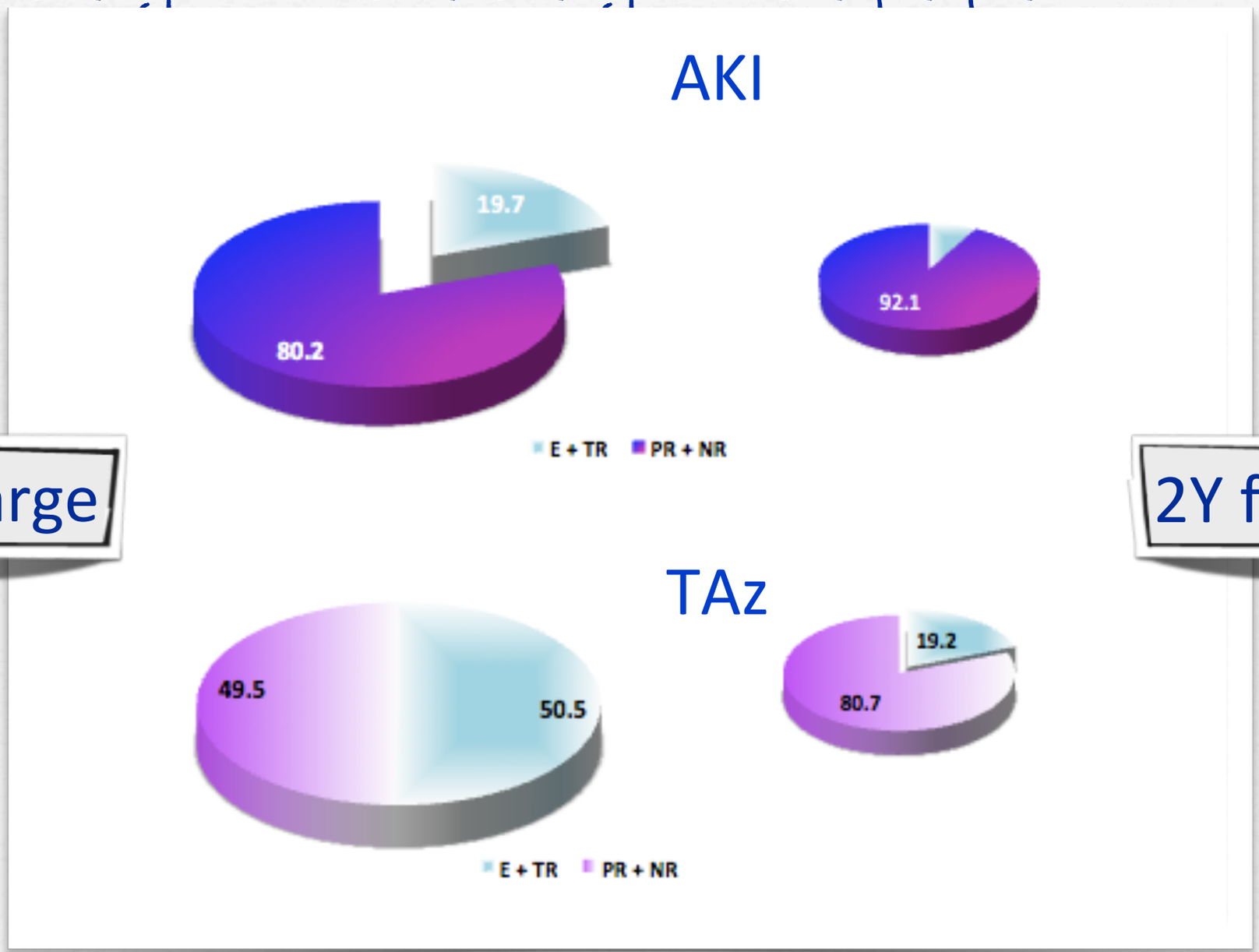
➡ Natural History of AKI leading to chronic disease



Sutton TA et al. Kidney Int 62, 2002; modified by Okusa et al. CAJSN 4, 2009

Changing concepts

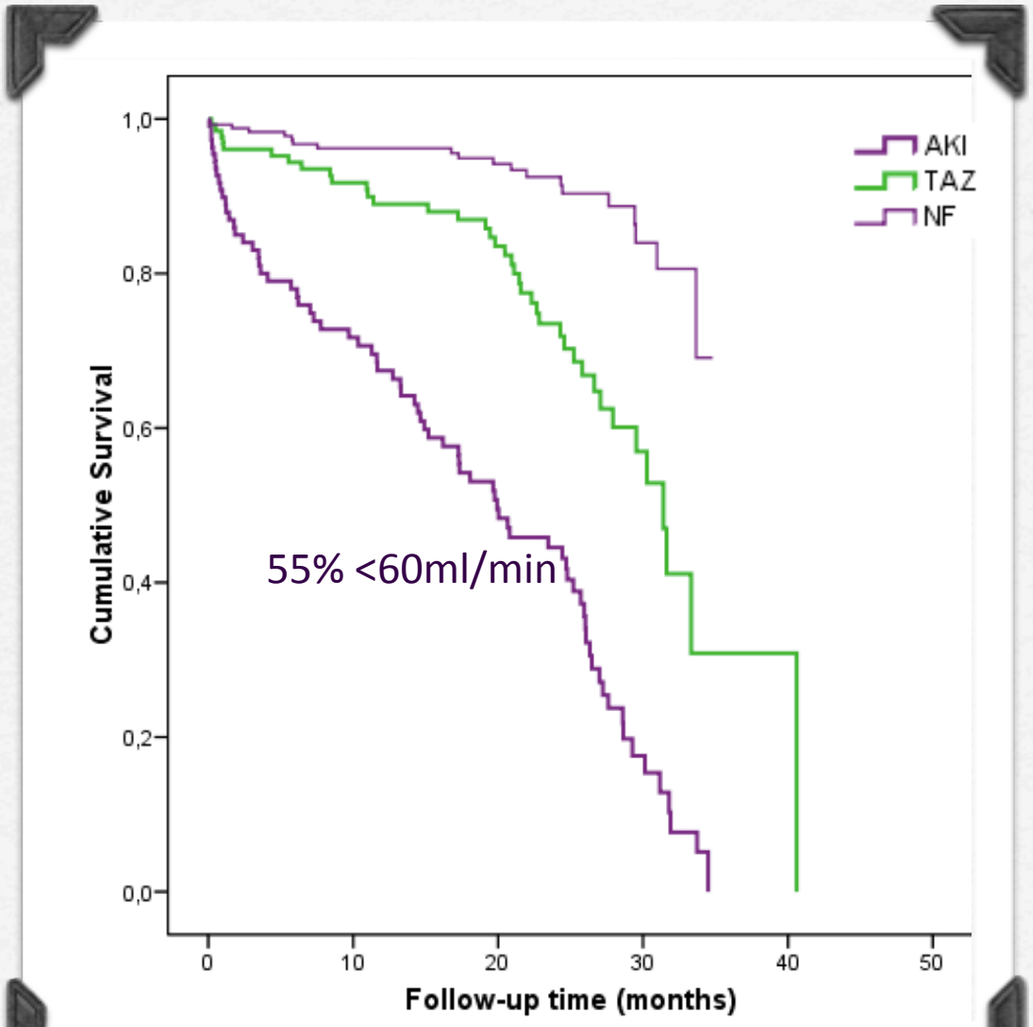
- Partial recovery and No-recovery is more frequent than we thought



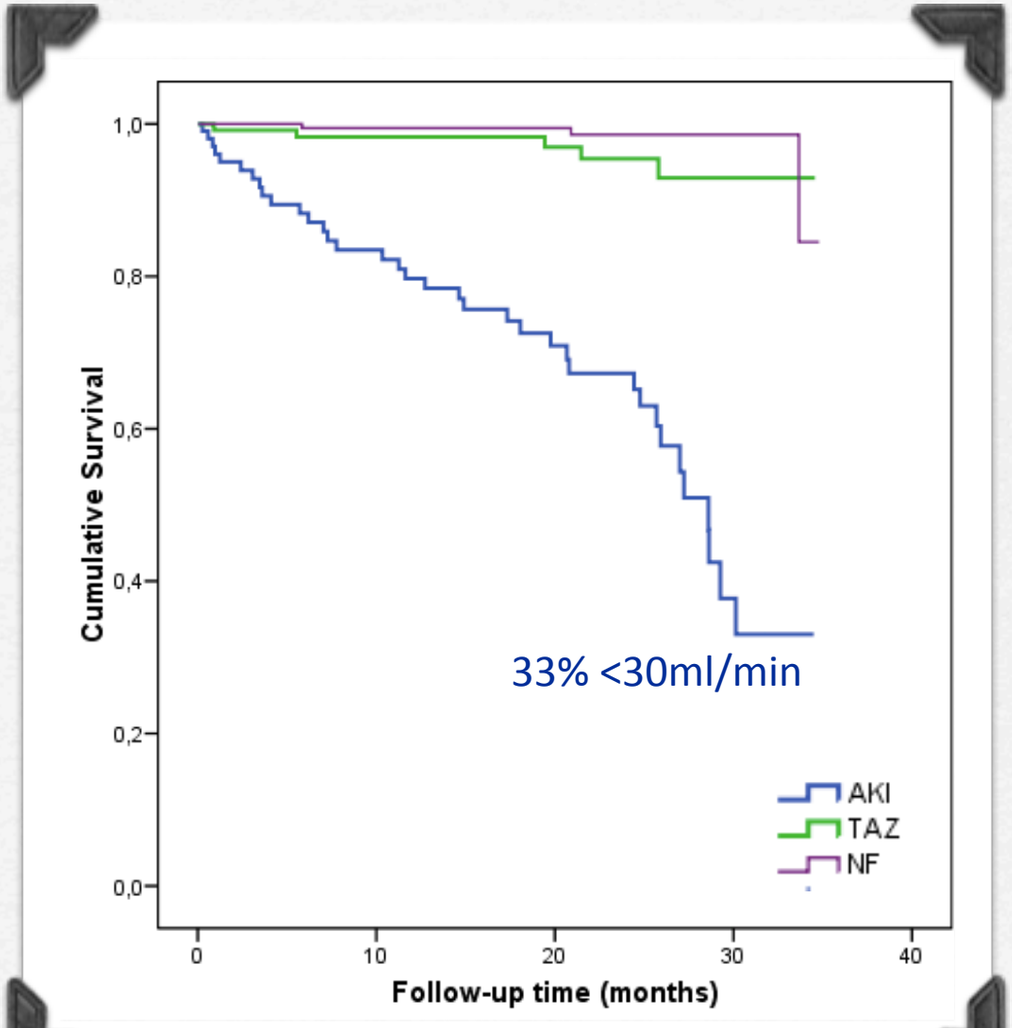
Soto et. al 2012

Changing concepts

➡ Renal survival decrease after an AKI episode



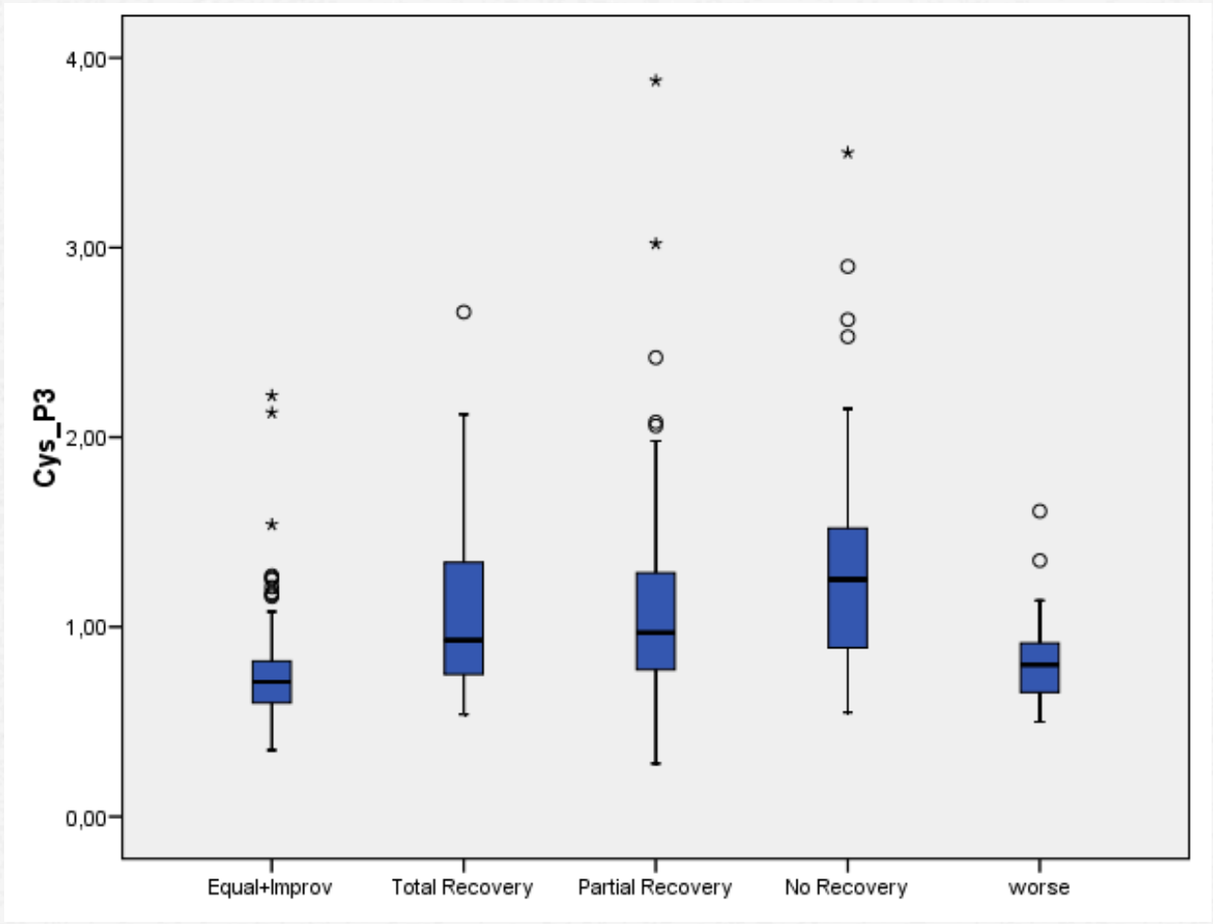
Survival to CKD3

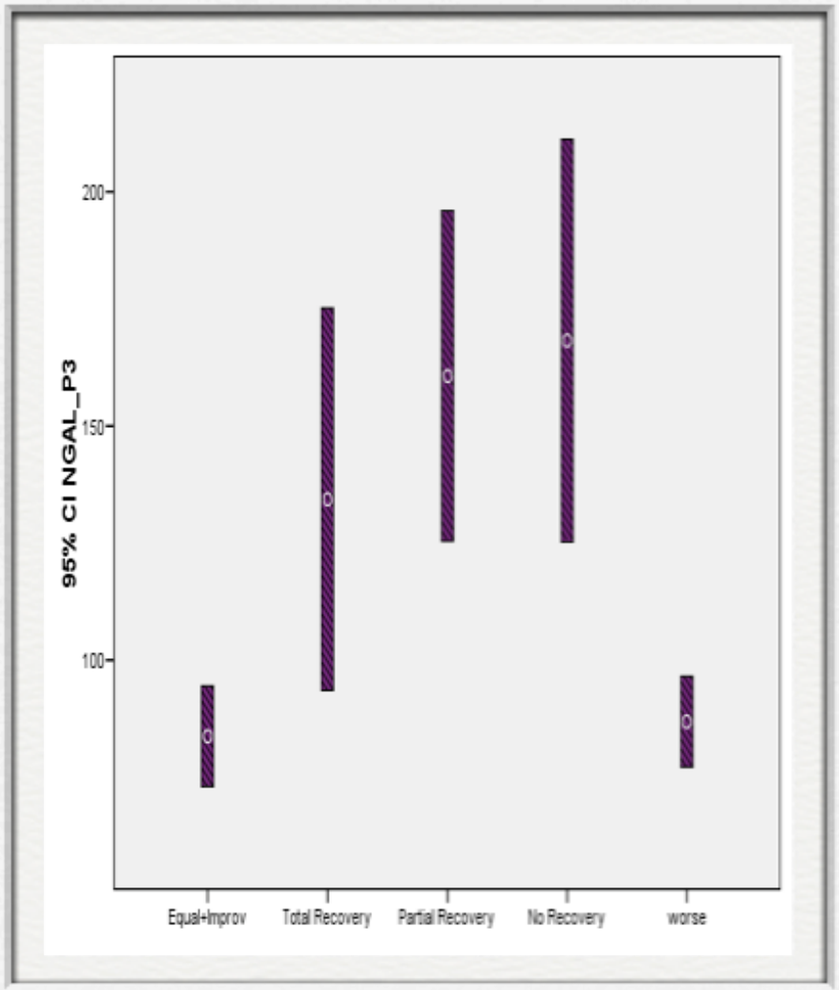


Survival to CKD4

Soto et. al 2012

Searching for predictors of renal outcome

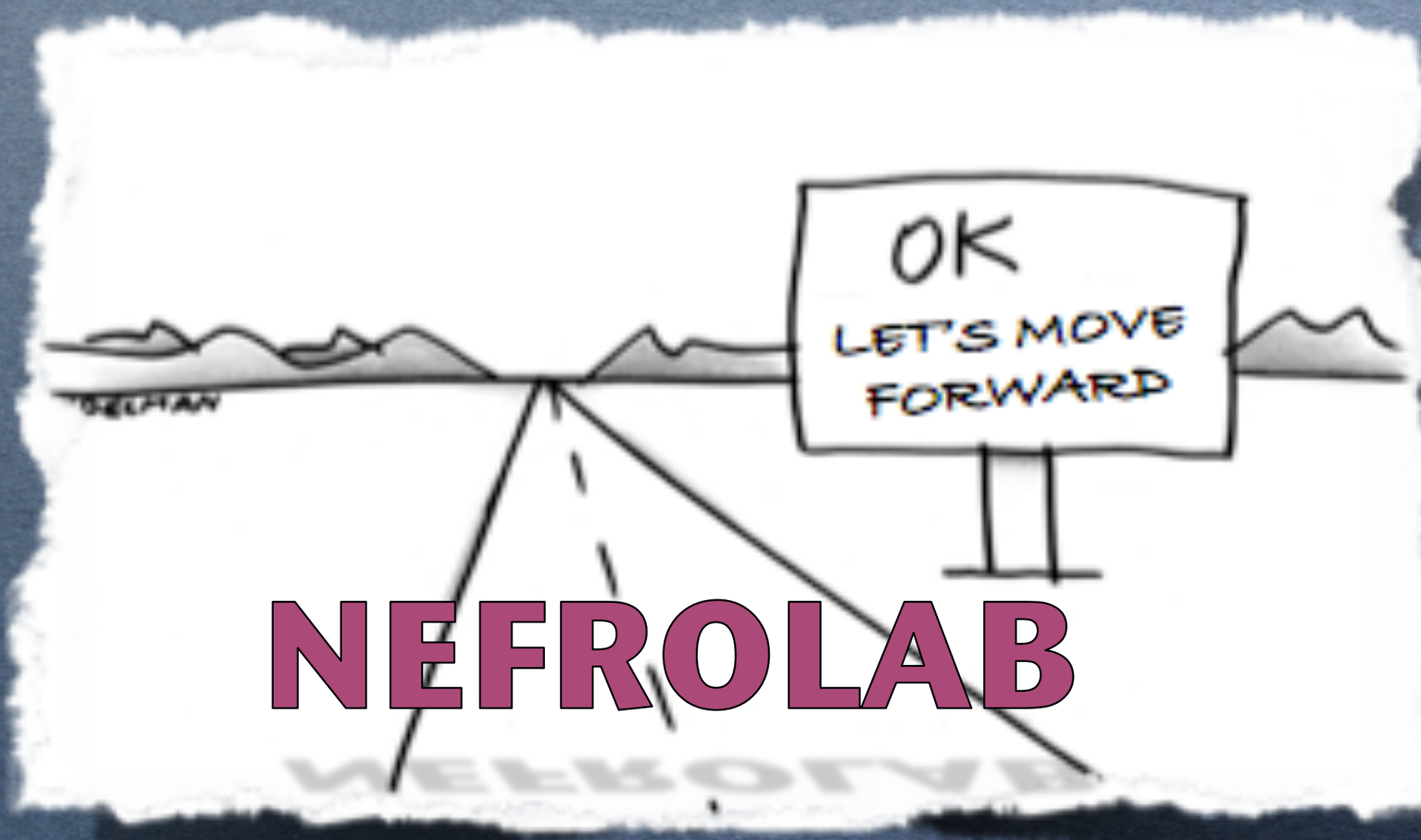




pNGAL and CysC as a biomarkeres of kidney evolution

Soto et. al 2012

And now?



NEFROLAB

for homework:

- change our point of view about AKI, as a continuous disease that leads to renal imprint
- we have a lot to do, let's start using clinical markers
- Applying concepts to clinical practice
- following those patients emphasizing nephroprotection
- let's work together searching for solutions

thanks for sharing our concerns