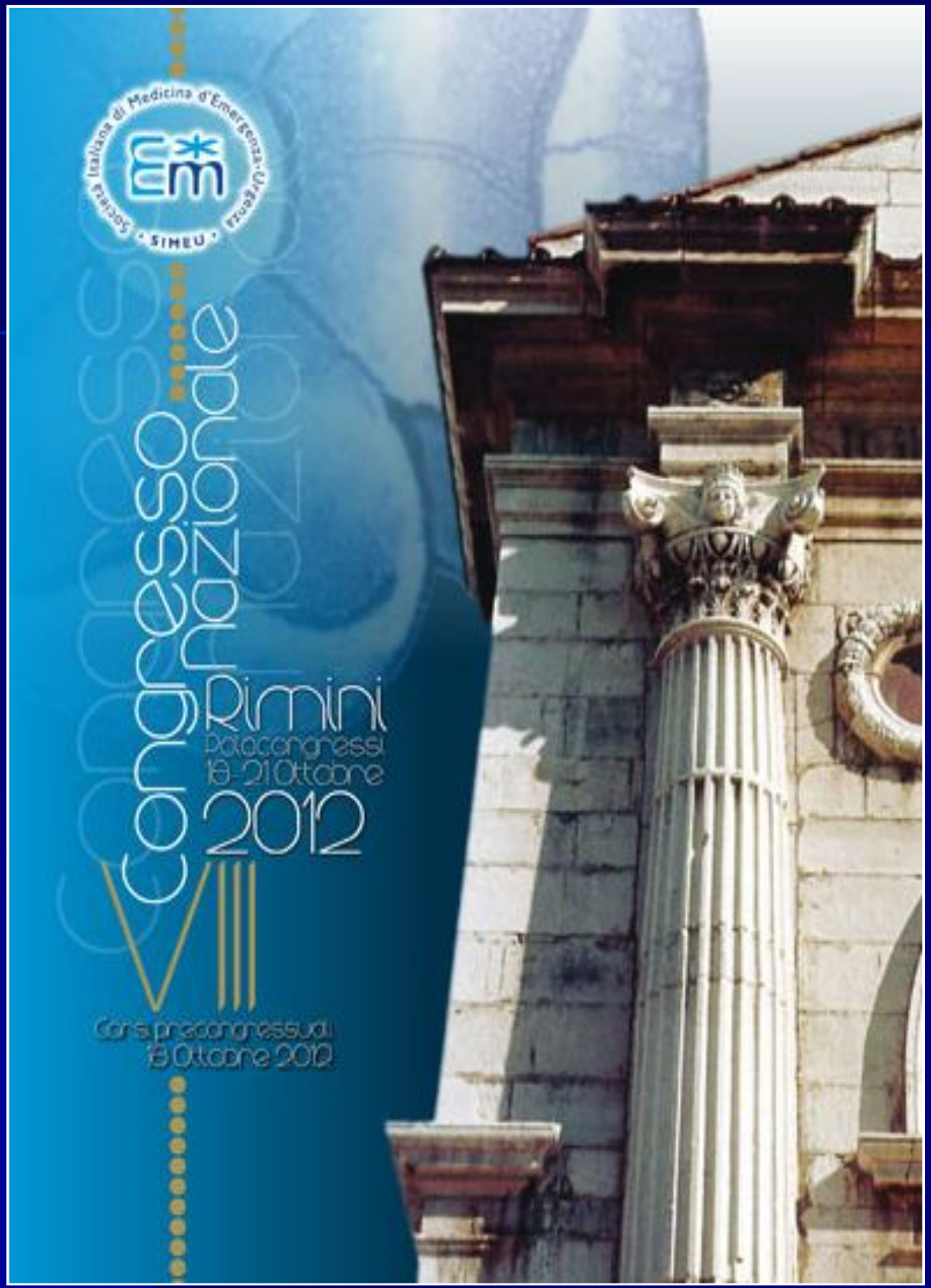
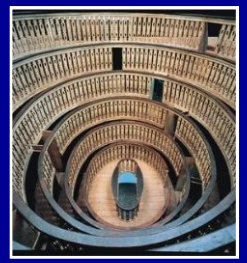


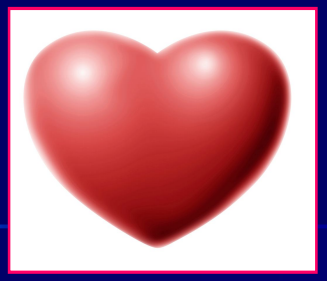
INSUFFICIENZA RENALE ACUTA

Marcatori precoci di danno



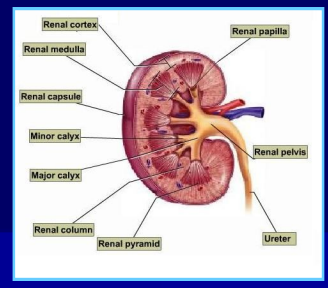
Mario Plebani

University-Hospital of Padova, Italy



Myocardial Diseases

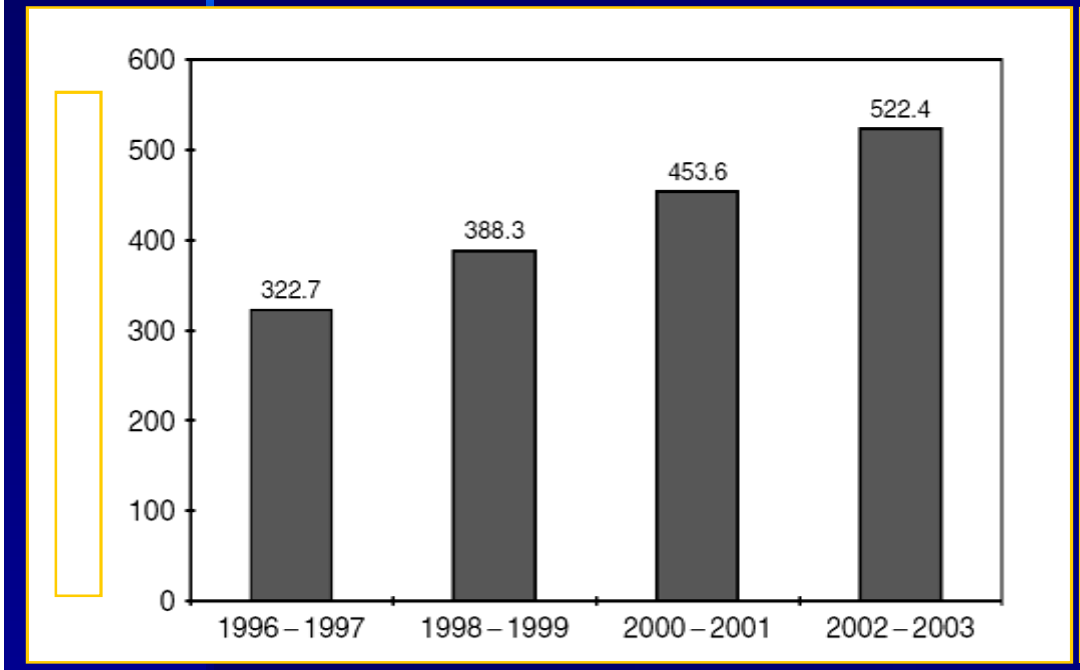
Kidney Diseases



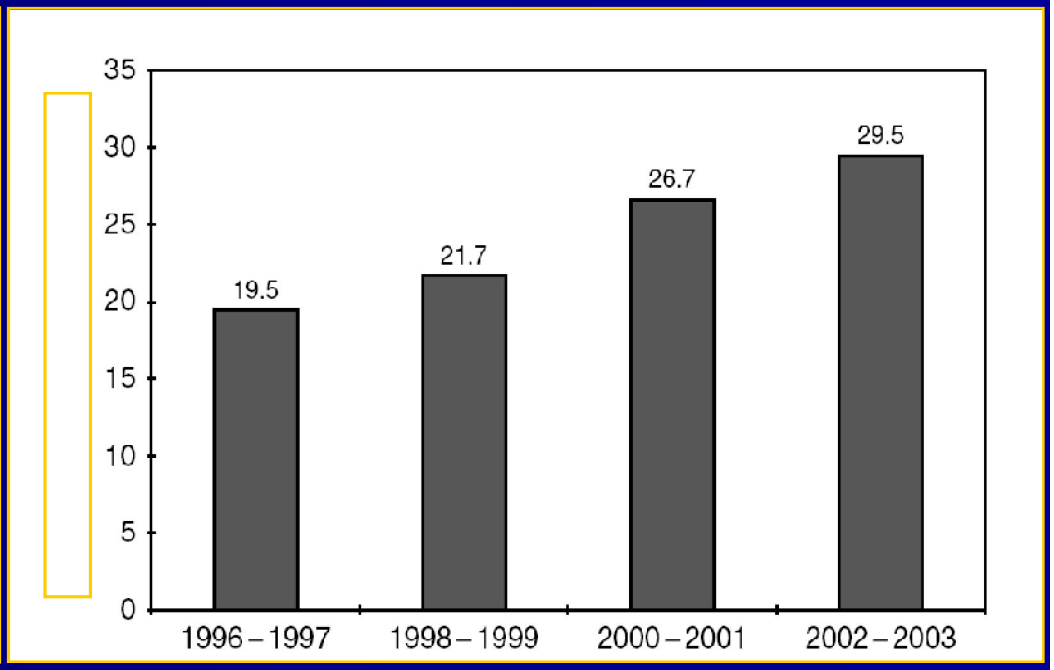
- **1886$_s$** - **Creatinine (Jaffe reaction)**
- **1950$_s$** **AST**
- **1960$_s$** **CK**
- **1970$_s$** **CK and LDH Isoenzymes**
- **1980$_s$** **CK-MB Mass**
- **1990$_s$** Troponins

Community-based incidence rates of AKI

AKI non requiring dialysisis



AKI requiring dialysisis

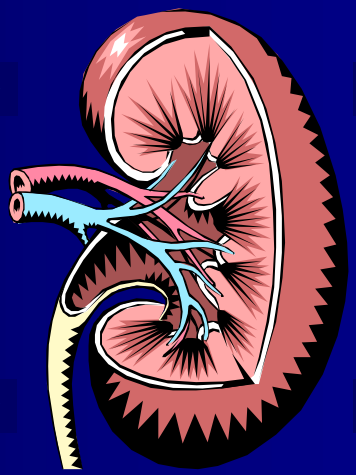


The number of cases of AKI is progressively increasing
The demand for renal replacement therapy is increasing
The cost for patients requiring RRT is higher than average

Le cause più comuni di AKI in ambito ospedaliero

Interventi chirurgici (es. bypass coronarico)

Agenti nefrotossici (es. mezzi di contrasto)

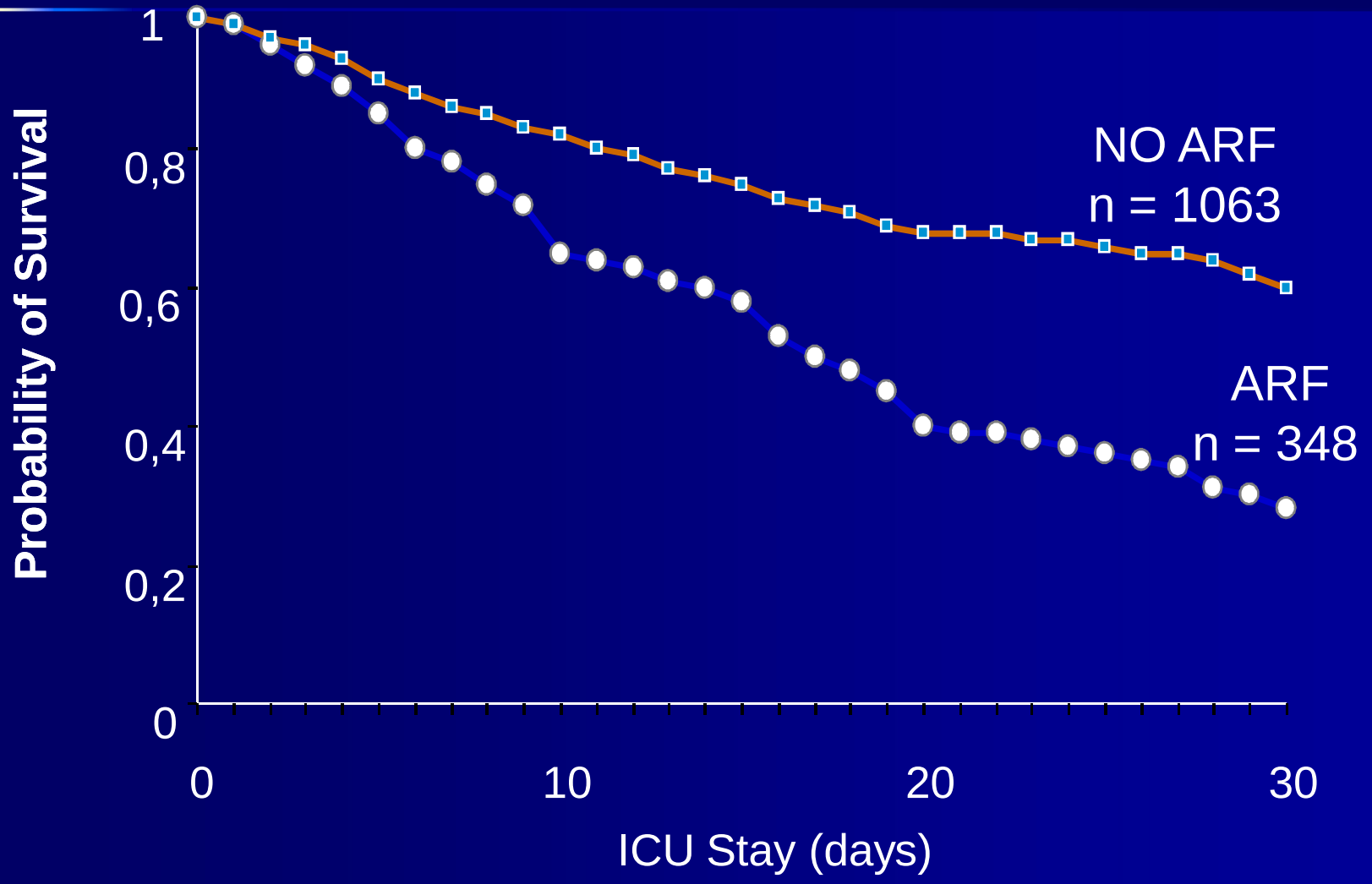


Sepsi, insufficienza multisistemica

Malattie critiche (es. scompenso cardiaco)

Adattata da: Parikh CR e Devarajan P, Crit Care Med 2008; 36: S159-S165

AKI:
an independent risk factor of mortality

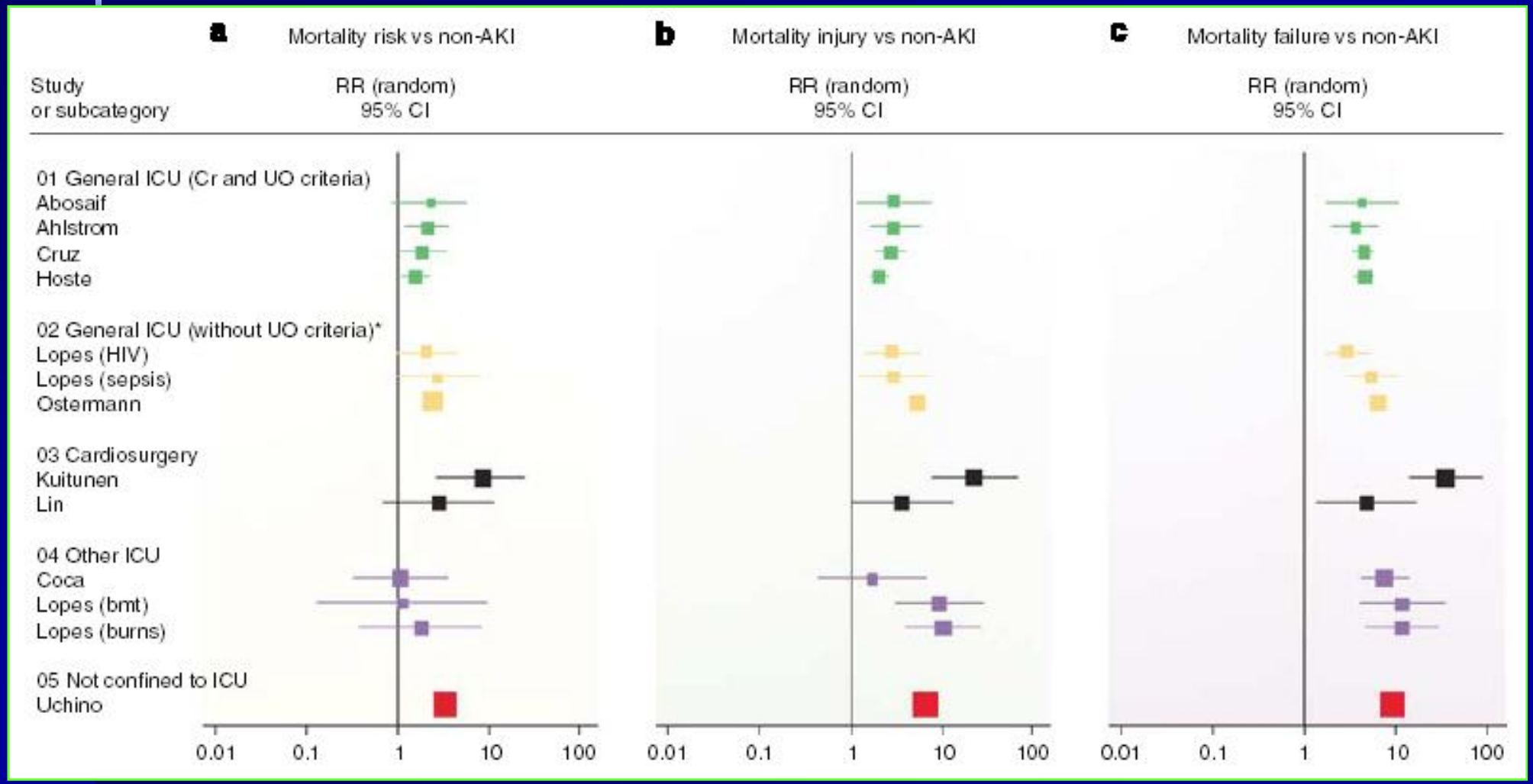


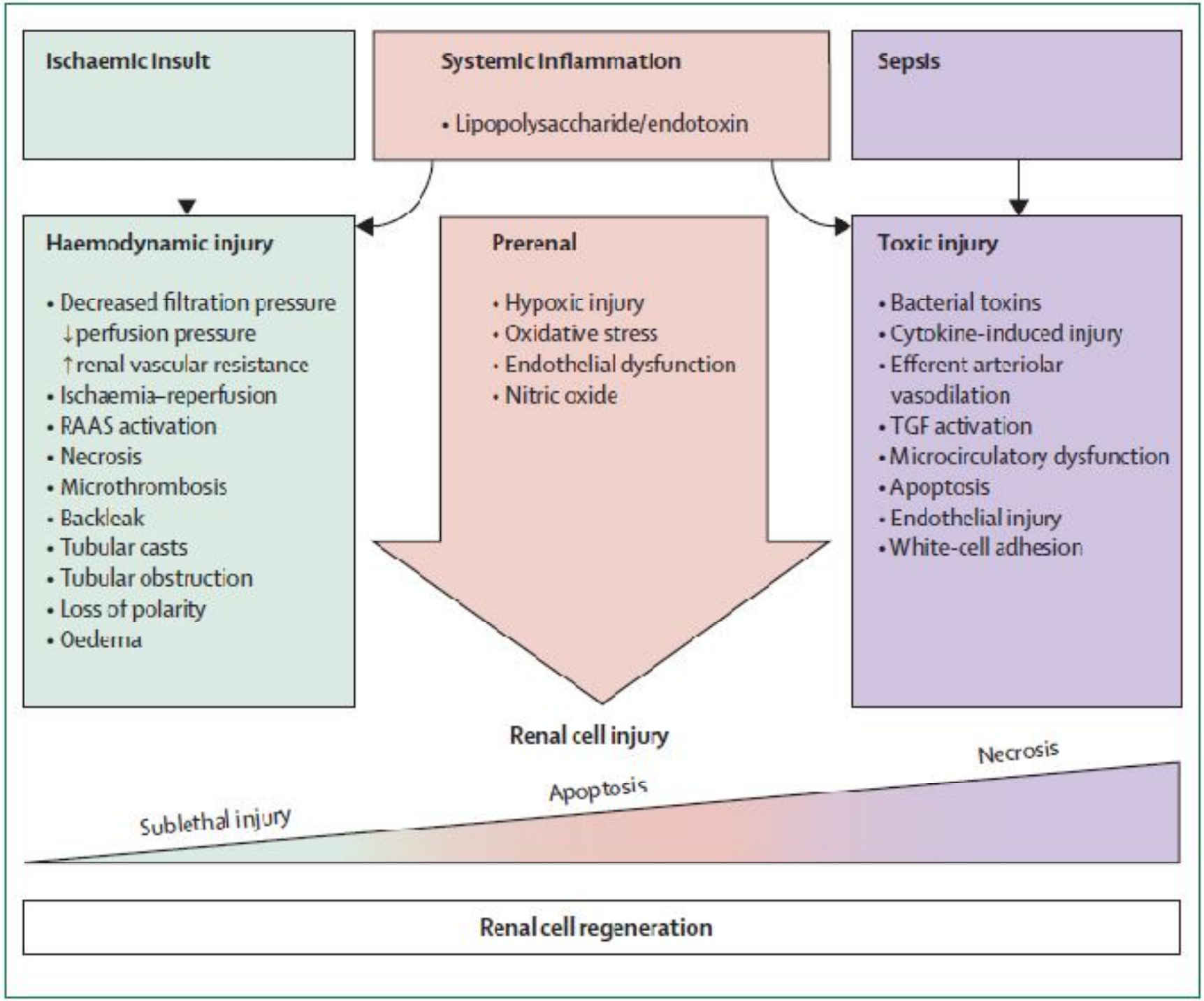
De Mendonça A et al. Intensive Care Med 26 : 915-921, 2000

The RIFLE criteria and mortality in acute kidney injury: A systematic review

Z Ricci[1], D Cruz[2,3] and C Ronco[2,3]

[1]Department of Pediatric Cardiosurgery, Bambino Gesù Hospital, Rome, Italy; [2]Department of Nephrology, Dialysis and Transplantation, S Bortolo Hospital, Vicenza, Italy and [3]International Renal Research Institute Vicenza (IRRIV), Vicenza, Italy

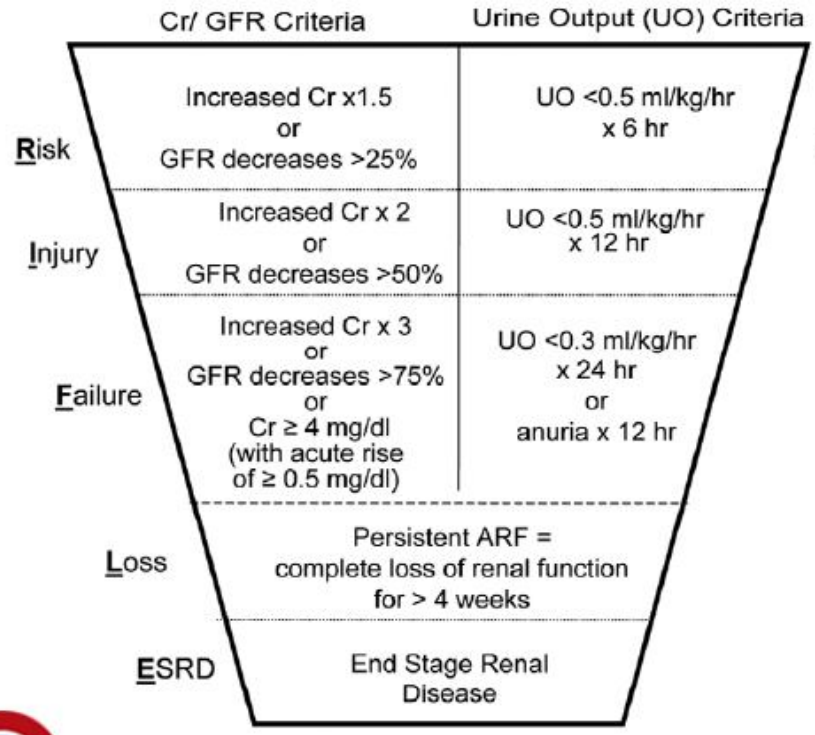



Ischaemic insult
Systemic inflammation
• Lipopolysaccharide/endotoxin
Sepsis
Haemodynamic injury
• Decreased filtration pressure
↓perfusion pressure
↑renal vascular resistance
• Ischaemia–reperfusion
• RAAS activation
• Necrosis
• Microthrombosis
• Backleak
• Tubular casts
• Tubular obstruction
• Loss of polarity
• Oedema
Prerenal
• Hypoxic injury
• Oxidative stress
• Endothelial dysfunction
• Nitric oxide
Toxic injury
• Bacterial toxins
• Cytokine-induced injury
• Efferent arteriolar vasodilation
• TGF activation
• Microcirculatory dysfunction
• Apoptosis
• Endothelial injury
• White-cell adhesion
Renal cell injury
Sublethal injury
Apoptosis
Necrosis
Renal cell regeneration

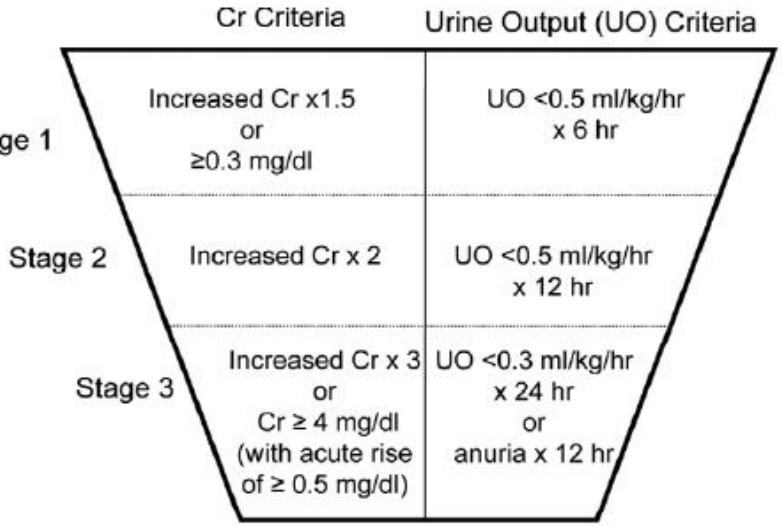
AKI: a problem of definition

CRITERI RIFLE E AKIN PER LA DIAGNOSI DI AKI

RIFLE



AKIN



Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

Cruz DN. *Crit Care, 2009*, 13: 211-220

CRITERI RIFLE e LIMITI

- I segni clinici di AKI compaiono solo dopo significative diminuzioni del GFR;
- I campioni di urina di 6 e 12 h non vengono usualmente raccolti e non possono perciò essere considerati negli studi retrospettivi;
- I valori di creatinina e GFR fanno riferimento ad un basale che spesso non è disponibile;
- Il calcolo di eGFR con MDRD non è appropriato in caso di modifiche rapide della funzionalità renale;
- Anche modeste variazioni della creatinina si associano a “poor outcomes”;
- Non considerano il sito e la natura del danno che fa precipitare la funzione renale.

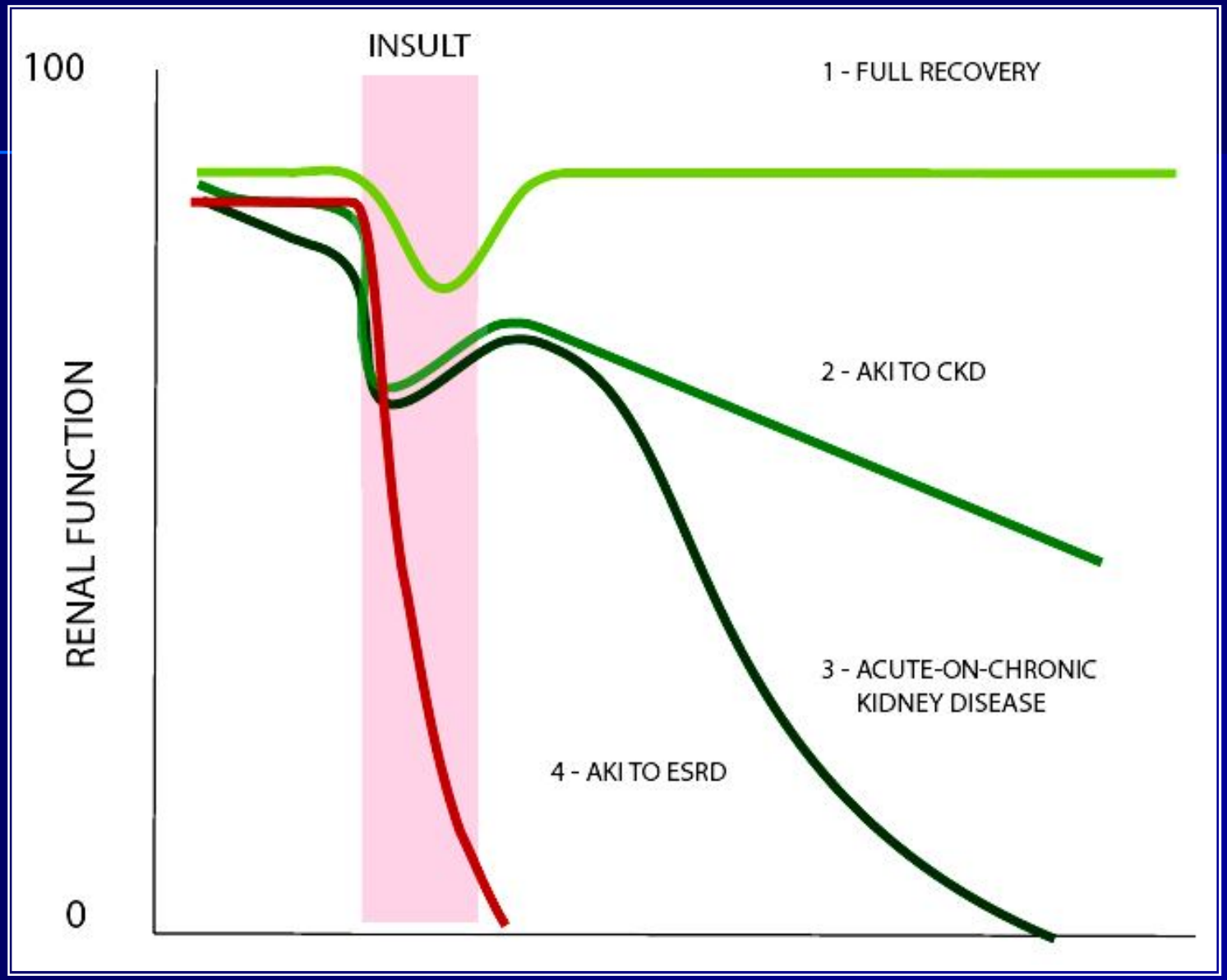
AKI stage e misura surrogata della creatinina basale

Table 2 | Surrogate measures for baseline serum creatinine used to establish AKI diagnosis and severity[24]

Surrogate measures for baseline serum creatinine level	AKI diagnosis (%)			Misclassification of AKI severity by AKIN Stage (%)	
	Frequency*	Sensitivity	Specificity	Any AKIN stage	AKIN Stage 1 and 2 only
MDRD back-estimation	38.3	84.2	77.4	29.5	11.6
Nadir level in hospital	35.9	81.7	79.8	24.0	5.2
Level at hospital admission	13.7	38.9	94.9	18.0	4.9

*For comparison purposes, the frequency of AKI in patients for whom baseline serum creatinine levels were available was 25.5%.[24] Values <0.1 were imputed at 0.05 to compose this table.[24] Abbreviations: AKI, acute kidney injury; AKIN, AKI Network; MDRD; Modification of Diet in Renal Disease.

AKI: storia naturale



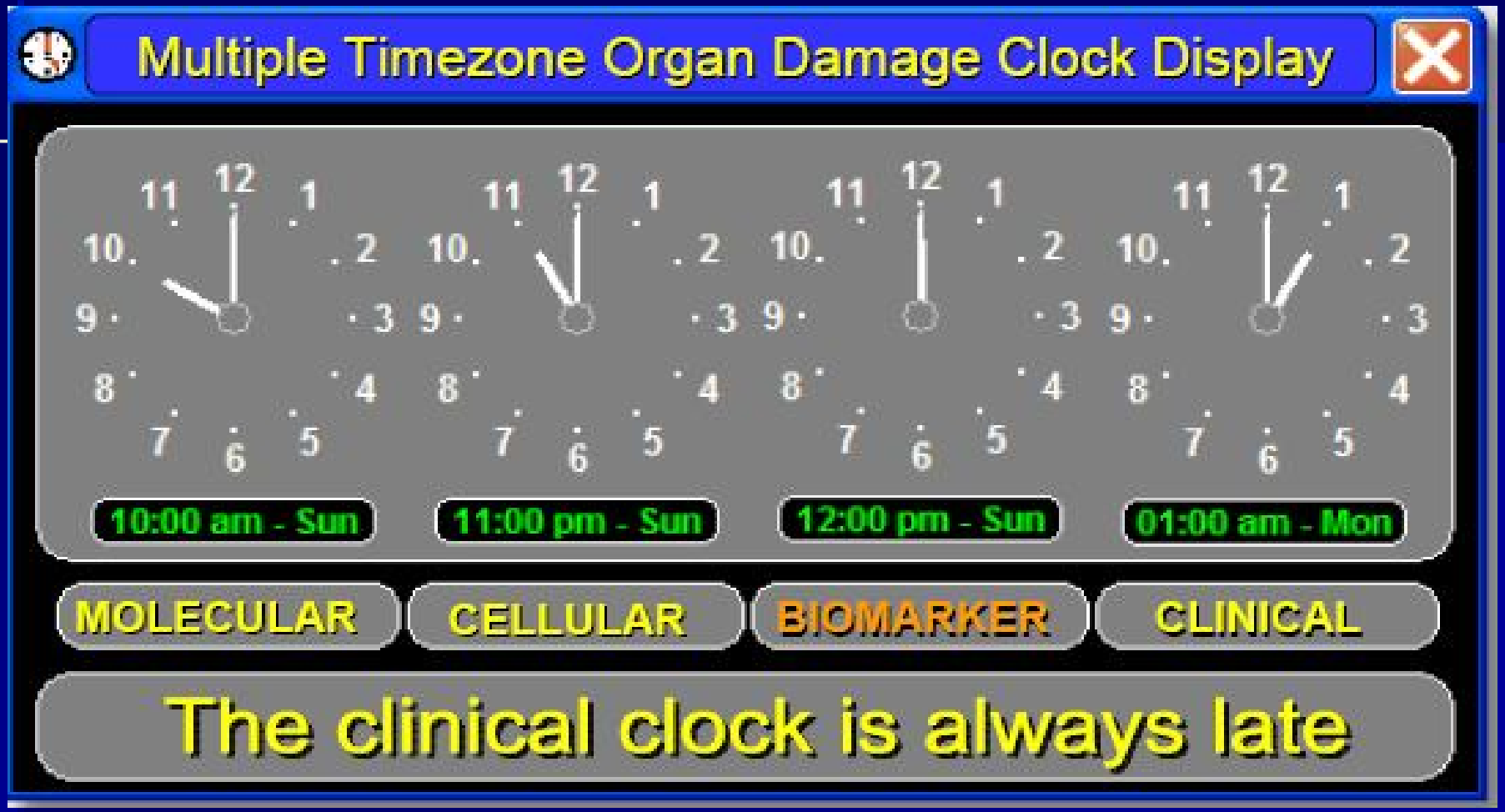
Cerdà J et al, Clin J Am Soc Nephrol 2008; 3: 881-886

ACUTE KIDNEY INJURY

- "Because ***acute kidney injury is asymptomatic untile extremes of loss of function*** are reached and has no characteristic clinical findings, diagnosis typically occurs in the context of another acute illness.
- Under most circumstances, ***AKI is diagnosed*** in high-risk contexts (eg, sepsis, major surgery, bleeding, volume losses) by ***laboratory tests.***
- Creatinine and urea concentrations are the standard diagnostic analytes".

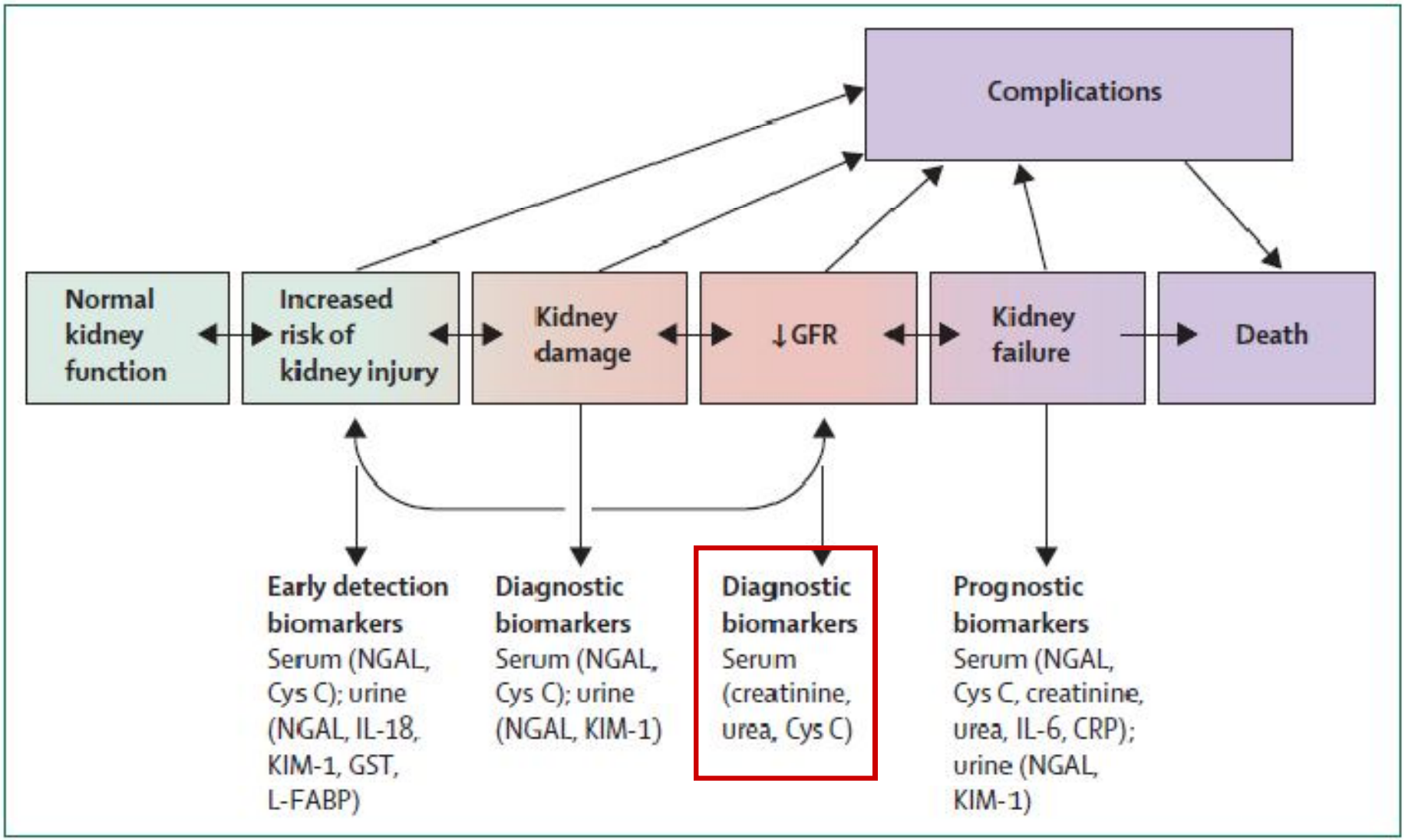
Bellomo R, et al. Lancet 2012

AKI: é possibile una diagnosi precoce?



Le manifestazioni cliniche di un danno renale acuto (aumento creatinina, contrazione diuresi) si manifestano molte ore dopo il danno molecolare

L'esigenza di disporre di nuovi biomarcatori che evidenzino l'insorgere di AKI ben prima dell'aumento della creatininemia costituisce una priorita'



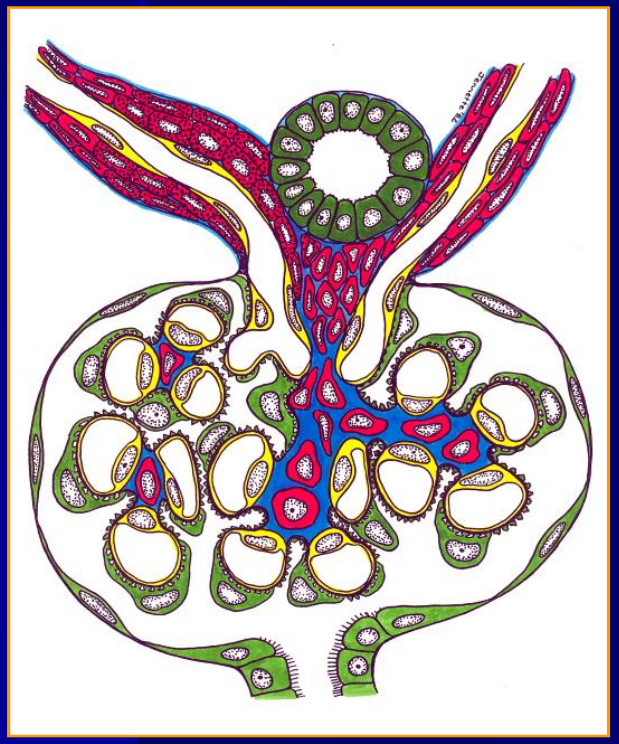
Bellomo R, et al. Lancet 2012

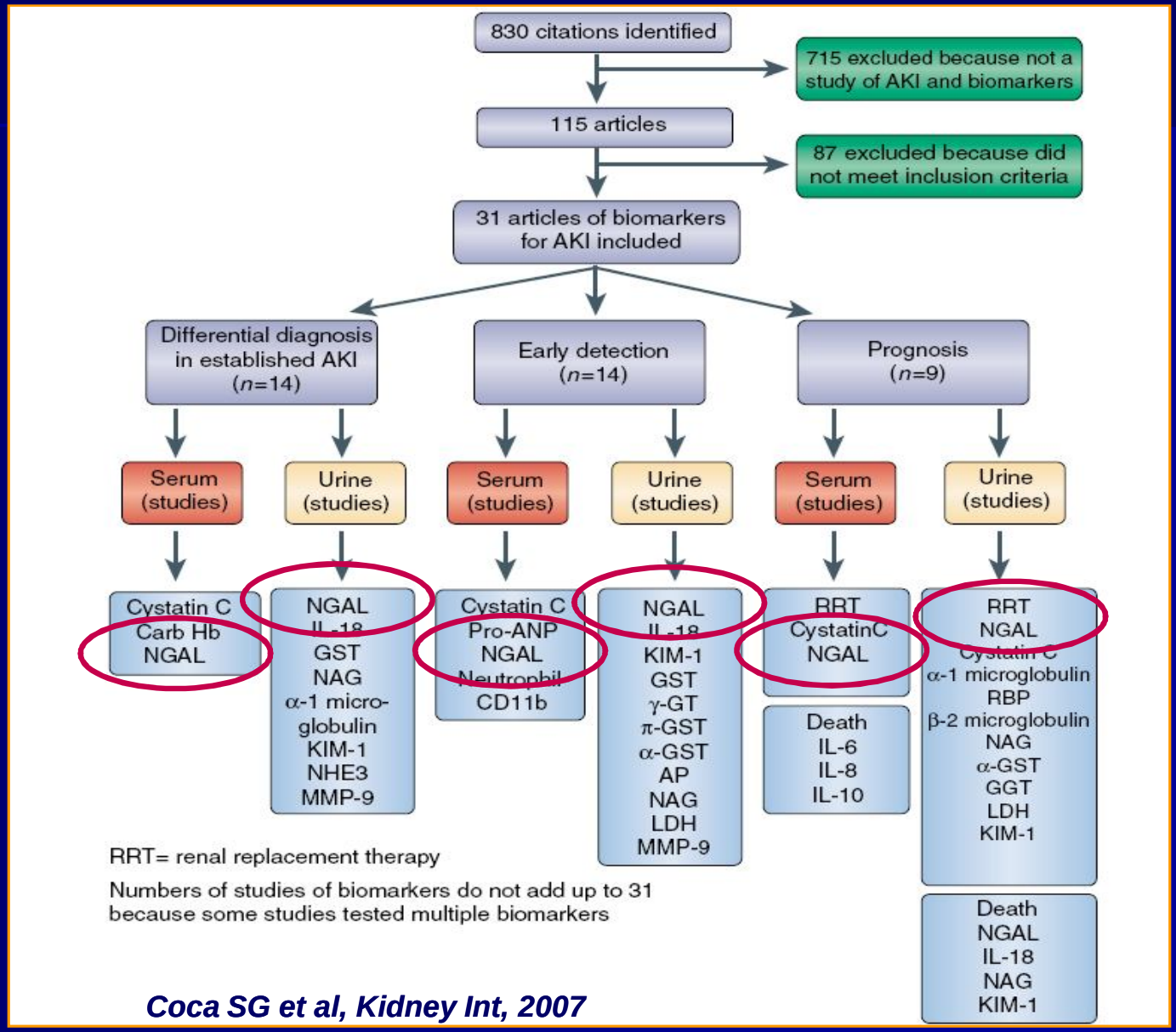
Diagnosis and Monitoring of AKI

Established AKI

Early AKI

Severity of AKI

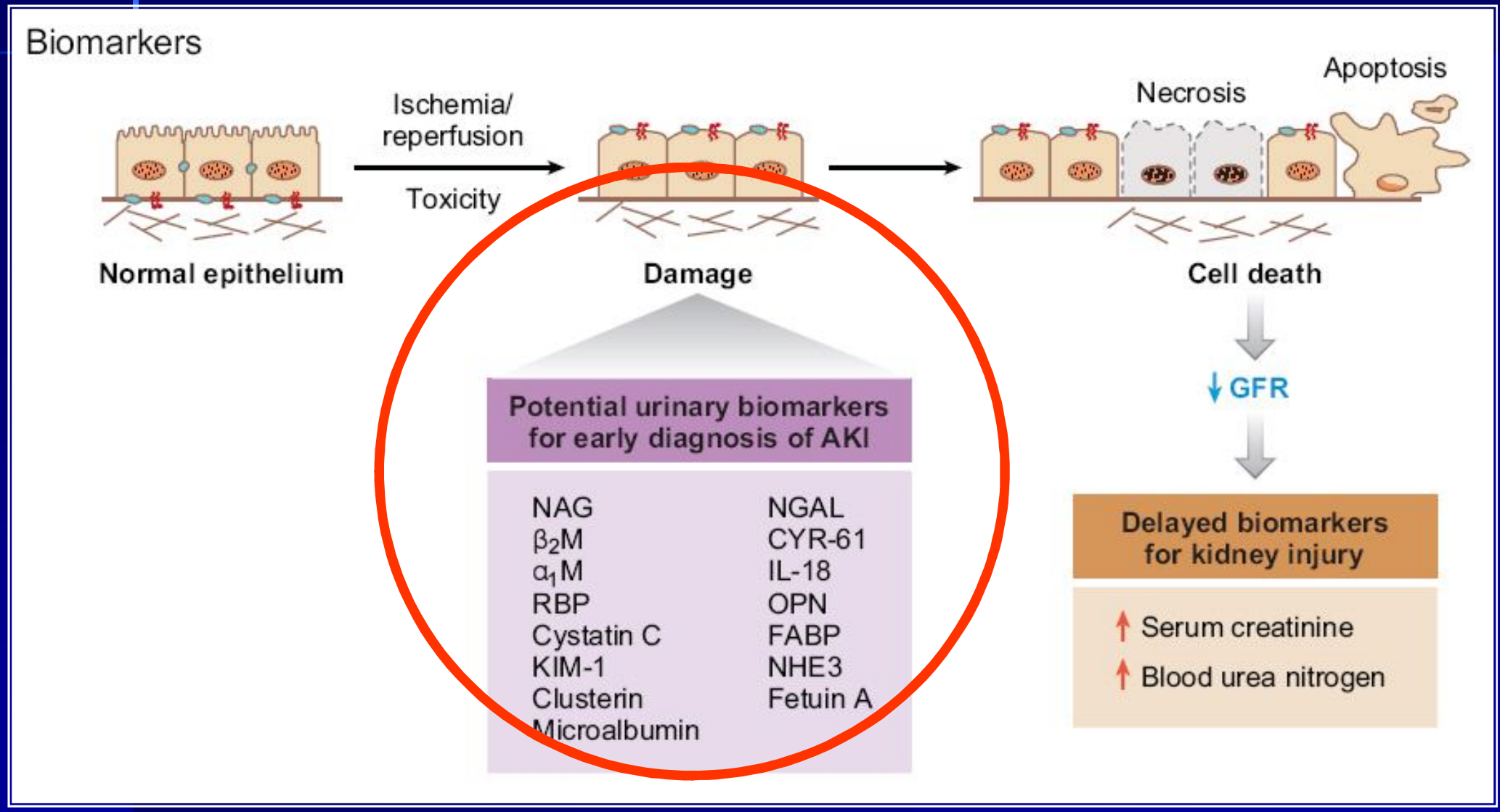




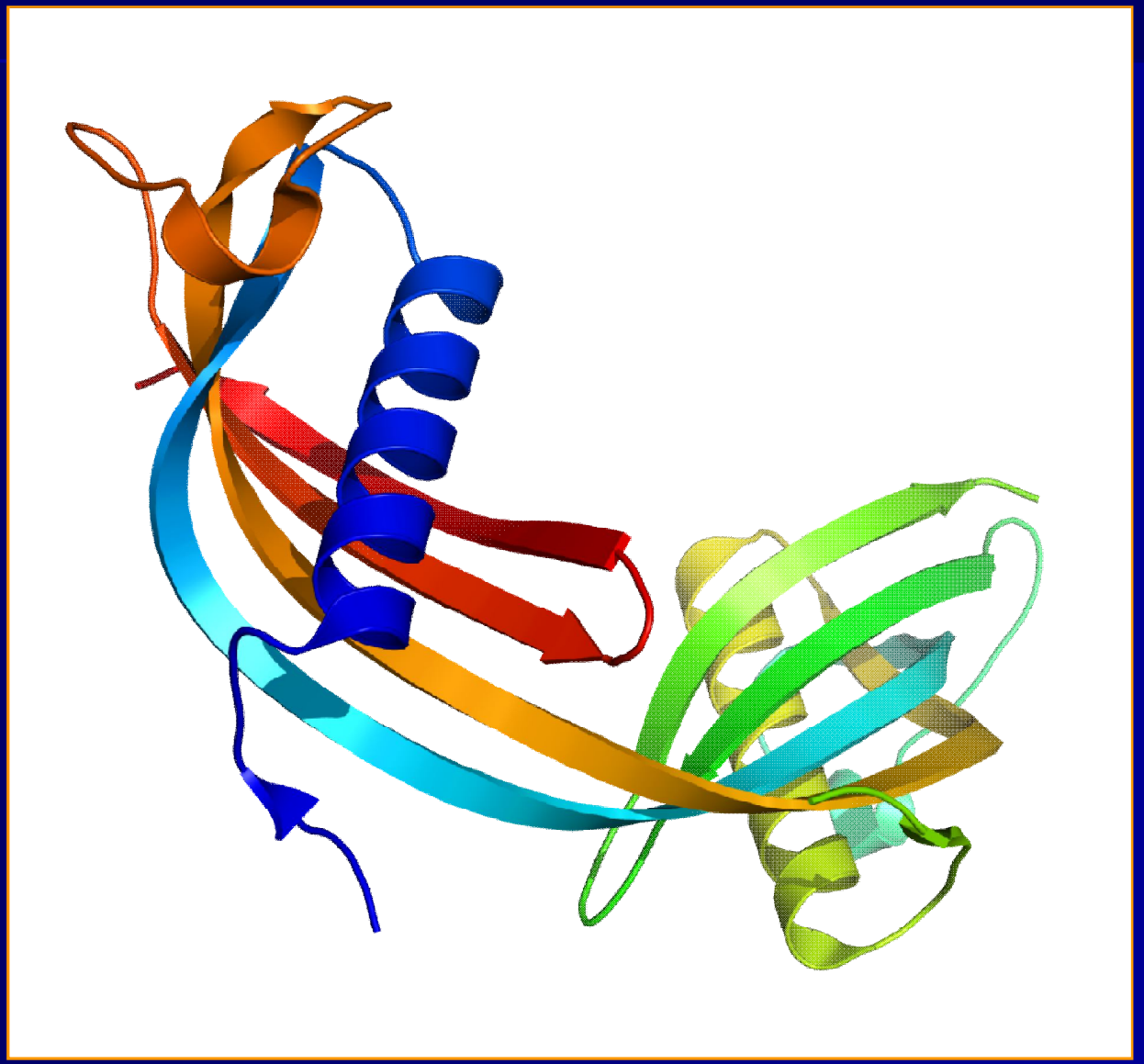
Coca SG et al, Kidney Int, 2007

Acute Kidney Injury Biomarkers

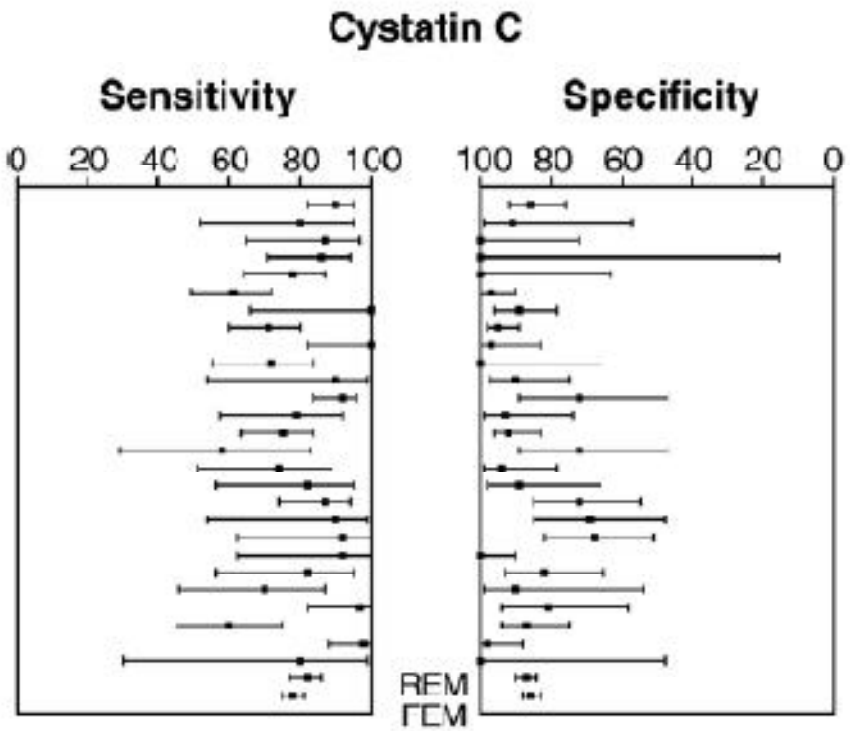
Vaidya VS, Ferguson MA, Bonventre JV.
Biomarkers of Acute Kidney Injury.
Annu Rev Pharmacol Toxicol 2008;48:463-493

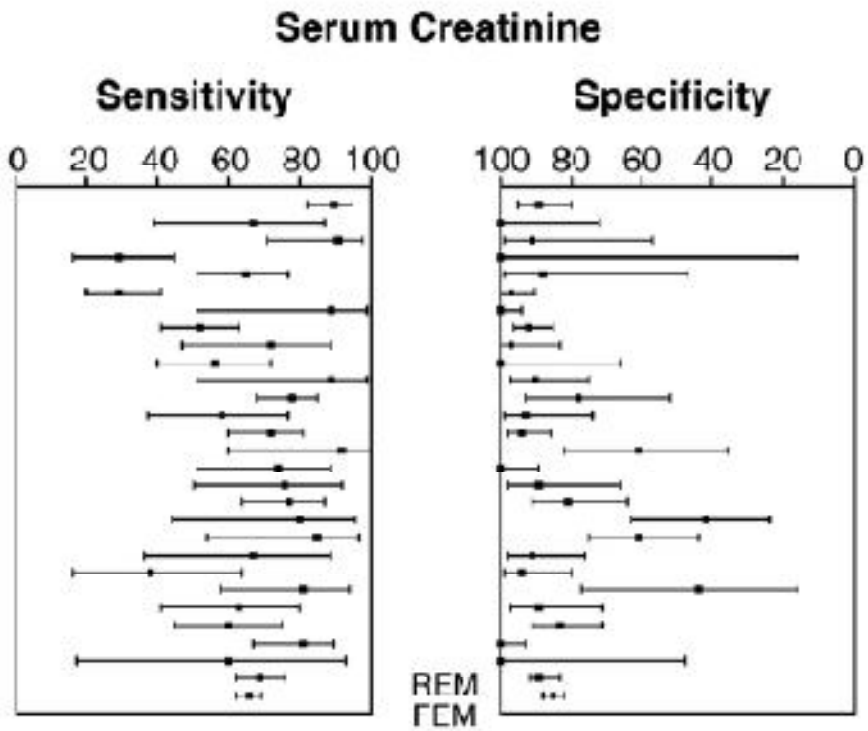


CISTATINA C



Forest plots of sensitivity and specificity shows for each of the diagnostic tests forCysC and SCr. REM:random effects model; FEM: fixed effects model





	Sens	95% CI	Spec	95% CI
REM Pooled	0.81	0.76-0.85	0.88	0.84-0.91
FEM Pooled	0.78	0.75-0.80	0.86	0.83-0.88

	Sens	95% CI	Spec	95% CI
REM Pooled	0.69	0.61-0.76	0.88	0.83-0.92
FEM Pooled	0.65	0.62-0.68	0.84	0.81-0.87

Ross JF et al., Clin Biochem 40, 2007

Positive and negative likelihood ratios and heterogeneity (p-values) for cystatin C (CysC) and serum creatinine (SCr), using a cut-off value for renal impairment for the 'gold standard' inulin between 60 and 79 mL/min/1.73 m^2 and cystatin C (CysC) concentrations between 0.9 and 1.4 mg/L

Diagnostic test (cut-off between 60 and 79 mL/min/1.73 m^2)	Likelihood ratios (LRs)		Heterogeneity (P-values)	
	Positive (95% CI)	Negative (95% CI)	Positive LR	Negative LR
Cystatin C	10.11 (4.12–24.81)	0.23 (0.16–0.34)	$P=0.87$	$P=0.82$
Serum creatinine	8.57 (3.02–24.36)	0.34 (0.23–0.48)	$P=0.35$	$P=0.35$

$P<0.1$ = statistically significant.

Ross JF et al., Clin Biochem 40, 2007

CISTATINA C e CREATININA

Diagnostic Odd ratio (95% CI)

- **Cistatina C 54.001 (30.175 - 96.641)**
- **Creatinina 16.297 (8.348 – 31.785)**

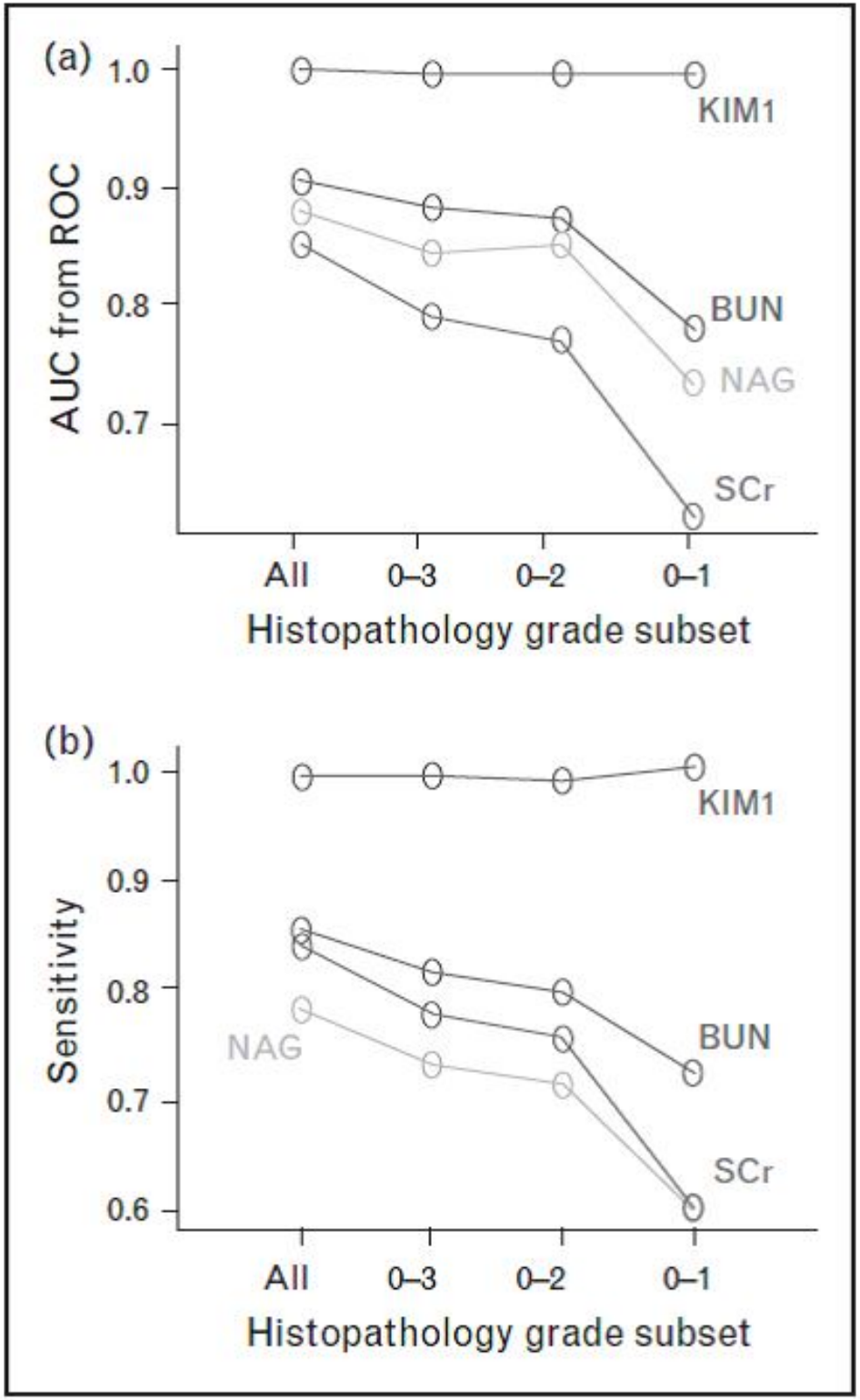
Ross JF Clin Biochem 2007

KIM-1

- Proteina transmembrana contenente un domain simil-Ig appartenente alla classe delle proteine di adesione cellulare (CAM)
- Espressa dalle cellule epiteliali renali (tubulo prossimale) nella fase rigenerativa dopo un insulto ischemico o tossico
- Gene principalmente espresso (su 30.000 screenati) dopo danno renale sperimentale da cis-platino
- La proteina è rilasciata nelle urine

Cause di aumento dei livelli ematici

- Interventi di cardiochirurgia con Bypass Cardio-Polmonare
- Necrosi tubulare acuta da danno ischemico renale
- Tossicità renale da chemioterapici (Cis-platino)
- Tossicità renale da metalli pesanti per esposizione professionale (Cadmio)
- Danno renale da ischemia/riperfusione dopo trapianto di rene



Kidney injury molecule-1

Joseph V. Bonventre[a,b] and Li Yang[a,b,c]

Current Opinion in Critical Care 2010, 16:556–561

Interleukin-18

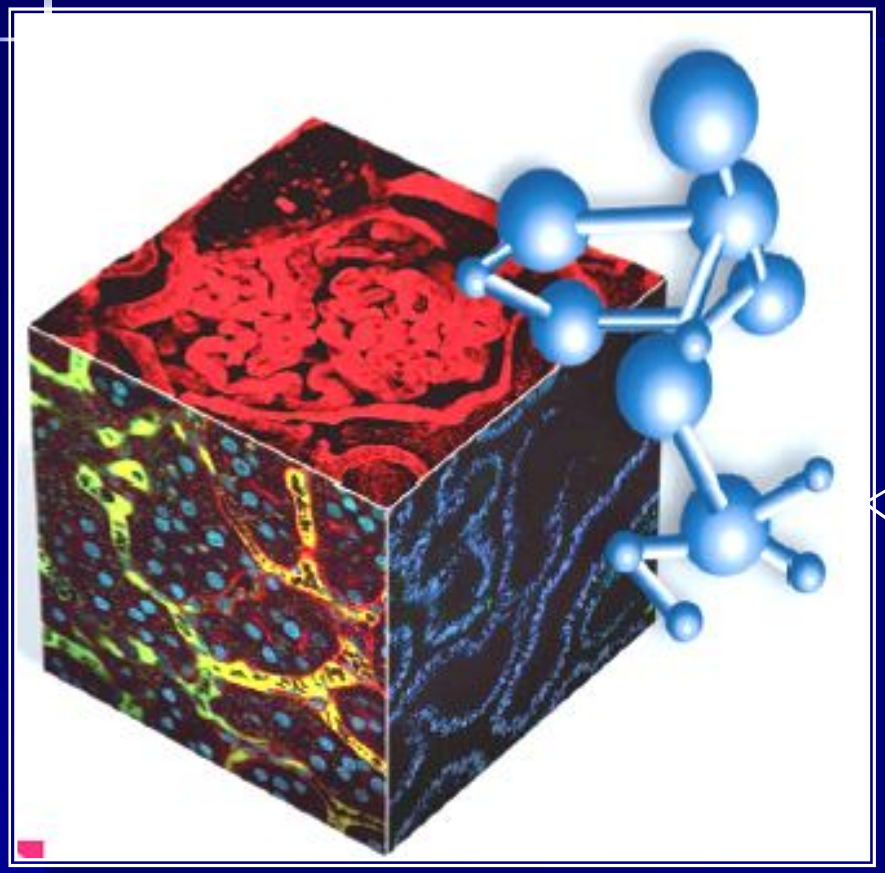
- Interleuchina (IL) -18 è sintetizzata come un precursore inattivo di 23 kDa da diversi tessuti quali monociti, macrofagi e cellule tubulari prossimali epiteliali. Stati infiammatori generalizzati, come il danno da ischemia/riperfusione dei tubuli prossimali, inducono il clivaggio intracellulare del precursore, che porta alla forma matura di IL-18.

- Studi su modelli animali indicano che IL-18 è un mediatore di necrosi tubulare acuta, che induce infiltrazione del parenchima renale sia da parte di neutrofili che di monociti.

- Studi trasversali indicano che i livelli urinari di IL-18 sono notevolmente elevati nei pazienti con necrosi tubulare acuta rispetto ai controlli sani e una varietà di altre patologie renali, tra cui infezioni delle vie urinarie, insufficienza renale cronica, e azotemia prerenale.

- Tuttavia, nonostante sia stata evidenziata l'associazione tra IL-18 e AKI, l'utilità di diagnostica si è dimostrata limitata in quanto l'aumento dell'IL-18 non anticipava di molto l'incremento della creatinina.

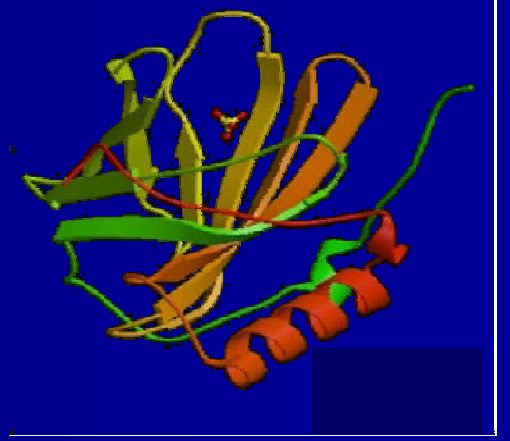
Biomarkers in AKI: NGAL



NGAL

Plasma

Urine



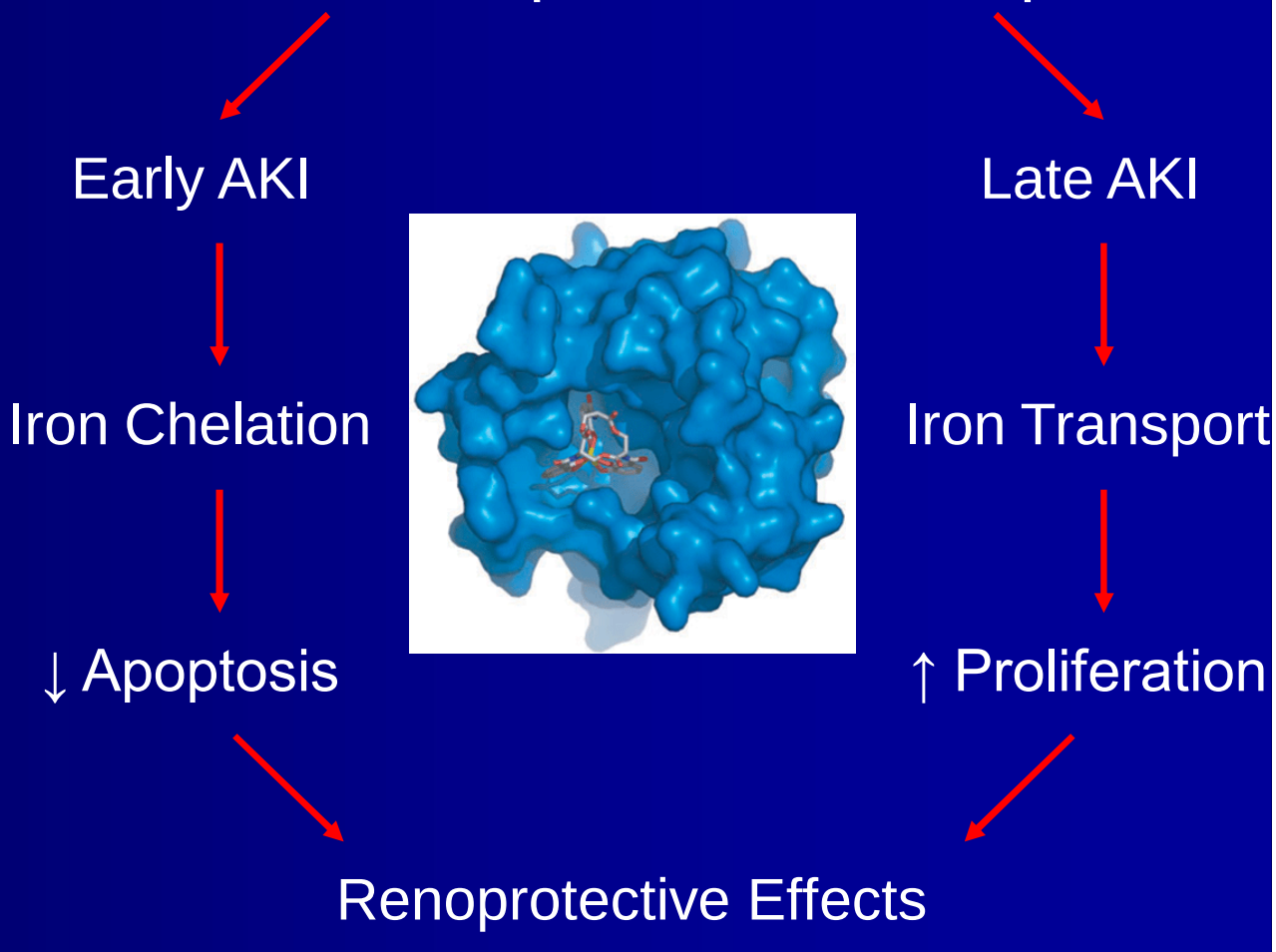
Using cDNA microarray as a screening technique, a subset of genes whose expression is up-regulated within the first few hours after renal injury can be discovered. (Or early ↓ GFR)

Biomarkers of AKI: NGAL

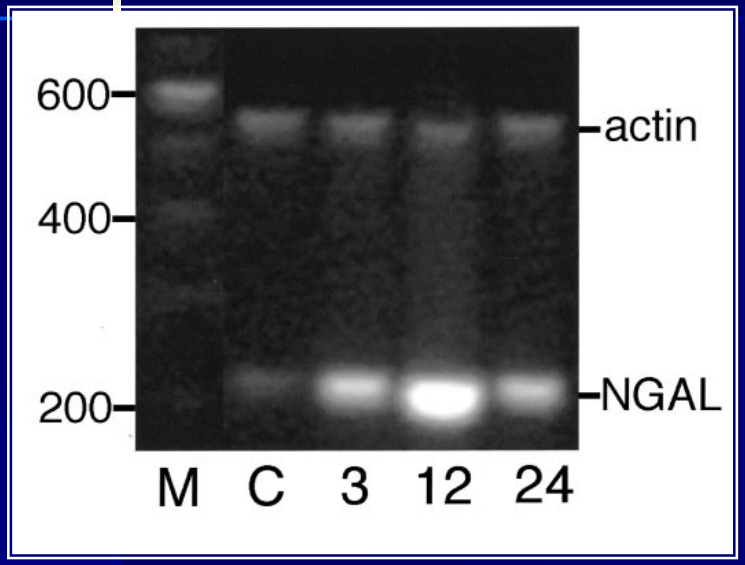
Neutrophil gelatinase-assoc. lipocalin (NGAL) produced by neutrophils in response to specific stimuli Also known as lipocalin-2 and siderocalin it is known to play a role in *fighting bacteria infections.*

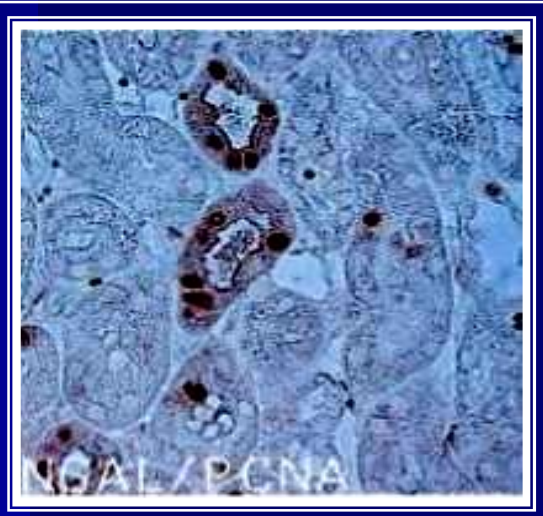
It is detectable in urine and plasma of patients with AKI 24-48 h before creatinine rise.

Animal studies have shown NGAL is one of the earliest proteins induced in the kidney after ischemic or nephrotoxic insult.

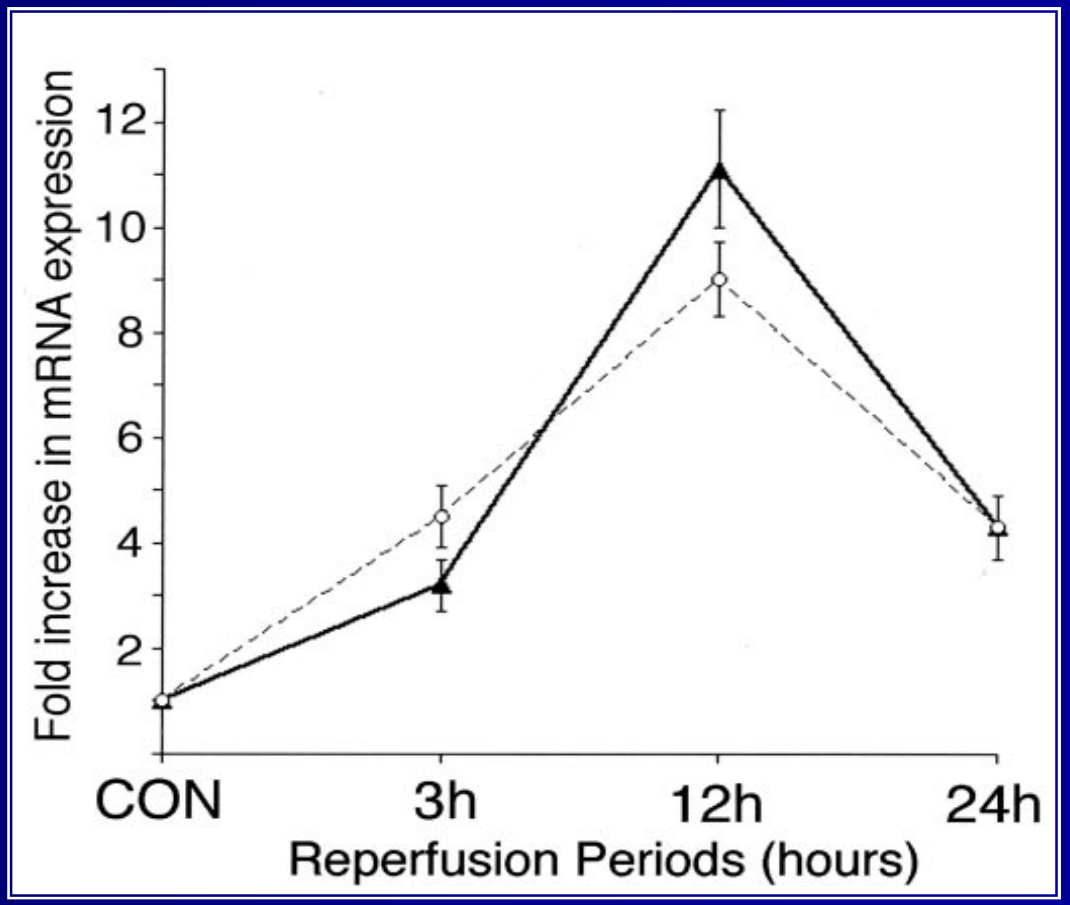


NGAL mRNA is markedly induced in the early post-ischemic kidney



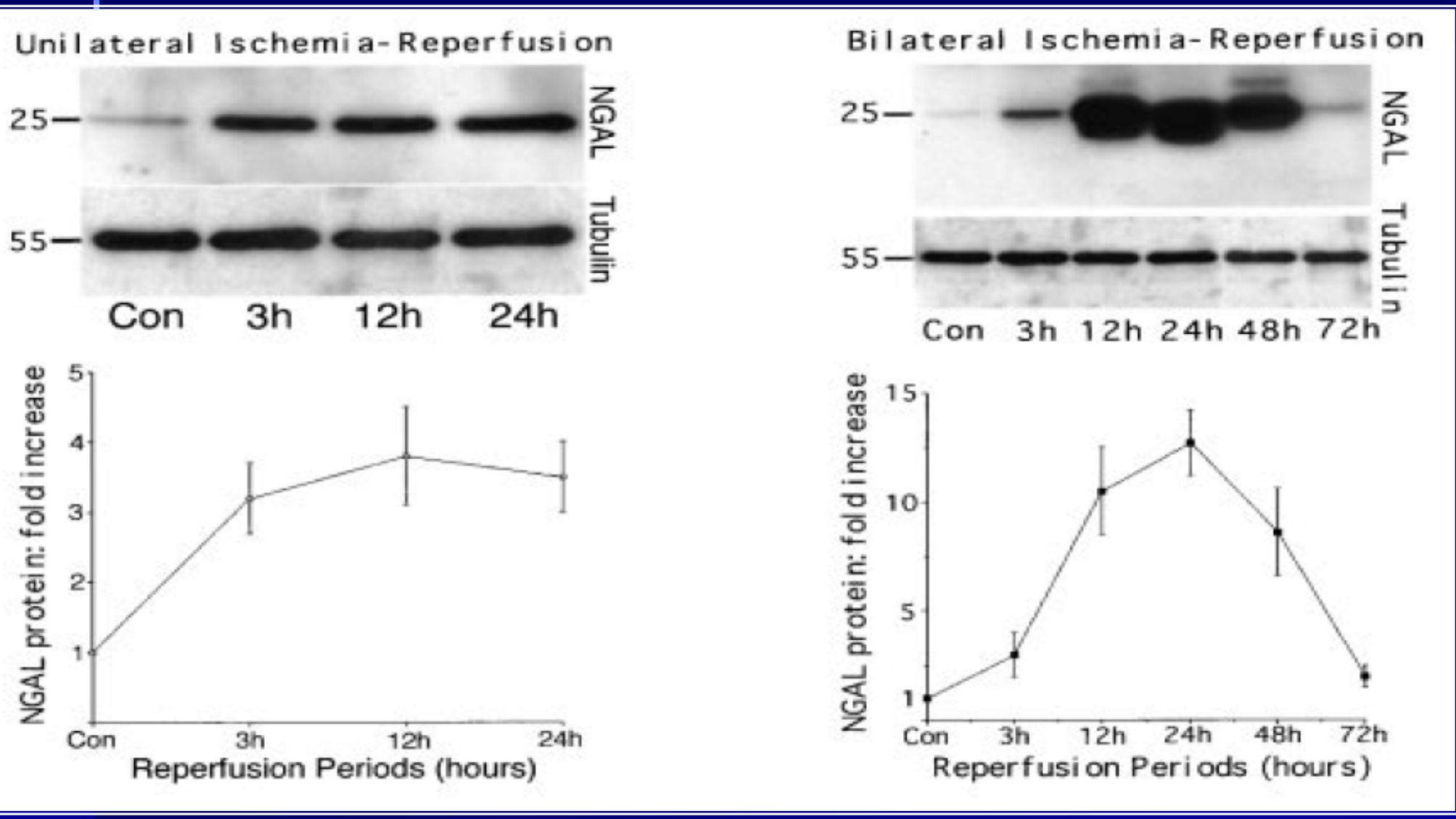


Ischemic kidneys synthesize NGAL !

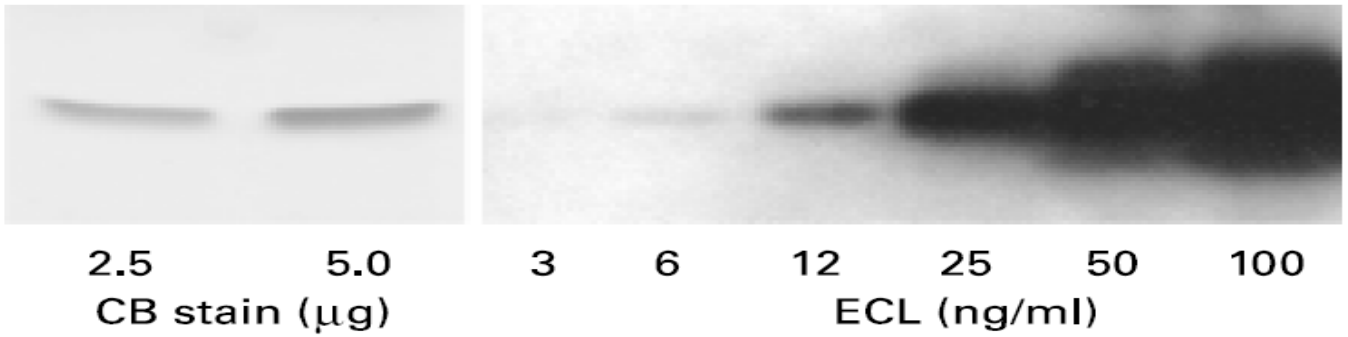


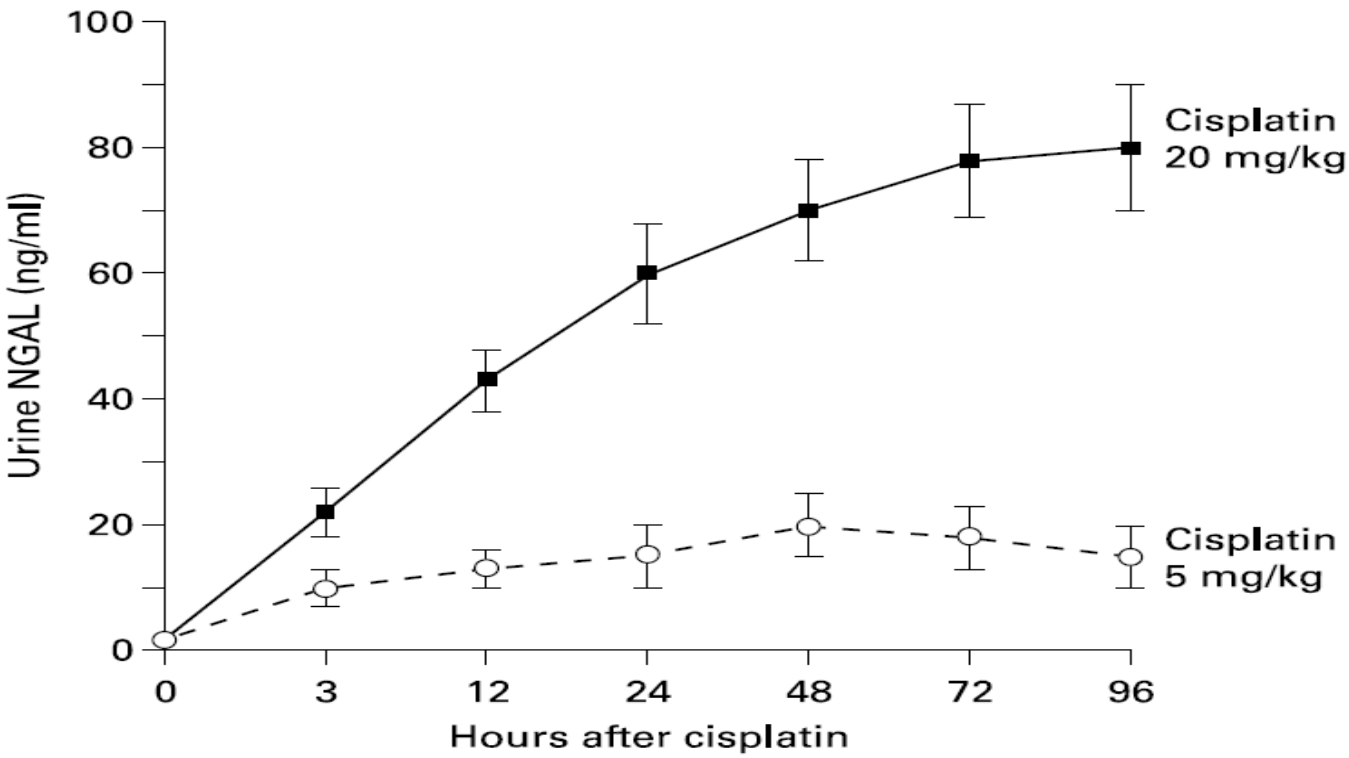
MISHRA J.,et al., J Am Soc Nephrol 14: 2534-2543, 2003

Induction of mouse kidney NGAL protein after unilateral or bilateral ischaemia



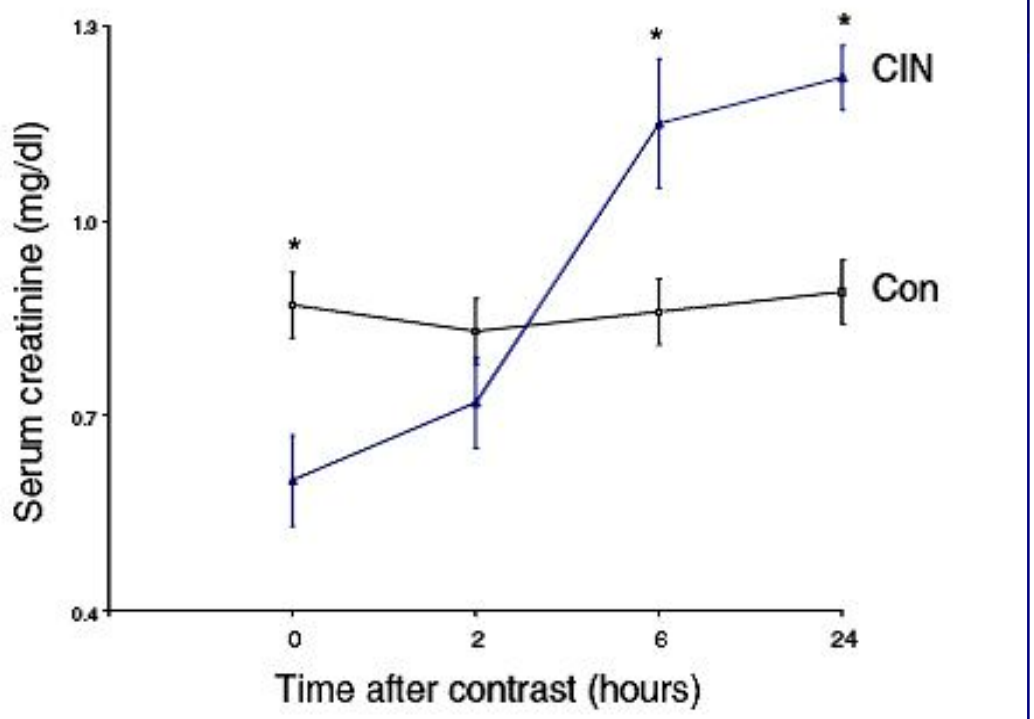
Urinary NGAL following cisplatin

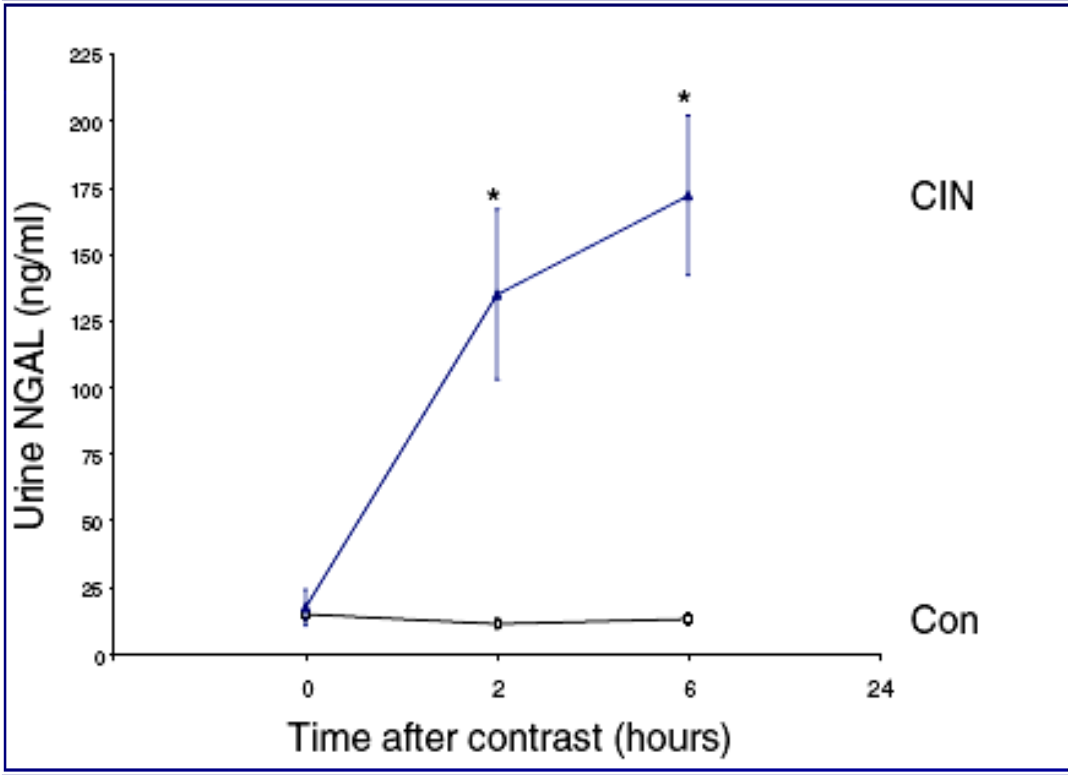




Mishra J et al. Am J Nephrol 2004;24:307-315

NGAL e nefropatia da mezzo di contrasto (CIN)



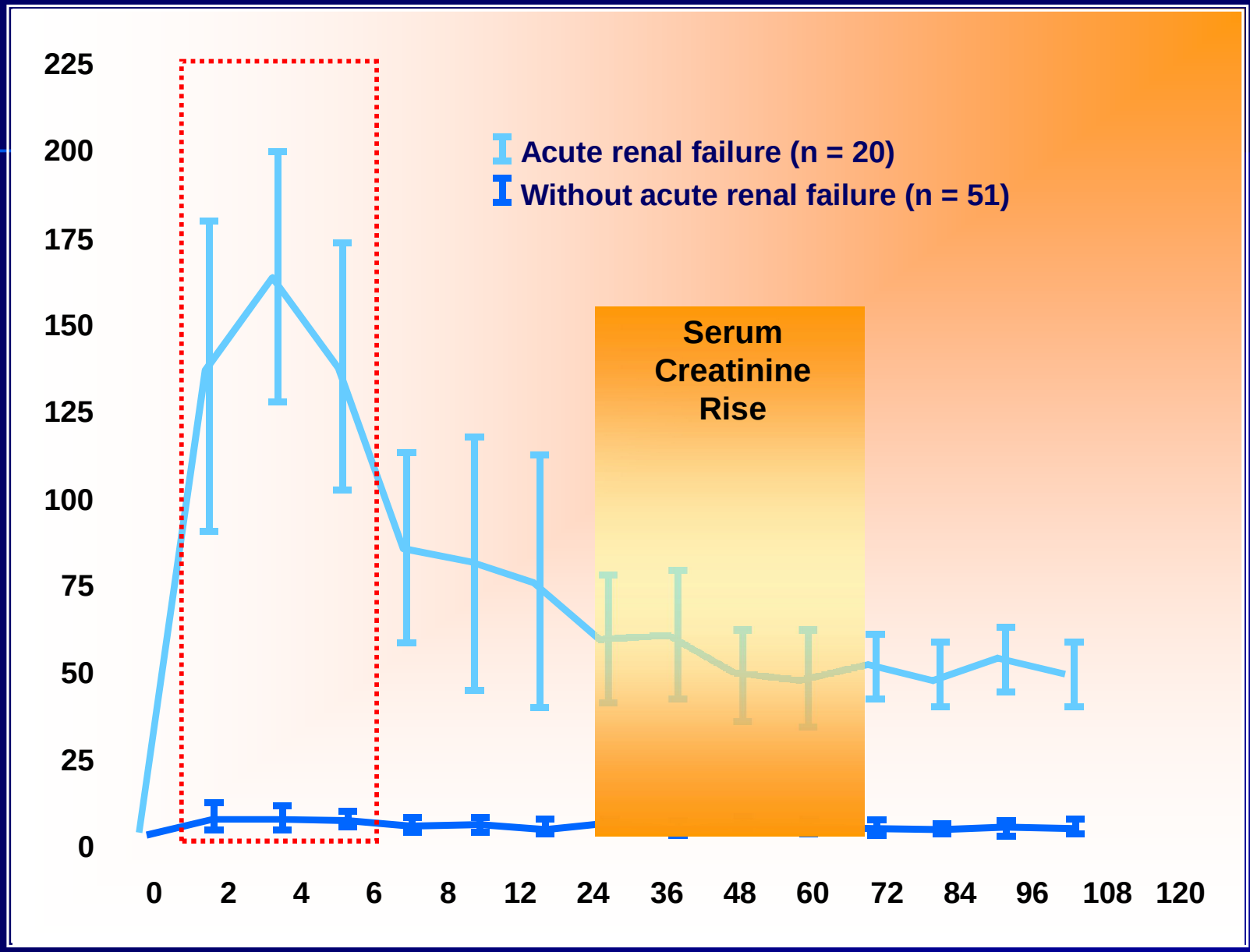


Creatinina

uNGAL

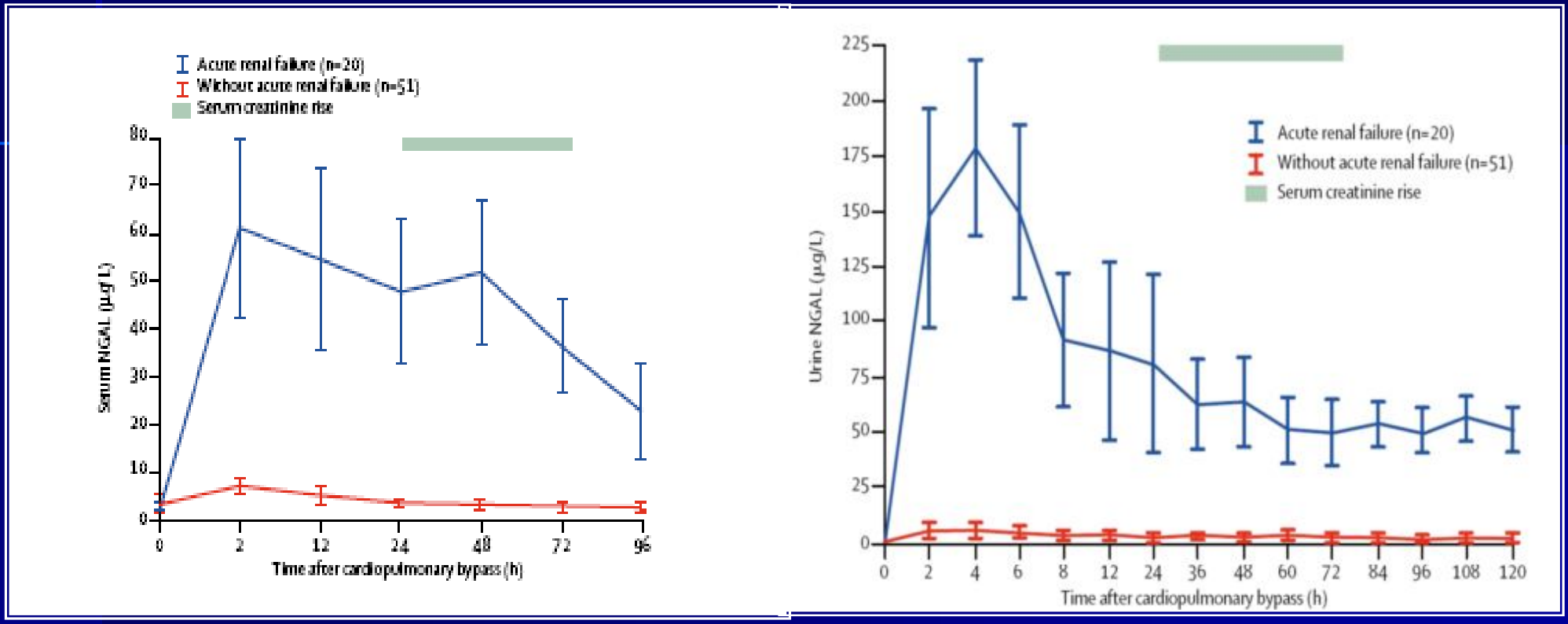
Da: Hirsch R et al. Pediatr Nephrol 2007, 22 (12); 2089-2095

NGAL urinaria e cardiochirurgia



Mishra J et al. Lancet 2005; 365: 1231-1238

NGAL urinaria e cardiochirurgia



- **Un aumento sensibile e precoce dei livelli sierici ed ancor più urinari di NGAL si osserva solo nei soggetti che sviluppano danno renale acuto.**

- **In questi pazienti, la diagnosi di AKI basata sull'incremento della creatinina poteva essere effettuata solo 24/48ore dopo l'insulto iniziale.**

Mishra J et al. Lancet 2005; 365: 1231-1238

URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN IN ADULT PATIENTS AFTER CARDIAC SURGERY

C. Cosma [(1)], D. Faggian [(1)], M. M. Mion [(1)], R. Bianco [(2)], M. Zaninotto [(1)], M. Plebani [(1)].

1) Dep. Of Laboratory Medicine, University of Padua, Italy
2) Dep. Of Medical and Surgical Sciences, U.O. Cardiosurgery, University of Padua, italy

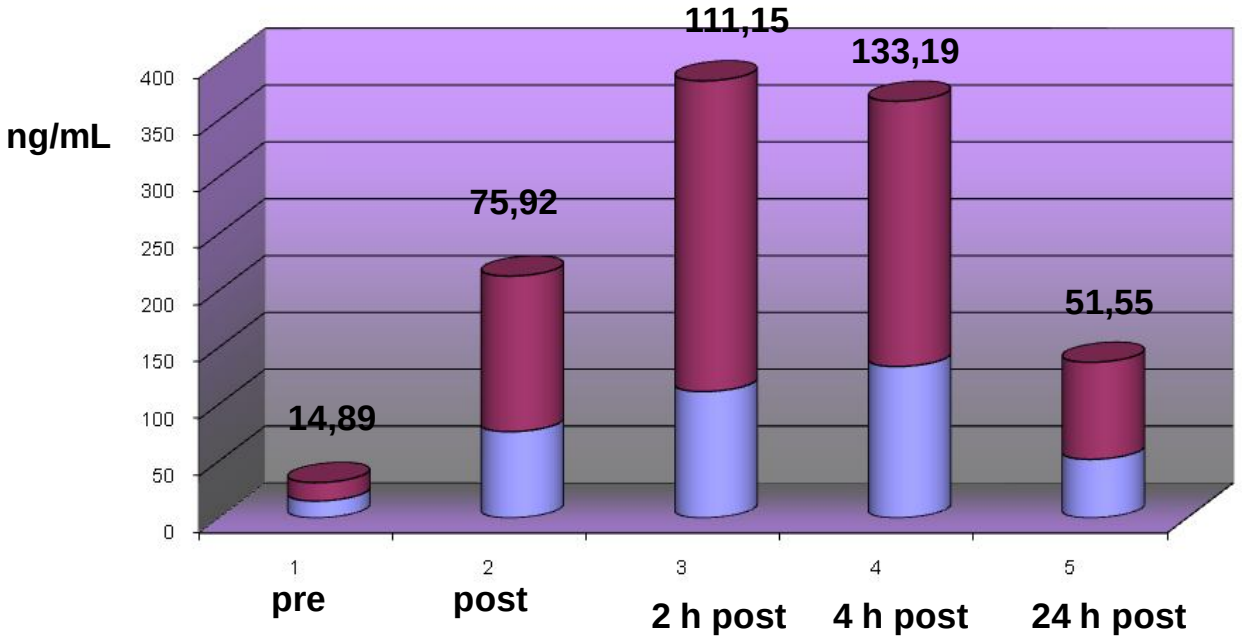
INTRODUCTION

…….Recent studies had demostrated that NGAL is highly expressed in various pathological states like acute kidney injury (AKI). Serum creatinine is an insensitive and later marker for AKI, while an early diagnosis is a fundamental aspect in order to facilitate effective interventions. This had led to an aggressive research for new biomarkers for AKI. NGAL appears to be the most promising molecule among the new molecules.

AIM OF THIS STUDY

The aim of this study was to investigate the NGAL's role as biomarker of AKI in patients undergoing cardiac surgery

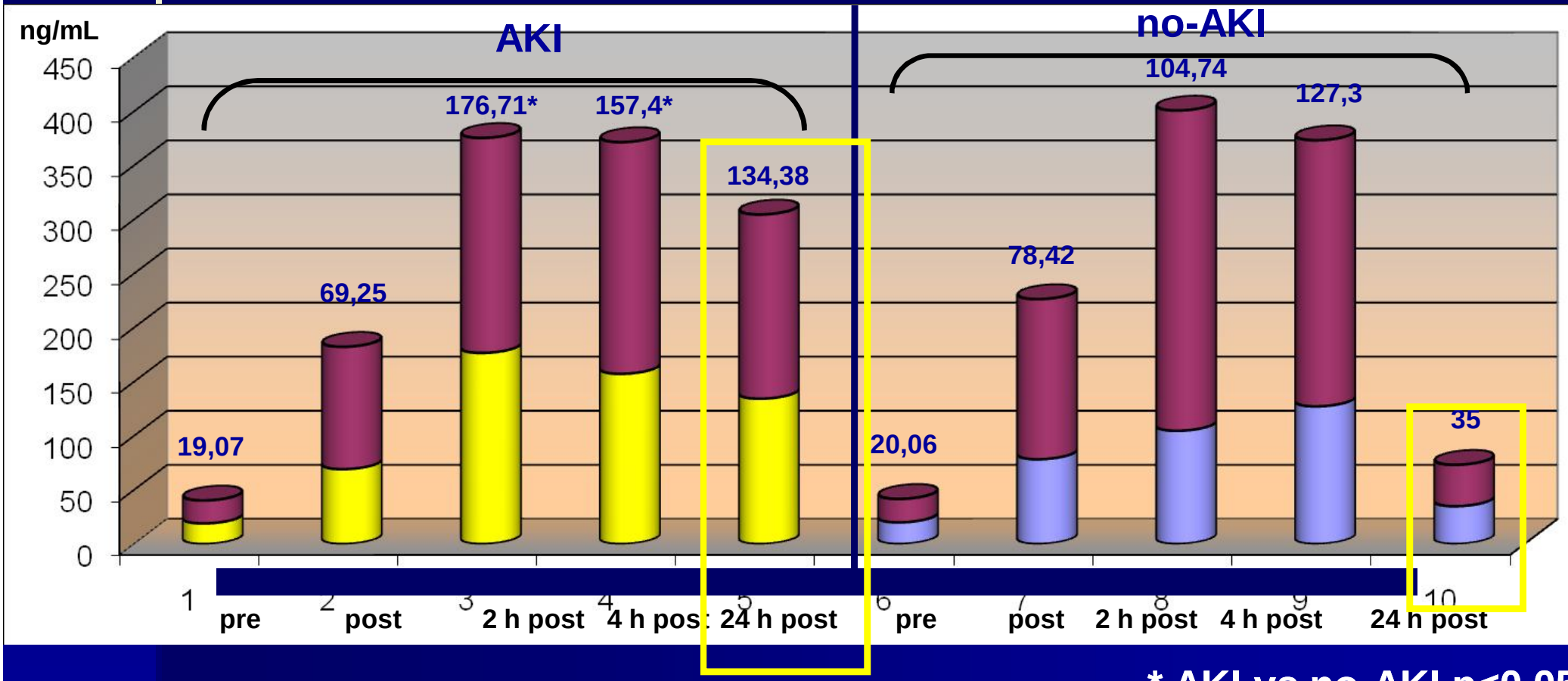
NGAL after cardiac surgery
All patients (n=150)



mean

SD

NGAL after cardiac surgery
AKI vs no-AKI



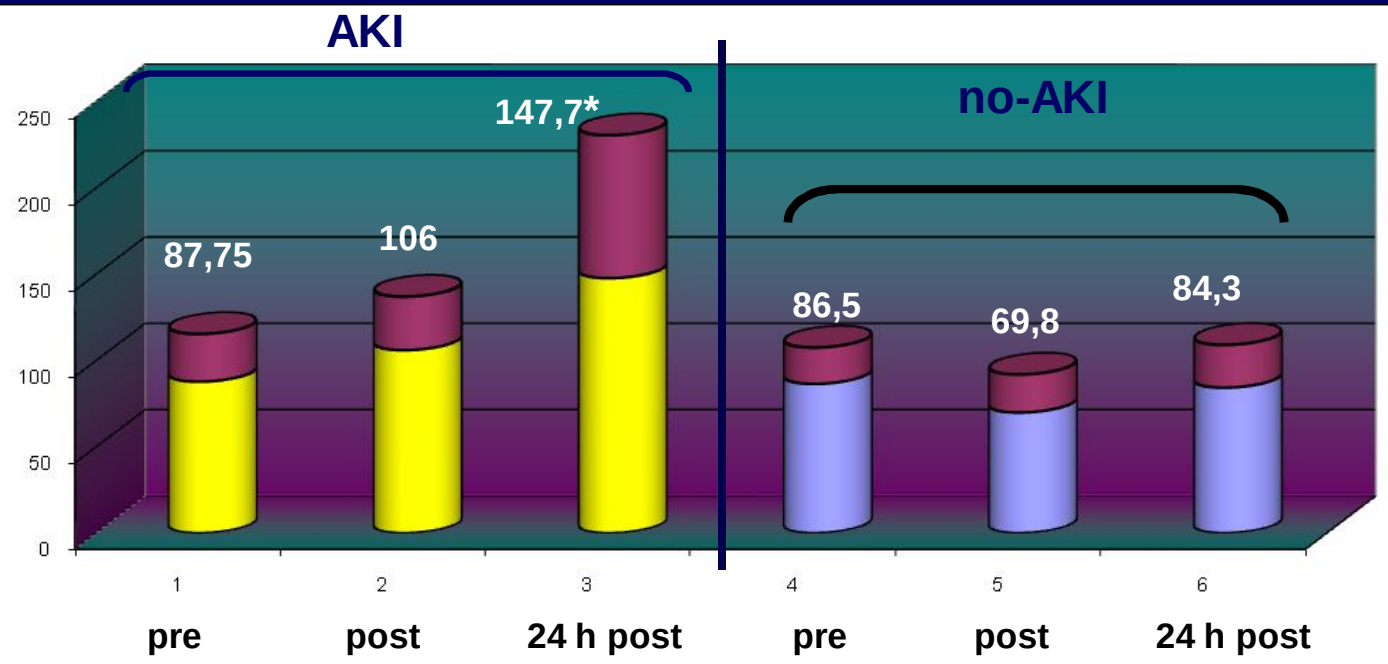
* AKI vs no-AKI p<0.05

Mean AKI

SD

Mean non AKI

Creatinine after cardiac surgery
AKI vs no-AKI



* AKI *vs* no-AKI p<0.05

Mean AKI

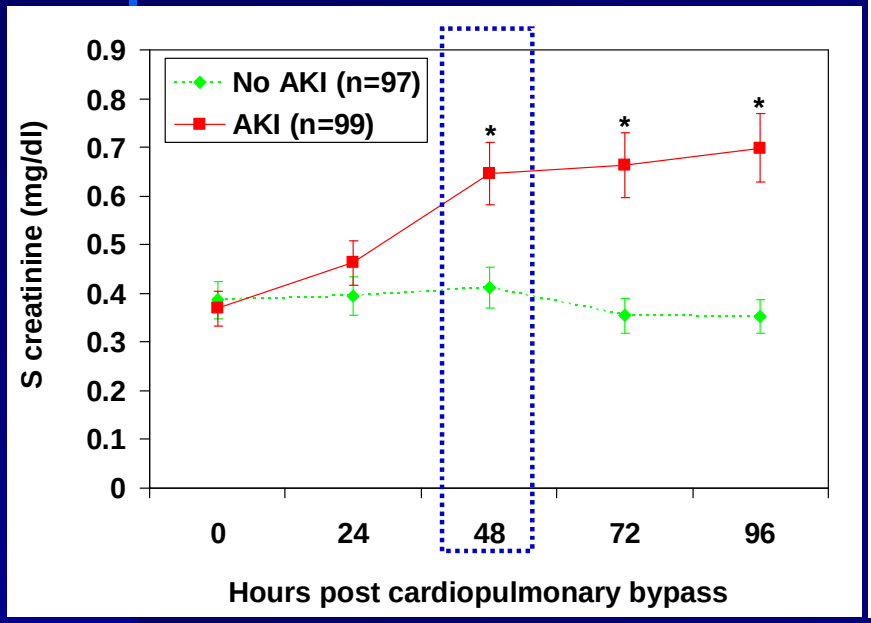
SD

Mean Non AKI

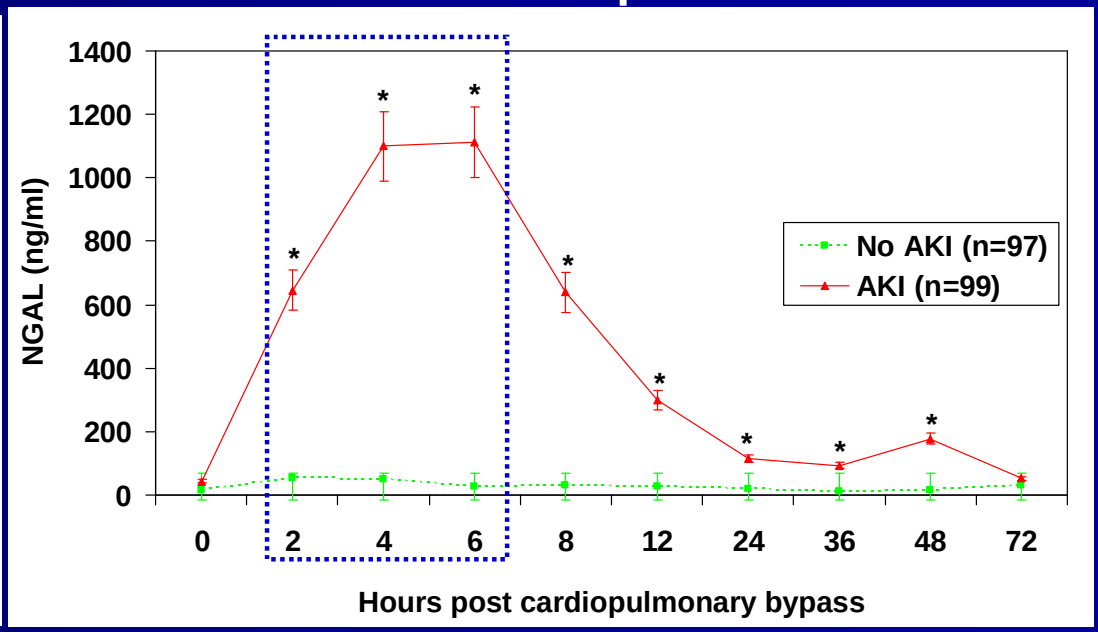
Urine NGAL Predicts Severity of Acute Kidney Injury After Cardiac Surgery: A Prospective Study

Prospective study on 196 children undergoing elective CPB for surgical correction or palliation of congenital heart lesions

Serum creatinine post-CPB



Urine NGAL post-CPB



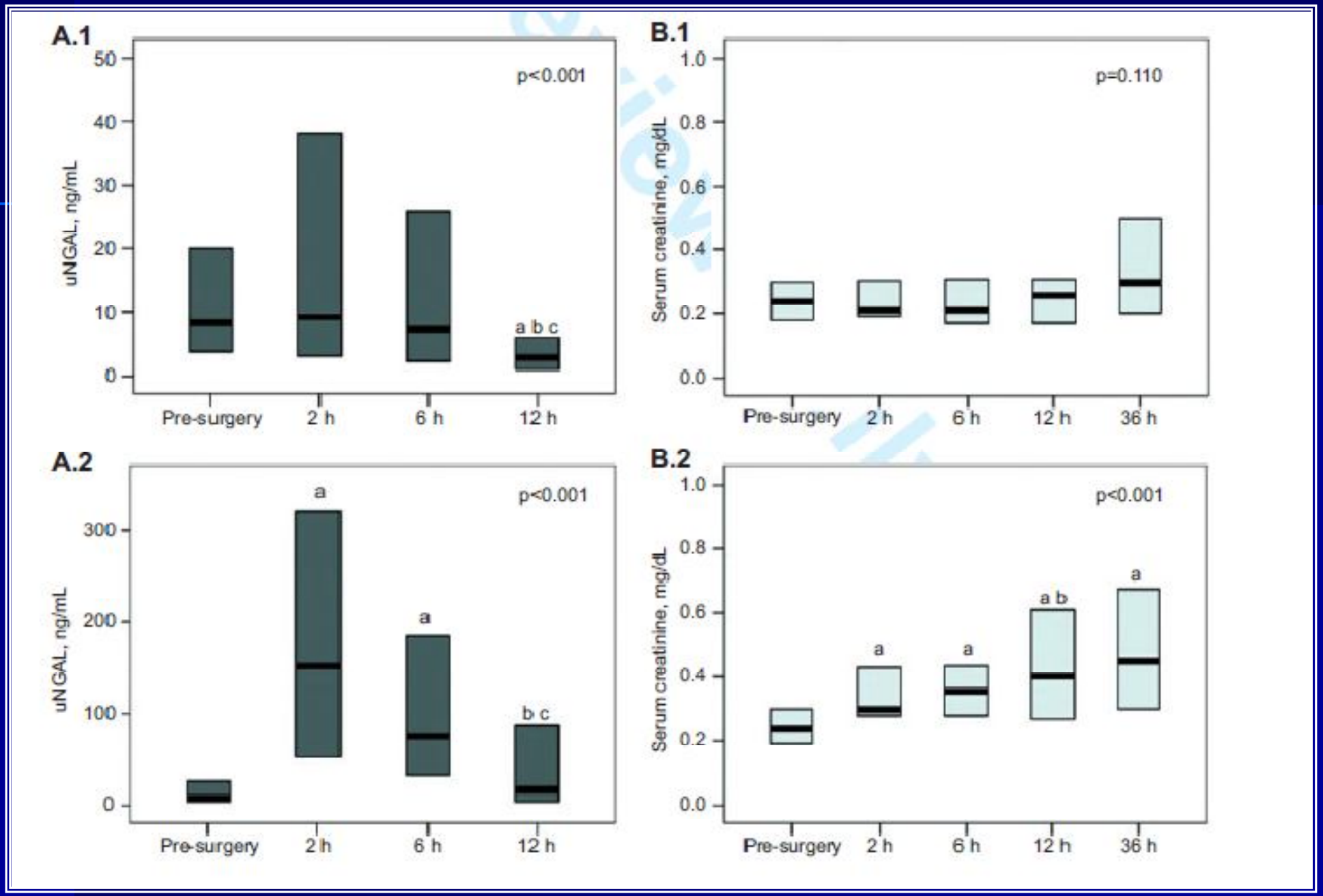
AUC	0.93	0.96	0.98

Urine NGAL was associated with key clinical factors, including:
length of stay ($p < 0.0001$), duration of AKI ($p < 0.001$)
need for dialysis ($p = 0.01$, AUC = 0.86), death ($p = 0.01$, AUC = 0.91)

Bennett et al., Clin J Am Soc Nephrol 2008

The combined use of neutrophil gelatinase-associated lipocalin and brain natriuretic peptide improves risk stratification in pediatric cardiac surgery

Clerico A et al, 2012


A.1
p<0.001
uNGAL, ng/mL
50
40
30
20
10
0
a b c
Pre-surgery
2 h
6 h
12 h
B.1
p=0.110
Serum creatinine, mg/dL
1.0
0.8
0.6
0.4
0.2
0.0
Pre-surgery
2 h
6 h
12 h
36 h
A.2
p<0.001
uNGAL, ng/mL
300
200
100
0
a
a
b c
Pre-surgery
2 h
6 h
12 h
B.2
p<0.001
Serum creatinine, mg/dL
1.0
0.8
0.6
0.4
0.2
0.0
a
a
a b
a
Pre-surgery
2 h
6 h
12 h
36 h

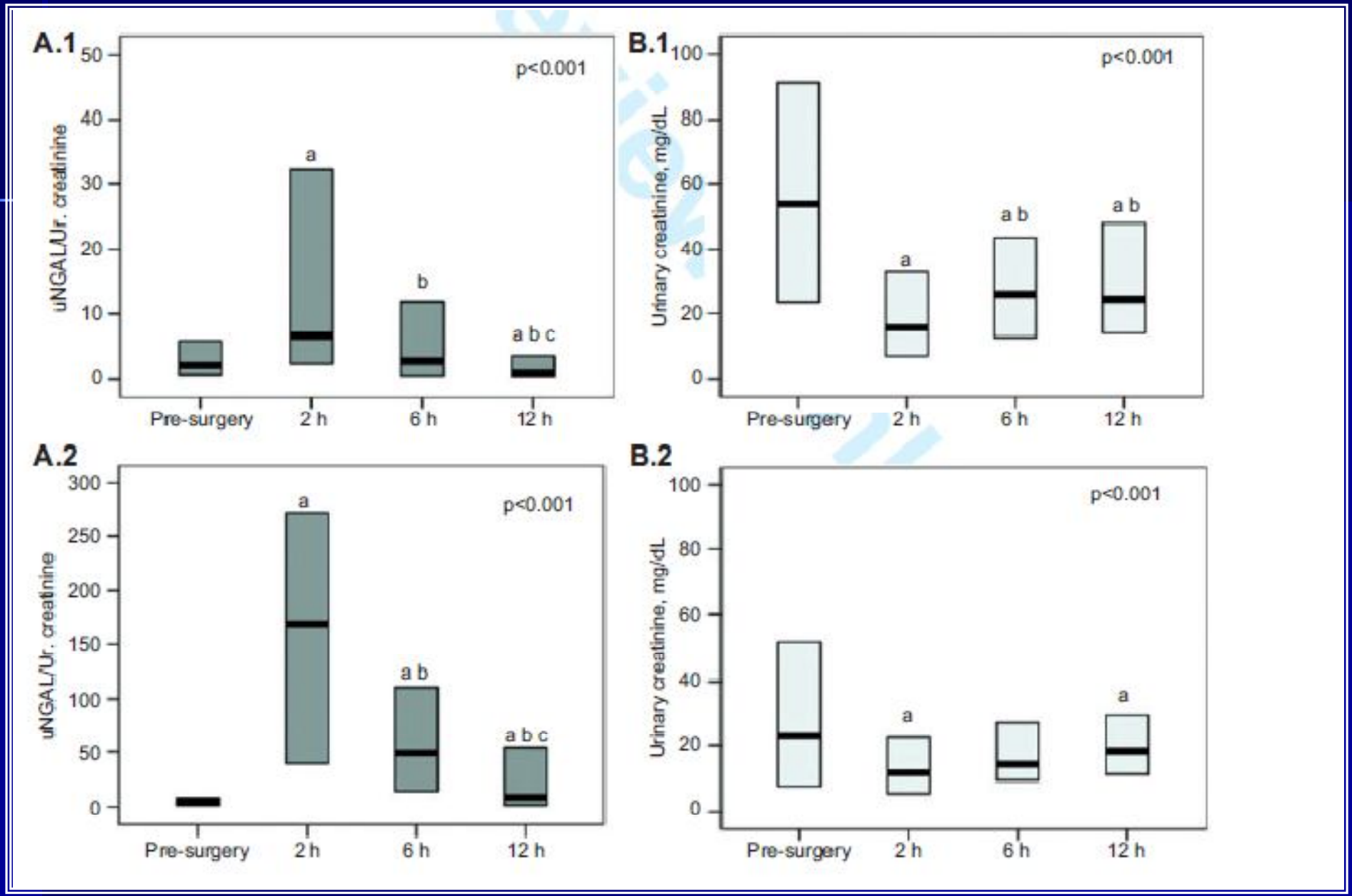

A.1
p<0.001
uNGAL/Ur. creatinine
50
40
30
20
10
0
a
b
a b c
Pre-surgery
2 h
6 h
12 h
B.1
p<0.001
Urinary creatinine, mg/dL
100
80
60
40
20
0
a
a b
a b
Pre-surgery
2 h
6 h
12 h
A.2
p<0.001
uNGAL/Ur. creatinine
300
250
200
150
100
50
0
a
a b
a b c
Pre-surgery
2 h
6 h
12 h
B.2
p<0.001
Urinary creatinine, mg/dL
100
80
60
40
20
0
a
a
Pre-surgery
2 h
6 h
12 h

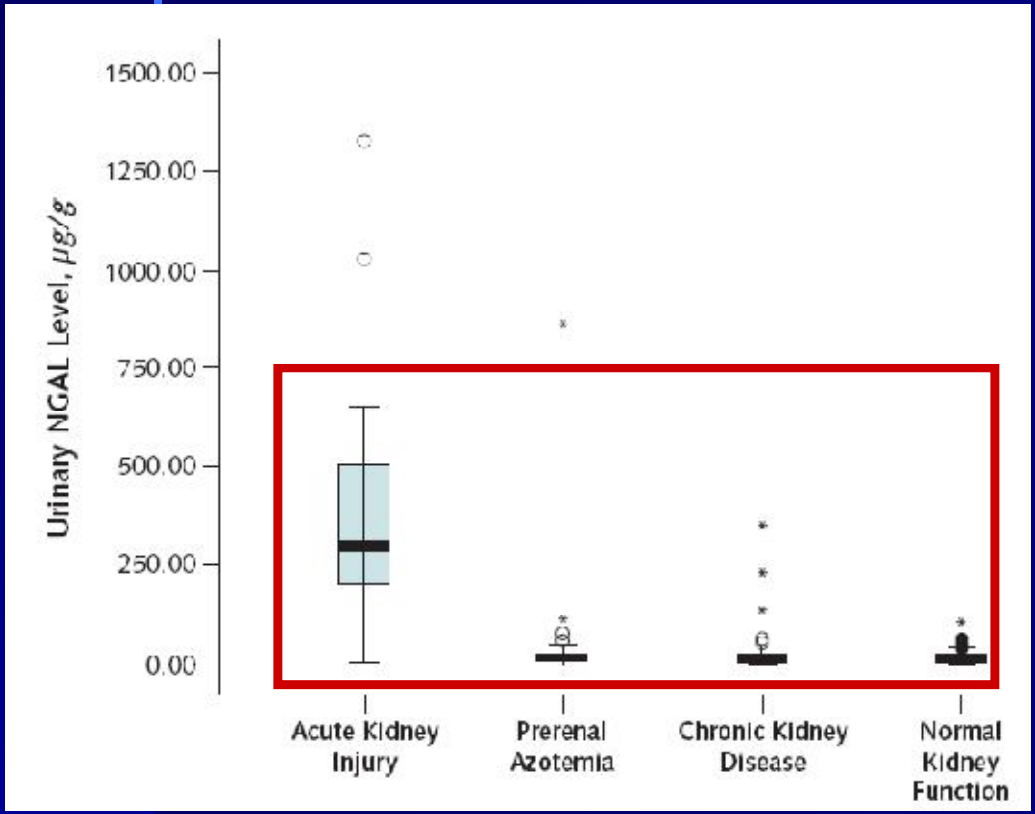
Table 3 Data of ROC analysis. The values of best cut-off value, AUC, sensitivity and specificity (calculated at the best cut-off) are reported.

Data group	uNGAL, ng/mL	AUC (SE)	Sensitivity	Specificity
2 h post-surgery	49.95	0.85 (0.034)	0.784	0.815
6 h post-surgery	22.00	0.85 (0.036)	0.813	0.734
12 h post-surgery	3.55	0.78 (0.042)	0.766	0.610
Peak among 12 h post-surgery	64.75	0.87 (0.036)	0.824	0.802

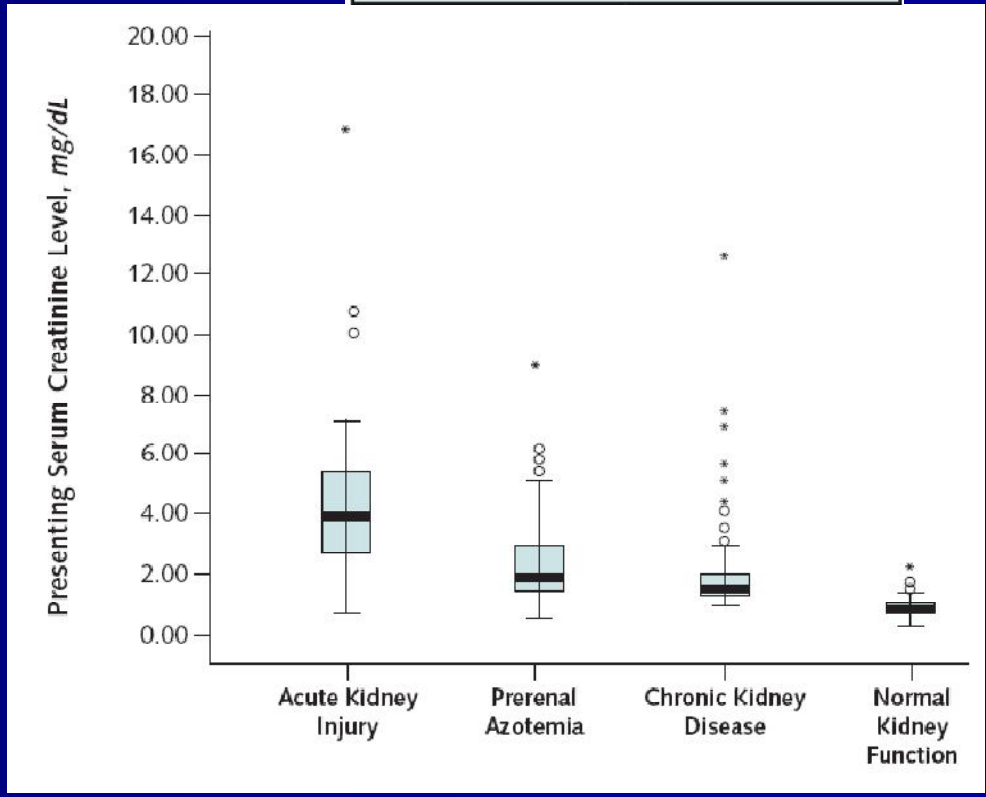
Peak within 12 h after surgery: the highest value measured within 12 h after surgery.

Sensitivity and Specificity of a Single Emergency Department Measurement of Urinary Neutrophil Gelatinase–Associated Lipocalin for Diagnosing Acute Kidney Injury

Thomas L. Nickolas, MD, MS; Matthew J. O'Rourke, BS; Jun Yang, MD, PhD; Meghan E. Sise, BS; Pietro A. Canetta, MD;

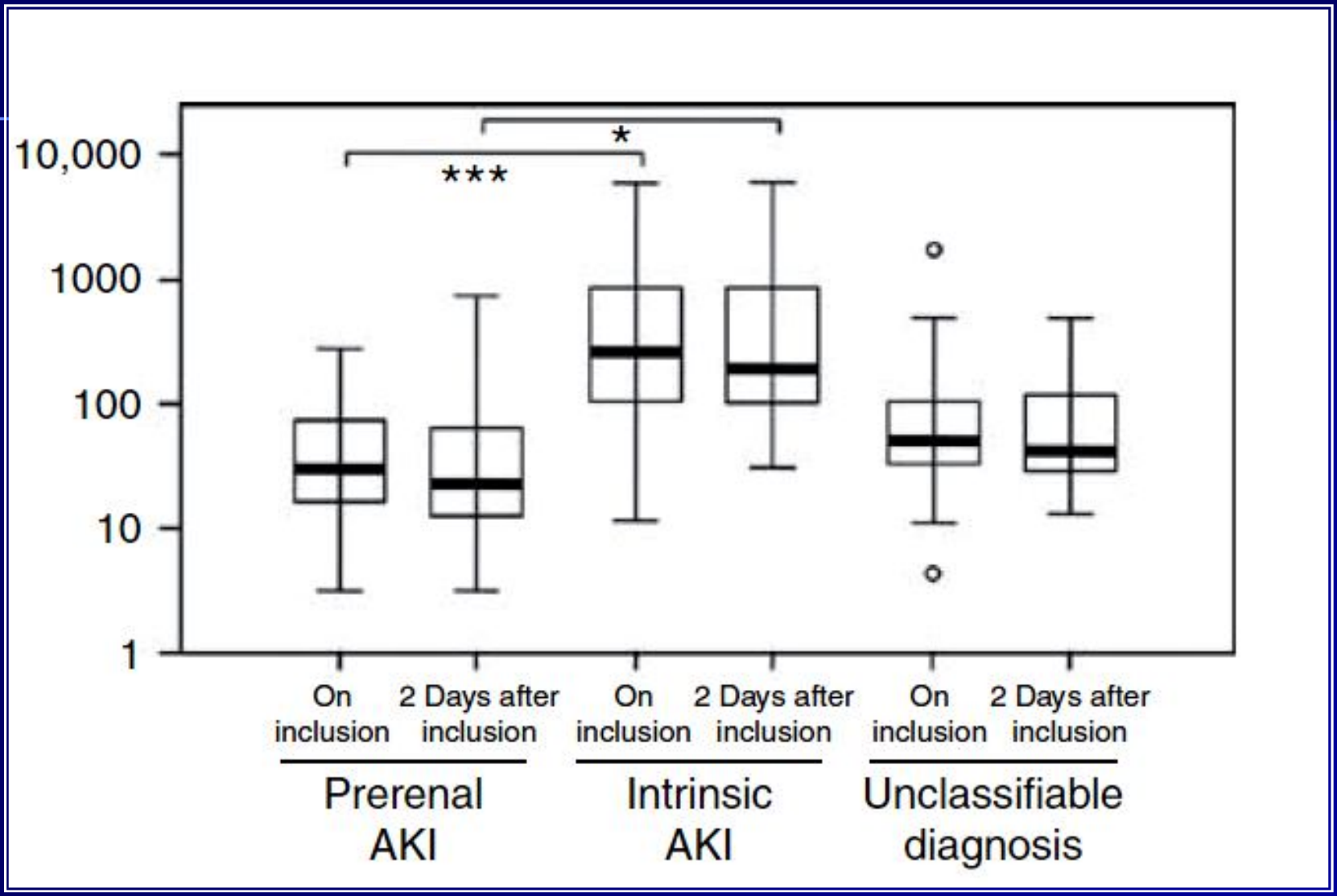


Patients recruited during the process of hospitalization (n = 882)



Single ED measurement of NGAL was useful to identify AKI and to distinguish it from other morbid conditions in which creatinine was altered. NGAL was highly predictive of clinical outcomes including nephrology consultation, ICU admission and need for dialysis

NGAL urinaria e AKI pre-renale e renale



Singer E et al, Kidney Internat 2011, doi:10.1038/ki.2011 .41

NGAL - una meta-analisi

ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease

Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis

Michael Haase, MD,[1] Rinaldo Bellomo, MD,[2] Prasad Devarajan, MD,[3] Peter Schlattmann, MD, MSc,[4] and Anja Haase-Fielitz, PharmD,[1] and the NGAL Meta-analysis Investigator Group

Limitations: Serum creatinine level was used for AKI definition.

Conclusions: NGAL level appears to be of diagnostic and prognostic value for AKI.

Am J Kidney Dis 54:1012-1024.

INDEX WORDS: Neutrophil gelatinase-associated lipocalin (NGAL); plasma NGAL; urine NGAL; meta-analysis; acute kidney injury (AKI).

Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis

Michael Haase, MD, Rinaldo Bellomo, MD, Prasad Devarajan, MD, Peter Schlattmann, MD, MSc, and Anja Haase-Fielitz, PharmD, and the NGAL Meta-analysis Investigator Group

Background: Neutrophil gelatinase-associated lipocalin (NGAL) appears to be a promising biomarker for the early diagnosis of acute kidney injury (AKI); however, a wide range in its predictive value has been reported.

Study Design: Meta-analysis of diagnostic test studies using custom-made standardized data sheets sent to each author.

Setting & Population: Different clinical settings of AKI.

Selection Criteria for Studies: MEDLINE, EMBASE, and CENTRAL databases and congress abstracts were searched for studies reporting the value of NGAL to predict AKI.

Index Tests: Plasma/serum and urine NGAL within 6 hours from the time of insult (if known) or 24-48 hours before the diagnosis of AKI if the time of insult was not known.

Reference Tests: The primary outcome was AKI, defined as an increase in serum creatinine level > 50% from baseline within 7 days or contrast-induced nephropathy (creatinine increase > 25% or concentration > 0.5 mg/dL in adults or > 50% increase in children within 48 hours). Other outcomes predicted using NGAL were renal replacement therapy initiation and in-hospital mortality.

Results: Using a hierarchical bivariate generalized linear model to calculate the diagnostic odds ratio (DOR) and sample size–weighted area under the curve for the receiver-operating characteristic (AUC-ROC), we analyzed data from 19 studies and 8 countries involving 2,538 patients, of whom 487 (19.2%) developed AKI. Overall, the DOR/AUC-ROC of NGAL to predict AKI was 18.6 (95% CI, 9.0-38.1)/0.815 (95% CI, 0.732-0.892). The DOR/AUC-ROC when standardized platforms were used was 25.5 (95% CI, 8.9-72.8)/0.830 (95% CI, 0.741-0.918) with a cutoff value > 150 ng/mL for AKI compared with 16.7 (95% CI, 7.1-39.7)/0.732 (95% CI, 0.656-0.830) for "research-based" NGAL assays. In cardiac surgery patients, the DOR/AUC-ROC of NGAL was 13.1 (95% CI, 5.7-34.8)/0.775 (95% CI, 0.669-0.867); in critically ill patients, 10.0 (95% CI, 3.0-33.1)/0.728 (95% CI, 0.615-0.834); and after contrast infusion, 92.0 (95% CI, 10.7-794.1)/0.894 (95% CI, 0.826-0.950). The diagnostic accuracy of plasma/serum NGAL (17.9 [95% CI, 6.0-53.7]/0.775 [95% CI, 0.679-0.869]) was similar to that of urine NGAL (18.6 [95% CI, 7.2-48.4]/0.837 [95% CI, 0.762-0.906]). We identified age to be an effective modifier of NGAL value with better predictive ability in children (25.4 [95% CI, 8.9-72.2]/0.930 [95% CI, 0.883-0.968]) compared with adults (10.6 [95% CI, 4.8-23.4]/0.782 [95% CI, 0.689-0.872]). NGAL level was a useful prognostic tool with regard to the prediction of renal replacement therapy initiation (12.9 [95% CI, 4.9-33.9]/0.782 [95% CI, 0.648-0.917]) and in-hospital mortality (8.8 [95% CI, 1.9-40.8]/0.706 [95% CI, 0.530-0.747]).

Limitations: Serum creatinine level was used for AKI definition.

Conclusions: NGAL level appears to be of diagnostic and prognostic value for AKI.

Am J Kidney Dis 54:1012-1024.

NGAL - METANALISI

Table 1. Characteristics of Studies

Reference	Sample Size	Population Type	Age (y)	Women (%)	Mean Baseline Serum Creatinine (mg/dL)	Impaired Renal Function (%)	Setting	NGAL Measurement	Country
Mishra et al, 2005[13]	71	Children	3.0	36.6	0.45	0	CS	Plasma + urine	United States
Wagener et al, 2006[15]	81	Adults	64.7	34.6	1.10	32.1	CS	Urine	United States
Dent et al, 2007[25]	123	Children	4.2	48.8	0.50	0	CS	Plasma	United States
Zappitelli et al, 2007[18]	39	Children	7.1	48.7	0.44	0	ICU	Urine	United States
Hirsch et al, 2007[23]	91	Children	6.9	44.0	0.73	0	CIN	Plasma + urine	United States
Wagener et al, 2008[26]	426	Adults	63.2	33.8	1.08	27.2	CS	Urine	United States
Bennett et al, 2008[16]	196	Children	4.0	46.4	0.39	0	CS	Urine	United States
Ling et al, 2008[20]	40	Adults	67.9	40.0	0.83	0	CIN	Urine	China
Koyner et al, 2008[22]	72	Adults	61.3	29.2	1.24	26.4	CS	Plasma + urine	United States
Nickolas et al, 2008[14]	541	Adults	59.2	48.4	1.20	26.8	ED	Urine	United States
Lima et al, 2008[27]	52	Adults	54.7	42.3	1.20	53.8	CS	Urine	Brazil
Wheeler et al, 2008[19]	143	Children	2.2	28.0	0.76	—	ICU	Plasma	United States
Xin et al, 2008[28]	33	Children + adults	38.0	42.4	0.77	0	CS	Urine	China
Cruz et al, 2009[29]	301	Adults	58.6	31.2	0.97	6.7	ICU	Plasma	Italy
Makris et al, 2009 (CIN)[30]	60	Adults	62.8	18.3	0.86	13.3	CIN	Urine	Greece
Makris et al, 2009 (ICU)[31]	31	Adults	41.9	19.4	0.97	—	ICU	Urine	Greece
Tuladhar et al, 2009[24]	50	Adults	66.7	30.0	1.10	42.0	CS	Plasma + urine	United Kingdom
Constantin et al, 2009[32]	88	Adults	57.0	45.5	0.81	—	ICU	Plasma	France
Haase-Fielitz et al, 2009[17]	100	Adults	69.5	39.0	1.04	27.0	CS	Plasma	Australia

Note: Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations and definitions: CIN, contrast-induced nephropathy; CS, cardiac surgery–associated acute kidney injury; ED, emergency department; ICU, intensive care unit; NGAL, neutrophil gelatinase-associated lipocalin.

Da: Haase M et al, Am J Kidney Dis 2009; 54: 1012-1024

0031-3998/09/6605-0528
PEDIATRIC RESEARCH

Vol. 66, No. 5, 2009
Printed in U.S.A.

Reference Values of Urinary Neutrophil Gelatinase-Associated Lipocalin in Very Low Birth Weight Infants

TRANG K. HUYNH, DAVID A. BATEMAN, ELVIRA PARRAVICINI, JOHN M. LORENZ, SHERI L. NEMEROFSKY, MEGHAN E. SISE, TERESA M. BOWMAN, ELENA POLESANA, AND JONATHAN M. BARASCH

Department of Pediatrics [T.K.H.], New York Presbyterian Hospital-Weill Cornell Medical College, New York, New York 10065; Departments of Pediatrics [D.A.B., E.P., J.M.L., T.M.B., E.P.] and Medicine [M.E.S., J.M.B.], Columbia University, New York, New York 10032; Department of Pediatrics [S.L.N.], Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York 10461

0031-3998/08/6404-0423
PEDIATRIC RESEARCH

Vol. 64, No. 4, 2008
Printed in U.S.A.

Urinary NGAL in Premature Infants

ADRIAN P. LAVERY, JAREEN K. MEINZEN-DERR, EDWARD ANDERSON, QING MA, MICHAEL R. BENNETT, PRASAD DEVARAJAN, AND KURT R. SCHIBLER

Division of Neonatology [A.P.L., K.R.S.], Center for Epidemiology and Biostatistics [J.K.M.-D.], Division of Nephrology and Hypertension [Q.M., M.R.B., P.D.], Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229; Department of Nursing [E.A.], Good Samaritan Hospital, Cincinnati, Ohio 45220

0031-3998/11/7004-0379
PEDIATRIC RESEARCH

Vol. 70, No. 4, 2011
Printed in U.S.A.

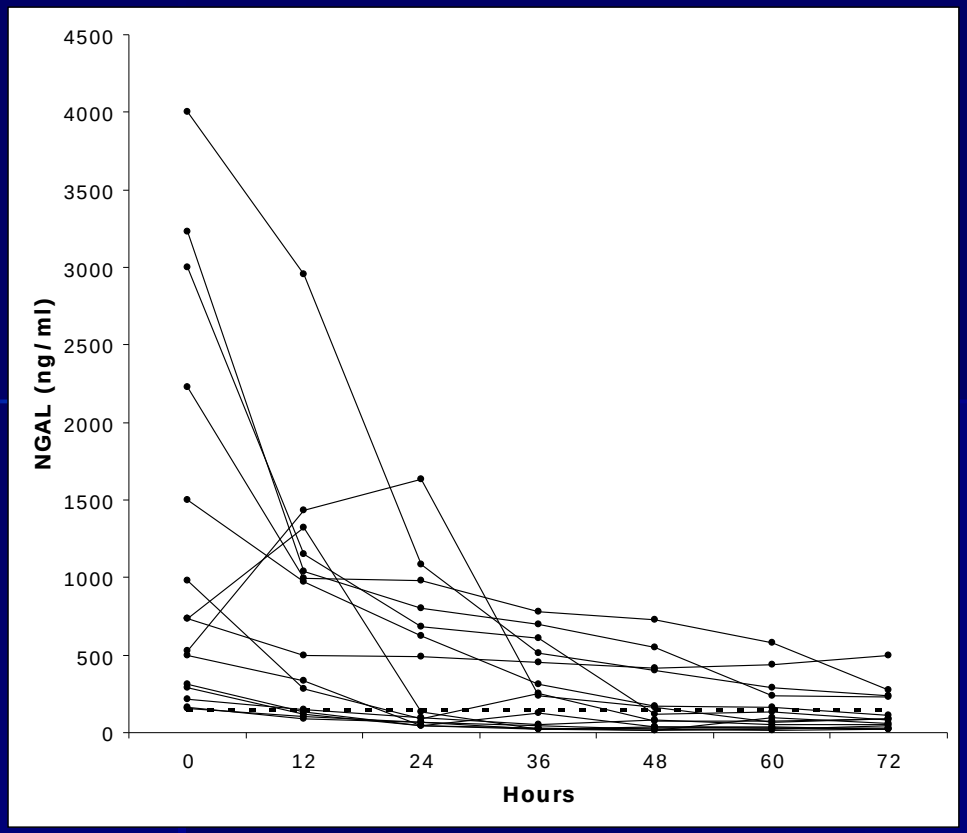
Urinary Neutrophil Gelatinase-Associated Lipocalin at Birth Predicts Early Renal Function in Very Low Birth Weight Infants

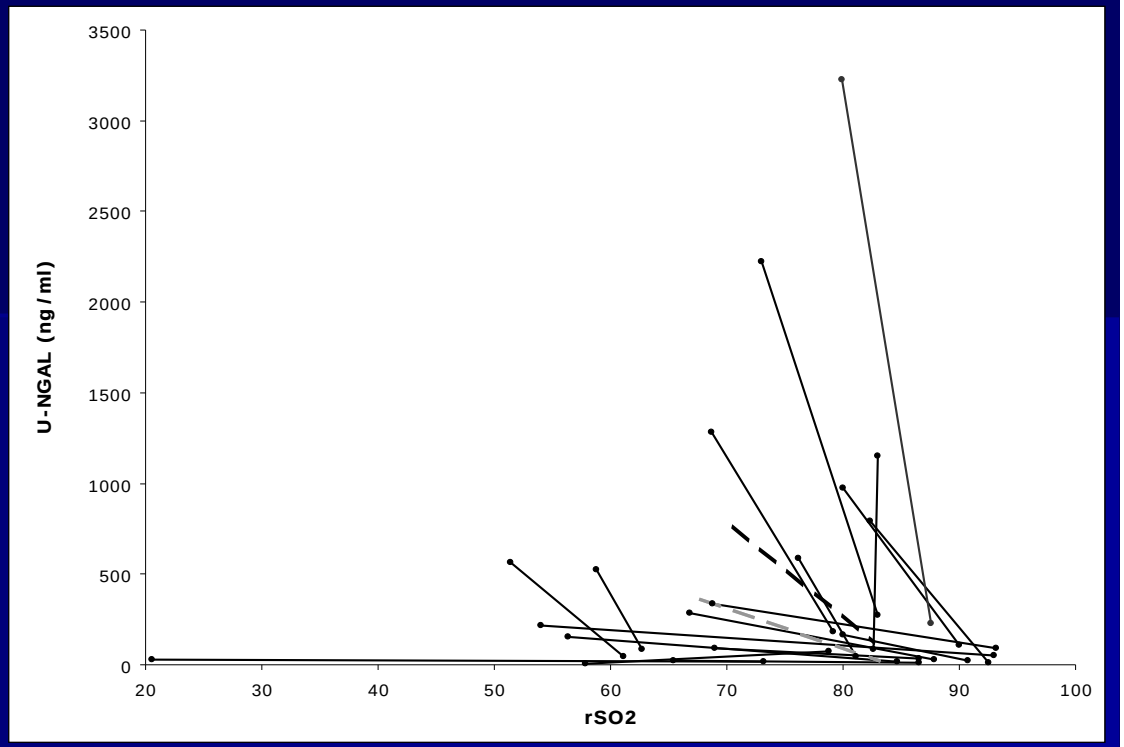
GAETANO LA MANNA, SILVIA GALLETTI, IRENE CAPELLI, SILVIA VANDINI, KATIA NISI, GIULIA AQUILANO, RITA MANCINI, ELISA CARRETTA, GIOVANNI MONTINI, GIACOMO FALDELLA, AND SERGIO STEFONI

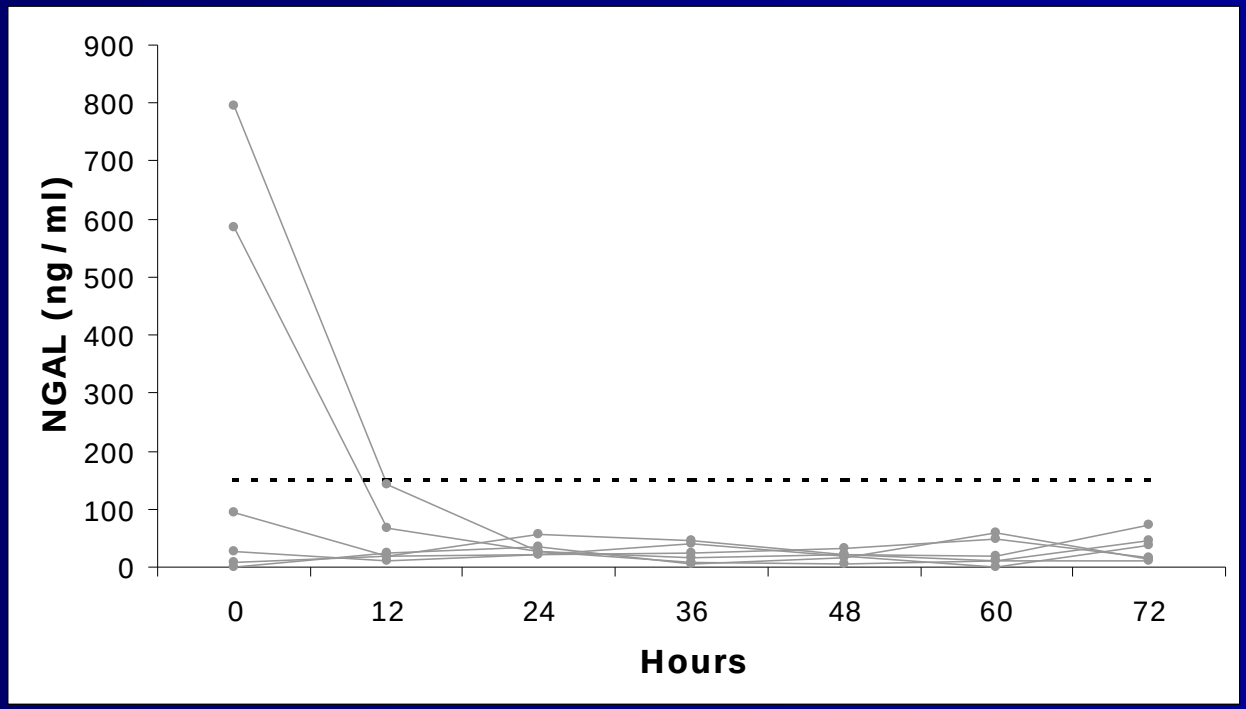
Department of Internal Medicine, Aging and Renal Disease [G.L.M., I.C., K.N., S.S.], Department of Woman Child and Adolescent Health [S.G., S.V., G.A., G.F.], Laboratory of Pathology and Clinical Chemistry [R.M.], Department of Pediatrics [G.M.], St. Orsola Hospital, University of Bologna, 40138 Bologna, Italy; Department of Medicine and Public Health [E.C.], University of Bologna, 40126 Bologna, Italy

First Pediatric Experience of Near-Infrared Spectroscopy (NIRS) as a Continuous Real-Time Monitoring for Kidney Graft Perfusion

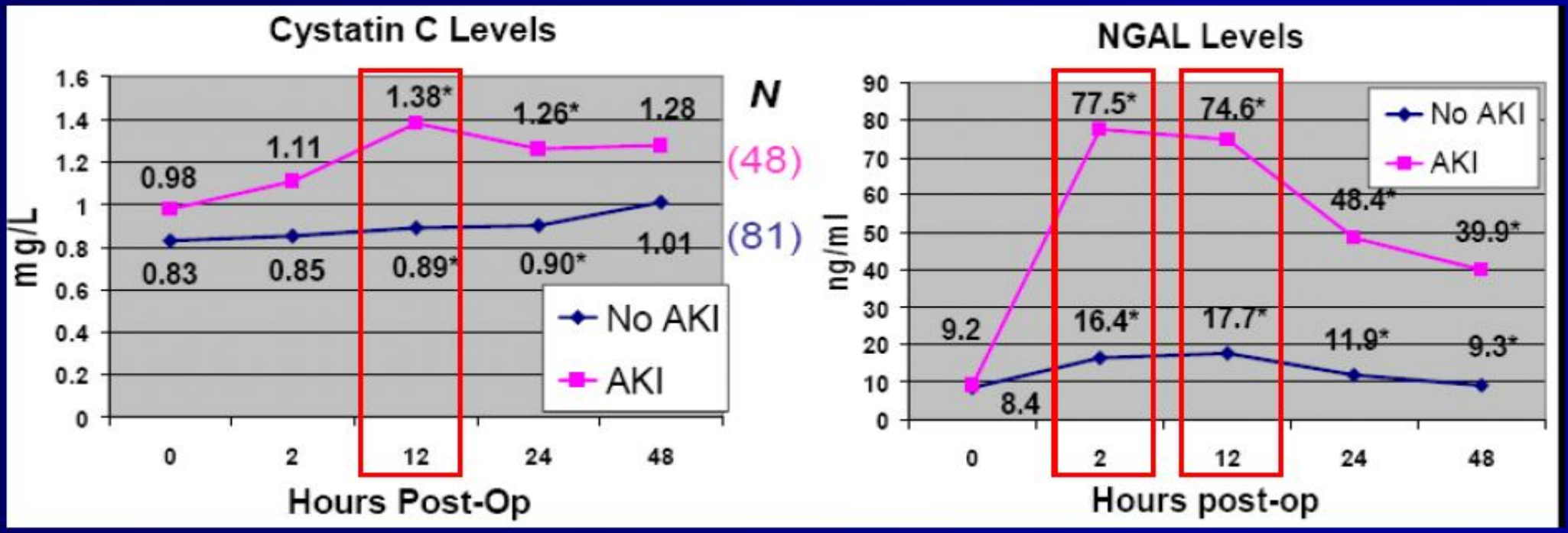
Post-revascularization time (hours)	DD KTP U-NGAL (ng/ml)	LRD KTP U-NGAL (ng/ml)	p
	Mean±DS	Mean±DS	
0	765.82±931.73	301.88±363.49	<0.05
12	729.63±721.18	47.08±50.94	
24	359.58±449.58	30.98±12.94	
36	260.78±301.07	23.46±16.47	
48	161.17±201.06	18.95±8.60	
60	126.80±152.13	29.42±22.97	
72	121.36±124.99	32.23±23.51	


NGAL (ng / ml)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
12
24
36
48
60
72
Hours


U-NGAL (ng / ml)
3500
3000
2500
2000
1500
1000
500
0
20
30
40
50
60
70
80
90
100
rSO2


NGAL (ng / ml)
900
800
700
600
500
400
300
200
100
0
0
12
24
36
48
60
72
Hours

NGAL e CISTATINA C [2]



Vandevoorde R. J Am Soc Nephrol 2006

I livelli di Cistatina C segnalano IRA dopo 12h

I livelli di NGAL dopo 2h e 12h

Clin Chem Lab Med 2012;50(9):1489–1493 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/cclm-2012-0433

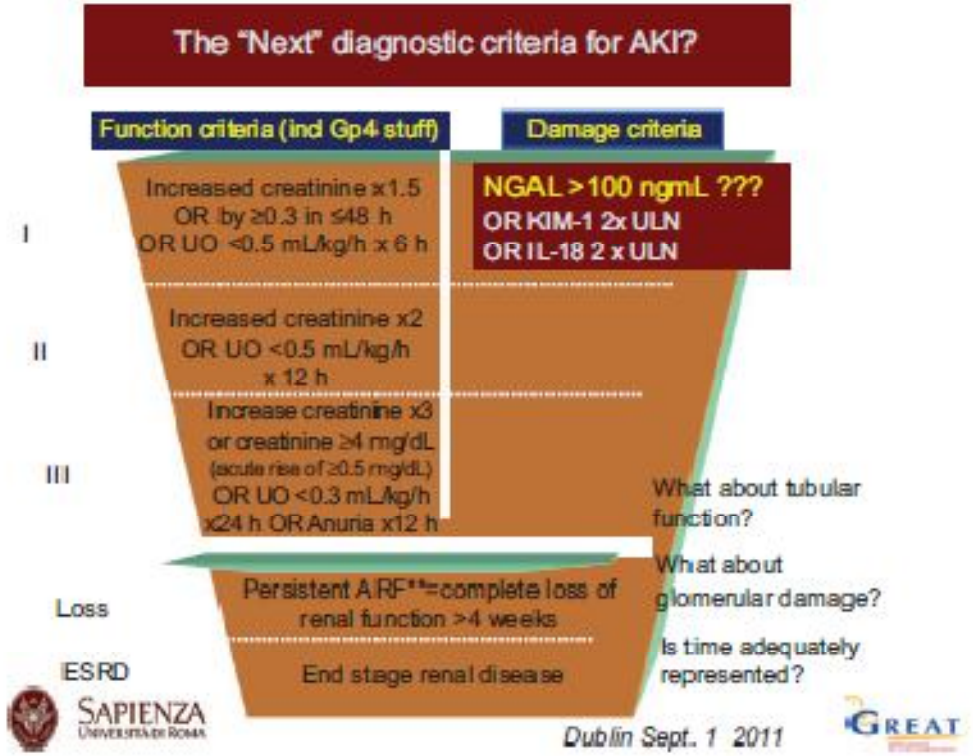
Editorial

Neutrophil gelatinase-associated lipocalin (NGAL): the clinician's perspective

Gianfranco Cervellin and Salvatore di Somma

Keyword
nase-assc

resulting in obstructive uropathy or postrenal AKI. If the site of obstruction is unilateral, then a rise in the serum creatinine level may be counterbalanced by contralateral renal function,
d patients
ss of GFR



Clin Chem Lab Med 2012;50(9):1483–1487 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/cclm-2012-0344

Editorial

Neutrophil gelatinase-associated lipocalin (NGAL): the laboratory perspective

Giuseppe Lippi and Mario Plebani

noticeably modified until the renal reserve has expired (e.g., up to 2–3 days post-injury), the reference range varies widely

Table 1 Leading issues in laboratory assessment of neutrophil gelatinase-associated lipocalin (NGAL).

1. Poor specificity of the current immunoassays for NGAL synthesized and released by the kidney tubule.
2. Insufficient data about biological variability and additional preanalytical sources of variations.
3. No definitive evidence about the optimal biological matrix (i.e., urine, blood, serum, EDTA plasma, heparin plasma).
4. Unavailability of definitive diagnostic thresholds.
5. Uncertainty about reporting test results.

Table 1 Origin of molecular forms of NGAL and NGAL/MMP9 complex in urine or blood.

Molecular form	Molecular weight	Origin
Urine		
Monomeric NGAL	25 kDa	De novo from injured kidney epithelial cells following AKI
Dimeric NGAL	45 kDa	1. From polymorphoneuclear neutrophils that infiltrate the damaged kidney 2. From neutrophils present in the urine of patients with localized urinary tract infections 3. Filtered systemic NGAL released from activated neutrophils in circulation (e.g., septic patients)
NGAL/MMP9 complexes	135 kDa	1. Complex formed in the urine from NGAL and MMP9 of systemic origin which were freely filtered through glomerulus 2. Complex formed in the urine from NGAL and MMP9 originating from kidney itself, following AKI
Blood		
Dimeric NGAL	45 kDa	From activated neutrophils. Can be filtered through intact glomerulus
NGAL/MMP9 complexes	135 kDa	Formed in the systemic circulation from NGAL and MMP9 produced by neutrophils, following production from inflamed or malignantly transformed epithelia. Cannot be filtered through glomerulus due to its large size

Clin Chem Lab Med 2012;50(9):1495–1499 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/cclm-2012-0099

Editorial

Serum creatinine and the search for new biomarkers of acute kidney injury (AKI): the story continues

Davide Bolignano

Failure were replaced with Stages 1, 2 and 3 and the outcome categories Loss and ESRD were eliminated. However, irrespective of the classification used, increasing evidence

Neutrophil gelatinase-associated lipocalin (NGAL) determined in urine with the Abbott Architect or in plasma with the Biosite Triage? The laboratory's point of view

Etienne Cavalier , Anne-Catherine Bekaert , Agnès Carlisi , Delphine Legrand , Jean-Marie Krzesinski and Pierre Delanaye

Clin Chem Lab Med 2011;49(2):339–341

Table 1 Precision and measurement uncertainty observed in six urine pools (Abbott Architect NGAL) and seven EDTA plasma pools (Biosite Triage NGAL).

Pool	n	Mean, µg/L	SD, µg/L	CV, %	Uncertainty, µg/L	Uncertainty, %	β-Expectation tolerance limit, µg/L	β-Expectation tolerance limit, %
Abbott Architect NGAL								
1	15	22.47	0.72	3.2	0.73	6.5	[21.0, 25.0]	[–6.7, 7.3]
2	15	81.07	2.80	3.5	3.0	7.3	[74.4, 87.8]	[–8.3, 8.3]
3	15	141.4	5.80	4.1	6.3	8.2	[124.9, 157.9]	[–11.7, 11.7]
4	15	460.0	26.3	5.7	28.7	12.5	[385.3, 534.7]	[–16.2, 16.2]
5	15	927.5	15.3	1.7	16.0	3.5	[892.6, 962.4]	[–3.8, 3.8]
6	15	1315	24.0	1.9	25.5	3.9	[1257, 1373]	[–4.4, 4.4]
Biosite Triage NGAL								
1	15	117	18.2	15.6	19.4	33.3	[72.22, 161.1]	[–38.1, 38.0]
2	15	163	25.3	15.5	26.1	32.0	[108.9, 221.3]	[–33.1, 35.7]
3	15	174	17.1	9.9	18.2	22.0	[132.6, 214.5]	[–23.6, 23.6]
4	15	199	29.0	14.6	30.0	30.2	[134.3, 263.2]	[–32.4, 32.4]
5	15	298	39.3	13.2	40.5	27.2	[210.6, 385.0]	[–29.2, 29.2]
6	15	427	67.6	15.8	69.8	32.7	[276.5, 576.6]	[–35.1, 35.1]
7	15	722	35.0	4.9	37.4	10.4	[636.0, 807.3]	[–11.8, 11.8]

The standard deviation (SD) and coefficient of variation (CV) correspond to the total variability observed during the 5 days of the experiment. Uncertainty characterizes the dispersion of the values around the (unknown) true value. The β-expectation tolerance limits show, for each level tested, where 95% of future results generated by the methods could be situated.

NGAL su urine plasma: sensibilità e specificità differenti

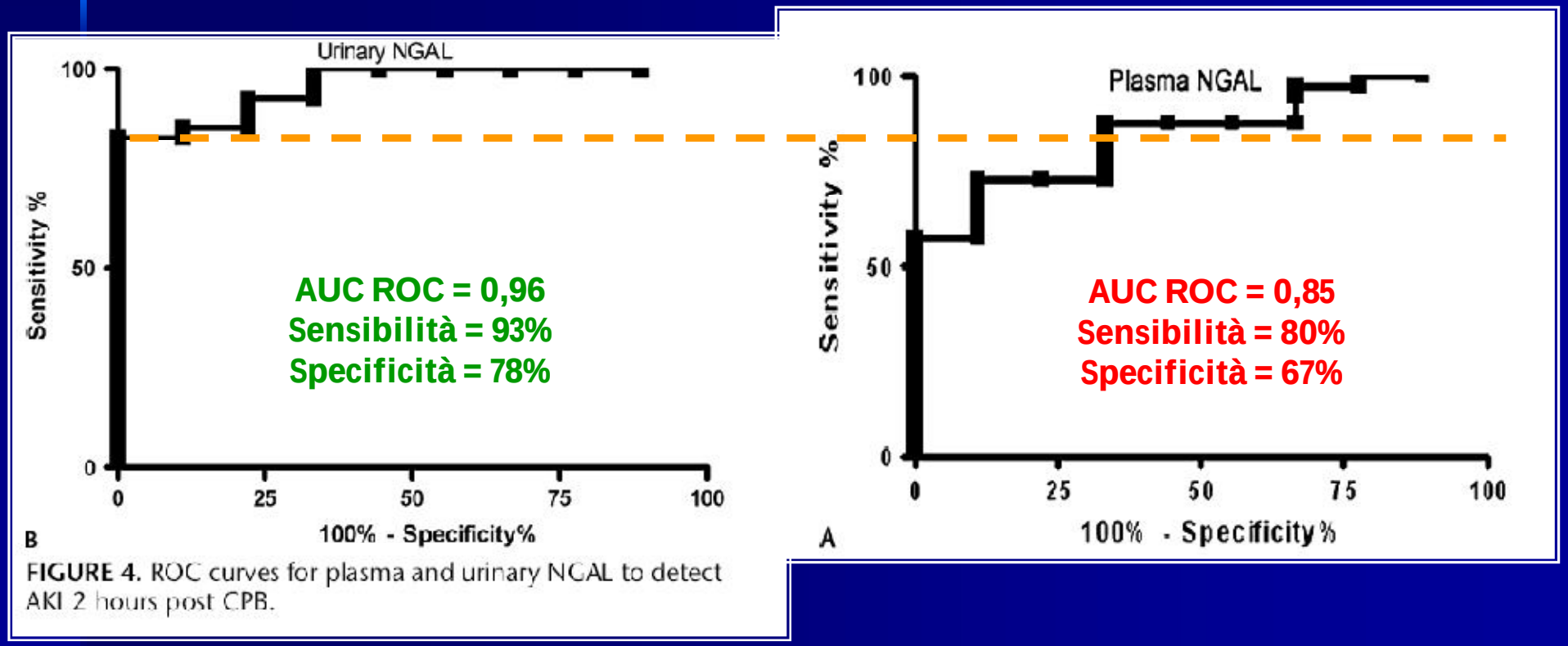


FIGURE 4. ROC curves for plasma and urinary NGAL to detect AKI 2 hours post CPB.

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REVIEW ARTICLE

Biomarkers of kidney injury

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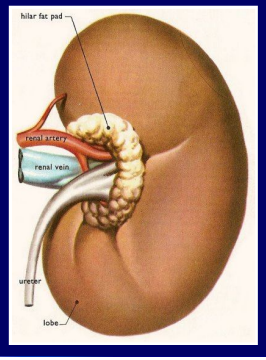
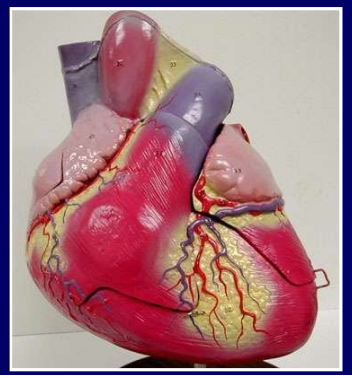
In conclusion, NGAL was found to be a useful early predictor of AKI, with urine or plasma/serum NGAL levels functioning as well. Additionally, NGAL level had prognostic value for clinical endpoints, such as initiation of dialysis and mortality (Haase et al., 2009). Unfortunately, substantial extrarenal NGAL generation in response to systemic stress can increase urinary NGAL excretion in the absence of AKI as well, and this may also arise from chronic and not just acute, renal disease (Haase et al., 2009).



nGAL e TROPONINA



- ***L'nGAL può essere per il rene il corrispettivo di quello che rappresenta la determinazione della troponina per il cuore?***
- La risposta, ad oggi, è interlocutoria: mancano le prove di modifiche del processo decisionale e di gestione del paziente sulla base del risultato di nGAL.

The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies

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Objectives The aim of this study was to test the hypothesis that, without diagnostic changes in serum creatinine, increased neutrophil gelatinase-associated lipocalin (NGAL) levels identify patients with subclinical acute kidney injury (AKI) and therefore worse prognosis.

Background Neutrophil gelatinase-associated lipocalin detects subclinical AKI hours to days before increases in serum creatinine indicate manifest loss of renal function.

Methods We analyzed pooled data from 2,322 critically ill patients with predominantly cardiorenal syndrome from 10 prospective observational studies of NGAL. We used the terms NGAL(−) or NGAL(+) according to study-specific NGAL cutoff for optimal AKI prediction and the terms sCREA(−) or sCREA(+) according to consensus diagnostic increases in serum creatinine defining AKI. A priori-defined outcomes included need for renal replacement therapy (primary endpoint), hospital mortality, their combination, and duration of stay in intensive care and in-hospital.

Results Of study patients, 1,296 (55.8%) were NGAL(−)/sCREA(−), 445 (19.2%) were NGAL(+)/sCREA(−), 107 (4.6%) were NGAL(−)/sCREA(+), and 474 (20.4%) were NGAL(+)/sCREA(+). According to the 4 study groups, there was a stepwise increase in subsequent renal replacement therapy initiation—NGAL(−)/sCREA(−): 0.0015% versus NGAL(+)/sCREA(−): 2.5% (odds ratio: 16.4, 95% confidence interval: 3.6 to 76.9, $p < 0.001$), NGAL(−)/sCREA(+): 7.5%, and NGAL(+)/sCREA(+): 8.0%, respectively, hospital mortality (4.8%, 12.4%, 8.4%, 14.7%, respectively) and their combination (4-group comparisons: all $p < 0.001$). There was a similar and consistent progressive increase in median number of intensive care and in-hospital days with increasing biomarker positivity: NGAL(−)/sCREA(−): 4.2 and 8.8 days; NGAL(+)/sCREA(−): 7.1 and 17.0 days; NGAL(−)/sCREA(+): 6.5 and 17.8 days; NGAL(+)/sCREA(+): 9.0 and 21.9 days; 4-group comparisons: $p = 0.003$ and $p = 0.040$, respectively. Urine and plasma NGAL indicated a similar outcome pattern.

Conclusions In the absence of diagnostic increases in serum creatinine, NGAL detects patients with likely subclinical AKI who have an increased risk of adverse outcomes. The concept and definition of AKI might need re-assessment.
(J Am Coll Cardiol 2011;57:1752–61)

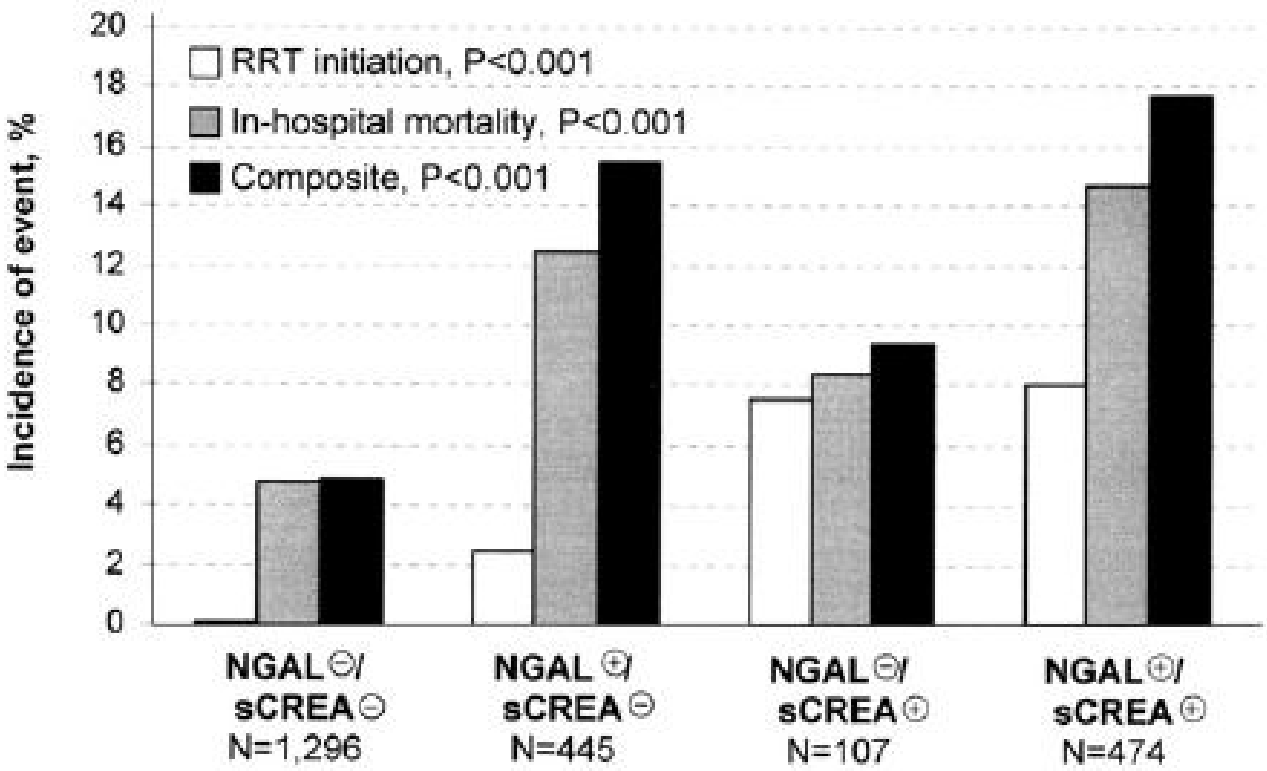

Figure 3 **Incidence of Events**

Incidence of RRT initiation, in-hospital morality, and a combination of both according to NGAL and sCREA. There was a stepwise increase in all outcomes. Abbreviations as in Figures 1 and 2.

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Una classificazione basata sui biomarcatori?

Table 3 | Relationship between biomarkers and RIFLE class or AKIN stage in adults

Study	Biomarker	Setting	AKI criteria	AKI severity by level of biomarkers
Siew *et al.* (2009)[32]	Urine NGAL*	ICU	AKIN	Non-AKI: 48.1 (12.7–179.3) ng/ml‡ Stage 1: 158 (27–430) ng/ml‡ Stage 2: 390 (39–4,317) ng/ml‡§ Stage 3: 390 (39–4,317) ng/ml‡§
Cruz *et al.* (2010)[31]	Plasma NGAL‖	ICU	RIFLE	Non-AKI: 102.4 (67.4–147.5) ng/ml‡ Risk: 171.4 (101.9–281.7) ng/ml‡ Injury 2: 214.9 (137.5–419.5) ng/ml‡ Failure: 620.3 (406.4–1,300.0) ng/ml‡
Haase-Fielitz *et al.* (2009)[40]	Plasma NGAL (ng/ml)¶	Undergoing cardiac surgery	RIFLE and AKIN	Non-AKI: ≤150 ng/ml Risk or Stage 1: >150 ng/ml Injury or Stage 2: >150 ng/ml Failure or Stage 3: >240 ng/ml
Herget-Rosenthal *et al.* (2004)[25]	Serum cystatin C (% increase from baseline)#	ICU and high risk of AKI	RIFLE	Non-AKI: 48.1 <50% increase Risk: ≥50% increase Injury: >100% increase Failure: ≥200% increase

Work in progress