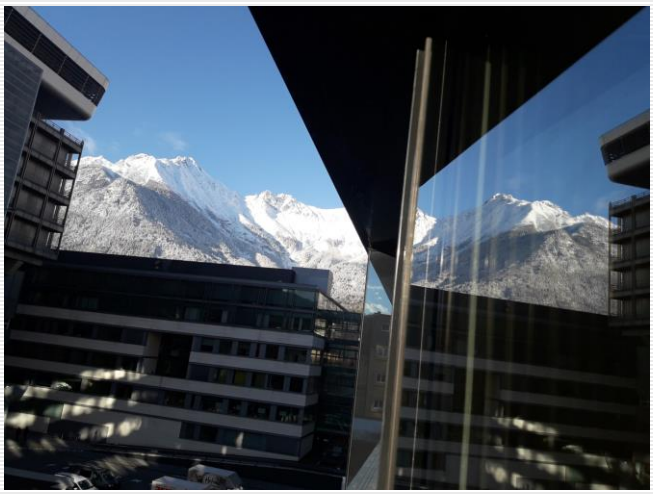
INTERNISTISCHE INTENSIVSTATION INNSBRUCK

Neue Biomarkers für Akute Nierenschädigung (AKI)

MEDIZINISCHE UNIVERSITÄT INNSBRUCK



Michael Joannidis
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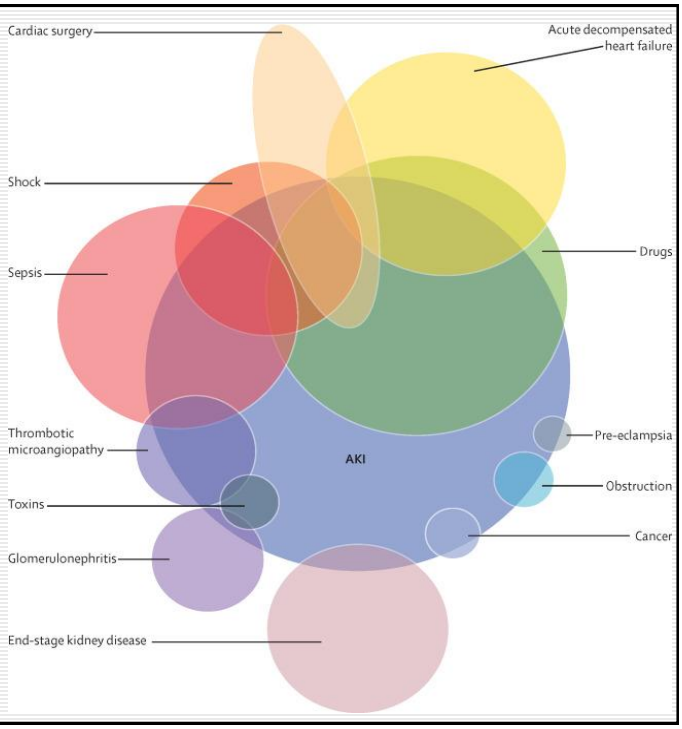
Director
Intensive Care and Emergency Medicine
Department Internal Medicine

Medical University Innsbruck, Austria

Why should we use Biomarkers?

- ✓ Redefining AKI for a more personalised diagnosis
- ✓ Coming closer to successful prevention/management of AKI
- ✓ Optimising timing of RRT

The clinical spectrum of AKI syndrome

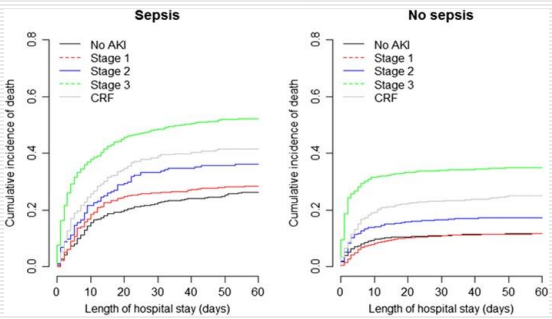


Ronco C et al, Lancet 2019; 394: 1949–64

A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit.

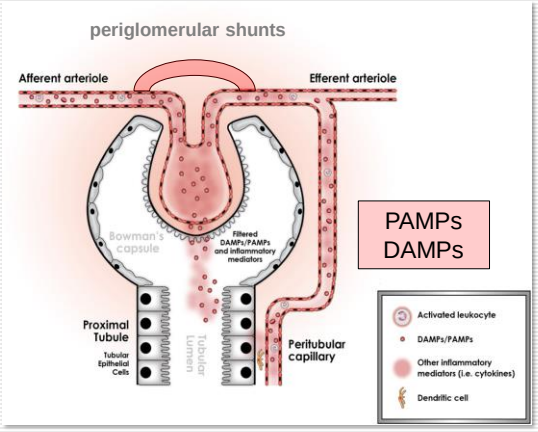
N=7970	Sepsis (N=1946)	No sepsis (n=6024)
AKI	68%	57%
AKI stage 3	40%	24%
RRT	20%	5%
Improvement to AKI<3 within 7days	21%	32%

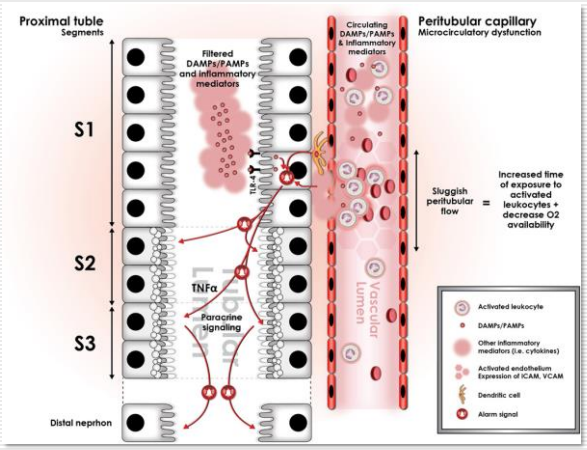
Mortality



Peters E. et al, Crit Care. 2018; 22: 188.

A Unified Theory of Sepsis-Induced Acute Kidney Injury: Inflammation, microcirculatory dysfunction, bioenergetics and the tubular cell adaptation to injury



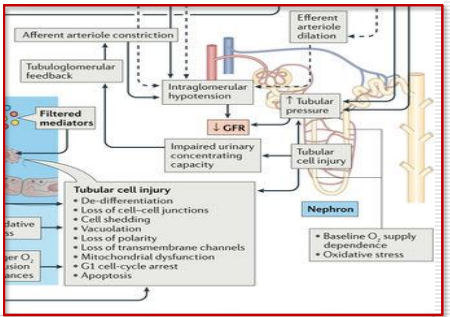


Gomez H et al, Shock 2014 Jan; 41(1): 3–11.

Pathophysiologie akuten Nierenschädigung (AKI)

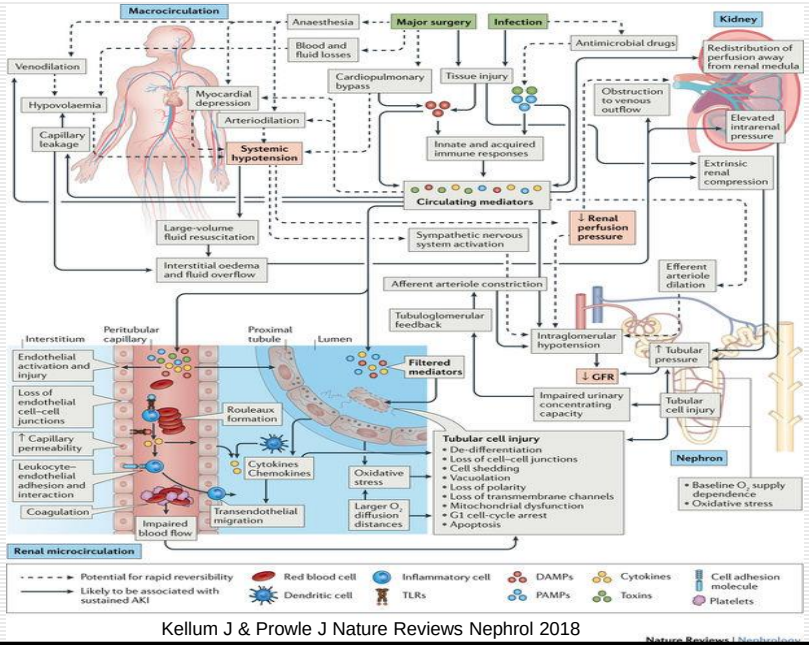
GFR Reduktion durch:

- Aktivierung des Tubuloglomerulären Feedback (TGF)
- Intraglomeruläre Hypotension
- Erhöhten Widerstand im Tubulus
- Intrarenales Ödem



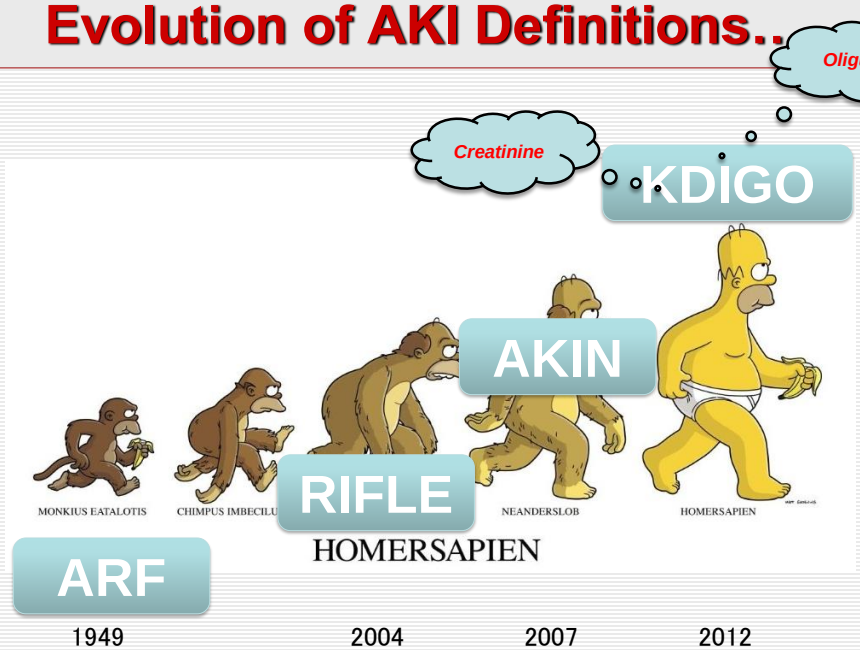
Kellum J & Prowle J Nature Reviews Nephrol 2018

Pathophysiologie der akuten Nierenschädigung (AKI)



Kellum J & Prowle J Nature Reviews Nephrol 2018

Evolution of AKI Definitions..



The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock

ProCESS trial- secondary analysis

Supplementary Table 1. New acute kidney injury as defined by Serum Creatinine or Urine Output Criteria by Treatment Arm Creatinine Criteria

	AKI Stage by Serum Creatinine Criteria				
Treatment arm	0	1	2	3	Total
EGDT	177 (85.9%)	17 (8.2%)	7 (3.4%)	5 (2.4%)	206
PSC	169 (80.9%)	24 (11.5%		7 (3.4%)	209
UC	164 (81.2%)	28 (13.9%		4 (2.0%)	202
Total	510	69	22	16	617

AKI ~ 17%

Fisher's exact test p-value = 0.59

Urinary Output Criteria

	AKI Stage by Urine Output Criteria				
Treatment arm	0	1	2	3	Total
EGDT	136 (66.0%)	15 (7.3%)		19 (9.2%)	206
PSC	157 (75.1%)	14 (6.7%		13 (6.2%)	209
UC	146 (72.3%)	12 (5.9%)	31 (15.4%)	13 (6.4%)	202
Total	439	41	92	45	617

AKI ~ 29%

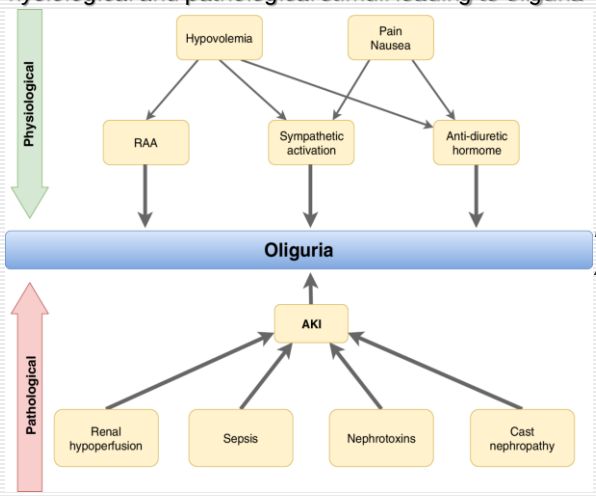
Chi-Square test p-value = 0.51

AKI, Acute Kidney Injury. Stage 0 = "no AKI" by serum creatinine (top) or urine output criteria (bottom). Analyses were restricted to patients without AKI at enrollment.

Kellum J et al, AJRCCM 2015, Epub September 2015

Oliguria as part of a spectrum

Physiological and pathological stimuli leading to oliguria

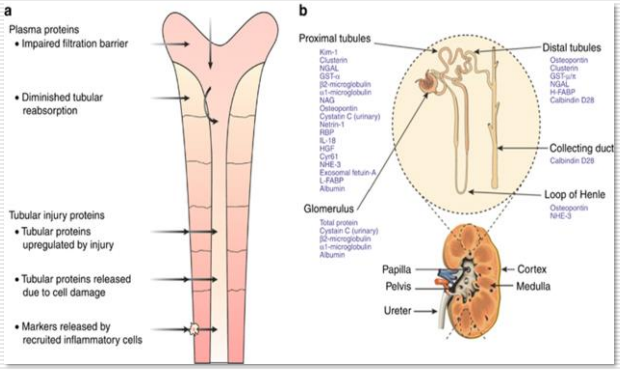


RAA renin–angiotensin–aldosterone system

AKI acute kidney injury

Klein S et al, J Nephrol. 2018 Dec;31(6):855-862

Proposed New Definition of AKI

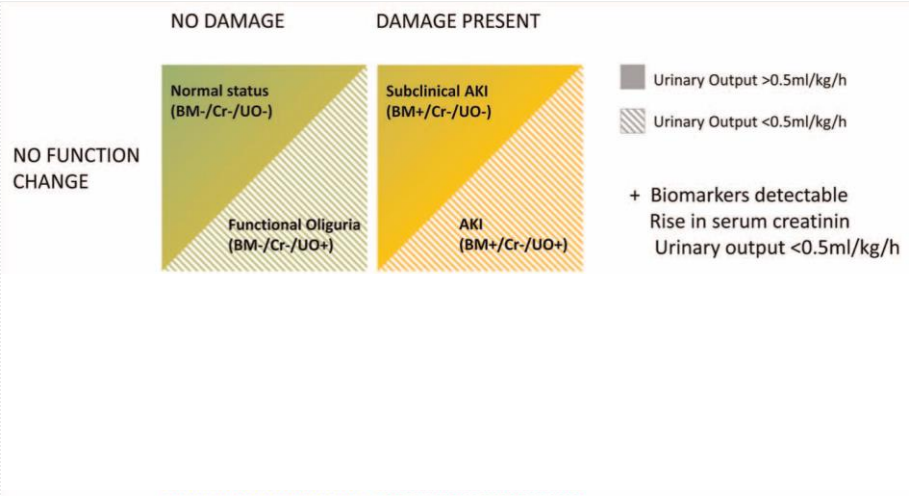


Functional criteria	Stage	Damage criteria
No change or sCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of sCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of sCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of sCr level by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

Murray PT et al , Kidney Int. 2014 Mar;85(3):513-21

Ostermann M et al, *JAMA Netw Open.* 2020;3(10):e2019209

The spectrum of acute kidney injury according to biomarkers of kidney injury, urine output, and serum creatinine



Vaara S, Forni L, Joannidis M; Curr Opin Crit Care. 2022 Dec 1;28(6):599-604

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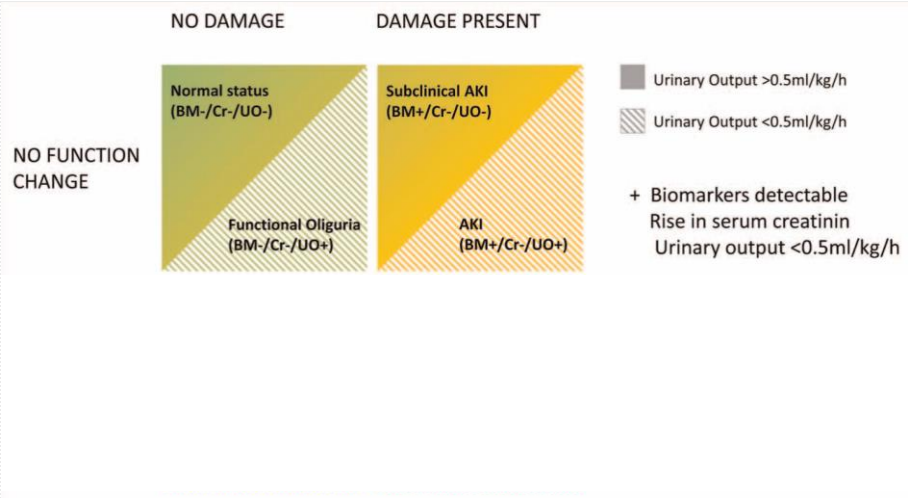
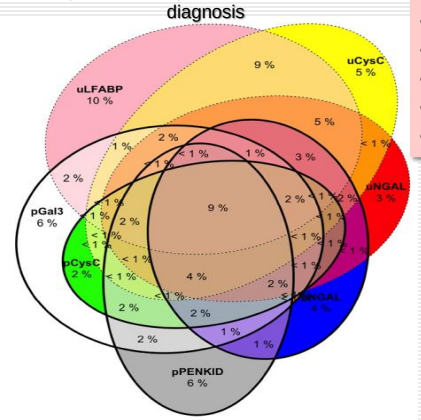


Vaara S, Forni L, Joannidis M; Curr Opin Crit Care. 2022 Dec 1;28(6):599-604

Subclinical and clinical acute kidney injury share similar urinary peptide signatures and prognosis

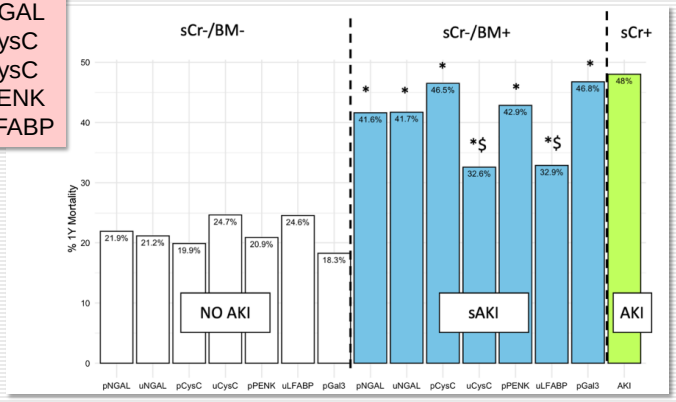
Ancillary analysis of the prospective, observational, multinational FROG-ICU cohort study
1885 patients had all biomarkers measured at inclusion, 1154 patients without AKI (non-AKIKDIGO subgroup)
AKI by creatinine criteria only!

Correspondence of positive biomarker for sAKI diagnosis



- pNAGL
- uNGAL
- pCysC
- uCysC
- pPENK
- uLFABP

The mortality rate of patients according to their AKI status



Boutin L et al, Intensive Care Med (2023) 49:1191–1202

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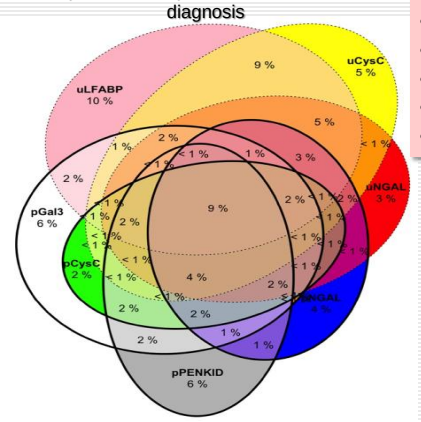

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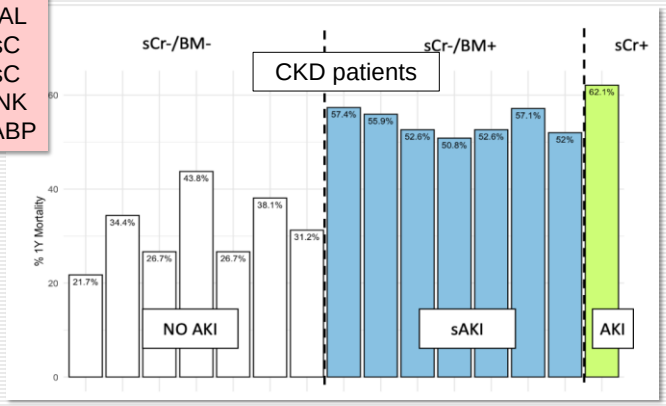
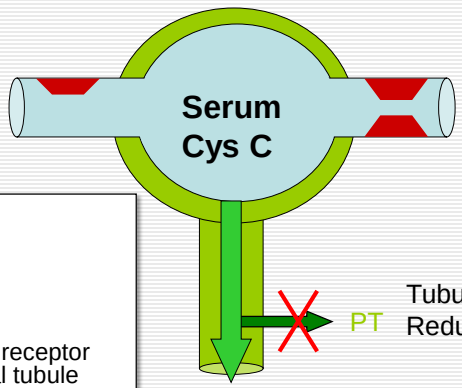


Boutin L et al, Intensive Care Med (2023) 49:1191–1202

Cystatin C

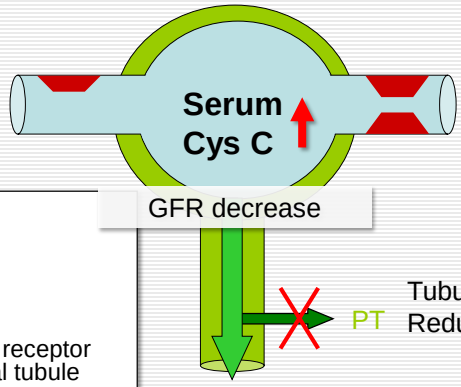


- MW : 13 kDa (protein)
- produced by nucleated cells
- constant production rate
- free glomerular filtration
- complete reabsorption via megalin receptor and degradation in proximal tubule
- small volume for distribution (high sensitivity for changes in GFR)

Tubular damage ->
Reduced reabsorption

Increased **urinary CysC**

Cystatin C



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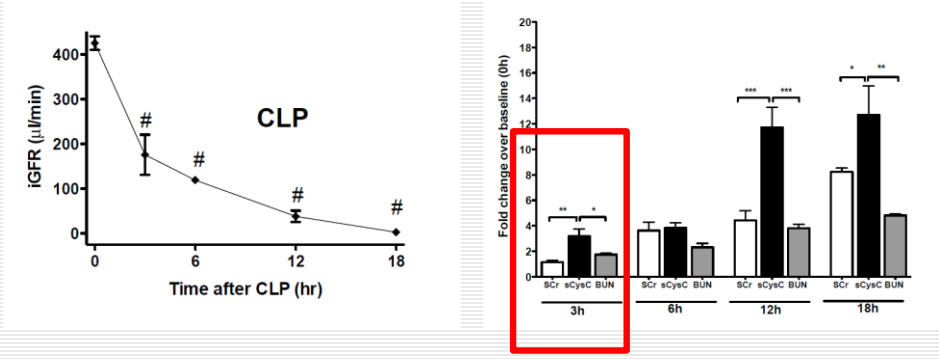
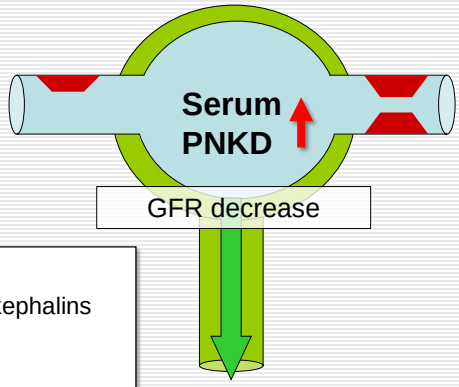
Comparison of serum creatinine and serum cystatin C as biomarkers to detect sepsis- induced acute kidney injury and to predict mortality in CD-1 mice



Leelahavanichkul A, Am J Physiol Renal Physiol (August 20, 2014)

PenKID



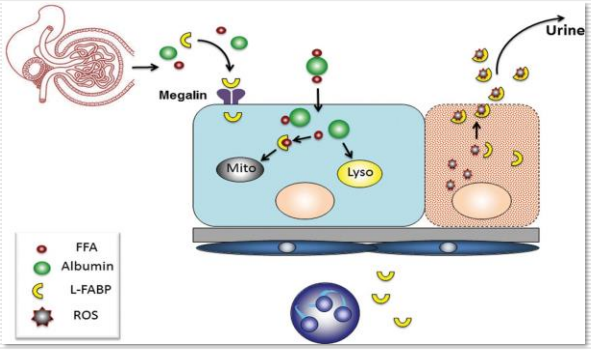
- MW : 5 kDa (protein)
- identical to the precursors of met-enkephalins and leu-enkephalins
- No plasma binding
- free glomerular filtration
- no tubular secretion
- high sensitivity for changes in GFR

NGAL
(Neutrophil gelatinase-associated lipocalin)

- MW : 25 kDa protein
- Released by activated neutrophils
- Filtered in the glomerulum
- Expression in kidney after Ischemia
- Appears in urine (secreted by TAL and CD)

Haase M et al, Am J Kidney Dis. 2009 Dec;54(6):1012-24

Liver Fatty Acid-Binding Protein (L-FABP)



Charlton J R et al. Nephrol. Dial. Transplant. 2014;29:1301-1311

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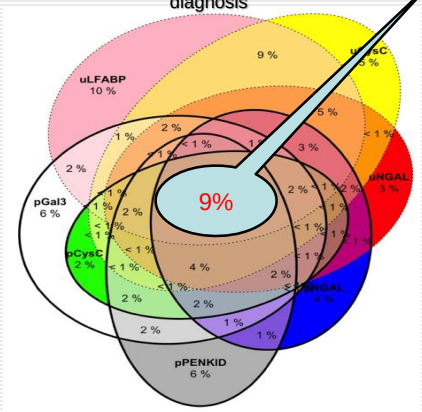
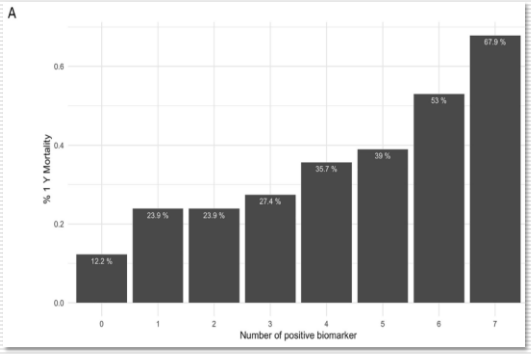


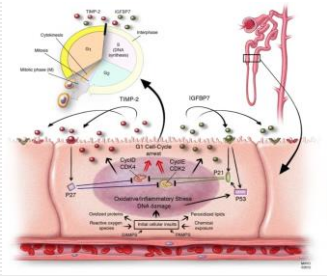
One biomarker can´t do the job

The mortality rate according to the number of positive biomarkers



Boutin L et al, Intensive Care Med (2023) 49:1191–1202

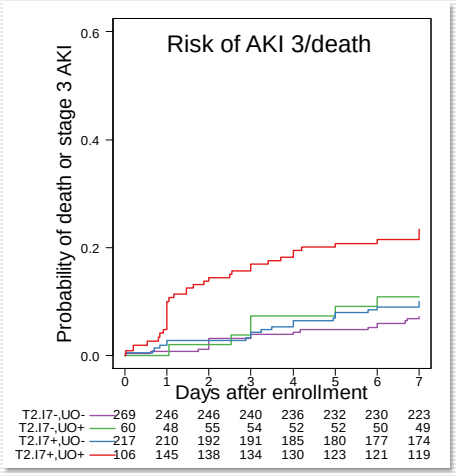
Cell Cycle Arrest Biomarkers for Differential Diagnosis in Oliguria in High Risk Patients.



Tissue Inhibitor of Metalloproteinases 2

Insulin-like Growth Factor Binding Protein 7

TIMP-2/IGFBP7 added to UO



Stage 1B

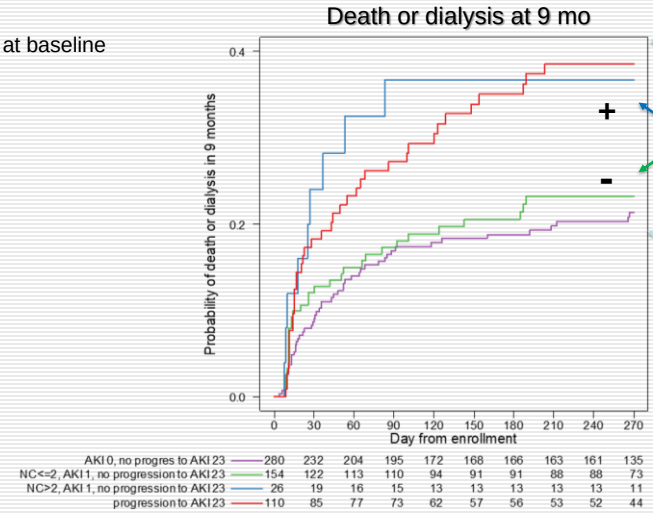
Stage 1A

Kashani et al. Critical Care 2013, 17:R25

Joannidis M et al, Critical Care Medicine 2019, 47(10):e820-e826

Oliguria, Azotemia and Cell Cycle Arrest Biomarkers as Predictors of Acute Kidney Injury in High Risk Patients.

[TIMP-2]*[IGFBP7] > 2.0 at baseline
AKI within 12h
Progression over 1wk
Death or dialysis 9mo



Progression to Stage 2-3

\+ AKI Stage 1 NO Progression to Stage 2-3 — Stage 1B

\- NO AKI NO Progression to Stage 2-3 — Stage 1A

Joannidis M et al, Critical Care Medicine 2019, 47(10):e820-e826

Prevention of AKI - the KDIGO – "Bundle"

KDIGO Consensus Guideline for AKI

KDIGO Staging of Acute Kidney Injury (AKI)

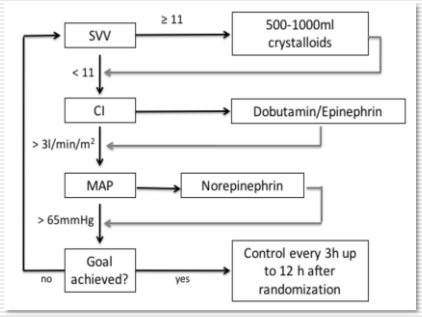
	AKI Stage		
High Risk	**Stage 1**	**Stage 2**	**Stage 3**
Discontinue all nephrotoxic agents when possible			
Ensure volume status and perfusion pressure			
Consider functional hemodynamic monitoring			
Monitor serum creatinine and urine output			
Avoid hyperglycemia			
Consider alternatives to radiocontrast procedures			
	Non-invasive diagnostic workup		
	Consider invasive diagnostic workup		
		Check for changes in drug dosing	
		Consider renal replacement therapy	
		Consider ICU admission	
			Avoid subclavian catheters if possible

Kidney Int 2012, Suppl. 2012, 2: 1-138

Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial

Patient selection by increased levels of cell cycle arrest markers (TIMP-2 * IGFBP7) > 0.3 ng/ml²/1000
267 patients randomized (138 control, 138 intervention)

Intervention:
- Avoiding nephrotoxins
- BS control in the first 72 h
- using alternatives to radiocontrast media
- hemodynamic monitoring by using a PICCO catheter with an optimization of the volume status and hemodynamic parameters according to a prespecified algorithm



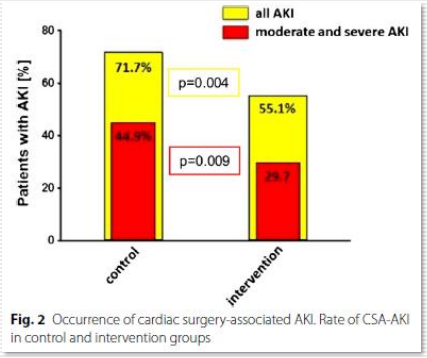


Fig. 2 Occurrence of cardiac surgery-associated AKI. Rate of CSA-AKI in control and intervention groups

Meersch M et al, Intensive Care Med 2016

Prevention of Cardiac Surgery–Associated Acute Kidney Injury by Implementing the KDIGO Guidelines in High-Risk Patients Identified by Biomarkers: The PrevAKI-Multicenter Randomized Controlled Trial

Patient selection by increased levels of cell cycle arrest markers (TIMP-2 * IGFBP7) > 0.3 ng/ml²/1000
280 patients randomized (138 control, 138 intervention), Multi-center RCT

Table 4. Secondary Outcomes

	Control (n = 142)	Intervention (n = 136)	OR (intervention versus control) (95% CI)	RRR[a] (%) (95% CI)	ARR[b] (%) (95% CI)
AKI within 72 h, no./total no. (%)	59/142 (41.5)	63/136 (46.3)	1.21 (0.76-1.95)	−11.5 (−45.5 to 14.6)	−4.8 (−16.4 to 6.9)
Diagnosis based on, no. (%)					
Creatinine	22 (37.3)	24 (38.1)			
Urine output	27 (45.8)	26 (41.3)			
Both	10 (16.9)	13 (20.6)			
Moderate to severe AKI, no./total no. (%)	34/142 (23.9)	19/136 (14.0)	0.52 (0.28-0.96)	41.7 (2.9-65.0)	10.0 (0.9-19.1)
Renal recovery at 90 d, no./total no. (%)	118/142 (83.1)	106/136 (77.9)	0.72 (0.40-1.31)	−30.5 (−111.5 to 19.4)	−5.2 (−14.5 to 4.1)
RRT during hospital stay, no./total no.(%)	9/142 (6.3)	6/136 (4.4)	0.68 (0.24-1.97)	30.4 (−90.3 to 74.5)	1.9 (−3.4 to 7.2)

Zarbock A et al, Anesth Analg 2021;133:292–302

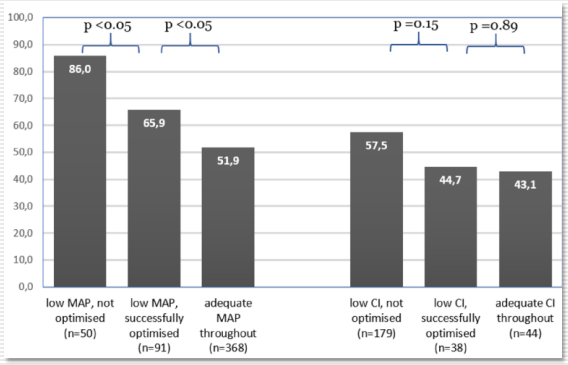
Not all interventions are equal

Analysis of the PrevAKI-Multicenter Randomized Controlled Trial

Univariate, binary logistic regression analysis for development of any AKI

Analysis:	Risk factor (intervention + control arms; n=554)		Individual treatment effect (intervention arm; n=274)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Hypotension	2.30 (1.61 - 3.27)	< 0.05	2.37 (1.41 – 3.98)	< 0.05
cardiac index < 3.0	1.93 (1.10 - 3.38)	< 0.05	1.97 (1.11 – 3.52)	< 0.05
cardiac index < 3.0 and/or hypotension	2.25 (1.15 - 4.39)	< 0.05	2.10 (1.06 – 4.17)	< 0.05
hyperglycemia	1.44 (0.99 - 2.10)	0.056	1.07 (0.64 – 1.77)	0.8
Use of ACEi or ARBs	1.19 (0.75 - 1.90)	0.456	0.85 (0.41 – 1.76)	0.85
Use of contrast agents	3.57 (1.55 - 8.24)	< 0.05	2.57 (0.81 – 8.18)	0.11
nephrotoxic drugs	1.58 (0.91 - 2.73)	0.107	8.19 (1.86 – 36.02)	< 0.05

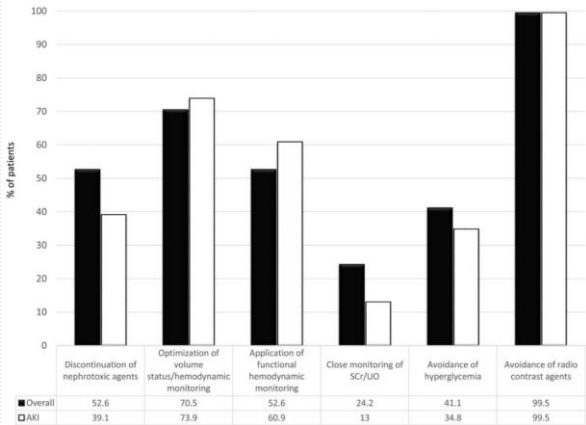
AKI Rate

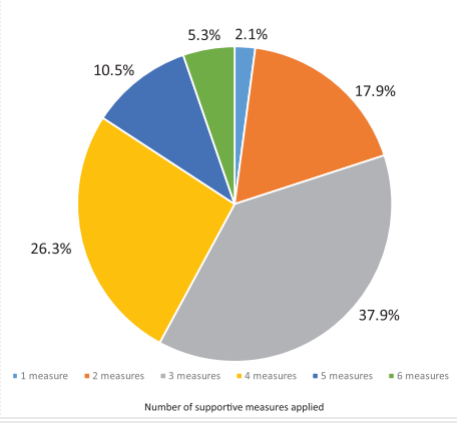


Von Groote TC et al, Intensive Care Med (2022) 48:242–245

Adherence to preventive measures

A 2-day observational prevalence study, 95 cardiac surgery patients enrolled in 12 participating hospitals





Külmar M. et al, Anesth Analg 2020;130:910–6

Predicting „persistent severe AKI“

Identification and Validation of Biomarkers of Persistent Acute Kidney Injury. The RUBY Study.

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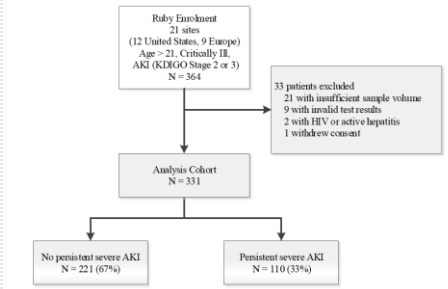
- ICU patients enrolled with 36h of *AKI stage 2+*
- Primary outcome
  - AKI stage 3 of >72h
  - dialysis
  - death following KDIGO stage 3 AKI



Prediction of persistent AKI
(= AKI stage 3 >72h)

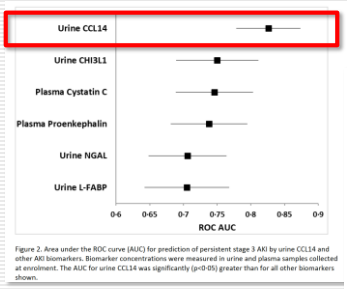
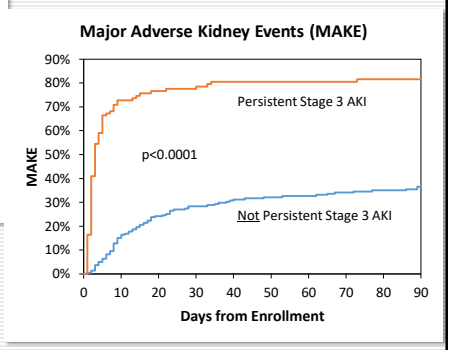


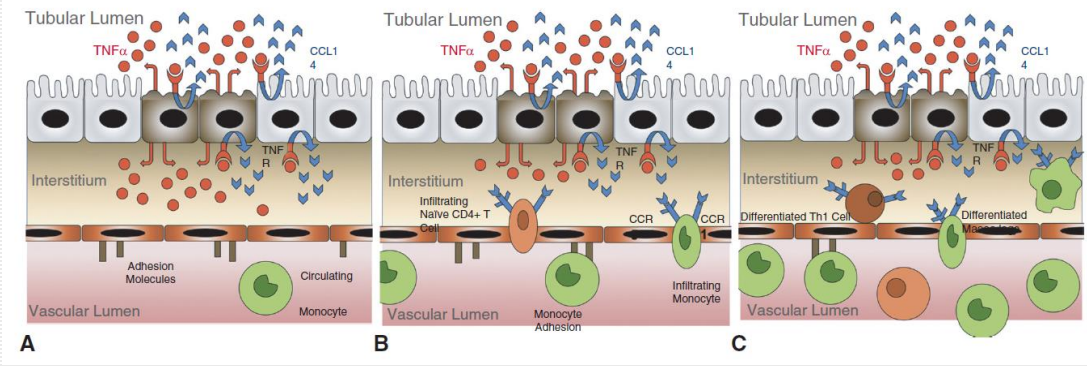
Figure 2. Area under the ROC curve (AUC) for prediction of persistent stage 3 AKI by urine CCL14 and other AKI biomarkers. Biomarker concentrations were measured in urine and plasma samples collected at enrolment. The AUC for urine CCL14 was significantly (p<0·05) greater than for all other biomarkers shown.

Persistent AKI predicts MAKE
(=dialysis, 25% eGFR loss, or death within 90 days)



E. Hoste et al, Intensive Care Med (2020) 46:943–953

CCL14 (CC-chemokine ligand 14) mechanism

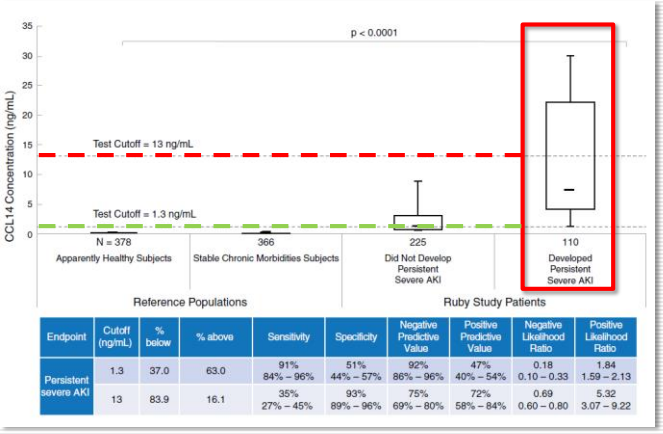


A, Injured cells release inflammatory mediators. These bind to tumor necrosis factor receptors leading to a release of CCL14 from tubular epithelial cells.
B, CCL14 binds to CCR receptors on monocytes and T cells leading to an induction of chemotaxis toward the site of injury.
C, Monocytes differentiate into macrophages, and naive T cells differentiate into proinflammatory T-helper 1 cells

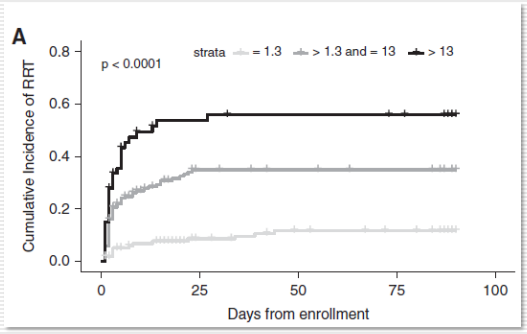
(based on Hoste E et al ICM 2020)

Biomarker of persistent AKI

Secondary analysis of the RUBY Study



Endpoint	Cutoff (ng/mL)	% below	% above	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Negative Likelihood Ratio	Positive Likelihood Ratio
Persistent severe AKI	1.3	37.0	63.0	91% 84% – 96%	51% 44% – 57%	92% 86% – 96%	47% 40% – 54%	0.18 0.10 – 0.33	1.84 1.59 – 2.13
	13	83.9	16.1	35% 27% – 45%	93% 89% – 96%	75% 69% – 80%	72% 58% – 84%	0.69 0.60 – 0.80	5.32 3.07 – 9.22



Koyner J. et al, KIDNEY360 3: 1158–1168, 2022.

Predicting the Development of Renal Replacement Therapy Indications by Combining the Furosemide Stress Test and Chemokine (C-C Motif) Ligand 14 in a Cohort of Postsurgical Patients

Prospective observational cohort study: critically ill adult patients with an oliguric stage 2 AKI were (n=208). At study inclusion, patients had to be either mechanically ventilated and/or receiving vasopressors.
Exclusion CKD < 20 ml/min/1.73 m²

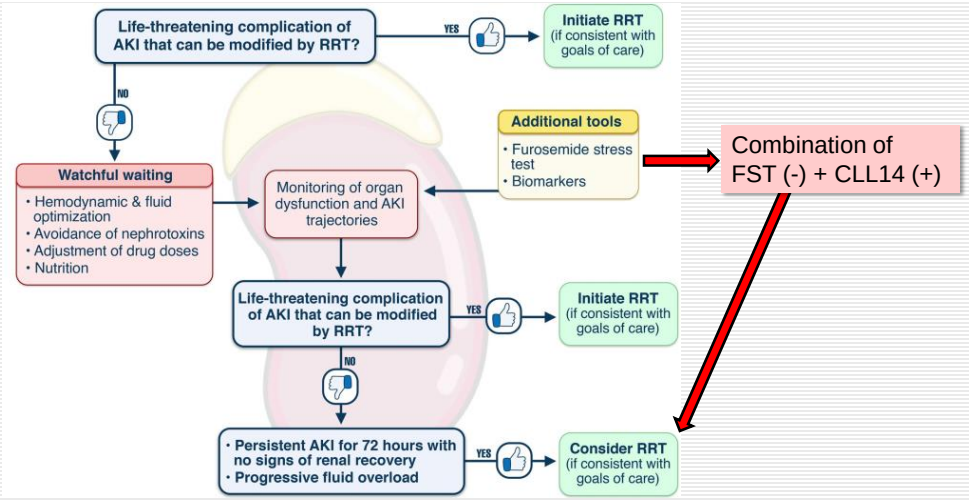
Biomarker	FST Negative (UO < 200 mL/2 hr), AUC (95% CI)	FST Positive (UO > 200 mL/2 hr), AUC (95% CI)	p[a]
Chemokine (C-C motif) ligand 14	0.855 (0.770–0.940)	0.658 (0.517–0.800)	0.019
Neutrophil gelatinase-associated lipocalin	0.716 (0.614–0.819)	0.718 (0.602–0.834)	0.98
Dipeptidyl peptidase 3	0.697 (0.568–0.826)	0.707 (0.572–0.843)	0.91

CCL14 : AUC 0.83 (95% CI, 0.77–0.89)
FST : AUC 0.79 (95% CI, 0.74–0.85)
Combination of FST and CCL14: AUC 0.87 (95% CI, 0.82–0.92)

Meersch M et al. Critical Care Med (2023) 51 EPUB

Delivering optimal renal replacement therapy to critically ill patients with acute kidney injury

A proposed algorithm for the initiation of renal replacement therapy



Wald R *et al. Intensive Care Med (2022) 48:1368–1381*

Biomarkers for AKI Diagnosis Summary

- AKI is a complex disease which requires additional diagnostic tools

- (Serum) biomarkers with increased sensitivity for *small changes of GFR (pCys C, pPENKid)*
- (Urinary) biomarkers indicating *stress/tubular damage (NGAL, TIMP-2/IGFBP-7, Kim-1)*
- (Urinary) biomarkers indicating *profound kidney inflammation (uCCL14)*
- New biomarker will help identify patients at risk for AKI and individualise therapy and preventive measures

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