The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

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Persistent AKI

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THE FATHER OF EXPERIMENTAL MEDICINE

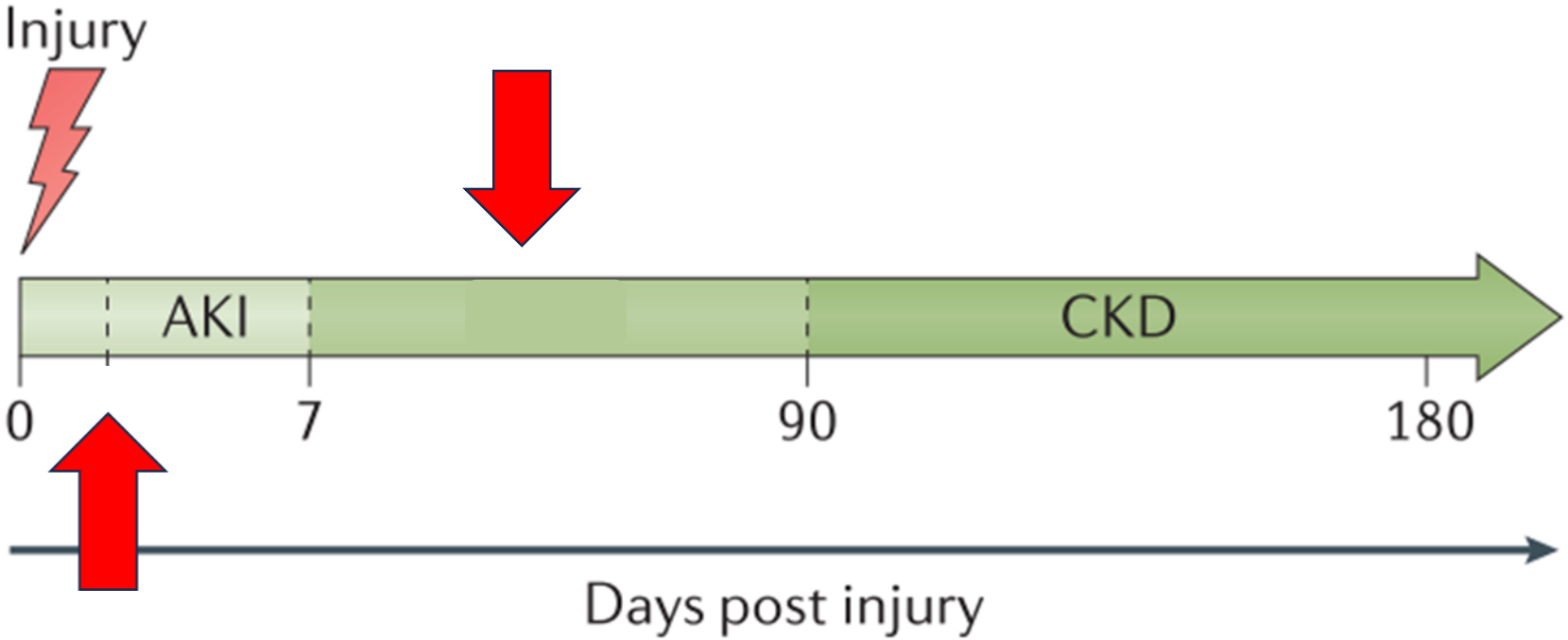
- ✓ *As far back as ancient times, it was appreciated that an "empty bladder" was a fatal disease although it wasn't until Galen who established the kidneys as the source of the problem.*

Section 2: AKI Definition

2.1.1: AKI is defined as any of the following (*Not Graded*):

- Increase in SCr by $\geqslant$0.3 mg/dl ($\geqslant$26.5 µmol/l) within 48 hours; or
- Increase in SCr to $\geqslant$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume $<$0.5 ml/kg/h for 6 hours.

Physiologic? Pathologic?


Injury
AKI
CKD
0
7
90
180
Days post injury

Outline

- What is persistent AKI?
- Persistent vs transient AKI
- What is acute kidney disease (AKD)?
- How to predict persistent AKI
- How to measure renal functional reserve

CONSENSUS STATEMENT

NATURE REVIEWS | NEPHROLOGY

Persistent AKI

OPEN

EXPERT CONSENSUS DOCUMENT

Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup

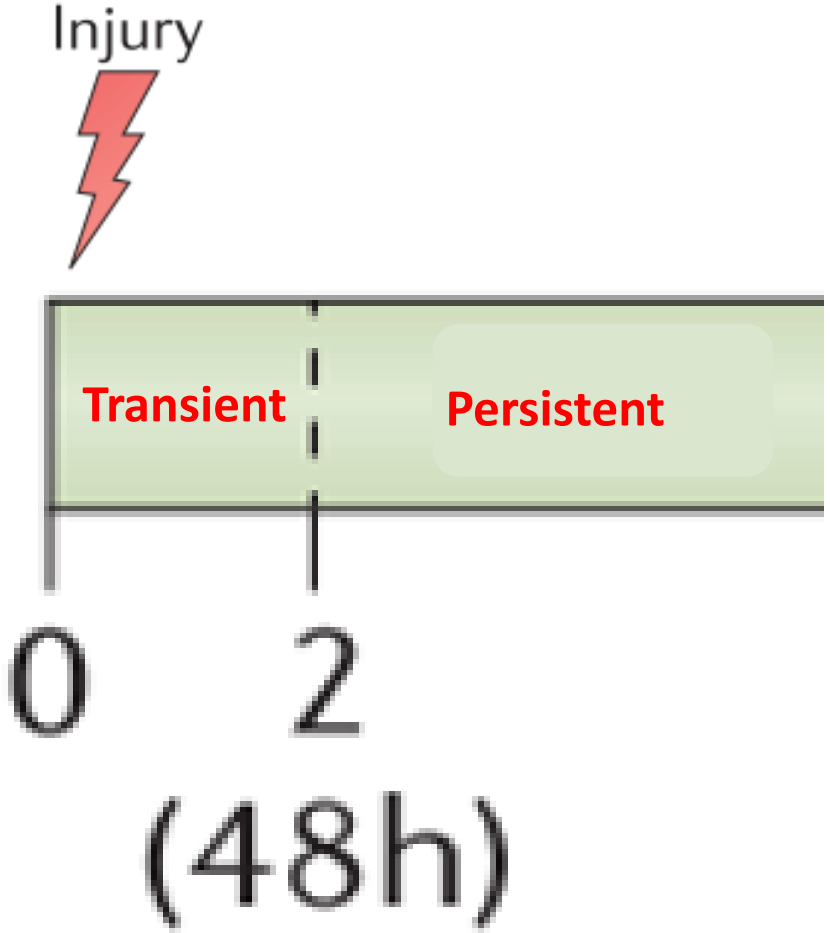
Box 1 | **Definitions of AKI and AKD, initial management of AKI, and assessment of kidney function**

Consensus statement 1A:

Persistent acute kidney injury (AKI) is characterized by the continuance of AKI by serum creatinine or urine output criteria (as defined by KDIGO) beyond 48 h from AKI onset. Complete reversal of AKI by KDIGO criteria within 48 h of AKI onset characterizes rapid reversal of AKI (evidence grade: level 5).

Nat Rev Nephrol. 2017;13(4):241-57

Transient vs Persistent AKI



48 HRS?

Reversal of an AKI episode within 48–72 h: Better outcomes

Transient and Persistent Acute Kidney Injury and the Risk of Hospital Mortality in Critically Ill Patients: Results of a Multicenter Cohort Study*

Six hospital ICUs

A total of 447 patients

283 patients with AKI

TABLE 2. Factors Independently Associated With Hospital Survival

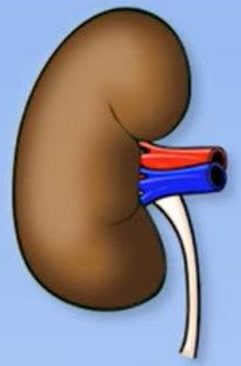
Variables	OR (95% CI)	*p*
Need for vasopressors	0.65 (0.43–0.98)	0.04
Age (per yr)	0.99 (0.98–1.0)	0.19
Type of AKI		
No AKI	1 (Reference)	–
Transient AKI	0.79 (0.45–1.39)	0.42
Persistent AKI	0.58 (0.36–0.95)	0.03

Crit Care Med. 2015;43(8):e269-75

Acute Kidney Injury (AKI)
Prerenal vs. Intrarenal vs. Postrenal Paradigm

Prerenal

- **Dehydration***
- **Heart failure**
  (a.k.a. cardiorenal syndrome)
- **Liver failure**
  (a.k.a. hepatorenal syndrome)



Intrarenal

- **Intrinsic renovascular disease**
  - Hypertensive emergency
  - Small vessel vasculitis
  - TTP / HUS
- **Glomerular disease**
  - Post-infectious glomerulonephritis
- **Tubulointerstitial disease**
  - Acute tubular necrosis (ATN)*
    (causes: sepsis, meds, contrast, rhabdo, prolonged prerenal AKI)
  - Acute interstitial nephritis (AIN)

Postrenal

- **Ureteral obstruction**
  (usually requires bilateral obstruction)
- **Neurogenic bladder**
- **Urinary tract infection**
- **Medications**
- **Benign prostatic hypertrophy (BPH)**

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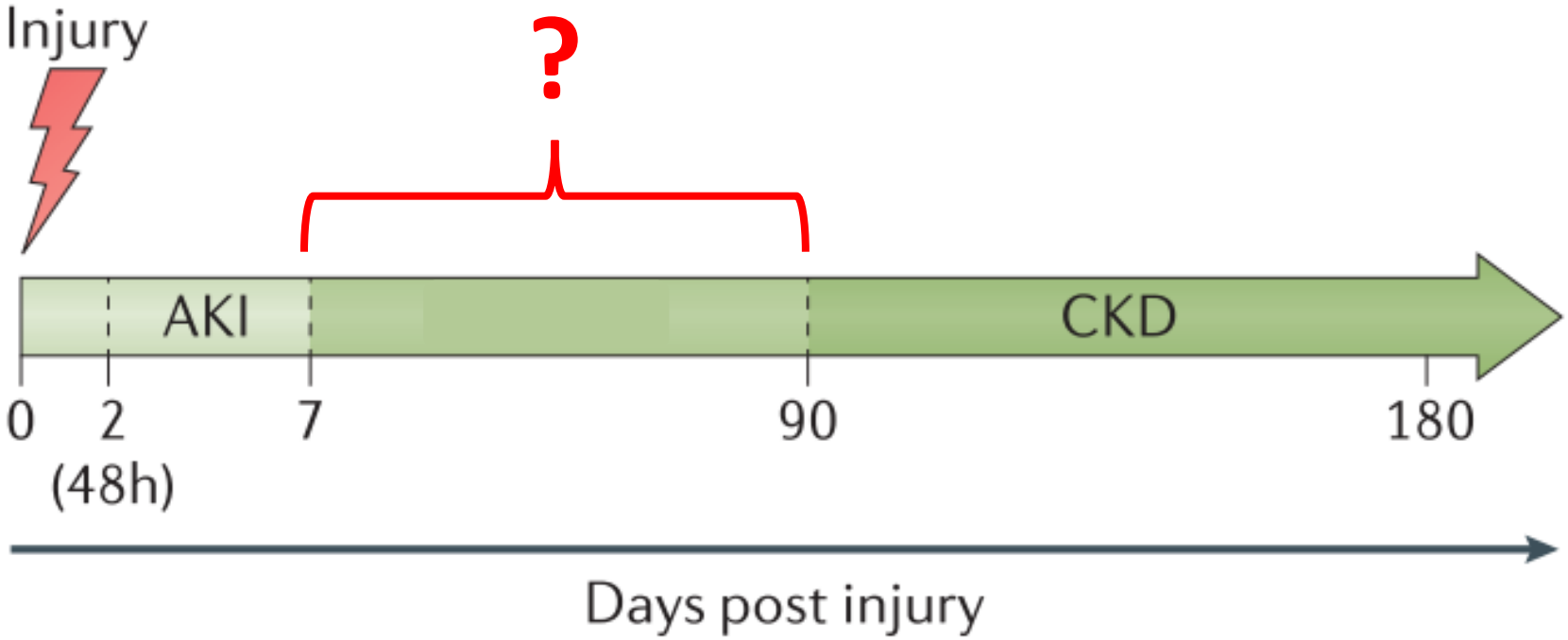
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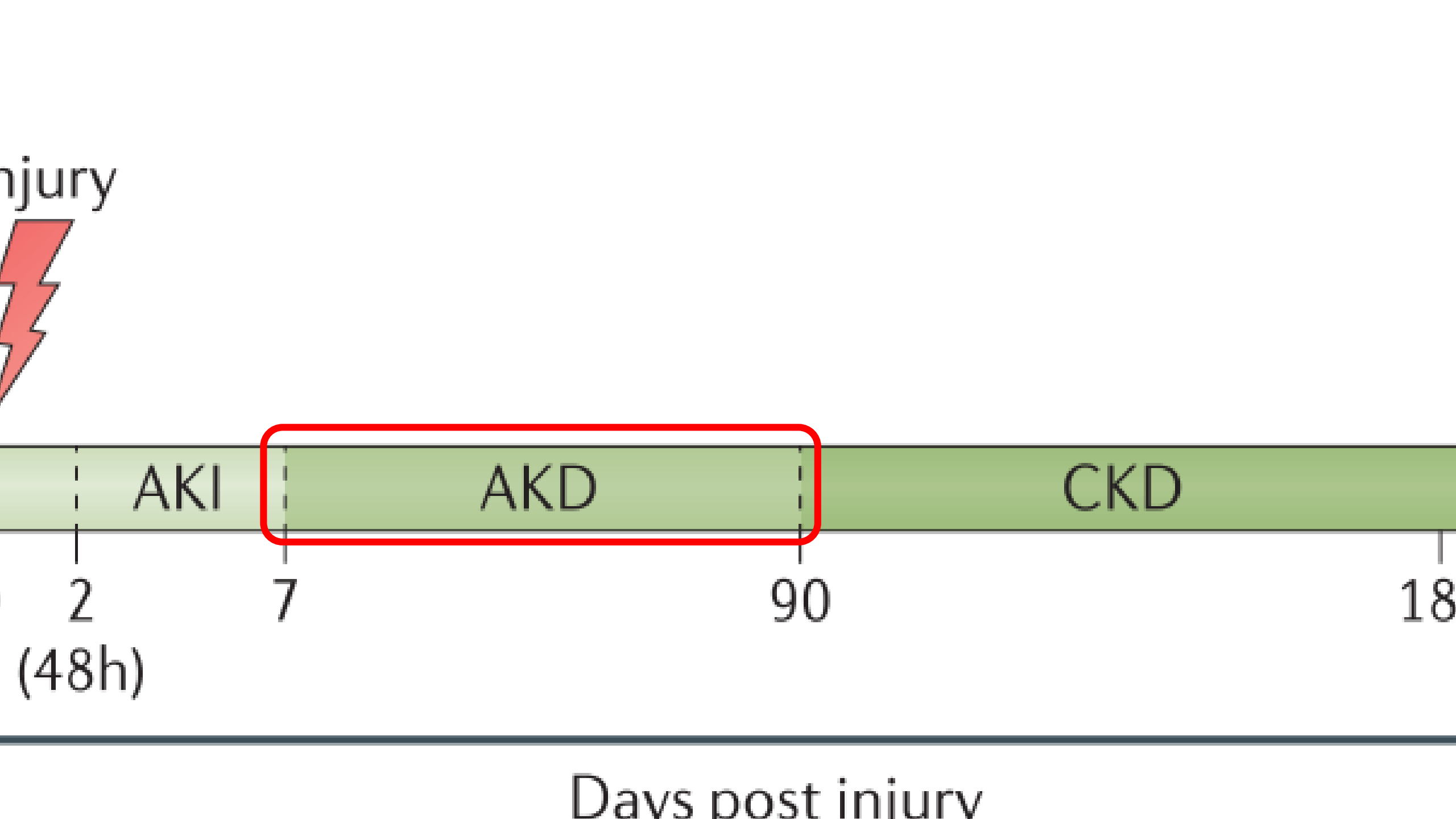
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CONSENSUS STATEMENT

NATURE REVIEWS | NEPHROLOGY

OPEN

EXPERT CONSENSUS DOCUMENT

Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup

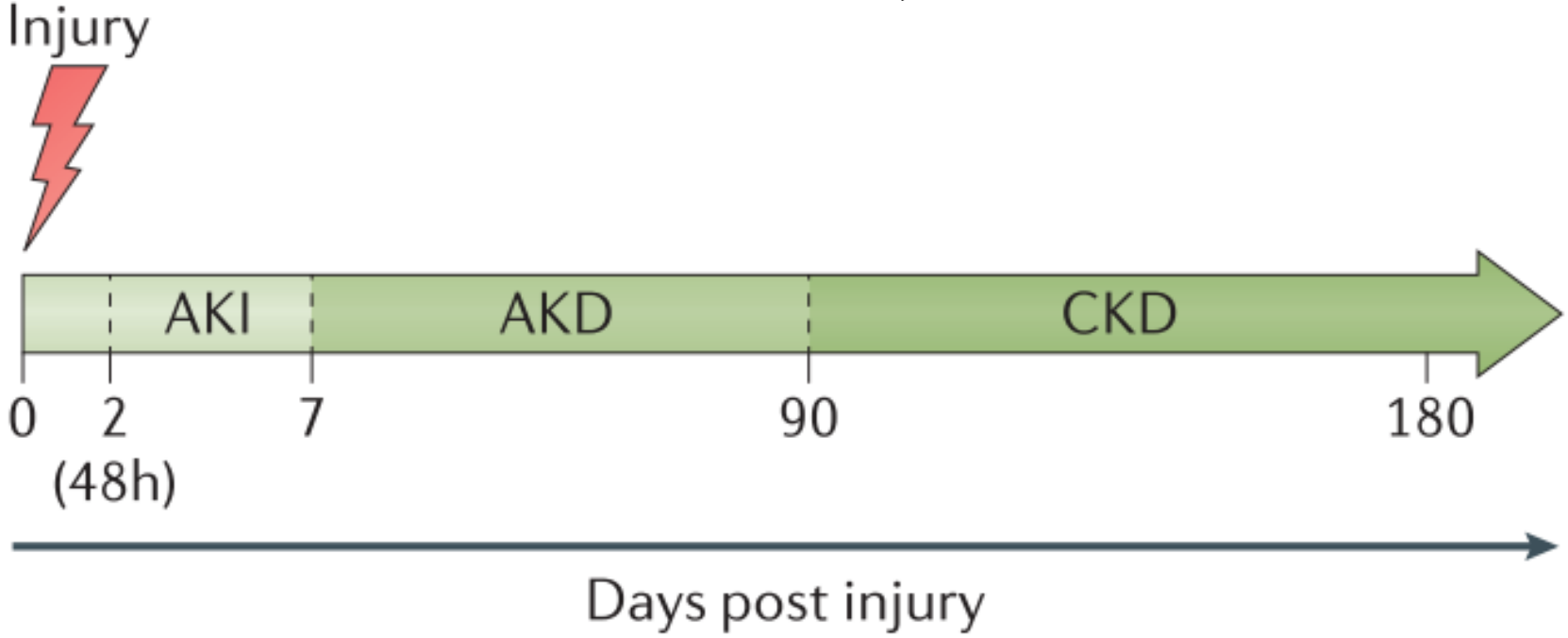
Box 3 | Definition of AKD and recovery from AKD

Consensus statement 2A:

- Acute kidney disease (AKD) describes acute or subacute damage and/or loss of kidney function for a duration of between 7 and 90 days after exposure to an acute kidney injury (AKI) initiating event.

Nat Rev Nephrol. 2017;13(4):241-57

The continuum of AKI, AKD and CKD

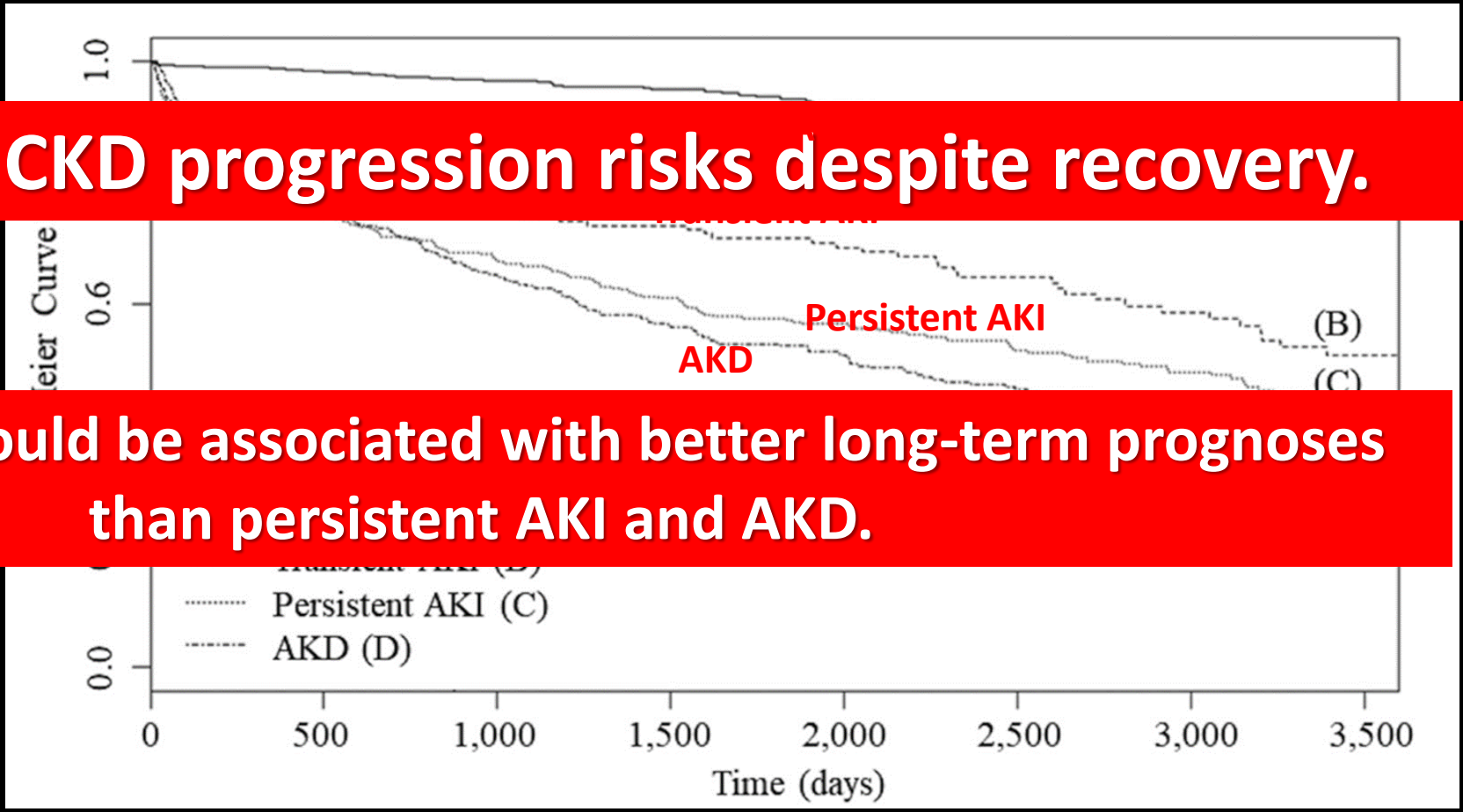


Consensus statement 1C:
AKI and acute kidney disease (AKD) are a continuum, and persistent AKI frequently becomes AKD, defined as a condition wherein criteria for AKI stage 1 or greater persists ≥7 days after an exposure (FIG. 2; TABLE 1; evidence grade: level 4).

Nat Rev Nephrol. 2017;13(4):241-57.

Survival free from kidney function decline after AKI recovery

AKI has rapid CKD progression risks despite recovery.

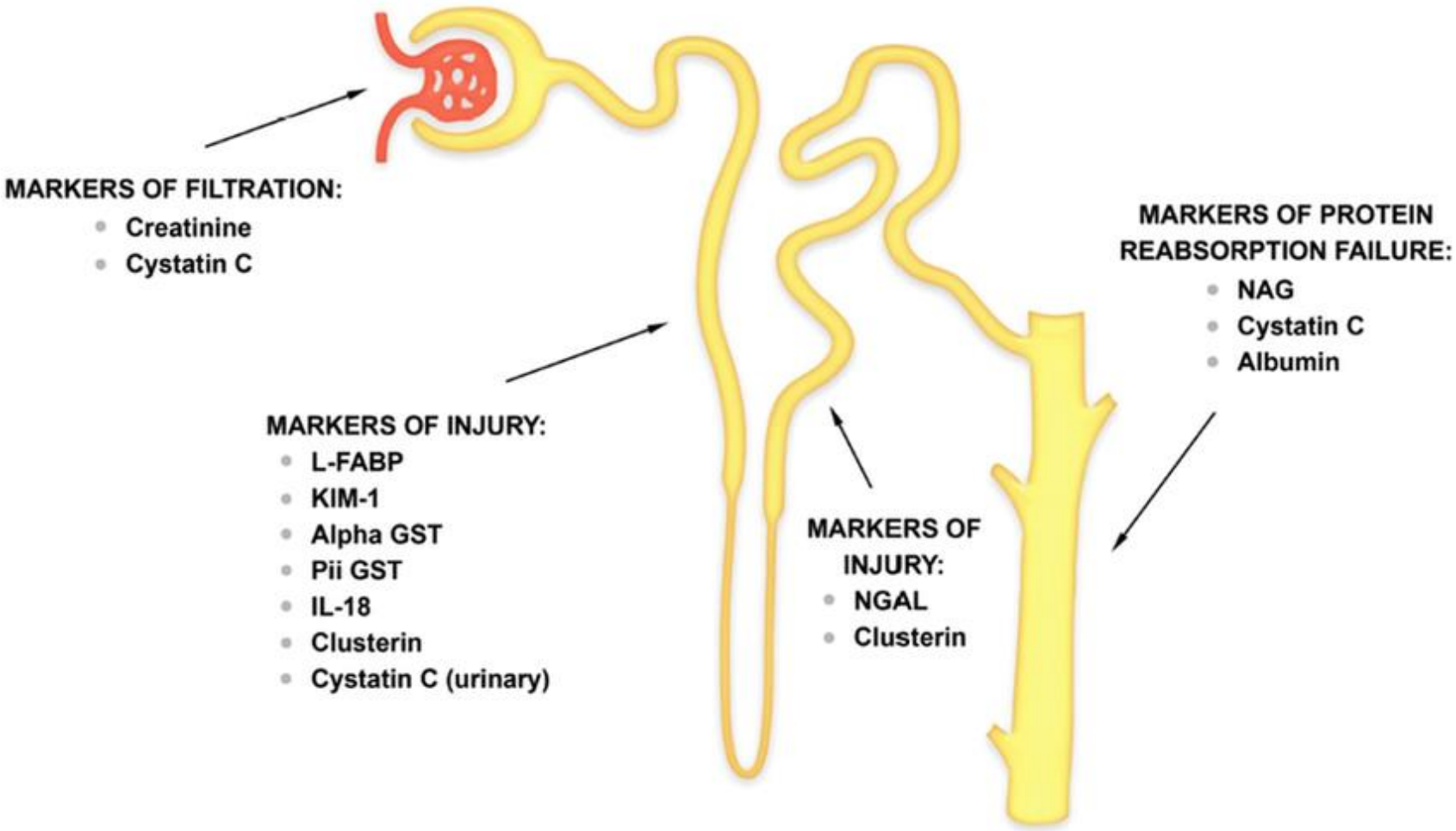


Transient AKI could be associated with better long-term prognoses than persistent AKI and AKD.

Nephrology. 2021;26(4):312-8

How To Predict And Early Diagnose Persistent AKI

Biomarkers of AKI



CCL14

Urinary C–C motif chemokine ligand 14

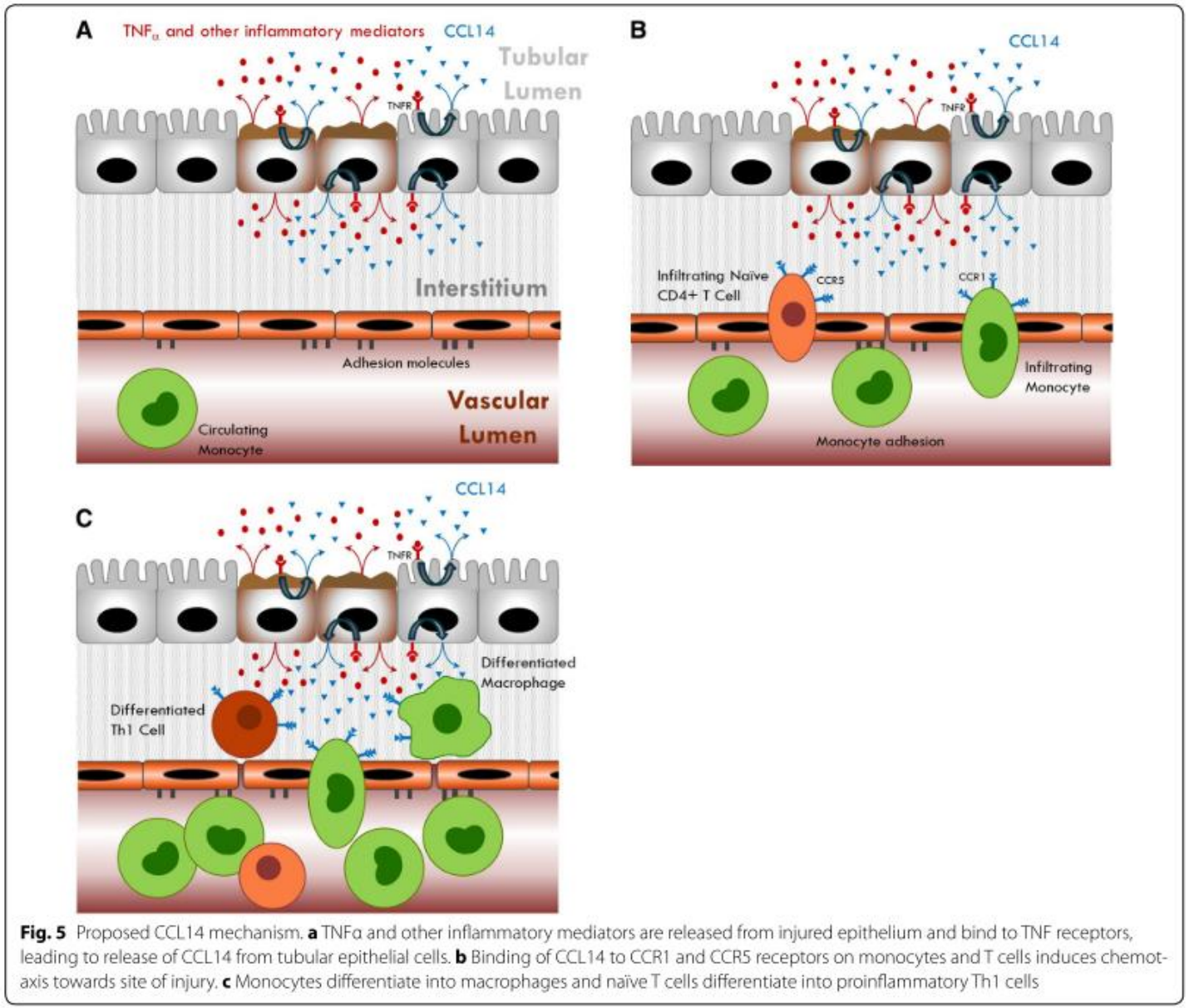


Fig. 5 Proposed CCL14 mechanism. **a** TNFα and other inflammatory mediators are released from injured epithelium and bind to TNF receptors, leading to release of CCL14 from tubular epithelial cells. **b** Binding of CCL14 to CCR1 and CCR5 receptors on monocytes and T cells induces chemotaxis towards site of injury. **c** Monocytes differentiate into macrophages and naïve T cells differentiate into proinflammatory Th1 cells

Intensive Care Med. 2020;46(5):943-53

Urinary C–C motif chemokine ligand 14 (CCL14)

Elevated urinary CCL14 predicts persistent AKI in a large heterogeneous cohort of critically ill patients with severe AKI.

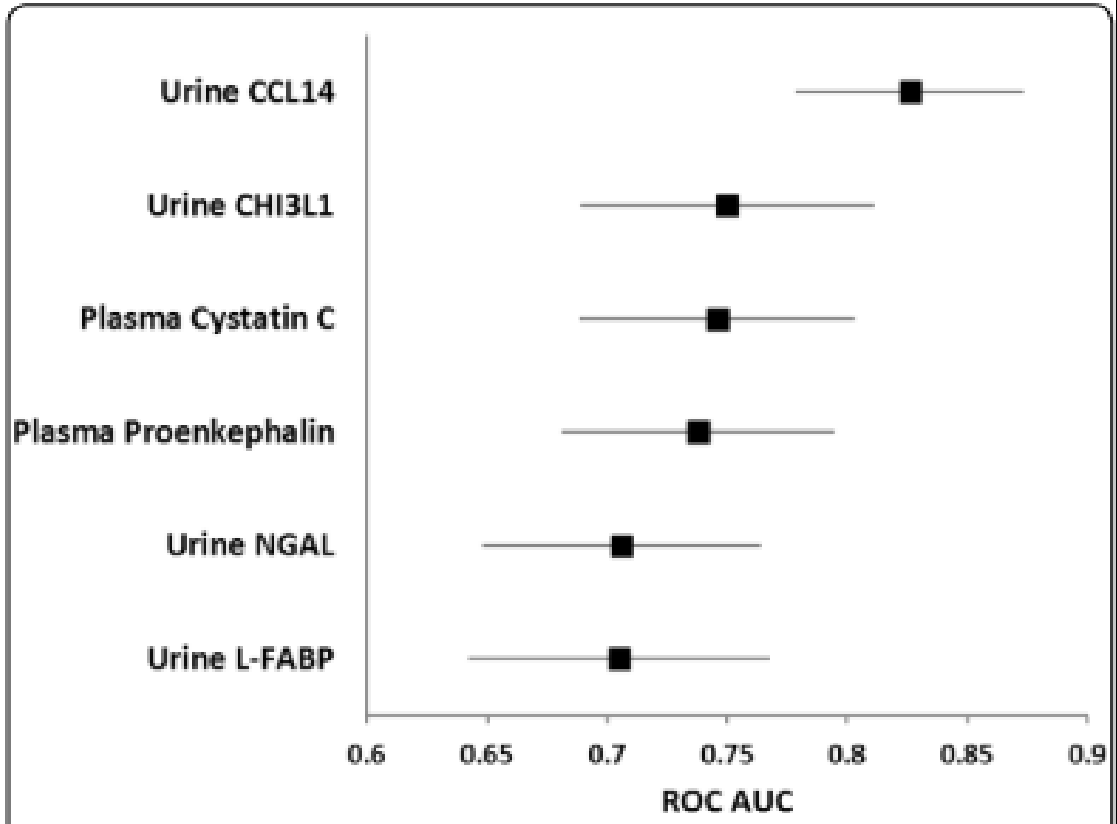


Fig. 2 Area under the ROC curve (AUC) for prediction of persistent stage 3 AKI by urine CCL14 and other AKI biomarkers, including both injury and functional biomarkers. Biomarker concentrations were measured in urine and plasma samples collected at enrollment. The AUC for urine CCL14 was significantly ($p < 0.05$) greater than for all other biomarkers shown

Intensive Care Med. 2020;46(5):943-53

JAMA Network | Open

Consensus Statement | Critical Care Medicine

Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference

A Consensus Statement

AKI biomarker	Biological role	Source	Stress marker[a]	Damage marker[b]	Functional marker[c]	Potential role in clinical practice				
						Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI	Kidney recovery
Alanine aminopeptidase; alkaline phosphatase; γ-glutamyl transpeptidase	Enzymes located on the brush border villi of the proximal tubular cells; released into urine after tubular damage	Coca et al,[2] 2008		Urine				X	X	
Calprotectin	Cytosolic calcium-binding complex; derived from neutrophils and monocytes; detectable in urine in intrinsic AKI	Charlton et al,[3] 2014; Heller et al,[4] 2011		Urine				X		
C-C motif chemokine ligand 14	Pro-inflammatory chemokine; released into urine following stress or damage of tubular cells	Hoste et al,[5] 2020		Urine						X
Chitinase 3-like protein 1	39 kDa intracellular protein of glycoside hydrolase family; expressed by endothelial cells, macrophages, and neutrophils	De Loor et al,[6] 2016		Urine and plasma				X		
Cystatin C	13 kDa cysteine protease inhibitor produced by nucleated human cells; freely filtered	Coca et al,[2] 2008; Ho et al,[7] 2015; Ravn et al,[8] 2019			Plasma			X	X	
Dickkopf-3	38 kDa stress-induced, kidney tubular epithelia-derived glycoprotein; secreted into urine under tubular stress conditions	Schunk et al,[9] 2019	Urine			X	X			
α glutathione S-transferase	Cytoplasmic enzyme in proximal tubule	Koyner at al,[10] 2010		Urine				X		
π glutathione S-transferase	Cytoplasmic enzyme in distal tubules	Coca et al,[2] 2008; Charlton et al,[3] 2014		Urine				X		
Hepatocyte growth factor	Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	Heller et al,[4] 2011; Vaidya et al,[11] 2008		Plasma					X	X

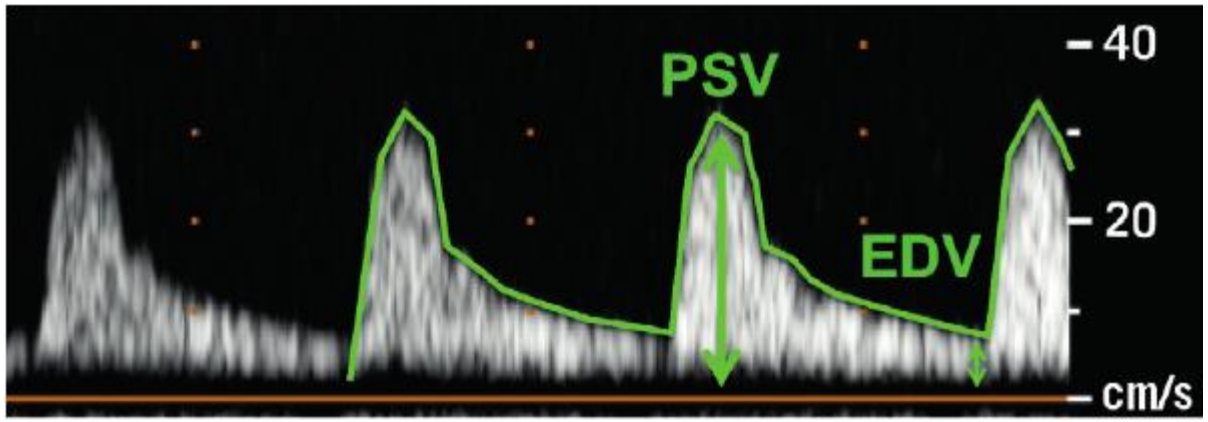
Intensive Care Med. 2020;46(5):943-53

	Stress marker[a]	Damage marker[b]	Functional marker[c]	Potential role in clinical practice				
				Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI	Kidney recovery
		Urine				X	X	
		Urine				X		
		Urine						X
		Urine and plasma				X		
			Plasma			X	X	
	Urine			X	X			
		Urine				X		

Intensive Care Med. 2020;46(5):943-53

Renal resistive index (RRI) value

measured in a segmental artery, is commonly used to assess blood flow in renal intra-parenchymal vessels.



$$\frac{(\textit{Peak systolic velocity} - \textit{end diastolic velocity})}{\textit{peak systolic velocity}}.$$

CLINICAL JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

CJACN 9(2):382-394, February 2014.

Renal Resistive Index In Predicting Persistent AKI

Table 3. Summary of studies examining the use of resistive index (RI) in AKI

Study (Reference)	Renal RI/Group	Study Notes
Healthy volunteers (20)	0.60±0.07/Normal	
Predicting AKI post-CPB (26)	0.68±0.06/No AKI 1–5 d later	Single-center, prospective, n=65
	0.77±0.08/AKI without RRT 1–5 d later	RI was determined immediately after CPB
	0.84±0.03/AKI requiring RRT 1–5 d later	Presence of AKI was assessed on days 1–5 An RI>0.74 had an AUC of 0.91 to predict AKI with 85% sensitivity and 94% specificity
Predicting AKI in septic shock (27)	0.68±0.08/No AKI 5 d later	Single-center, prospective, n=35
	0.77±0.08/AKI 5 d later	RI was obtained within 24 h of ICU admission Presence of AKI was assessed on day 5 AKI was defined as RIFLE stage 2 or greater (*i.e.*, doubling of serum creatinine or greater) An RI>0.74 predicted AKI with 78% sensitivity and 77% specificity
Predicting AKI in the ICU (28) (sepsis and trauma)	0.66±0.08/No AKI 3 d later	Single-center, prospective, n=58
	0.80±0.08/AKI 3 d later	RI was obtained within 12 h of ICU admission Presence of AKI was assessed on day 3 AKI was defined as stage 2 AKIN or greater (*i.e.*, doubling of serum creatinine or greater) An RI of 0.71 predicted AKI with an AUC of 0.91

CJACN 9(2):382-394, February 2014.

Renal Resistive Index In Predicting Persistent AKI

Identifying prerenal azotemia (29)	0.67±0.90/Prerenal azotemia 0.74±0.13/Non-ATN AKI (mostly HRS) 0.85±0.60/ATN	Single-center, $n=91$ An RI≥0.75 occurred in 91% of patients with ATN and 20% of patients with prerenal azotemia
Identifying prerenal azotemia (30)	0.76±0.06/Prerenal azotemia 0.82±0.07/ATN	Single-center, $n=50$ An RI≥0.75 had 91.3% sensitivity and 85.2% specificity to distinguish ATN from prerenal azotemia
Identifying prerenal azotemia/assessing severity (31)	0.52–0.71/Prerenal azotemia 0.77–1.0/ATN	Single-center, $n=40$ Decreasing RI predicted renal recovery
Assessing severity (57)	0.71 (0.62–0.77)/Transient AKI 0.82 (0.80	Single-center, $n=51$

An RI>0.795 had 82% sensitivity and 92% specificity for persistent AKI

CJACN 9(2):382-394, February 2014.

Early diagnose persistent versus transient AKI

Furosemide
1 mg/Kg IV. if Furosemide – Naïve

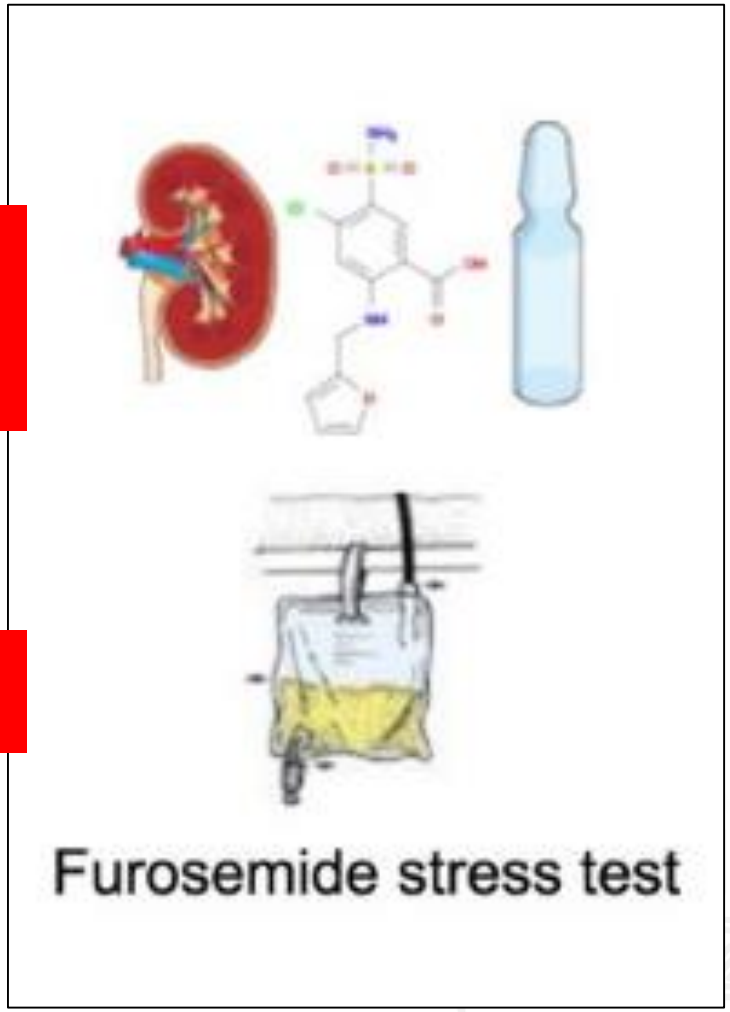
Indicates good functional reserve of the kidneys in patients with AKI

Urine flow rate (UFR)

Assess the integrity of tubular function

FST responsive

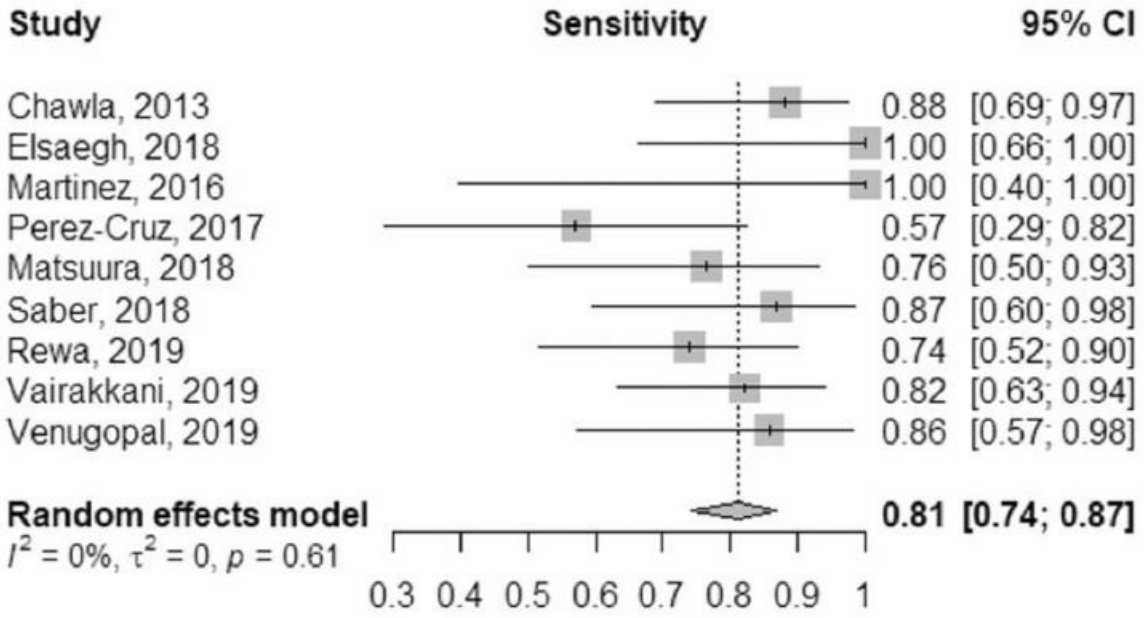
FST non-responsive

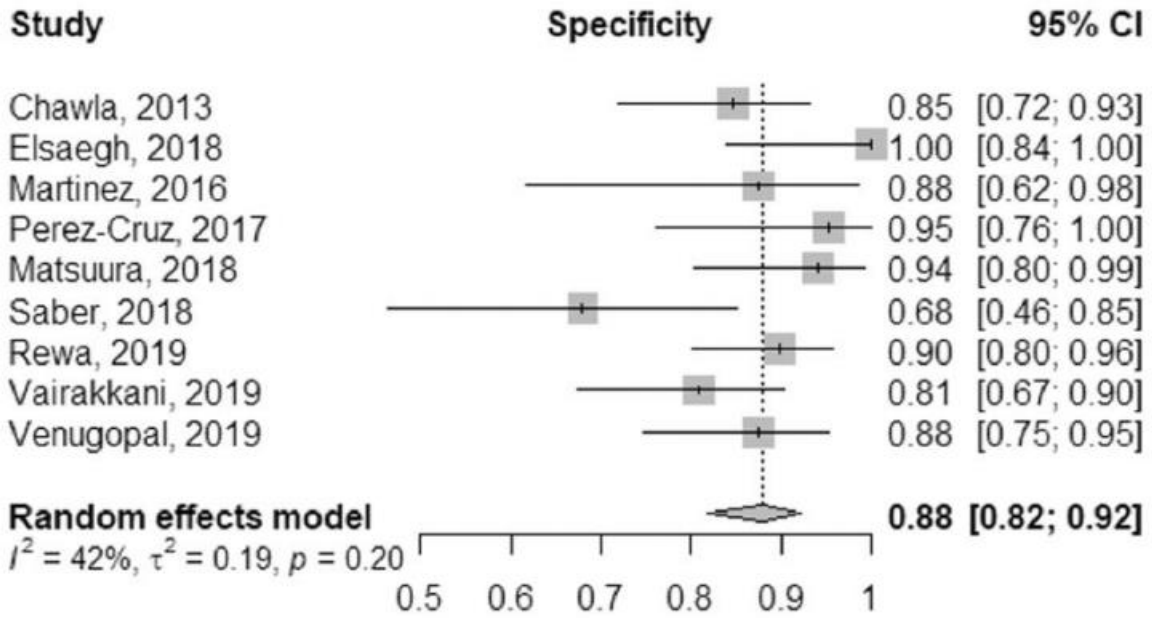


Indian J Crit Care Med. 2020;24(Suppl 3):S100-s1

RESEARCH

Furosemide stress test as a predictive marker of acute kidney injury progression or renal replacement therapy: a systemic review and meta-analysis



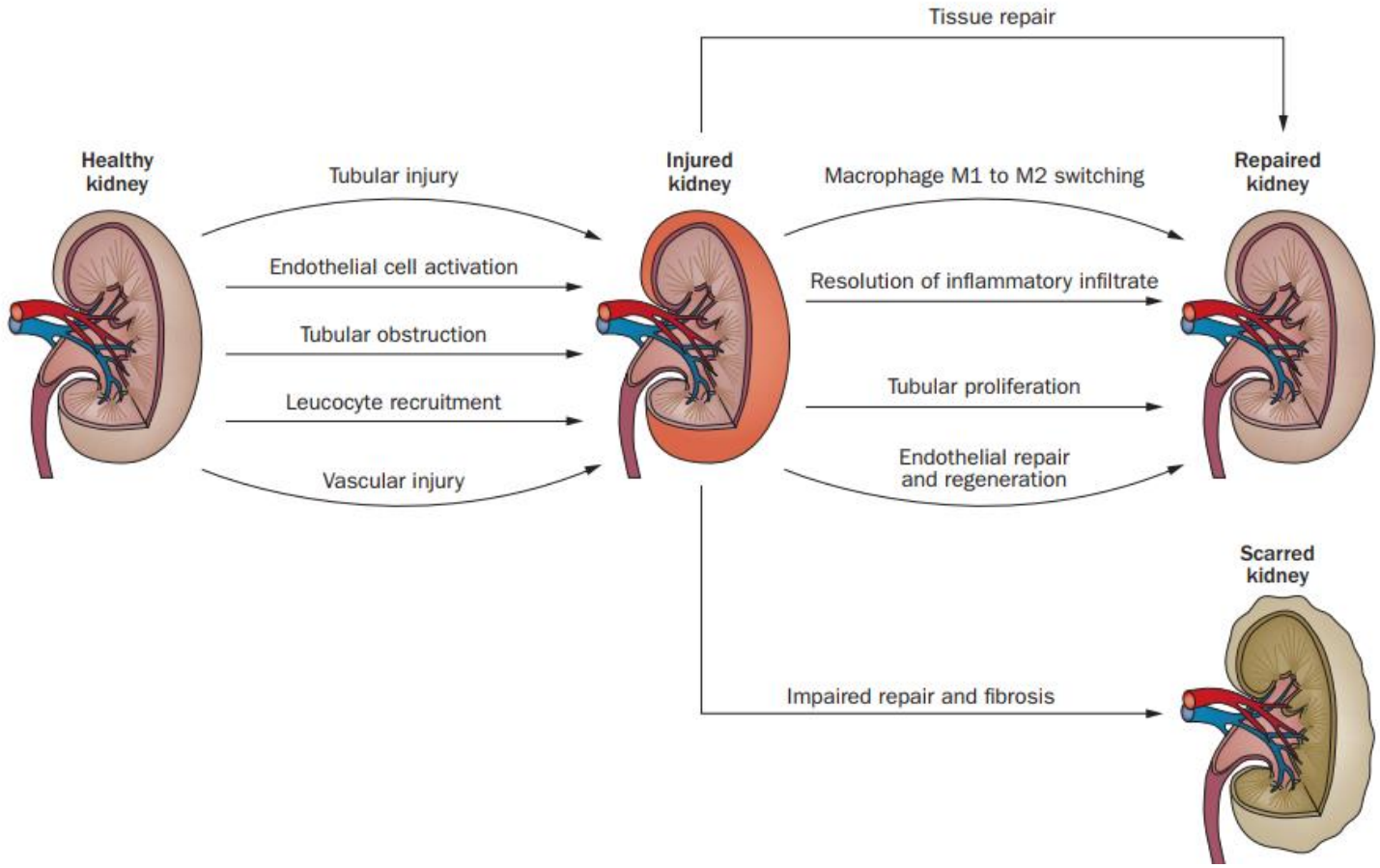


Conclusion: The FST is a simple tool for the identification of AKI populations at high risk of AKI progression and the need for RRT, and the diagnostic performance of FST in RRT prediction is better in early AKI population.

Critical Care. 2020;24(1):202

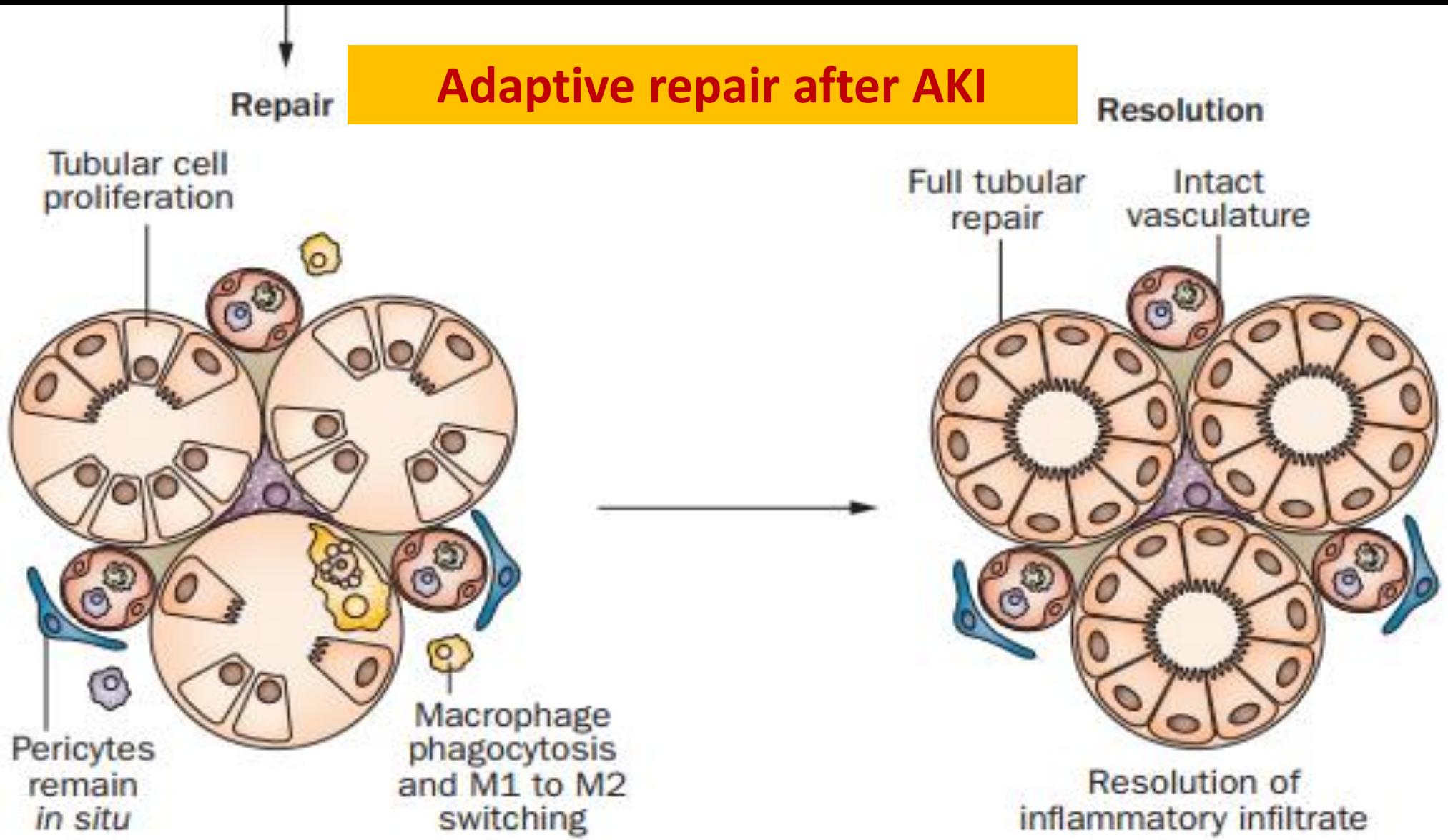
Adaptive vs Maladaptive repair

Mechanisms involved in initial tissue injury and subsequent repair of the kidney after AKI



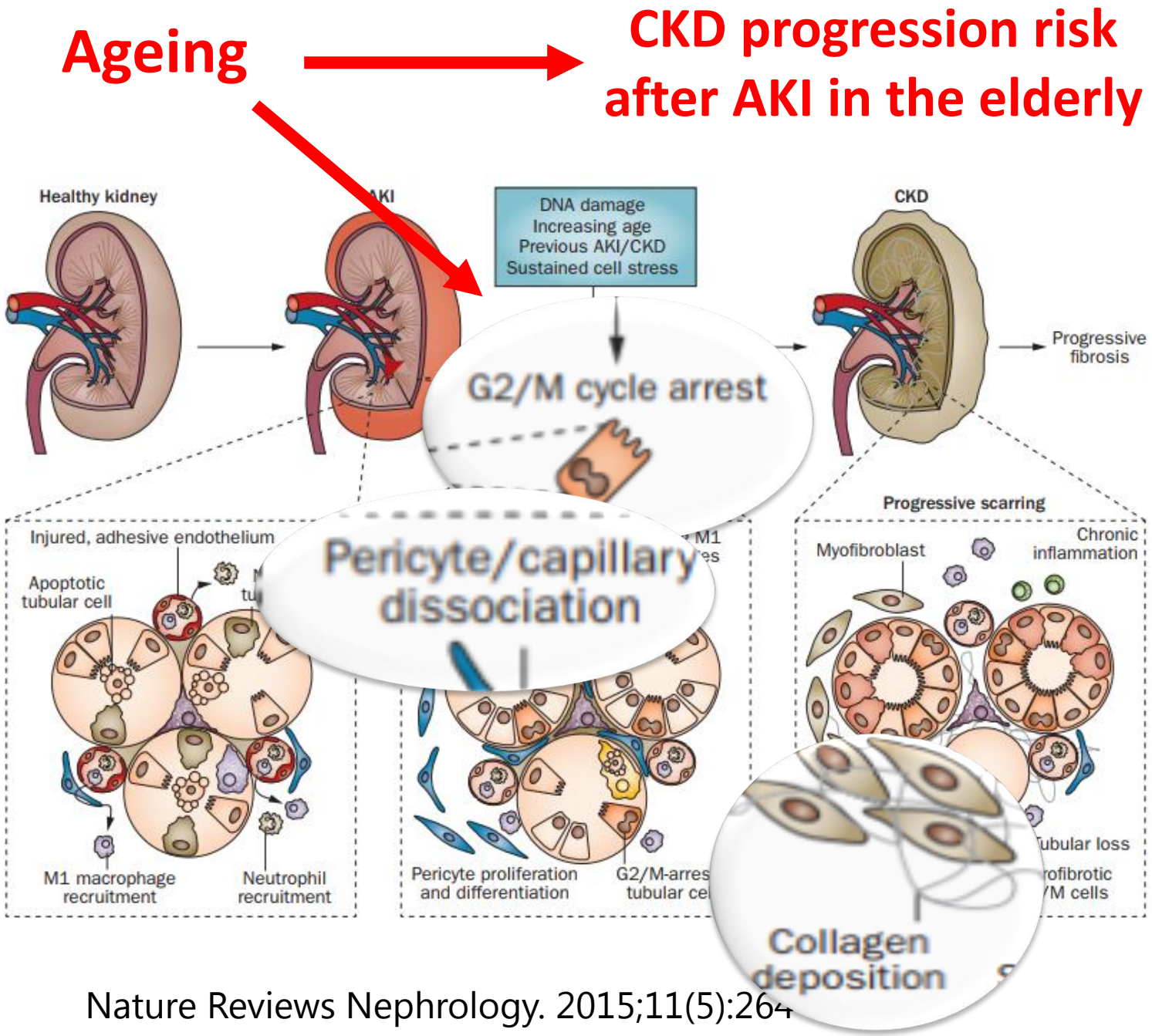
Nature Reviews Nephrology. 2015;11(5):264-76

Adaptive repair after AKI



Nature Reviews Nephrology. 2015;11(5):264-76

Maladaptive repair of AKI leads to CKD



Nature Reviews Nephrology. 2015;11(5):264

Treatment and follow-up

Kidney DAMAGE–An Approach to Patients with Persistent AKI

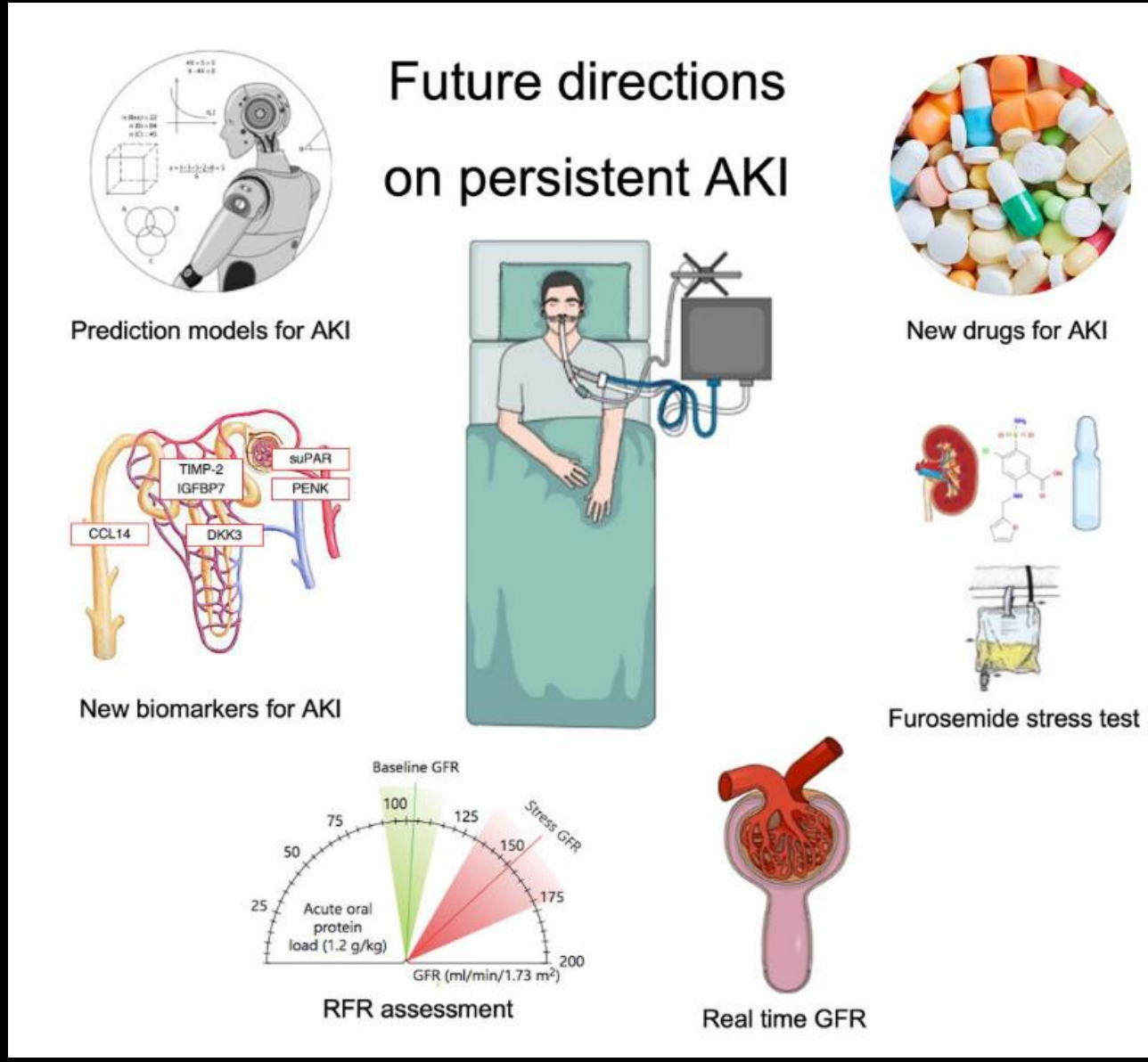
Goal	Recommendations	Comment
Determine Etiology	• Evaluate for ongoing drivers of injury (e.g. sepsis, drugs) • Consider less common causes of AKI (e.g. vasculitis, interstitial nephritis) • Consider kidney biopsy • Nephrology consultation	Persistent AKI is more likely to be due to conditions that are less easily reversed (e.g. sepsis) or have not been recognized (e.g. drug-induced, cardiorenal).
Avoid further injury	• Avoid unnecessary nephrotoxic drug and IV radio-contrast exposure • Consider patient location that minimizes risk (e.g. ICU vs. ward)	New nephrotoxic drug and radio-contrast exposures as well as fluid overload or hemodynamic instability may result further kidney injury
Monitor	• Serum creatinine (daily) • Urine output • Consider hemodynamic monitoring	Monitoring is helpful not only to assess recovery but also fluid balance and in select patients, cardiac function.

Crit Care Med. 2015;43(8):1785-6.

Kidney DAMAGE–An Approach to Patients with Persistent AKI

Monitor	• Serum creatinine (daily) • Urine output • Consider hemodynamic monitoring	Monitoring is helpful not only to assess recovery but also fluid balance and in select patients, cardiac function.
Adverse drug events	• Adjust medication selection and dosing	Not only are drugs important potential causes of persistent AKI but drugs may need to changed or dosed differently in these patients
Goals of treatment	• Assess treatment goals with respect to dialysis and other therapy	Patients with persistent AKI may ultimately require dialysis or other life support—a reassessment of goals and preferences may be warranted
Ensure follow-up	• Assess renal function within 30 days • Assess cardiovascular risk • Monitor/treat hypertension	Patients with persistent AKI, especial those without recovery at discharge are at high risk for chronic kidney disease, and for cardiovascular events

Crit Care Med. 2015;43(8):1785-6.

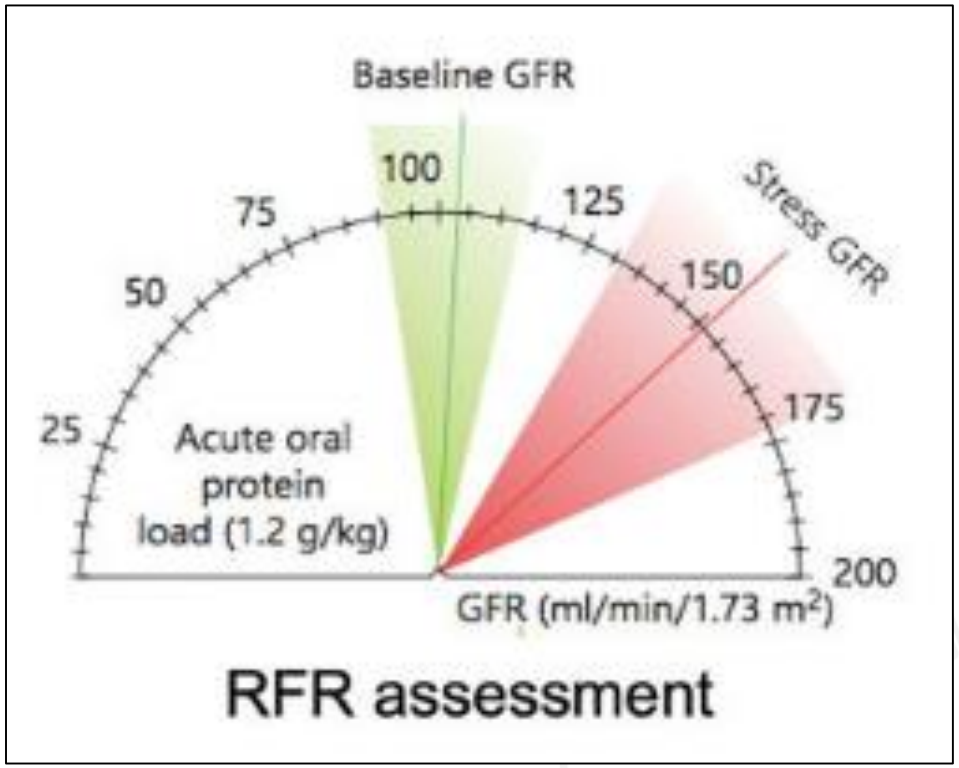


Clinical Kidney Journal. 2023;16(11):1813-23.

Renal Functional Reserve

Renal capacity to increase baseline GFR in response to higher functional demand
(e.g. pregnancy, solitary kidney).

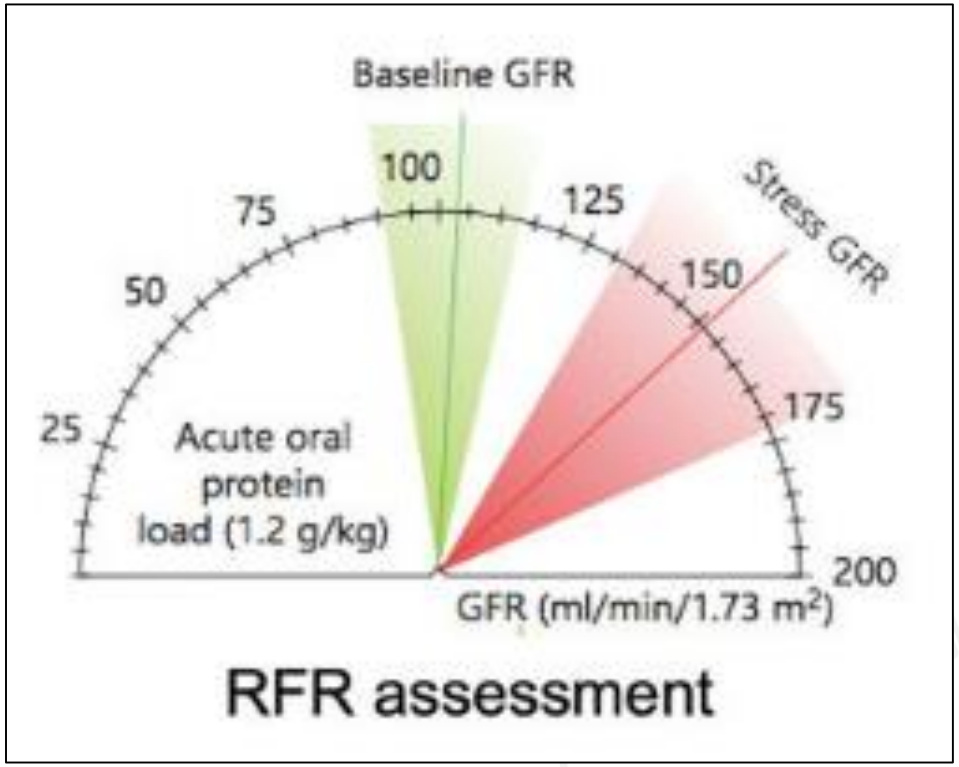
Maximum achievable (stress) GFR - baseline GFR (resting)



Journal of Nephrology. 2021;34(2):403-9

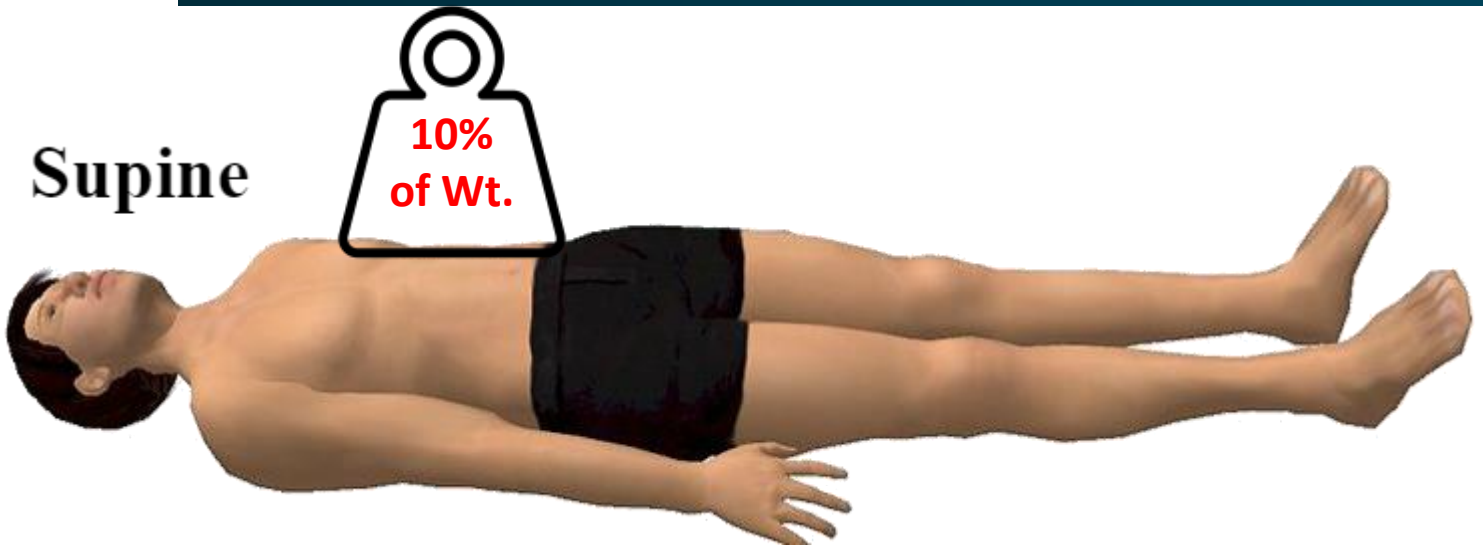
RFR test, when?

- The risk of AKI after stress exposure
- Detect early-stage CKD



Journal of Nephrology. 2021;34(2):403-9

The relationship between intra-parenchymal renal resistive index variation and renal functional reserve in healthy subjects



RRIs were recorded in a middle interlobular artery every minute for 10 min

IRRIV (%): Baseline RRI - stress RRI

Journal of Nephrology. 2021;34(2):403-9

Take Home Messages

Persistent AKI is an AKI which lasts more than 48 h from its onset is associated with worse outcome compared to transient AKI.

AKD is acute or subacute damage and/or loss of kidney function for a duration of between 7 and 90 days.

New biomarkers and FST to predict persistent AKI.


Thanks For Your Attention