DEFINITIONS AND EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

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AKI 2010
Acute Kidney Injury and Renal Support

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Disclosures

I have no actual or potential conflict of interest in relation to this program or presentation.

AKI 2010
Acute Kidney Injury and Renal Support

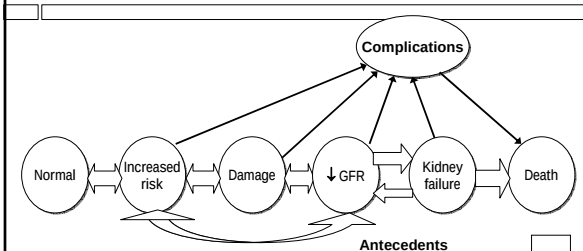
Issues

- Current Status
- Controversies
- Future directions

Human Data on AKI
Areas for Discussion

- Conceptual Model for AKI

Conceptual Model for AKI



Human Data on AKI
Areas for Discussion

- Conceptual Model
- Diagnosis

Research

Open Access

Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury

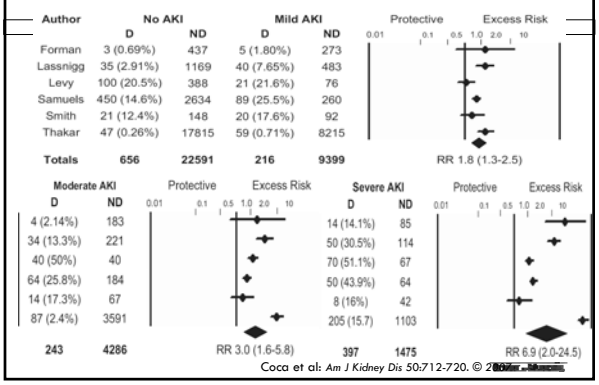
Ravindra L Mehta[1], John A Kellum[2], Sudhir V Shah[3], Bruce A Molitoris[4], Claudio Ronco[5], David G Warnock[6], Adeera Levin[7] and the Acute Kidney Injury Network

Diagnostic criteria for acute kidney injury

An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours).

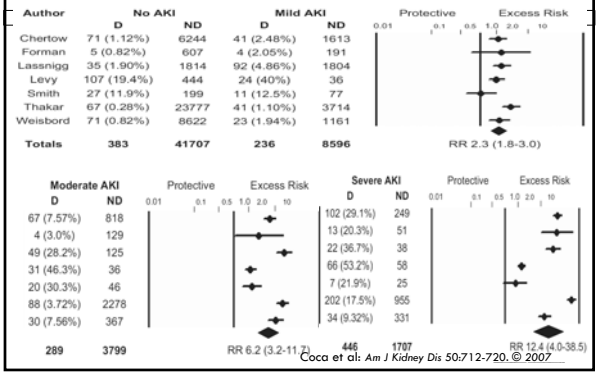
Critical Care 2007, 11:R31 (doi:10.1186/cc5713)
This article is online at: http://ccforum.com/content/11/2/R31

Relative Change from Baseline Creatinine



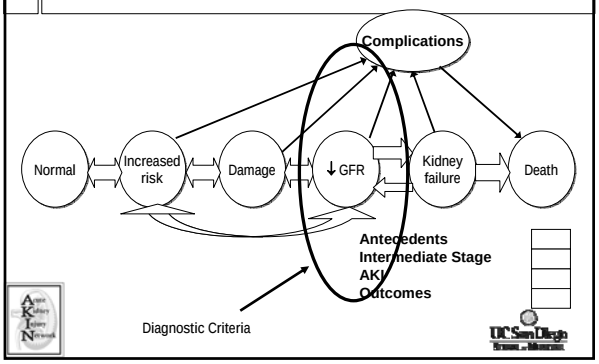
Coca et al: *Am J Kidney Dis* 50:712-720. © 2007

Absolute Change from Baseline Creatinine



Coca et al: *Am J Kidney Dis* 50:712-720. © 2007

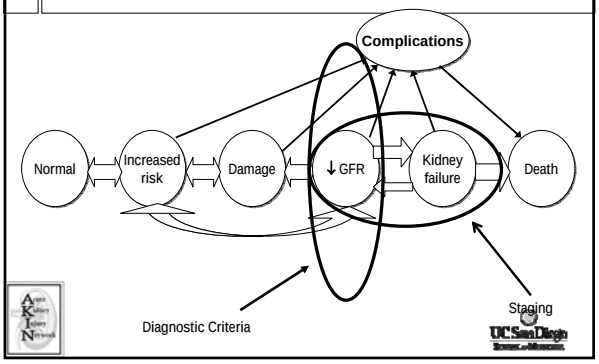
Conceptual Model for AKI



Human Data on AKI
Topics for Consideration

- Conceptual Model
- Diagnosis
- Staging

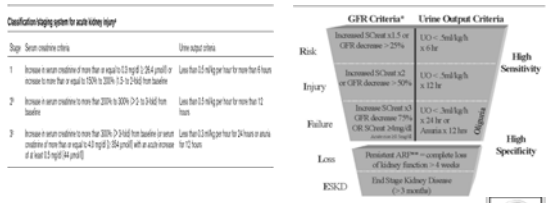
Conceptual Model for AKI



Proposed Staging Criteria for AKI

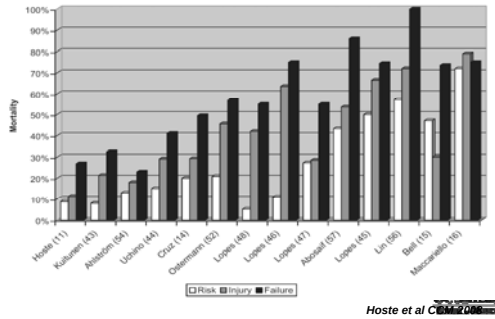
AKIN

RIFLE



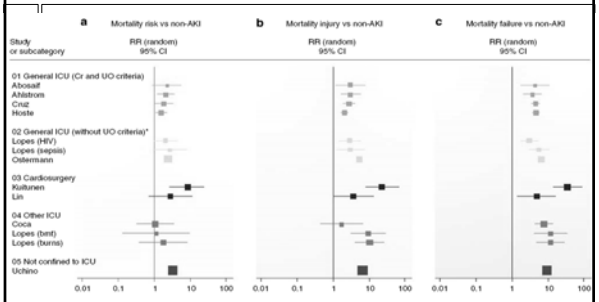
Mehta et al: Crit Care. 2007 Mar 1;11(2):R31

Effect of RIFLE Class on Mortality



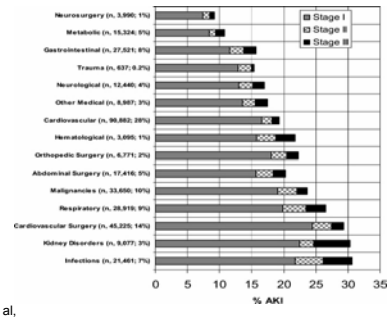
Hoste et al CCM 2008

RIFLE-Criteria and Outcome



Ricci Z et al, Kidney Int 2008

Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study



CV Thakar et al,
Crit Care Med 2009

Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study

Table 3. Odds of death associated with AKI in ICU

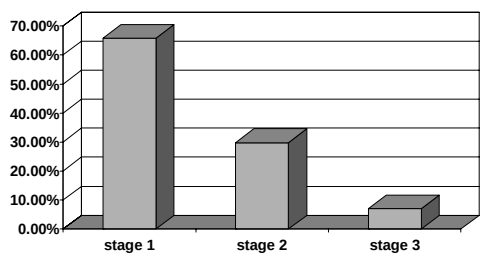
AKI Category	N	Odds Ratio	95% CI
Stratified by Time Taken to Meet AKI Criteria in ICU			
AKI <48 hrs	52,884	2.52	2.45–2.60
AKI >48 hrs	18,602	4.66	4.47–4.85
Stratified by Severity of AKI Reached during ICU			
Stage I AKI	57,126	2.23	2.17–2.30
Stage II AKI	7934	6.08	5.74–6.44
Stage III AKI	6426	8.6	8.07–9.15
AKI requiring dialysis (subgroup of Stage III AKI)	3140	5.78	5.30–6.31

AKI, acute kidney injury; ICU, intensive care unit; CI, confidence interval.

CV Thakar et al, Crit Care Med 2009

Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study

Renal Recovery Rate in AKI stage



CV Thakar et al, Crit Care Med 2009

Costantini et al: Redefining Renal Dysfunction in Trauma: Implementation of the Acute Kidney Injury Network Staging System (*J Trauma. 2009;67: 283–288*)

Design: Retrospective analysis of 571 concurrent cohort of trauma patients in ICU in single center.

Comparison of ASCOT (serum creatinine 3.5, blood urea nitrogen 100, or renal replacement therapy) to AKIN criteria for AKI.

TABLE 2. Demographics for Patients Admitted to the ICU for ≥48 h

	No AKI	AKI	ACSCOT Criteria
Patients	401	170	17
Age	42.3 ± 21.3*	52.9 ± 22.5	52.8 ± 23.8
Male sex	292 (72.8%)	111 (65.3%)	14 (82.4%)
Blunt mechanism	385 (96.0%)	164 (96.5%)	16 (94.1%)
Admission SBP	136.2 ± 31.8	137.6 ± 36.4	118.0 ± 38.1†
ISS	20.2 ± 10.7‡	22.8 ± 11.8‡	19.7 ± 13.9‡
ICU LOS	7.0 ± 7.5§	13.6 ± 13.2§	22.7 ± 16.2§
Hospital LOS	15.8 ± 17.5§	25.0 ± 36.7§	40.8 ± 45.9§

* $p < 0.001$ vs. AKI and ACS-COT criteria.
† $p < 0.05$ vs. no AKI and AKI.
‡ $p < 0.05$ ANOVA with variance between all the groups.
§ $p < 0.001$ ANOVA with variance between all the groups.

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TABLE 4. Morbidity and Mortality of Patients Admitted to the ICU for ≥48 h

	No AKI	AKI	ACS-COT Criteria
Dialysis	0*	12 (7.1%)	12 (70.6%)*
ARDS	9 (2.2%)	9 (5.3%)	2 (11.8%)
MOF	0†	3 (1.8%)	2 (11.8%)
Death	22 (5.5%)*	27 (15.9%)	7 (41.2%)†

* $p < 0.001$ vs. AKI.
† $p < 0.03$ vs. AKI.

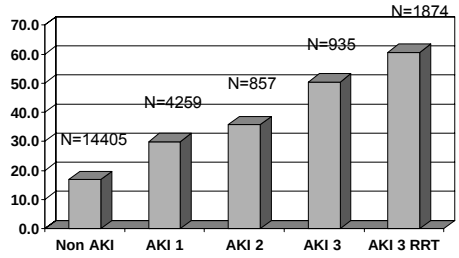
TABLE 5. Morbidity and Mortality of Patients Meeting AKIN Criteria

	No AKI (n = 401)	Stage 1 (n = 146)	Stage 2 (n = 15)	Stage 3 (n = 9)
Dialysis	0	1 (0.7%)	5 (33.3%)*	6 (66.7%)*
ICU LOS	7.0 ± 7.5	13.1 ± 13.2*	15.7 ± 13.4*	19.1 ± 13.8*
Hospital LOS	15.8 ± 17.5	24.0 ± 25.5*	31.1 ± 38.9†	32.1 ± 22.2†
ARDS	9 (2.2%)	6 (4.1%)	1 (6.7%)	2 (22.2%)*
MOF	0	0	1 (6.7%)†	2 (22.2%)†
Death	22 (5.5%)	14 (9.6%)	9 (60%)*	4 (44.4%)*

* $p < 0.001$ vs. no AKI.
† $p < 0.01$ vs. no AKI.

Mortality is associated with severity of AKI

The Riyadh ICU Program Users Group (22.303 patients, 1989-1999)



Ostermann M, Crit Care 2008

Acute kidney injury criteria predict outcomes of critically ill patients

	Risk Ratio	95% CI
Univariate analysis		
AKI	2.8	2.0–3.9
APACHE II modified (≥15)	1.7	1.2–2.4
Comorbidities (≥2)	1.3	0.9–1.9
Nephrotoxic medications (≥1)	0.9	0.6–1.3
NROF (≥2)	1.7	1.2–2.5
Sepsis	1.9	1.4–2.7
	Odds Ratio	95% CI
Multivariate logistic regression		
AKI	3.7	2.2–6.1
Sepsis	1.8	1.8–2.9

Barrantes F 2008, Crit Care Med

Barrantes et al: Acute Kidney Injury Predicts Outcomes of Non–Critically Ill Patients Mayo Clin Proc. 2009;84(5):410-416

Study Design: Retrospective cohort study.

6,033 patients admitted to medical wards of a community teaching hospital between 2005 and 2007.

Predictor: AKN criteria for AKI within 48 hours.

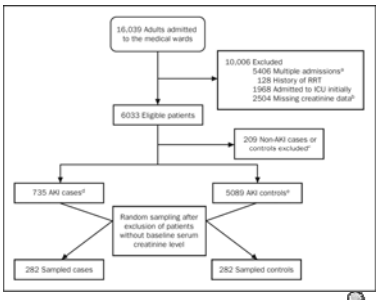


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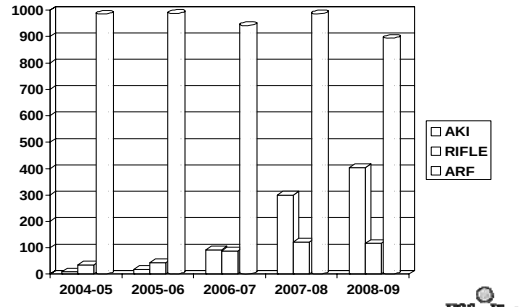
TABLE 2. **Outcomes of AKI Cases and Controls vs Outcomes of Patients With ≥0.3 mg/dL Increase in Serum Creatinine Level After >48 Hours or Uncertain Creatinine Velocity[a]**

	AKI controls (n=5089)	AKI cases (n=735)	Patients with creatinine increase ≥0.3 mg/dL[b] in ≥48 h (n=209)
Age (y), mean ± SD	65.4±19.2	72.9±15.0	71.6±16.0
Female	2707 (53.2)	394 (53.6)	111 (53.1)
In-hospital mortality	75 (1.5)	109 (14.8)	10 (4.8)
Hospital length of stay (d)			
Mean ± SD	4.8±4.6	11.7±12.3	13.7±13.8
Median (IQR)	3.7 (2.2-5.9)	7.9 (4.7-14.2)	8.5 (5.7-15.0)
New renal replacement therapy	0	73/564 (12.9)	0
Transfer to ICU	219 (4.3)	210 (28.6)	38 (18.2)
Discharge disposition of survivors			
Home	3998/5014 (79.7)	356/626 (56.9)	118/199 (59.3)
Extended-care facilities	1016/5014 (20.3)	270/626 (43.1)	81/199 (40.7)

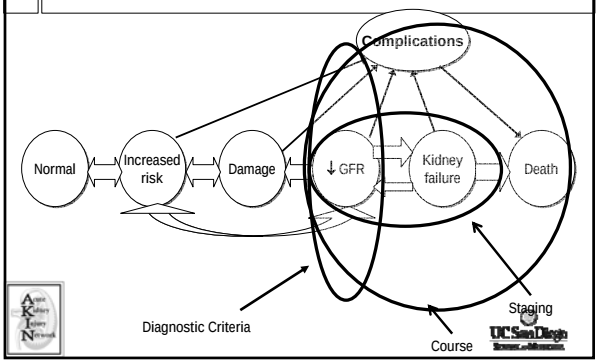
Publications citing AKI, RIFLE or ARF



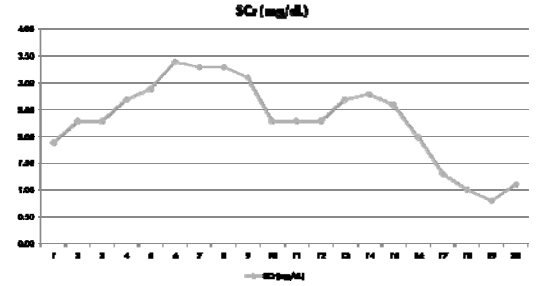
Human Data on AKI
Topics for Consideration

- Conceptual Model
- Diagnosis
- Staging
- Course

Conceptual Model for AKI

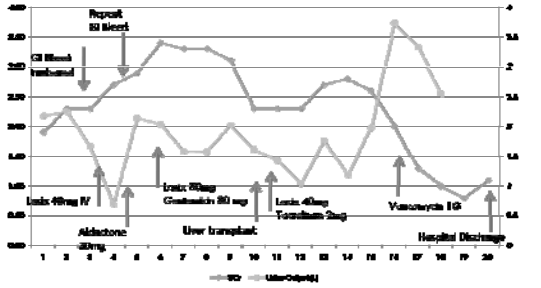


Course Of AKI: Characterization



50, Caucasian male, weight 87kg, height 78 in,
Baseline SCr = 1.3 - History of Hep C, ETOH, Cirrhosis hepatic encephalopathy, Liver Transplant Never dialyzed, Survived

Course Of AKI: Characterization



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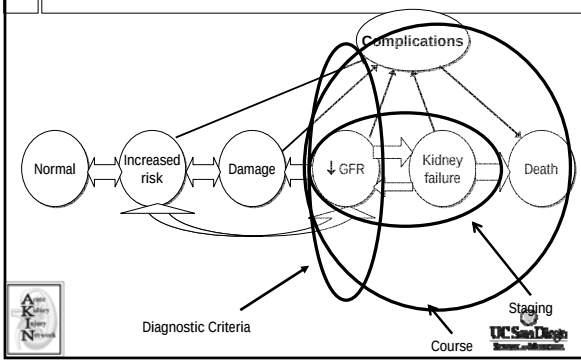
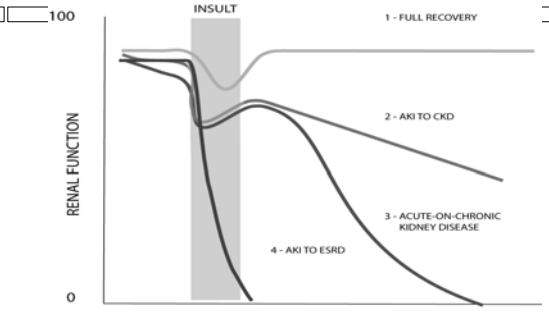
Conceptual Model for AKI



Natural History of AKI

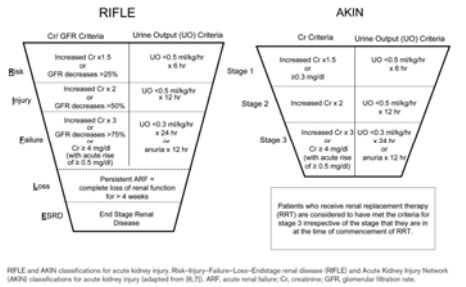


Cerda et al, CJASN 2008 AKIN, Vancouver 2006

Diagnosis of AKI: Controversies

- Which Criteria?
  - RIFLE vs AKIN

RIFLE vs AKIN



RIFLE and AKIN classifications for acute kidney injury. Risk-Injury-Failure-Loss-Endstage renal disease (RIFLE) and Acute Kidney Injury Network (AKIN) classifications for acute kidney injury (adapted from [6,7]). ARF, acute renal failure; Cr, creatinine; GFR, glomerular filtration rate.

Cruz D et al, Crit Care

RIFLE vs AKIN

Comparison between Risk–Injury–Failure–Loss–Endstage renal disease and Acute Kidney Injury Network classifications

RIFLE classification	AKIN classification
Risk, Injury, and Failure	Stages 1, 2 and 3
Loss and Endstage renal disease describe renal outcome after acute kidney injury episode	Not used
Uses change in creatinine or glomerular filtration rate, in addition to urine output criteria	Uses change in creatinine, in addition to urine output criteria
Risk: increased creatinine × 1.5 or glomerular filtration rate decrease >25%	Stage 1: increased creatinine x 1.5 or ≥0.3 mg/dl
Stage not specified for patients starting renal replacement therapy	Patients starting renal replacement therapy are classified as Stage 3, regardless of serum creatinine or urine output
Proposed timeframe of 1 week specified for making diagnosis of acute kidney injury	Acute kidney injury diagnosis is based on a change between two creatinine values within a 48-hour period*
Not specified	Diagnostic criteria to be used only "after an optimal state of hydration has been achieved"

*Although the diagnosis of acute kidney injury is based on changes over the course of 48 hours, staging occurs over a slightly longer timeframe. One week was the timeframe proposed by the Acute Dialysis Quality Initiative group [7].

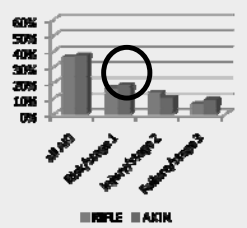
Cruz D et al, Crit Care

Comparison RIFLE vs AKIN

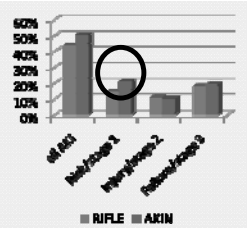
Retrospective Studies	Findings
Bagshaw et al. NDT 2008 (ICU ANZICS database)	increased sensitivity AKIN (n.s)
Lopes et al. Crit Care 2008 (Sepsis)	Increased sensitivity AKIN (n.s)
Lassnig et al JASN 2008 (cardiac surgery)	AKI stage 1 > RIFLE R
Joannidis et al Int Care Med 2009 (SAPS database)	Increased sensitivity RIFLE
Prospective Studies	
Haase 2009 (cardiac surgery)	Increased sensitivity AKIN

RIFLE vs. AKIN staging: Incidence

Bagshaw et al. NDT 2008

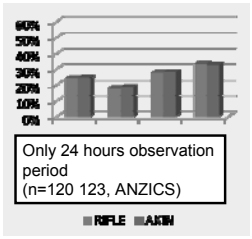


Lopes et al. Crit Care 2008



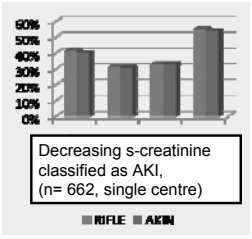
RIFLE vs. AKIN staging: Mortality

Bagshaw et al. NDT 2008



Only 24 hours observation period
(n=120 123, ANZICS)

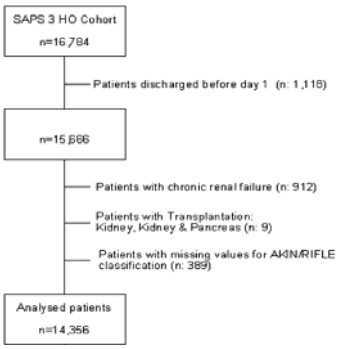
Lopes et al. Crit Care 2008



Decreasing s-creatinine classified as AKI,
(n= 662, single centre)

SAPS 3 database

- *303 ICUs*
- *35 countries*
- *basic cohort 19.557*



Joannidis M et al, Intensive Care Med 2009

SAPS 3 datal

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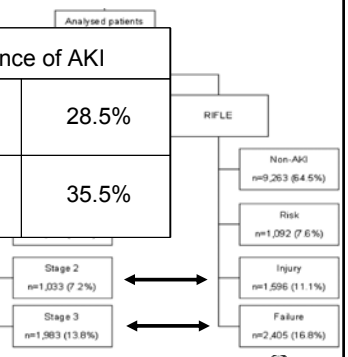
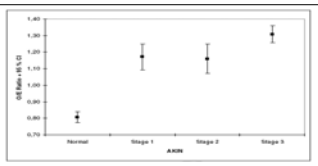
- *35 countries*
- *basic cohort*

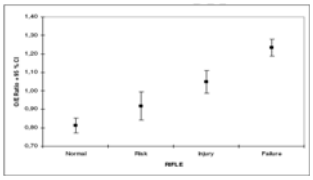
Incidence of AKI	
AKIN	28.5%
RIFLE	35.5%



Standardized mortality ratios (SMR) of RIFLE versus AKIN



AKIN



RIFLE

Classification of AKI RIFLE versus AKIN

AKIN		RIFLE				AKIN Total
		Normal	Risk	Injury	Failure	
Normal	n	**8759**	781	452	271	10263
	%	***(12,9%)***	*(27,7%)*	*(37,4%)*	*(41,3%)*	*(15,9%)*
Stage 1	n	457	**282**	243	95	1077
	%	*(25,2%)*	***(33,0%)***	*(44,0%)*	*(60,0%)*	*(34,5%)*
Stage 2	n	36	21	**885**	91	1033
	%	*(30,6%)*	*(47,6%)*	*(25,9%)*	*(54,9%)*	*(29,0%)*
Stage 3	n	11	8	16	**1948**	1983
	%	*(18,2%)*	*(12,5%)*	*(62,5%)*	***(41,3%)***	*(41,2%)*
Total RIFLE	n	9263	1092	1596	2405	**14356**
	%	*(13,6%)*	*(29,2%)*	*(32,3%)*	*(42,6%)*	***(21,7%)***

Joannidis M et al, Intensive Care Med 2009

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Classification of AKI
RIFLE versus AKIN

No increase in s-creatinine
between any 24 h interval
or
decrease within 48 h

AKIN		RIFLE				AKIN Total
		Normal	Risk	Injury	Failure	
Normal	n %	**8759** ***(12,9%)***	781 *(27,7%)*	452 *(37,4%)*	271 *(41,3%)*	10263 *(15,9%)*
Stage 1	n %	457 *(25,2%)*	**282** ***(33,0%)***	243 *(44,0%)*	95 *(60,0%)*	1077 *(34,5%)*
Stage 2	n %	36 *(30,6%)*	21 *(47,6%)*	**885** ***(25,9%)***	91 *(54,9%)*	1033 *(29,0%)*
Stage 3	n %	11 *(18,2%)*	8 *(12,5%)*	16 *(62,5%)*	**1948** ***(41,3%)***	1983 *(41,2%)*
Total RIFLE	n %	9263 *(13,6%)*	1092 *(29,2%)*	1596 *(32,3%)*	2405 *(42,6%)*	**14356** ***(21,7%)***

UC San Diego

Classification of AKI
RIFLE versus AKIN

AKIN		RIFLE				AKIN Total
		Normal	Risk	Injury	Failure	
Normal	n %	**8759** ***(12,9%)***	781 *(27,7%)*	452 *(37,4%)*	271 *(41,3%)*	10263 *(15,9%)*
Stage 1	n %	457 *(25,2%)*	**282** ***(33,0%)***	243 *(44,0%)*	95 *(60,0%)*	1077 *(34,5%)*
Stage 2	n %	36 *(30,6%)*	21 *(47,6%)*	**885** ***(25,9%)***	91 *(54,9%)*	1033 *(29,0%)*
Stage 3	n %	11 *(18,2%)*	8 *(12,5%)*	16 *(62,5%)*	**1948** ***(41,3%)***	1983 *(41,2%)*
Total RIFLE	n %	9263 *(13,6%)*	1092 *(29,2%)*	1596 *(32,3%)*	2405 *(42,6%)*	**14356** ***(21,7%)***

UC San Diego

Classification of AKI
RIFLE versus AKIN

- Admission-Creatinine < 0.8 mg/dl (249)
- AKI 1 for increase > 0,3 mg/dl but less
  x 1,5 admission creatinine (208)

AKIN		RIFLE				AKIN Total
		Normal	Risk	Injury	Failure	
Normal	n %	**8759** ***(12,9%)***	781 *(27,7%)*	452 *(37,4%)*	271 *(41,3%)*	10263 *(15,9%)*
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UC San Diego

Haase et al: A Comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: A prospective cohort study J Thorac Cardiovasc Surg 2009;-:1-7

Design: Prospective observational cohort study of 282 post cardiac surgery patients in a single center. The incidence of AKI and in-hospital mortality across classes was compared by using the c2 test, and their prognostic value was compared using AUROC characteristic for in-hospital mortality.

TABLE 3. Agreement of AKIN with RIFLE classifications according to identification of AKI across classes

		RIFLE				
		No AKI	Risk	Injury	Failure	Total
AKIN	No AKI	146	8	0	1	155
	Stage 1	6	76	13	0	95
	Stage 2	0	0	19	0	19
	Stage 3	0	1	2	9	12
	Total	152	85	34	10	282

AKIN, Acute Kidney Injury Network; *RIFLE*, R–renal risk, I–injury, F–failure, L–loss of kidney function, E–end-stage renal disease; *AKI*, acute kidney injury.

Haase et al: A Comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: A prospective cohort study J Thorac Cardiovasc Surg 2009;-:1-7

TABLE 4. Association of RIFLE or AKIN classifications with mortality

	RIFLE	R*	I*	F*	AKIN	1*	2*	3*
	RIFLE classes (total)				AKIN stages (total)			
AUC–ROC	0.91	0.82	0.91	0.97	0.94	0.81		0.98
(95% CI)	(0.82–0.99)	(0.62–0.99)	(0.84–0.98)	(0.88–0.99)	(0.81–0.97)	(0.59–0.99)	–‡	(0.89–1.00)
P value	.001	.266	.016	.022	<.001	.283		<.001
	RIFLE classes (creatinine value increase)				AKIN stages (creatinine value increase)			
AUC–ROC	0.93	0.95	0.97		0.88	0.88	0.98	
(95% CI)	(0.88–0.97)	(0.89–0.99)	(0.91–0.99)	–‡	(0.81–0.95)	(0.81–0.96)	(0.91–0.99)	–‡
P value	<.001	.030	.001		.001	.008	.021	
	RIFLE classes (urine output)				AKIN stages (urine output)			
AUC–ROC	0.76	0.56	0.64	0.70	0.76	0.56	0.64	0.70
(95% CI)	(0.51–0.99)	(0.21–0.90)	(0.27–0.97)	(0.40–0.99)	(0.51–0.99)	(0.21–0.90)	(0.27–0.97)	(0.40–0.99)
P value	.030	.734	.395	.136	.030	.734	.395	.136

RIFLE, R–renal risk, I–injury, F–failure, L–loss of kidney function, E–end-stage renal disease; *AKIN*, Acute Kidney Injury Network; *AUC–ROC*, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval. *Versus 0 (no AKI). †All patients who died in the hospital and who were classified as AKIN stage 2 with creatinine value or urine output switched to AKIN stage 3 because all of them received postoperative renal replacement therapy. ‡None of the patients with a postoperative greater than 200% creatinine value increase died in hospital.

Haase et al: A Comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: A prospective cohort study J Thorac Cardiovasc Surg 2009;-:1-7

- Results: According to the RIFLE (45.8%) or Acute Kidney Injury Network (44.7%) classification, a similar proportion of patients had acute kidney injury.
- There was large agreement between classifications according to patients graded as having nonacute kidney injury; however, there was some disagreement across classes for staging the severity of acute kidney injury
- The area under the curve for in-hospital mortality was similar for all classifications: 0.91 for the RIFLE classification (95%confidence interval, 0.82–0.99) and 0.94 for the Acute Kidney Injury Network classification (95%confidence interval, 0.81–0.97; P ¼ .6 for area under the curve comparison).

Diagnosis of AKI: Controversies

- Which Criteria?
  - Baseline creatinine

Unresolved Issues in RIFLE

Criteria for RIFLE classification	Controversial issue	Suggested remedies
Increase in serum creatinine	Uncertainty about baseline values of patients; Reliability of calculated baseline by MDRD formula based on 75ml/min/1.72m²	Increase in serum creatinine during a certain observation period
RRT	Influence of initiation of RRT on RIFLE classification	Requirement of RRT classified as FAILURE or introduction of a separate class

M. Joannidis, Intensive Care Med 2007

In case of missing baseline serum creatinine

Calculation of serum creatinine by using the MDRD formula assuming an eGFR of 75 ml/min/1,73m²

GFR (mL/min per 1.73 m2) =

186.3 x PCr (exp[-1.154]) x Age (exp[-0.203]) x (0.742 if female) x (1.21 if black)

Bellomo R et al, Crit Care 2004

Bagshaw et al: A comparison of observed versus estimated baseline creatinine for determination of RIFLE class in patients with acute kidney injury Nephrol Dial Transplant (2009) 24: 2739–2744

BEST Kidney study cohort: n= 1314/1753

Inclusion criteria: (1) oliguria defined as a urine output *<200 mL over 12 h, (2) marked azotaemia defined as a* serum urea *>30 mmol/L (84 mg/dL) and/or (3) need for acute RRT .*

Exclusion: Patients with pre-existing ESRD receiving chronic RRT and those treated with RRT prior to ICU admission or for drug toxicity not associated with AKI

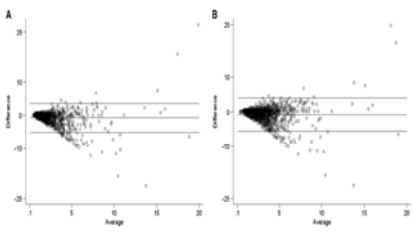


Fig. 1. (A) Bland–Altman plot of actual versus estimated baseline serum creatinine at ICU admission. X-axis, average of actual and measured baseline creatinine; Y-axis, difference between actual and measured baseline creatinine. (B) Bland–Altman plot of actual versus estimated baseline serum creatinine at study enrolment. X-axis, average of actual and measured baseline creatinine; Y-axis, difference between actual and measured baseline creatinine.

Use of eSCr to capture AKI by RIFLE category classified more patients as having AKI but was associated with an 18.8% false positive rate at ICU admission and 11.7% at study enrollment

Bagshaw et al: A comparison of observed versus estimated baseline creatinine for determination of RIFLE class in patients with acute kidney injury Nephrol Dial Transplant (2009) 24: 2739–2744

Table 2. Details of kidney function stratified by the RIFLE criteria

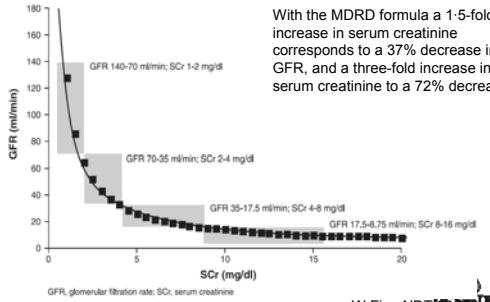
	Serum creatinine			
	Observed (%)	Estimated (%)	Absolute difference (%)	Correlation
At ICU admission				
None	723 (55.1)	477 (36.3)	246 (18.8)	0.49
Risk	209 (15.9)	199 (15.2)	10 (0.7)	
Injury	179 (13.6)	251 (19.1)	−72 (−5.5)	
Failure	202 (15.4)	386 (29.4)	−184 (−14)	
Any AKI	590 (44.9)	836 (63.7)	−246 (−18.8)	
At enrolment				
None	287 (21.9)	134 (10.2)	153 (11.7)	0.39
Risk	233 (17.8)	138 (10.5)	95 (7.3)	
Injury	313 (23.9)	316 (24.1)	−3 (−0.2)	
Failure	479 (36.5)	724 (55.2)	−245 (−18.7)	
Any AKI	1025 (78.1)	1178 (89.8)	−153 (−11.7)	

Use of eSCr to capture AKI by RIFLE category classified more patients as having AKI but was associated with an 18.8% false positive rate at ICU admission and 11.7% at study enrollment

Diagnosis of AKI: Controversies

- Which Criteria?
  - Baseline creatinine
  - Absolute vs Relative change in creatinine

Serum Creatinine and GFR Relationships



With the MDRD formula a 1·5-fold increase in serum creatinine corresponds to a 37% decrease in GFR, and a three-fold increase in serum creatinine to a 72% decrease.

W Finn NDT

Solomon et al: Defining acute kidney injury: what is the most appropriate metric?
www.nature.com/clinicalpractice doi:10.1038/ncpneph0746

Table 3 Amount of GFR lost to achieve an absolute increase (of ≥44.2 μmol/l or ≥0.5 mg/dl) in serum creatinine level as a definition of CIN.

Baseline serum creatinine level		Increase in serum creatinine level of ≥44.2 μmol/l (0.5 mg/dl)		Change in GFR[a] (ml/min per 1.73 m²)	Loss of GFR	
μmol/l	mg/dl	μmol/l	mg/dl		ml/min per 1.73 m²	%
88.4	1.0	133	1.5	100→67	33	33
133	1.5	177	2.0	67→50	17	25
177	2.0	221	2.5	50→40	10	20

[a]Assuming a steady state. Abbreviations: CIN, contrast-induced nephropathy; GFR, glomerular filtration rate.

Table 4 Amount of GFR lost to achieve a relative increase (≥25% rise) in serum creatinine level as a definition of CIN.

Baseline serum creatinine level		Increase of ≥25% in serum creatinine level		Change in GFR[a] (ml/min per 1.73 m²)	Loss of GFR	
μmol/l	mg/dl	μmol/l	mg/dl		ml/min per 1.73 m²	%
88.4	1.0	111	1.25	100→80	20	20
133	1.5	166	1.88	67→53	14	20
177	2.0	221	2.5	50→40	10	20

[a]Assuming a steady state. Abbreviations: CIN, contrast-induced nephropathy; GFR, glomerular filtration rate.

Solomon et al: Defining acute kidney injury: what is the most appropriate metric?
www.nature.com/clinicalpractice doi:10.1038/ncpneph0746

Table 1 Hypothetical model of GFR and AKI in a 60-year-old white female.

Baseline GFR (ml/min per 1.73 m²)	Baseline serum creatinine level		New 'steady state' serum creatinine level predicted for a GFR loss of 10 ml/min per 1.73 m²		Absolute change in serum creatinine level		Satisfies definition of AKI (CIN) as ≥44.2 μmol/l (0.5 mg/dl) absolute increase in serum creatinine level	Satisfies definition of AKI (CIN) as ≥25% relative increase in serum creatinine level
	μmol/l	mg/dl	μmol/l	mg/dl	μmol/l	mg/dl		
30	161	1.82	226	2.56	67.1	0.76	Yes	Yes
35	141	1.60	189	2.14	47.7	0.54	Yes	Yes
40	126	1.42	161	1.82	35.4	0.40	No	Yes
45	113	1.28	141	1.60	28.3	0.32	No	Yes
50	104	1.18	126	1.42	21.2	0.24	No	No
55	99.5	1.08	113	1.28	17.7	0.20	No	No
60	88.4	1.00	104	1.18	15.9	0.18	No	No

Abbreviations: AKI, acute kidney injury; CIN, contrast-induced nephropathy; GFR, glomerular filtration rate.

Table 2 Hypothetical model of GFR and AKI in a 60-year-old white male.

Baseline GFR (ml/min per 1.73 m²)	Baseline serum creatinine level		New 'steady state' serum creatinine level predicted for a GFR loss of 10 ml/min per 1.73 m²		Absolute change in serum creatinine level		Satisfies definition of AKI (CIN) as ≥44.2 μmol/l (0.5 mg/dl) absolute increase in serum creatinine level	Satisfies definition of AKI (CIN) as ≥25% relative increase in serum creatinine level
	μmol/l	mg/dl	μmol/l	mg/dl	μmol/l	mg/dl		
30	201	2.27	281	3.18	80.4	0.91	Yes	Yes
35	175	1.98	230	2.60	54.8	0.62	Yes	Yes
40	156	1.76	201	2.27	45.1	0.51	Yes	Yes
45	140	1.58	173	1.96	33.4	0.40	No	Yes
50	127	1.44	156	1.76	28.3	0.32	No	No
55	117	1.32	136	1.54	19.4	0.22	No	No
60	109	1.23	127	1.44	18.6	0.21	No	No

Abbreviations: AKI, acute kidney injury; CIN, contrast-induced nephropathy; GFR, glomerular filtration rate.

Creatinine Kinetics Simulation in AKI

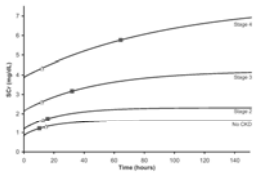


Figure 4. SCr concentrations after an abrupt 50% reduction in CrCl, superimposed on four different levels of baseline kidney function (no CKD and stages 2 through 4 CKD). Solid squares show the point at which a 100% increase in SCr has occurred; open triangles show the point at which a 1.0-mg/dl increase in SCr has occurred.

Table 3. Time (hours) to reach within 0.1 mg/dl of predicted steady-state SCr concentration after a given reduction in CrCl*

Parameter	Reduction in CrCl		
	75%	50%	25%
No CKD	102	34	10
Stage 2 CKD	159	59	21
Stage 3 CKD	223	139	62

*Results were obtained using a two-compartment model of creatinine

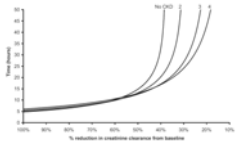


Figure 6. Time to reach a 0.5-mg/dl increase in SCr after a given percentage reduction in CrCl, according to the absence or presence of stages 2 through 4 CKD.

Waikar and Bonventre JASN 2009

Haase et al: A Comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: A prospective cohort study J Thorac Cardiovasc Surg 2009;-:1-7

Design:
Prospective observational cohort study of 282 post cardiac surgery patients in a single center. The incidence of AKI and in-hospital mortality across classes was compared by using the c2 test, and their prognostic value was compared using AUROC characteristic for in-hospital mortality.

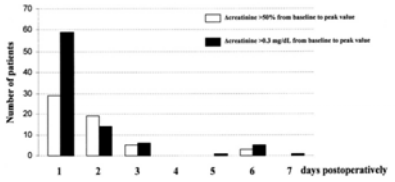
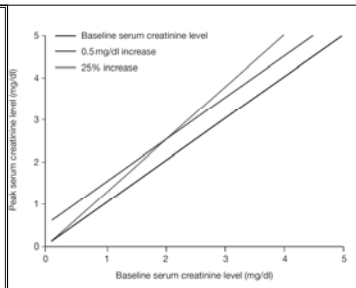


FIGURE 1. Timing of increase in serum creatinine value within 7 days postoperatively.

Solomon et al: Defining acute kidney injury: what is the most appropriate metric?
www.nature.com/clinicalpractice doi:10.1038/ncpneph0746

Hypothetical relationship between two definitions of acute kidney injury. The red line represents the definition of a 44.2 µmol/l (0.5 mg/dl) increase above the baseline serum creatinine level (black line); the blue line represents a 25% increase above the baseline serum creatinine level. The two definitions meet at a baseline serum creatinine concentration of 176.8 µmol/l (2.0 mg/dl), which, according to the MDRD equation, is an estimated GFR of 36 ml/min per 1.73 m2 for a 60-year-old white man. The relative increase (blue line) dominates for patients whose baseline serum creatinine concentration is less than 176.8 µmol/l (2.0 mg/dl; estimated GFR >40 ml/min per 1.73 m2). The absolute increase of 44.2 µmol/l (0.5 mg/dl; red line) dominates when baseline serum creatinine level is greater than 176.8 µmol/l (2.0 mg/dl; estimated GFR <40 ml/min per 1.73 m2).



Diagnosis and Staging of Acute Kidney Injury (AKI) in Critically ill patients: Comparison of AKIN, RIFLE and Waikar criteria

Rakesh Malhotra [1], Etienne Macedo [1], Josee Bouchard [1], Susan Wynn [1] and Ravindra Mehta [1] [1] University of California – San Diego

Parameter	Stage	Creatinine/GFR criteria
Acute Kidney Injury Network[2]	1	absolute change in sCR≥0.3 mg/dl or 50% from baseline within 48 hrs
	2	increase in sCR ≥100% over baseline
	3	increase in sCR ≥200% over baseline or sCR ≥ 4mg/dl with an acute rise of at least 0.5 mg/dl
Waikar et al.[1]	1	absolute change in sCR of 0.3 mg/dl in 24 hrs or a 0.5 mg/dl in 48 hrs
	2	absolute change in sCR of 0.5 mg/dl in 24 hrs or a 1.0 mg/dl in 48 hrs
	3	absolute change in sCR of 1.0 mg/dl in 24 hrs or a 1.5 mg/dl in 48 hrs
Acute dialysis quality initiative[3]	Risk	increase in sCR ≥50% from baseline or GFR decrease > 25% within 7 days
	Injury	increase in sCR ≥100 % from baseline or GFR decrease > 50%
	Failure	increase in sCR ≥200 % from baseline or GFR decrease > 75%

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Rakesh Malhotra [1], Etienne Macedo [1], Josee Bouchard [1], Susan Wynn [1] and Ravindra Mehta [1] [1] University of California – San Diego

		Waikar						RIFLE					
		No AKI	Waikar 1	Waikar 2	Waikar 3	Total	Total	RIFLE F	RIFLE I	RIFLE R	No AKI		
AKIN	No AKI	514	0	0	0	514	514	0	3	66	445	No AKI	AKIN
	AKIN 1	37	68	29	13	147	147	0	18	106	23	AKIN 1	
	AKIN 2	4	4	19	16	43	43	0	43	0	0	AKIN 2	
	AKIN 3	1	0	4	8	13	13	13	0	0	0	AKIN 3	
	Total	556	72	52	37	717	717	13	64	172	468	Total	

Diagnosis and Staging of Acute Kidney Injury (AKI) in Critically ill patients: Comparison of AKIN, RIFLE and Waikar criteria

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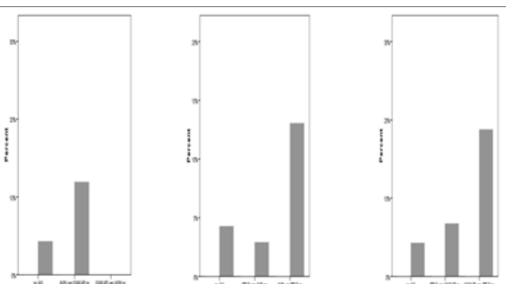


AKIN vs Waikar

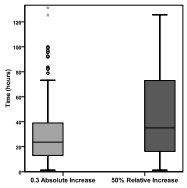
AKIN vs RIFLE

RIFLE vs Waikar

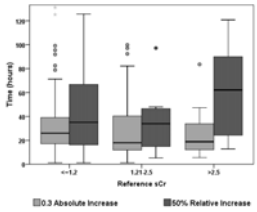
Diagnosis and Staging of Acute Kidney Injury (AKI) in Critically ill patients: Comparison of AKIN, RIFLE and Waikar criteria

Rakesh Malhotra [1], Etienne Macedo [1], Josee Bouchard [1], Susan Wynn [1] and Ravindra Mehta [1] [1] University of California – San Diego

Time to reach AKI diagnosis by absolute and relative change in sCR



Time to reach AKI diagnosis (absolute vs. relative change in sCR) by first sCR at ICU



ASN Abstract Thursday TH-PO0033

Diagnosis of AKI: Controversiies

- Which Criteria?
  - Absolute vs Relative change in creatinine?
  - Absolute change in sCR is more consistent and occurs earlier than relative changes in sCR and is not influenced by baseline kidney function. Relative changes in sCr are influenced by baseline renal function particularly above ? 2mg/dl

Diagnosis of AKI: Controversiies

- Which Criteria?
  - Absolute vs Relative change in creatinine?
  - Does a decrease in creatinine represent AKI?

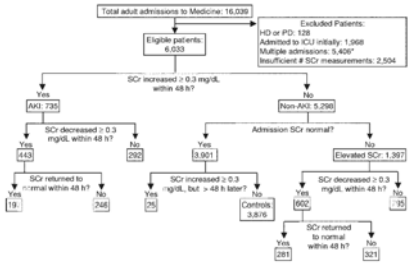
Tian et al: Rapid Reversal of Acute Kidney Injury and Hospital Outcomes: A Retrospective Cohort Study *Am J Kidney Dis 53:974-981.*

Study Design: Retrospective cohort study.

6,033 patients admitted to medical wards of a community teaching hospital between 2005 and 2007.

Predictor: AKN criteria for AKI N within 48 hours. Increased serum creatinine level on admission was defined as serum creatinine greater than1.2mg/dL on hospital admission in patients who did not subsequently meet criteria for AKI. Patients with a serum creatinine level of 1.2 mg/dL or less who had no increase of 0.3 mg/dL or greater within 48 hours

during their hospital stay served as controls.



Tian et al: Rapid Reversal of Acute Kidney Injury and Hospital Outcomes: A Retrospective Cohort Study *Am J Kidney Dis 53:974-981.*

Study Design: Retrospective cohort study.

6,033 patients admitted to medical wards of a community teaching hospital between 2005 and 2007.

Results: Of 6,033 patients, 735 had AKI. Of these, 443 (60%) had serum creatinine levels that subsequently decreased by 0.3 mg/dL or greater within 48 hours and 197 returned to normal levels within 48 hours. Overall, patients with AKI had significantly greater mortality rates (14.8%) than patients without AKI with increased serum creatinine levels on admission (2.5%) and controls (1.3%; *P 0.001*).

Patients with AKI with a serum creatinine level that returned to normal within 48 hours had substantially greater mortality rates (14.2%) than those who initially presented with an increased serum creatinine level on admission and subsequent serum creatinine level decrease of 0.3 mg/dL or greater to normal within 48 hours (2.5%; *P 0.01*).

Table 4. Logistic Analyses for Mortality With and Without Adjustment

	Unadjusted Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)
AKI fully reversed*†	12.9 (7.9-21.1)	4.4 (2.6-7.3)
AKI with SCr that did not return to normal*	11.3 (7.0-18.0)	4.4 (2.7-7.1)
AKI with SCr that did not decrease ≥ 0.3 mg/dL within 48 h*	16.1 (10.7-24.4)	8.0 (5.4-11.8)
Age (≥65 y)	4.3 (2.9-6.4)	3.2 (2.1-4.8)
Intensive care unit transfer	7.5 (5.5-10.3)	4.0 (2.8-5.8)
Deyo-Charlson comorbidity index score‡	2.5 (1.8-3.5)	1.4 (1.1-1.6)

Diagnosis of AKI: Controversies

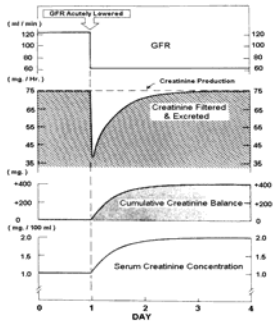
- Which Criteria?
  - Does a decrease in creatinine represent AKI?
    - Limited data suggests that a decrease in serum creatinine may be a marker of AKI however the risk for adverse events may not be the same as someone who has AKI based on AKIN criteria and then improves.
    - Further prospective studies needed to address this issue

Diagnosis of AKI: Controversies

- Which Criteria?
  - Absolute vs Relative change in creatinine?
  - Does a decrease in creatinine represent AKI?
  - What is the effect of fluid accumulation on serum creatinine?

Course of AKI: Issues

Response Variable is Affected by Various Factors



Factors Affecting Serum Creatinine

- Generation rate
- Volume of distribution
- Tubular Secretion
- Relationship to GFR
- Effect of Intervention

Kassirer JP, Clinical Evaluation of Kidney Function – Glomerular Function. N Engl J Med 1971, 285: 385-389.

Moran and Myers: Course of acute renal failure studied by amodel of creatinine kinetics. Kid Int 1985; 27: 928-937

Effects of increasing total body water on serum creatinine in ARF

	Day	Creat Cl	Weight	TBW	Lab Creat	Corrected Creat	TBW (wt %)
Patient A	-1	44	68	40.8	1.4	1.4	60
	0	44	68	40.8	1.4	1.4	60
	1	37	80.4	53.2	1.2	1.6	66
	2	35	82	54.8	1.1	1.5	67
	3	29	82.5	55.3	1.4	1.9	67
Patient B	-1	38	50.4	27.7	0.9	0.9	55
	0	38	52	29.3	0.9	1.0	56
	1	11	58	35.3	1.2	1.5	61
	3	12	65	42.3	1.6	2.3	65
	6	5	67.5	44.8	2.0	3.1	66
	10	5	69.4	46.7	3.9	6.2	67

Fluid Accumulation Underestimates Severity of Acute Kidney Injury in Critically-ill Patients

Etienne Macedo, MD[1], Josée Bouchard, MD[1], Sharon Soroko, MS[1], Glenn M. Chertow, MD, MPH[2], Jonathan Himmelfarb, MD[3], T. Alp Ikizler, MD[4], Emil P. Paganini, MD[5], Ravindra L Mehta, MD[1]. Program to Improve Care in Acute Renal Disease (PICARD) study

- **253 patients in PICARD database (n=618) with consecutive increase in serum creatinine over 3 to 7 days prior to any dialysis**
- ***Correction of Creatinine Values for Fluid Balance***
- Serum creatinine values were adjusted according to the cumulative daily fluid balance using the formula:
  - *Creatinine adjusted = serum creatinine x* ***correction factor***
  - ***Correction factor = [hospital admission weight (kg) x 0.6 + Σ (daily fluid balance)]/ hospital admission weight x 0.6***
- Reference creatinine → first value in the consecutive increase period of serum creatinine.
- Using creatinine non-adjusted and creatinine adjusted for fluid balance → We applied AKIN and RIFLE criteria to compare the timing of AKI diagnosis.
- → A delay in recognizing AKI (LAG) was defined as a difference in meeting SCr AKI criteria in one or more day.

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Daily Cumulative Fluid Balance and SCr (adjusted and non-adjusted)

	day 0	day 1	day 2	day 3	day 4	day 5	day 6
cumulative FB - Liters (median)		2.7	3.7	4.95	5.6	6	6.5
IQR 25%-75%		0.50 - 6.20	1.15 - 8.60	1.72 - 10.30	2.50 - 12.00	1.90 - 13.1	1.07 - 11.32
SCr non-adjusted	1.6	2.1	2.8	3.3	3.8	3.85	3.9
IQR 25% - 75%	1.2 - 2.20	1.5 - 2.80	2.1 - 3.75	2.6 - 4.60	2.9 - 5.50	2.9 - 5.55	2.825 - 5.58
SCr - FB adjusted	1.89	2.24	3	3.79	4.29	4.44	4.55
IQR 25% - 75%	1.20 - 2.32	1.61 - 3.06	2.31 - 4.24	2.86 - 5.23	3.23 - 6.29	3.44 - 6.31	3.42 - 6.68

Fluid Accumulation Underestimates Severity of Acute Kidney Injury In Critically-ill Patients

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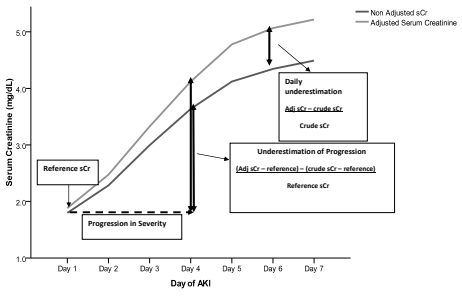


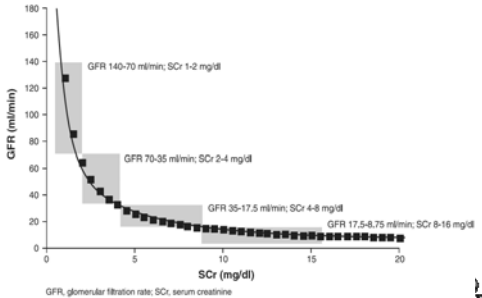
Diagnosis of AKI: Controversies

- Which Criteria?
  - What is the effect of fluid accumulation on serum creatinine?
    - Cumulative fluid gain masks the underlying severity of renal functional change based on serum creatinine and may lead to an underestimation of the rate of progression
    - Serum creatinine levels should be adjusted for fluid accumulation particularly in ICU patients.

Diagnosis of AKI: Controversies

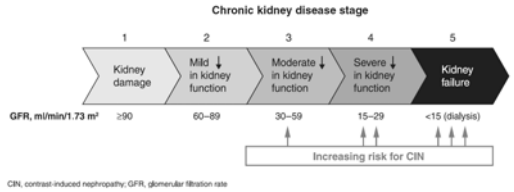
- Which Criteria?
  - Absolute vs Relative change in creatinine?
  - Does a decrease in creatinine represent AKI?
  - What is the effect of fluid accumulation on serum creatinine?
  - Can we use eGFR?

Serum Creatinine and GFR Relationships



W Finn NDT 2006

Influence of CKD on AKI
Example: Contrast Induced Nephropathy

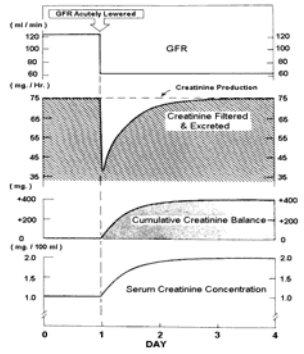


CIN, contrast-induced nephropathy; GFR, glomerular filtration rate

Fig. 2. Risk for CIN according to stage of CKD [5–7]. Reprinted with permission [7].

W Finn NDT

Changes in Serum Creatinine and eGFR after a Change in GFR



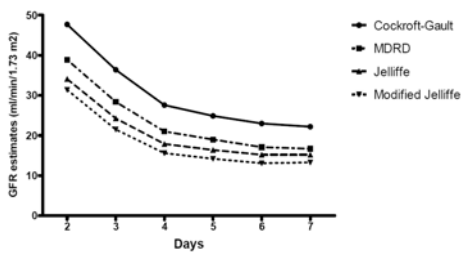
Day	Scr	eGFR
0	1.0	135
1.5	1.6	79
2.0	1.8	69
2.5	1.9	65
3.0	2.0	60

Kassirer JP, Clinical Evaluation of Kidney Function – Glomerular Function. N Engl J Med 1971, 285: 385-389.

Comparisons of different techniques for estimating glomerular filtration rate in critically ill patients with acute kidney injury

Josée Bouchard, MD[1], Etienne Macedo, MD[1], Sharon Soroko, MS[1], Glenn M. Chertow, MD, MPH[2], Jonathan Himmelfarb, MD[3], T. Alp Ikizler, MD[4], Emily Paganini, MS[5], Ravindra L. Mehta, MD[1], Program to Improve Care in Acute Renal Disease (PICARD) study

GFR estimates by Cockroft-Gault, MDRD, Jelliffe and Modified Jelliffe



Bouchard, NDT online on August, 2009

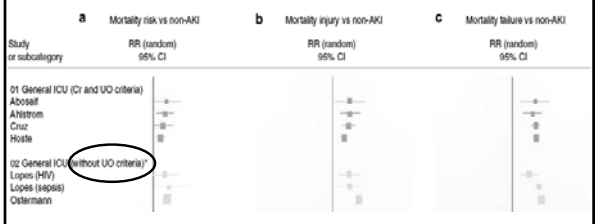
Diagnosis of AKI: Controversies

- Which Criteria?
  - Can we use eGFR?
    - eGFR based on Cockroft Gault and MDRD formulas significantly overestimate GFR and do not represent non-steady state conditions.
    - Modified Jelliffe GFR accounts for fluid accumulation and non-steady state generation of creatinine and needs to be validated prospectively

Diagnosis of AKI: Controversies

- Which Criteria?
  - Absolute vs Relative change in creatinine?
  - Does a decrease in creatinine represent AKI?
  - What is the effect of fluid accumulation on serum creatinine?
  - Can we use eGFR?
  - Is oliguria a valid criterion?

The RIFLE criteria and mortality in acute kidney injury: A systematic review the impact of UO criterion



Ricci Z et al, Kidney Int 2008

Haase et al: A Comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: A prospective cohort study J Thorac Cardiovasc Surg 2009;-:1-7

TABLE 5. Comparison of patients' outcomes according to the urine output criteria of the RIFLE versus AKIN classifications

RIFLE class/AKIN class	‚F'/3 (n = 5)	0/0, ‚R'/1, ‚I'/2 (n = 277)	*P* value
Length of stay in intensive care unit, h	266.6 ± 162.1	64.9 ± 88.2	.001
Length of stay in hospital, d	20.4 ± 13.1	9.7 ± 7.3	.001
Need for renal replacement therapy, no.	5 (100%)	4 (1.4%)	<.001
Died during hospital stay, no.	2 (40.0%)	4 (1.4%)	.004

The urine output criteria of both classifications apply the same cutoff values in urine output to allocate a patient to an acute kidney injury category. *RIFLE*, R–renal risk, I–injury, F–failure, L–loss of kidney function, E–end-stage renal disease; *AKIN*, Acute Kidney Injury Network; *AUC–ROC*, area under the receiver operating characteristic curve.; *AKIN*, Acute Kidney Injury Network.

Diagnosis of AKI: Issues

Response Variable is Affected by Various Factors

- **Factors Affecting Urine Output**
  - Hydration status
  - Hemodynamics
  - Autoregulation (TGF)
  - Intraglomerular capillary pressure
  - Diuretics
- **Issues**
  - What defines oliguria?
  - Is oliguria a valid marker of AKI?

Changes in Urine Output and Acute Kidney Injury in Critically ill patients

Etienne Macedo, Rakesh Malhotra, Rolando Claure, Peter Fedullo, and Ravindra Mehta
University of California – San Diego

Urinary Flow Measurements

- digital continuous urine meter *(Urinfo® system Med-Dynamix Inc, Israel):* infrared light to detect urinary flow drop by drop, providing an hourly accurate measurement of the urine flow.

AKI diagnosis

-SCr measurements were done at least once per 24hrs
- We applied the AKIN criteria to define AKI by sCr (creatinine change ≥ 0.3mg/dl or ≥ 50% from reference)

Changes in Urine Output and Acute Kidney Injury in Critically ill patients

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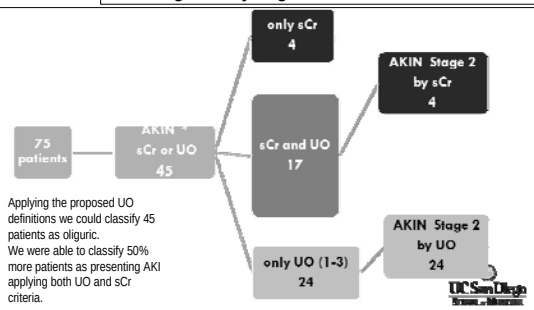
Results

- AKI Diagnosis by Oliguria Definitions and sCr criteria



Applying the proposed UO definitions we could classify 45 patients as oliguric.
We were able to classify 50% more patients as presenting AKI applying both UO and sCr criteria.

Changes in Urine Output and Acute Kidney Injury in Critically ill patients

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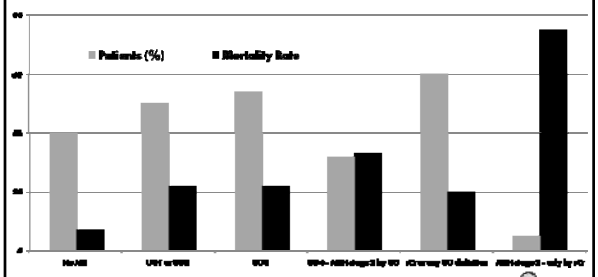
Mortality rate by AKI diagnosis criteria.



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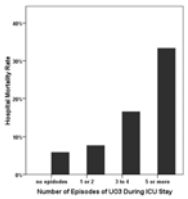
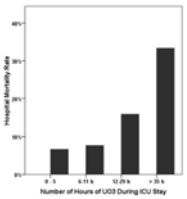
Changes in Urine Output and Acute Kidney Injury in Critically ill patients

Etienne Macedo, Rakesh Malhotra, Rolando Claure, Peter Fedullo, and Ravindra Mehta
University of California – San Diego

Episodes of Oliguria



Duration of Oliguria



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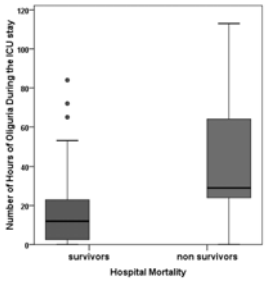
Changes in Urine Output and Acute Kidney Injury in Critically ill patients

Etienne Macedo, Rakesh Malhotra, Rolando Claure, Peter Fedullo, and Ravindra Mehta
University of California – San Diego

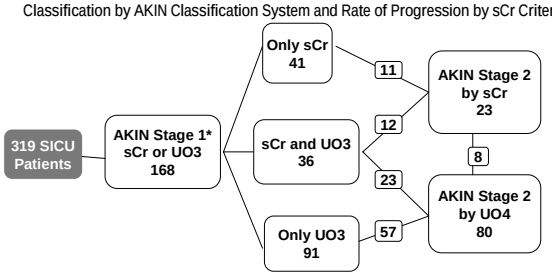
Hours of Oliguria During ICU Stay in Survivors and Non-Survivors



Do Episodes of Oliguria Reflect Acute Kidney Injury in Critically ill Patients?

Etienne Macedo , Rakesh Malhotra , Josee Bouchard , Susan Wynn and Ravindra Mehta
University of California – San Diego

Classification by AKIN Classification System and Rate of Progression by sCr Criterion



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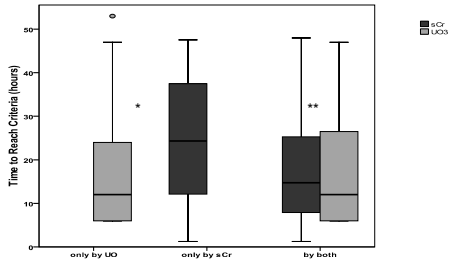
Do Episodes of Oliguria Reflect Acute Kidney Injury in Critically ill Patients?

Etienne Macedo , Rakesh Malhotra , Josee Bouchard , Susan Wynn and Ravindra Mehta
University of California – San Diego

Time to Reach sCr and UO Criteria



*p<0.01;**p=0.226

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Do Episodes of Oliguria Reflect Acute Kidney Injury in Critically ill Patients?

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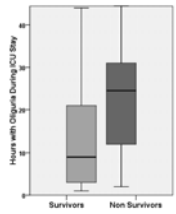
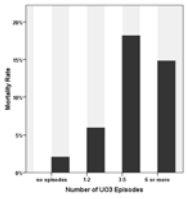
Hours of Oliguria During ICU Stay in Survivors and Non-Survivors



Mortality Rate by Number of UO3 Episodes



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P<0.001

Diagnosis of AKI: Controversies

- Which Criteria?
  - Is oliguria a valid criterion?

- ✓ The AKIN UO criteria for AKI diagnosis is sensitive and identifies additional patients with AKI compared to the sCr criterion alone.
- ✓ The diagnosis of AKI by UO alone is associated with an increased mortality, need for RRT and longer length of ICU and hospital stay.
- ✓ Oliguria is a valid marker of altered renal function in ICU patients and should be included in future studies in AKI.

Future Directions

- How will biomarkers change diagnosis and staging criteria?
- How will the gap between AKI and CKD definitions be addressed?
- Harmonization across settings

Defining Acute Kidney Injury: Summary

- Standardized criteria for diagnosis and staging allow earlier recognition of AKI
- Controversies exist on best criteria for each situation
- New conceptual model describes a series of stages, antecedents and outcomes for AKI
- Emerging discoveries of novel markers in AKI provide opportunities for an improved understanding of the pathophysiology and natural history of AKI.
- Need for ongoing research to develop knowledge base and provide practical tools to manage patients with AKI
- Ultimate goal is to improve outcomes from AKI.

Research Group

- PICARD
- UCSD AKI research group
  - **Josee Bouchard**, Rolando Claure, Sam Kuo, Yang Luo, **Etienne Macedo, Rakesh Malhotra, Sharon Soroko,** Guillermo Sanz, Jiandong Wei