Kidney Attack

John A. Kellum, MD

Professor of Critical Care Medicine, Medicine,
Bioengineering and Clinical and Translational Science
Vice Chair for Research

The CRISMA Center

Department of Critical Care Medicine
School of Medicine

Center for Inflammation and Regenerative Modeling
McGowan Institute for Regenerative Medicine

Health Policy and Management
Graduate School of Public Health

University of Pittsburgh

Disclosures

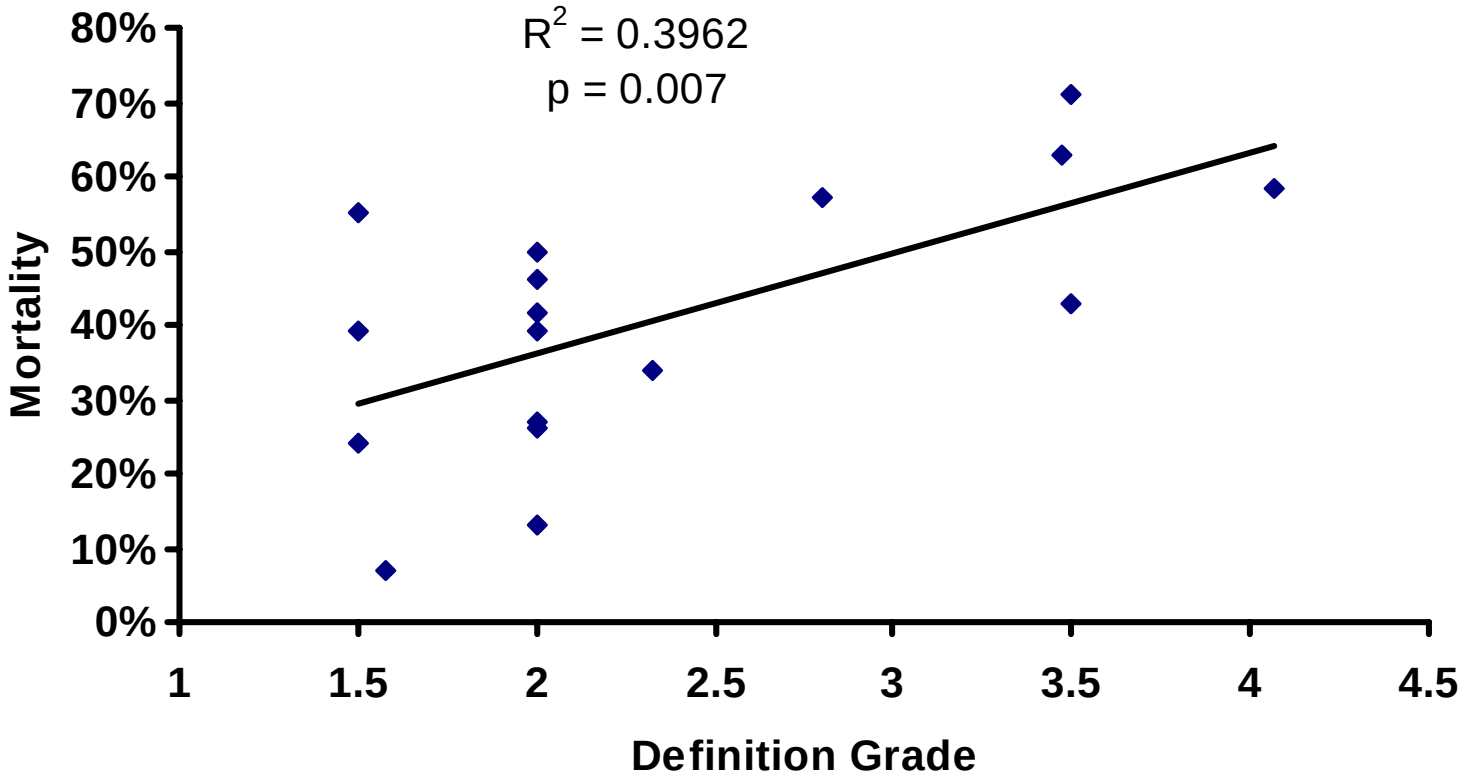
- **Consultant**
  - Gambro
  - Baxter
  - Fresenius
  - CytoSorbents
  - Alere
  - Astute Medical
- **Grant Support**
  - Gambro
  - Baxter
  - CytoSorbents
  - Astute Medical

Consider

- **Millions of patients are admitted to Intensive care units.**
  - As many as 2/3 will develop evidence of acute kidney injury (AKI)
  - Nearly half will be at increased risk of death because of AKI
  - 6% of critically ill patients world-wide will loose kidney function completely –60% of these will die

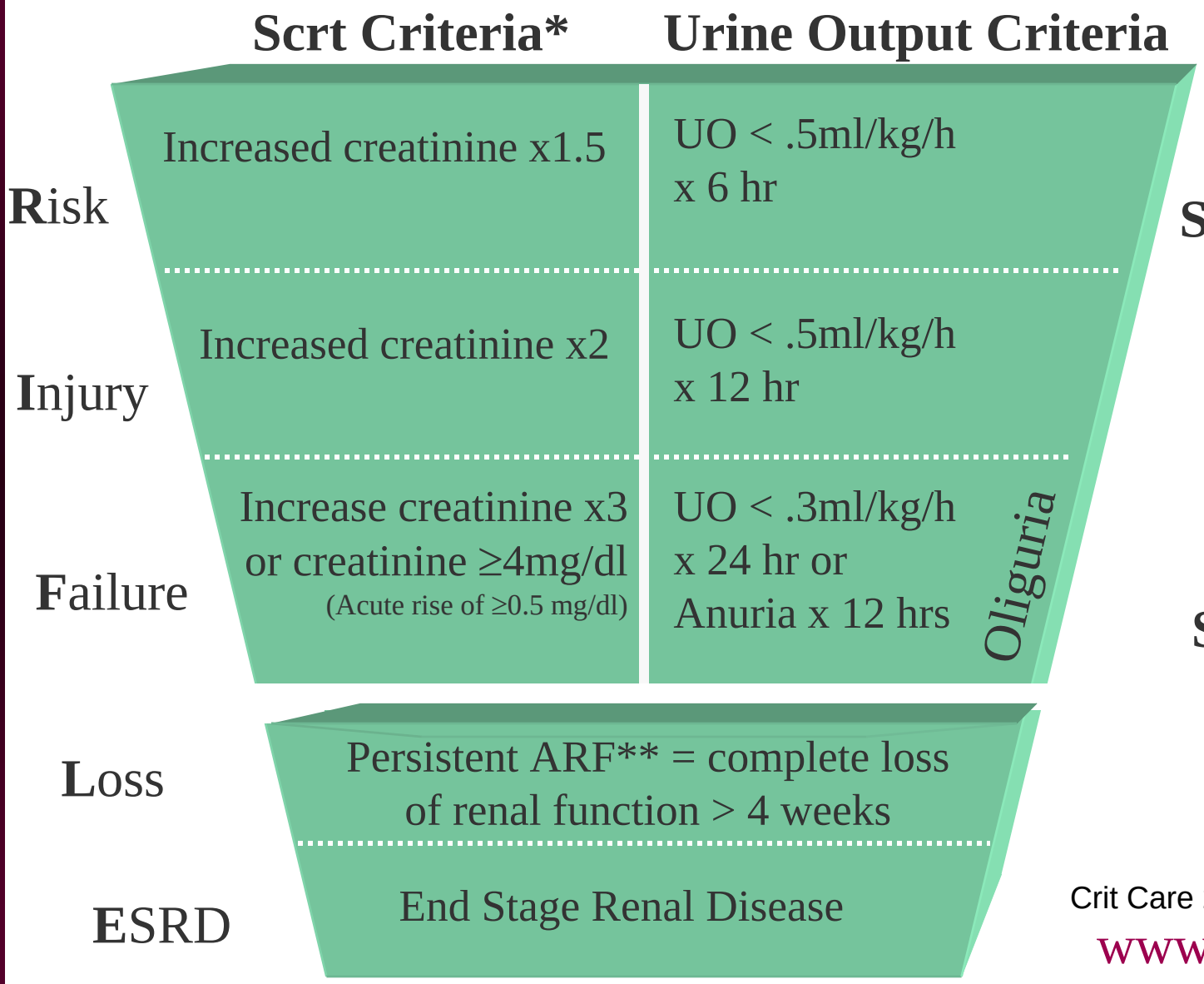
    JAMA. 2005; 294: 813-818.
- **We have no real idea why AKI occurs, why the kidneys fail or why, despite hemodialysis, mortality is so high.**
- **Throughout the world ~2 million will die this year of a disease whose pathophysiology we do not understand and for which no effective treatment exists.**

Definitions of ARF



Kellum et al. Current Opin in Crit Care 2002

RIFLE Criteria for Acute Kidney Injury

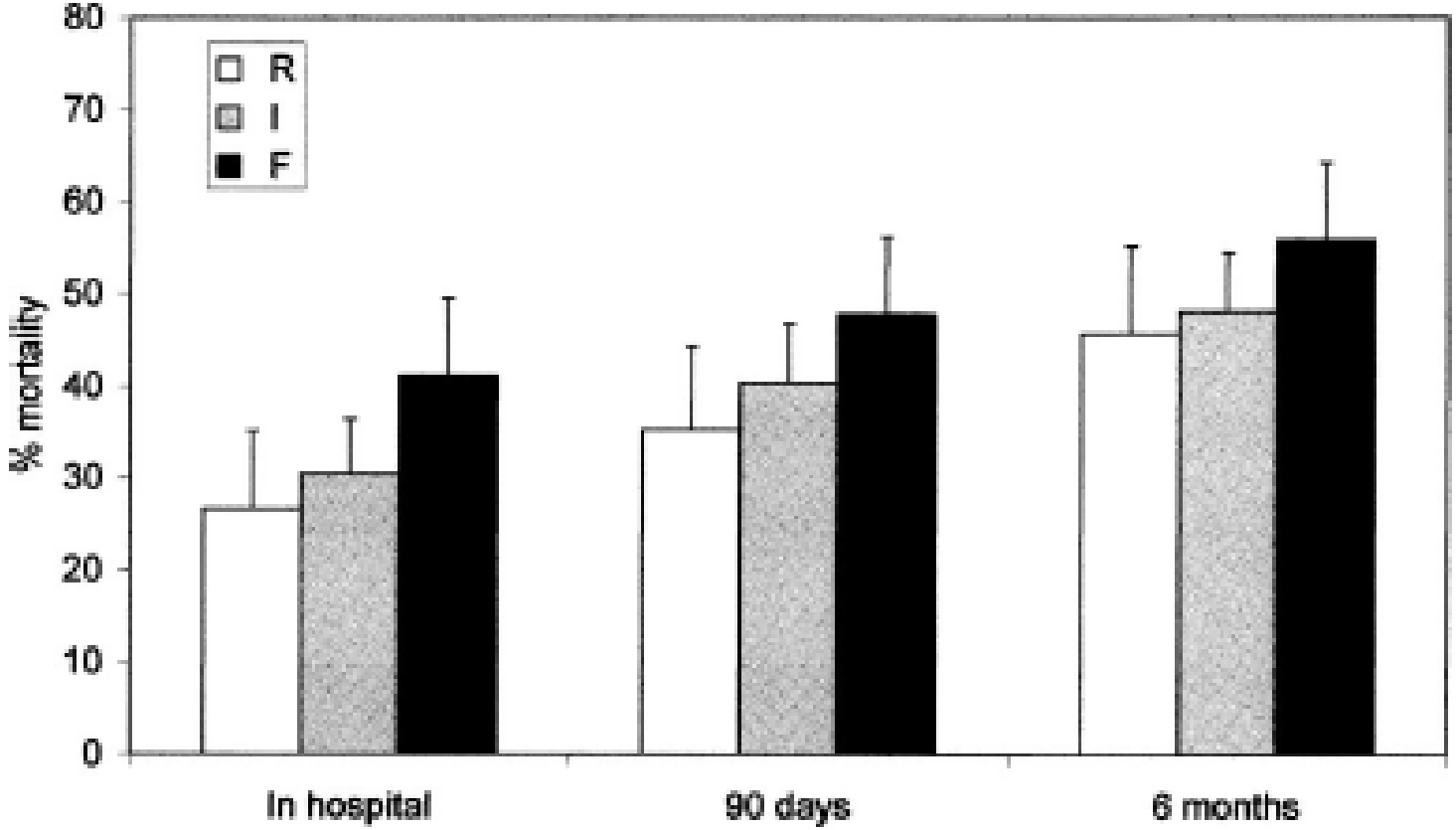


Crit Care 2004, 8:R204-12

www.ADQI.net

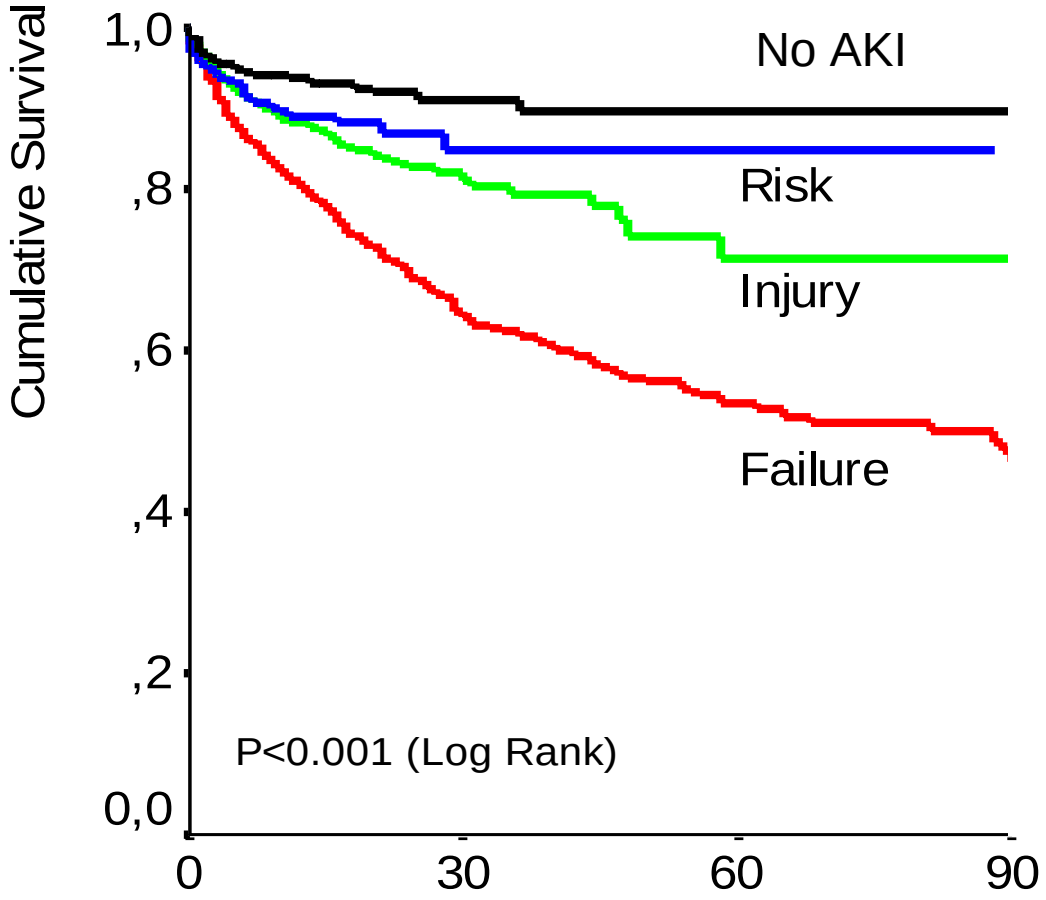
RIFLE has been validated in >500,000 pts

- **Hospital and ICU based studies**
  - Recent studies
    - 120,123 patients in 57 ICUs in Australia (Bagshaw et al)
      - 36.1% developed AKI
      - Hosp Mortality: R:17.9%, I:27.7%, F:33.2%
    - 41,972 patients in 22 ICUs in Europe (Ostermann et al.)
      - 35.8% developed AKI
      - Hosp Mortality: R:20.9%, I:45.6%, F:56.8%
- **Population based studies**
  - Northern Scotland (pop 523,390) (Ali et al.)
    - AKI incidence 2147 pmp (16% CKD)
    - By comparison the incidence of acute MI in US is approximately 2667 pmp



Ali et al. *J Am Soc Nephrol* 18: 1292–1298, 2007

RIFLE max



Hoste et al. Crit Care 2006;10:R73

RIFLEmax and mortality (Covariate-adjusted Cox proportional hazard regression analysis).

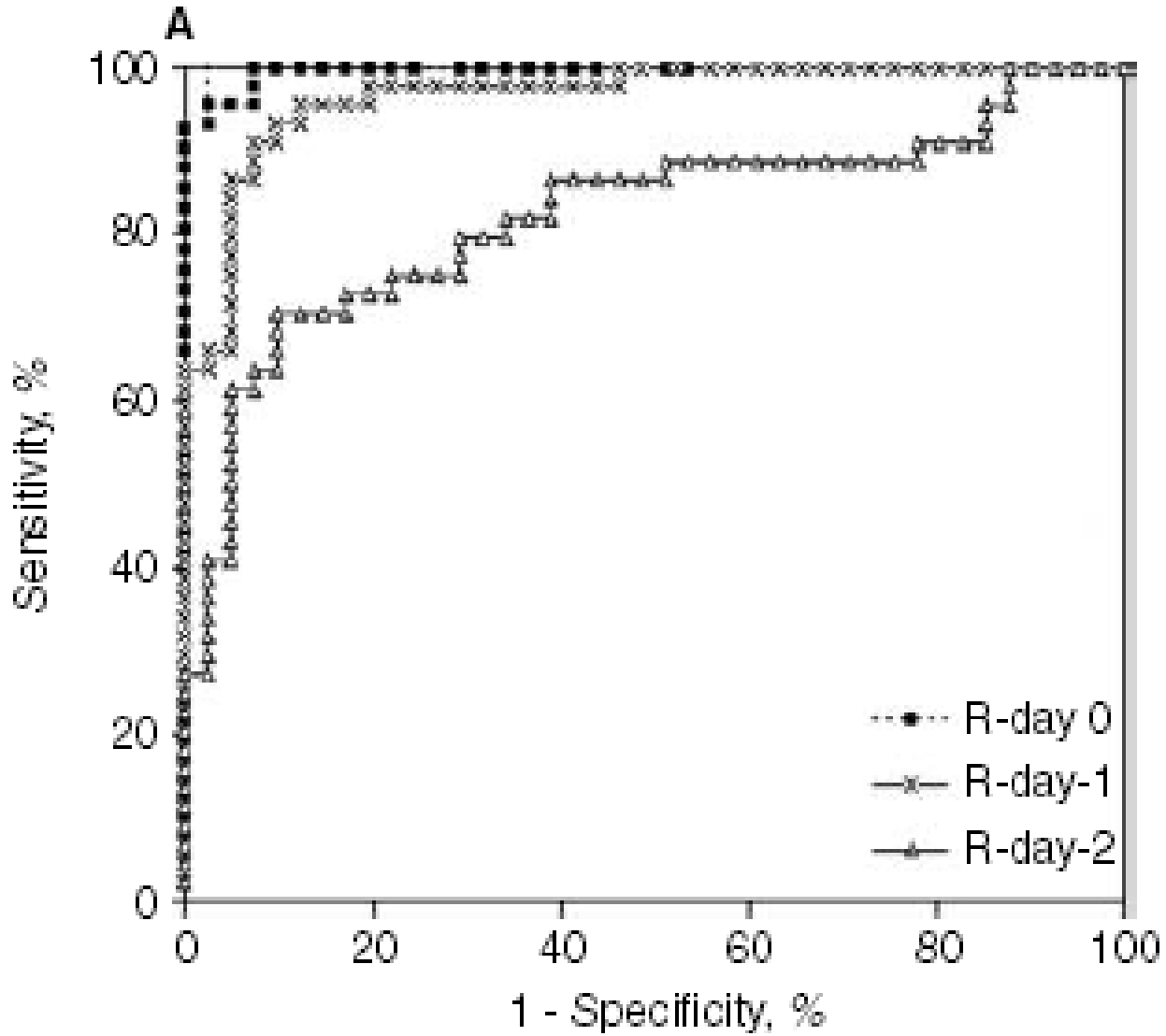
	B (SE)	P	HR	95% CI
$RIFLE_{max}$		<0.001		
Risk	0.072 (0.207)	0.728	1.075	0.716-1.614
Injury	0.465 (0.147)	0.002	1.592	1.192-2.124
Failure	1.130 (0.132)	<0.001	3.096	2.392-4.006
$SOFA_{non\text{-}renal}$ (/point)	0.092 (0.010)	<0.001	1.096	1.075-1.117
Age (/10 yr)	0.151 (0.026)	<0.001	1.163	1.106-1.223

Hoste et al. Crit Care 2006;10:R73

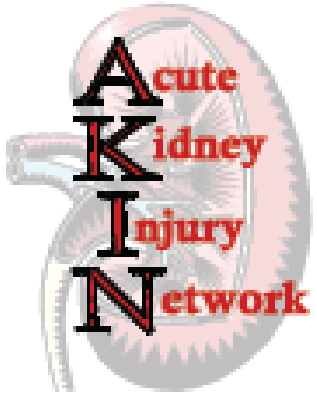
Evolution of ARF by RIFLE

	Evolution rate*	Time (days)
Risk		
No evolution	**24.2 %**	
Risk to Injury	**49.9 %**	**1.3 (0.5-3.4)**
Risk to Failure	**25.9 %**	**4.2 (1.4-9.3)**
Injury (development)		
Injury from Risk	**32.7 %**	**1.3 (0.5-3.4)**
Started as Injury	**67.3 %**	
Injury (progression)		
No Evolution	**62.6 %**	
Injury to Failure	**37.4 %**	**2.0 (0.5-6.3)**
Failure		
Failure from Risk	**24.7 %**	**4.2 (1.4-9.3)**
Failure from Injury	**55.9 %**	**2.0 (0.5-6.3)**
Started as Failure	**19.4 %**	

Hoste et al. Crit Care. 2006;10(3):R73



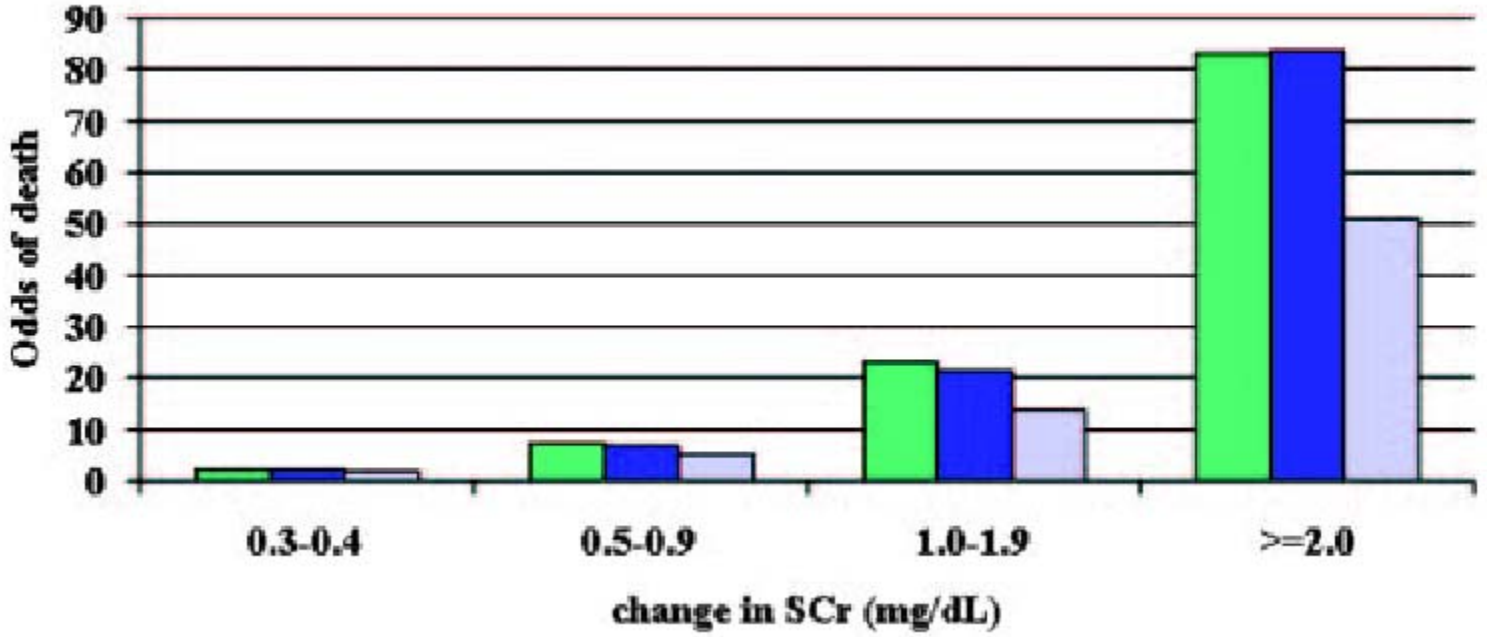
Herget-Rosenthal et al: Cystatin C and detection of ARF
Kidney International, Vol. 66 (2004), pp. 1115–1122



Recommendations for diagnosis and staging of Acute Kidney Injury

American College of Chest Physicians (ACCP), Acute Dialysis Quality Initiative (ADQI), Australian and New Zealand Intensive Care Society (ANZICS), Asia Pacific Association of Critical Care Medicine (APACCM), Asian Pacific Society of nephrology (APSN), American Society of Nephrology (ASN), American Society of Pediatric Nephrologists (ASPN), American Thoracic Society (ATS), Chinese Society of Nephrology (CSN), European Dialysis and Transplant Association-European Renal Association (EDTA-ERA), European Society of Intensive Care Medicine (ESICM), International Pediatric Nephrology Association (IPNA), Indian Society of Nephrology (ISN), International Society of Nephrology (ISN), National Kidney Foundation (NKF), Society of Critical Care Medicine (SCCM), Sociedade Latino-Americana de Nefrologia e Hipertensão (SLANH), Société de Réanimation de Langue Française (SRLF)

JASN 16:3365-70, 2005



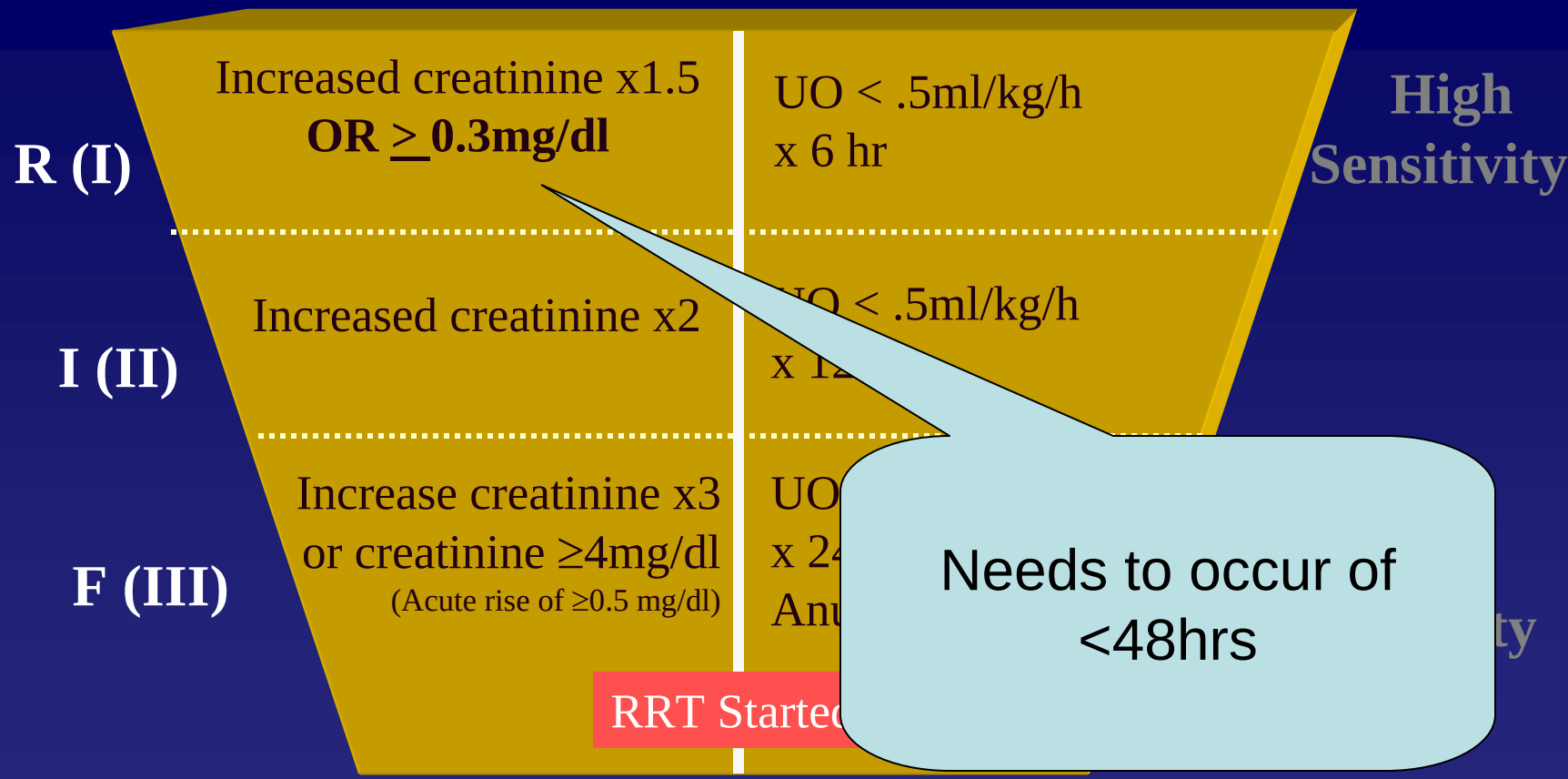
Unadjusted

Age and sex adjusted

Multivariable adjusted

"It is noteworthy that even very small increases in SCr (0.3 to 0.4 mg/dl) were significantly associated with mortality (multivariable OR 1.7; 95% CI, 1.2 to 2.6)."

Modified RIFLE Criteria for AKI Staging



Modifications proposed by AKIN
Amsterdam, 2005

Sepsis and AKI

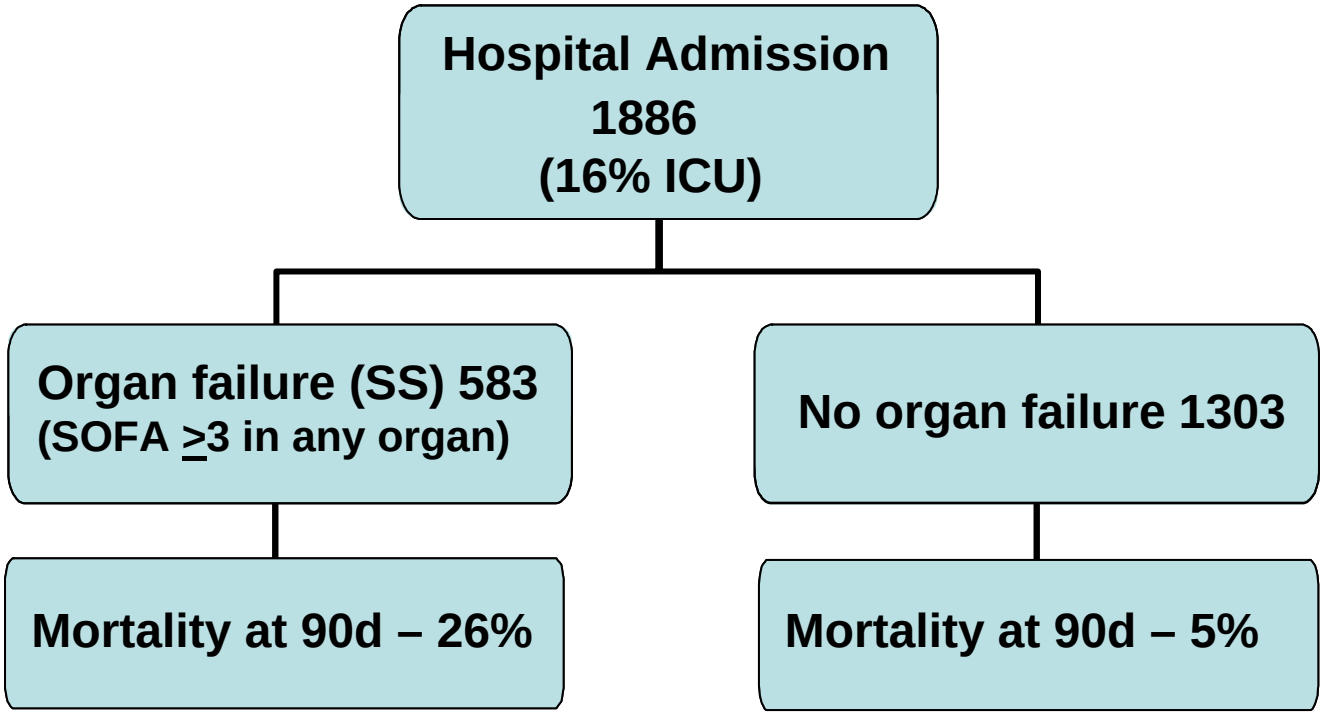
- **Severe sepsis is the leading cause of AKI and its incidence is increasing.**
  - 120,123 patients in 57 ICUs in Australia (NDT 2007)
    - 36.1% developed AKI
    - Hosp Mortality: R:17.9%, I:27.7%, F:33.2%
    - 42% with sepsis
  - BEST Kidney: 54 Centers in 28 countries (JAMA 2005)
    - 4.3% received RRT
    - Hospital mortality 60%
    - 47% with sepsis
  - Incidence of AKI specific patient types
    - Sepsis 37% (Lopes Crit Care 2007;11:408)
    - Cardiac surgery 16% (Heringlake Min Anest 2006;72:645)
    - Cardiac surgery 19% (Kuitunen Ann Thor Surg 2006;81:542)
    - CABG 7% (Dasta Nephrol Dial Transplant 2008)

Genetic and Inflammatory Markers of Sepsis (GenIMS)

- **Inception cohort study of patients presenting to ED with CAP**
  - 28 hospitals clustered in 4 regions
    - Pennsylvania (SW)
    - Connecticut
    - Michigan (Detroit area)
    - Tennessee (Memphis area)
- **Serial blood sampling and clinical data collection**
- **Characterize genotype, serum inflammatory and coagulation markers, and clinical outcomes**
  - CAP but no progress to severe sepsis
  - CAP progressing to severe sepsis

The GenIMS study of Sepsis in Community Acquired Pneumonia

A multicenter study of pneumonia and sepsis
GenIMS
Genetic and Inflammatory Markers of Sepsis



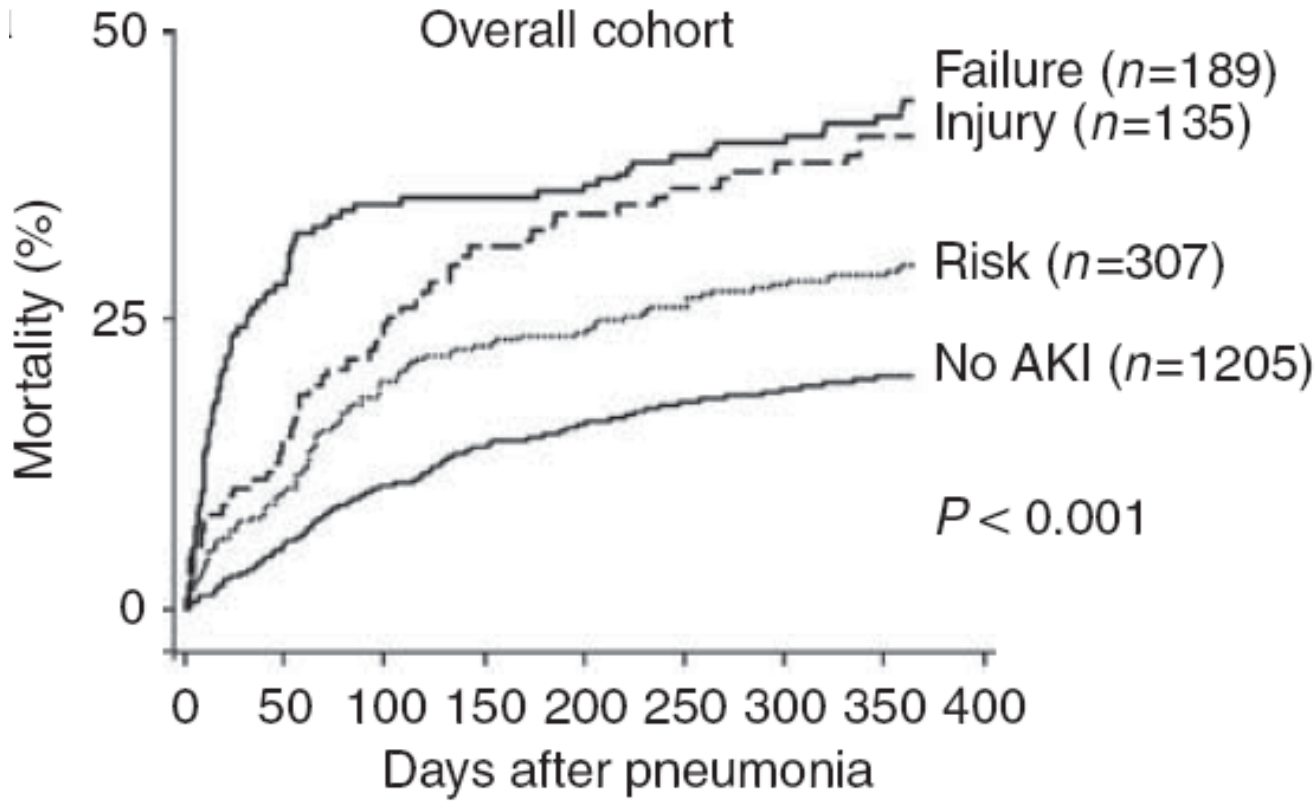
Kellum JA et al. Arch Intern Med 2007; 167(15):1655-63

AKI Incidence and Survival

A multicenter study of pneumonia and sepsis
GenIMS
Genetic and Inflammatory Markers of Sepsis

AKI 631 (34 %)

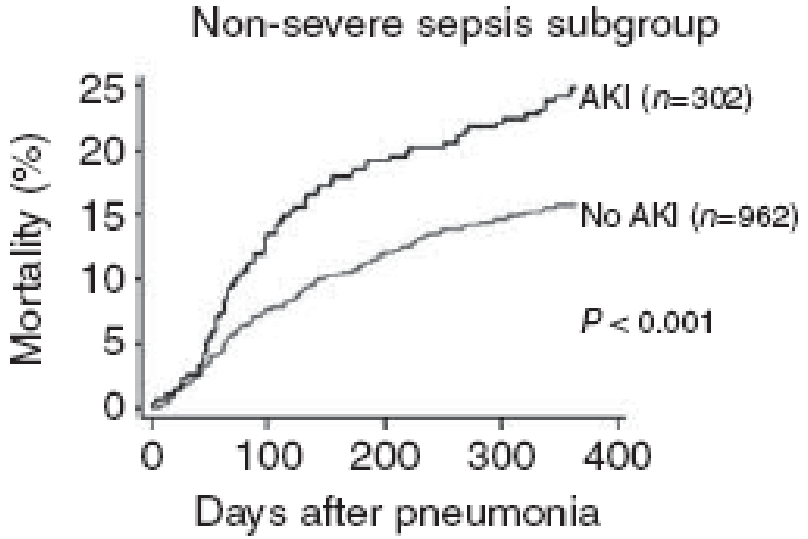
Risk 307 (49%)	Injury 135 (21%)	Failure 189 (30 %)

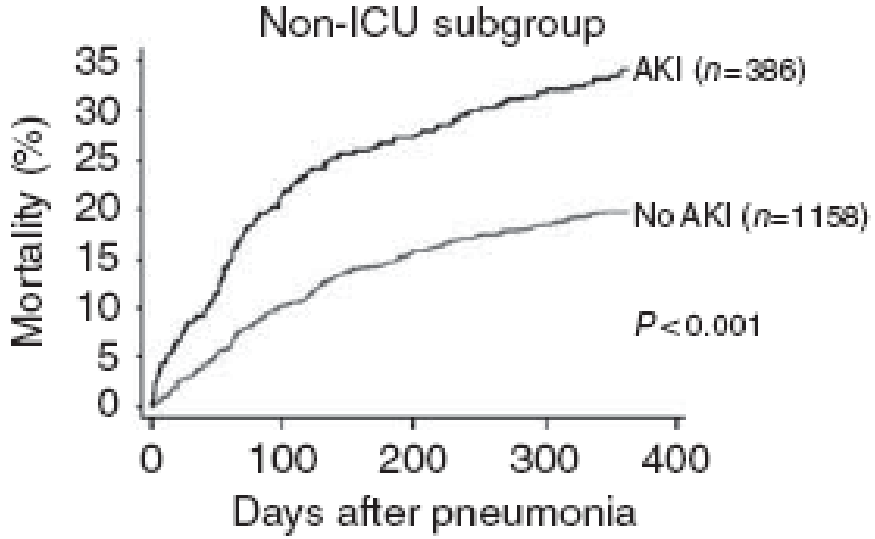


Murugan et al. Kidney Int *Mar 2010*

Not just an ICU disease

A multicenter study of pneumonia and sepsis
GenIMS
Genetic and Inflammatory Markers of Sepsis





Characteristic[a]	No. (%) AKI	No AKI	P-value
Developed severe sepsis	329 (52.1)	243 (20.1)	<0.001
Intensive care unit admission	245 (39)	47 (4)	<0.001
Mechanical ventilation	116 (18.4)	13 (1)	<0.001
Length of hospital stay, median (IQR)	8 (12–5)	5 (7–4)	<0.001
Hospital mortality	70 (11.1)	16 (1.3)	<0.001
90-day mortality	151 (24)	118 (9.8)	<0.001
1-year mortality	229 (36.3)	242 (20.1)	<0.001

Murugan et al. Kidney Int *Mar 2010*

Specific Treatment

- **Extracorporeal Kidney Support**
  - Intensity
  - Modality
  - Membranes
  - Timing (initiation and discontinuation)

The NEW ENGLAND JOURNAL of MEDICINE

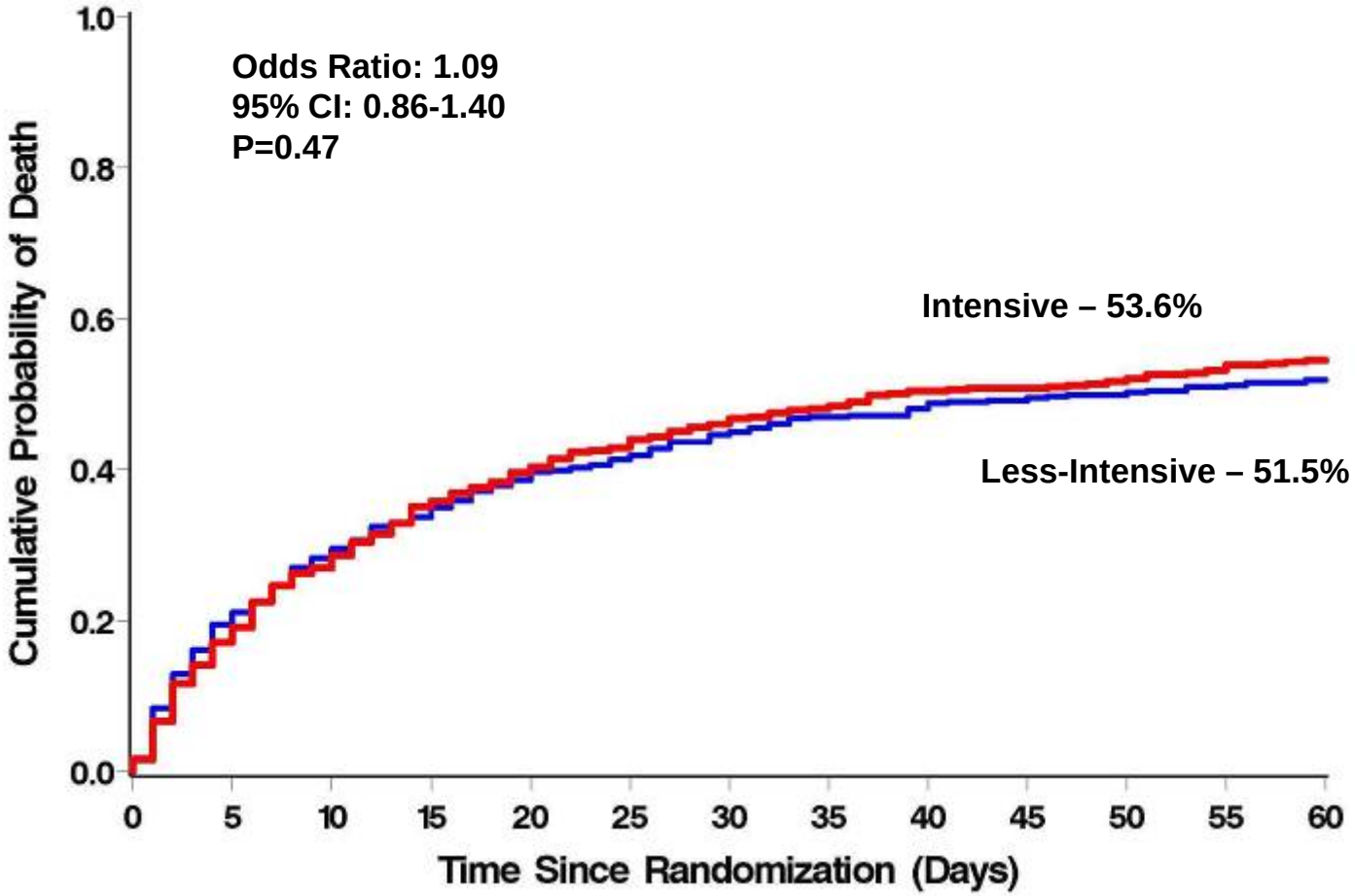
Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

This article (10.1056/NEJMoa0802639) was published at www.nejm.org on May 20, 2008.

N Engl J Med 2008;359.

60-Day All Cause Mortality

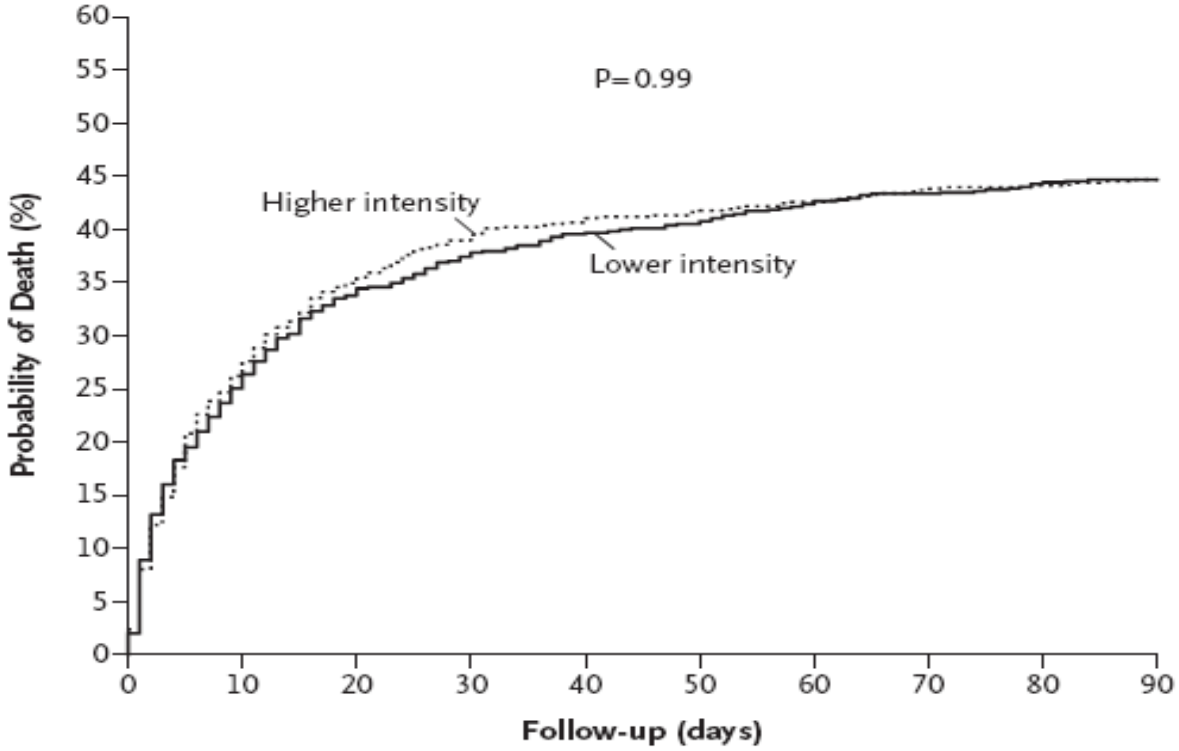


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

	Higher-Intensity CRRT	Lower-Intensity CRRT
RRT dependence among survivors		
At day 28	64/443 (14.4)	57/469 (12.2)
At day 90	27/399 (6.8)	18/411 (4.4)
ATN		
At day 28	131/275 (47.6)	134/292 (45.9)

CLINICAL CHARACTERISTICS BY RIFLEmax

	All n=5383	Non AKI N=1766	Risk n=670	Injury n=1436	Failure n=1511
Baseline characteristics					
N	100 %	32.8 %	12.4 %	26.7 %	28.1 %
Gender (male)	56.6 %	55.6 %	55.3 %	58.2 %	56.8 %
Age (yrs) *	60.5 (17.2)	56.7 (18.1)	63.3 (16.9)	62.5 (16.5)	61.7 (16.1)
APACHE III †	45 (33-59)	36 (26-47)	46 (35-57)	46 (36-59)	56 (41-74)
SOFA ‡	6.0 (4.3)	4.9 (3.6)	5.9 (4.1)	6.3 (4.3)	6.9 (4.8)
$SOFA_{non\text{-}renal}$ *	4.9 (3.7)	4.3 (3.2)	5.0 (3.6)	5.2 (3.7)	5.3 (4.0)
In-hospital before ICU admission §	34.3 %	30.1 %	36.4 %	33.0 %	39.0 %
Pre-ICU LOS ¶	2 (1-5)	1 (1-4)	2 (1-4)	2 (1-5)	2 (1-6)
Outcome:					
RRT §	4.1 %	0.1 %	0 %	0.3 %	14.2 %
LOS ICU (d) **	4 (2-10)	2.0 (2-4)	3 (2-6)	5 (3-10)	9 (4-21)
LOS Hospital (d) **	8 (4-17)	5 (3–10)	7 (4-13)	9 (5-17)	14 (7-28)
Mortality §	13.3 %	5.5 %	8.8 %	11.4 %	26.3 %

Hoste et al. Crit Care 2006;10:R73

Are we waiting too long?

- **RIFLE-F (n=1511)**
  - 14.2% received renal support
- **Mortality**
  - Overall 26.3%
  - Renal support *~50%*
  - No renal support *~23%*
  - *No AKI 5.5%*

What are the risks of renal support?

- **Bankruptcy**
- **Access and anti-coagulation**
  - <1% vascular injury/major bleeding
- **Membranes and fluids**
  - Subramanian et al. Kidney Int. 2002; 62: 1819-23
- **Hypotension**
  - Manns et al. Nephrol Dial Transplant 1997; 12: 870-872
  - Conger JD. Semin Dial 3: 146-148, 1990
- **Renal recovery**
  - HD-associated oliguria
  - Loss of renal (blood flow) auto-regulation

Conclusions

- **AKI is a disease of critical illness**
  - Sepsis is the leading cause
  - Hemodynamics are important
  - AKI leads to MOF
  - AKI is in the causal pathway for mortality
- **The care of patients with AKI needs to be improved**
  - Prevention
  - Fluid/electrolyte/nutrition management
  - Renal support
    - Timing
    - Intensity
    - Modality
- **Patients with AKI are often not…**
  - Going to ICU
  - Receiving renal support

…justifiably?