Disclosures

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Acute Kidney Injury: **EPIDEMIOLOGY**

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Outline

- Defining AKI
- Basic epidemiologic features
- Recent notable findings from the literature
- Controversies

Case overview: Ms. B

- Maintenance hemodialysis patient of mine this summer
- 80 year old woman, baseline SCr 1.4, admitted from nursing home in March 2009 for fever, abdominal pain
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Case overview

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Case overview

- **Pre-renal azotemia after admission**

  Is this *acute kidney injury? What is the definition?*

- **Laparoscopic cholecystectomy complicated by intraoperative hypotension, AKI**

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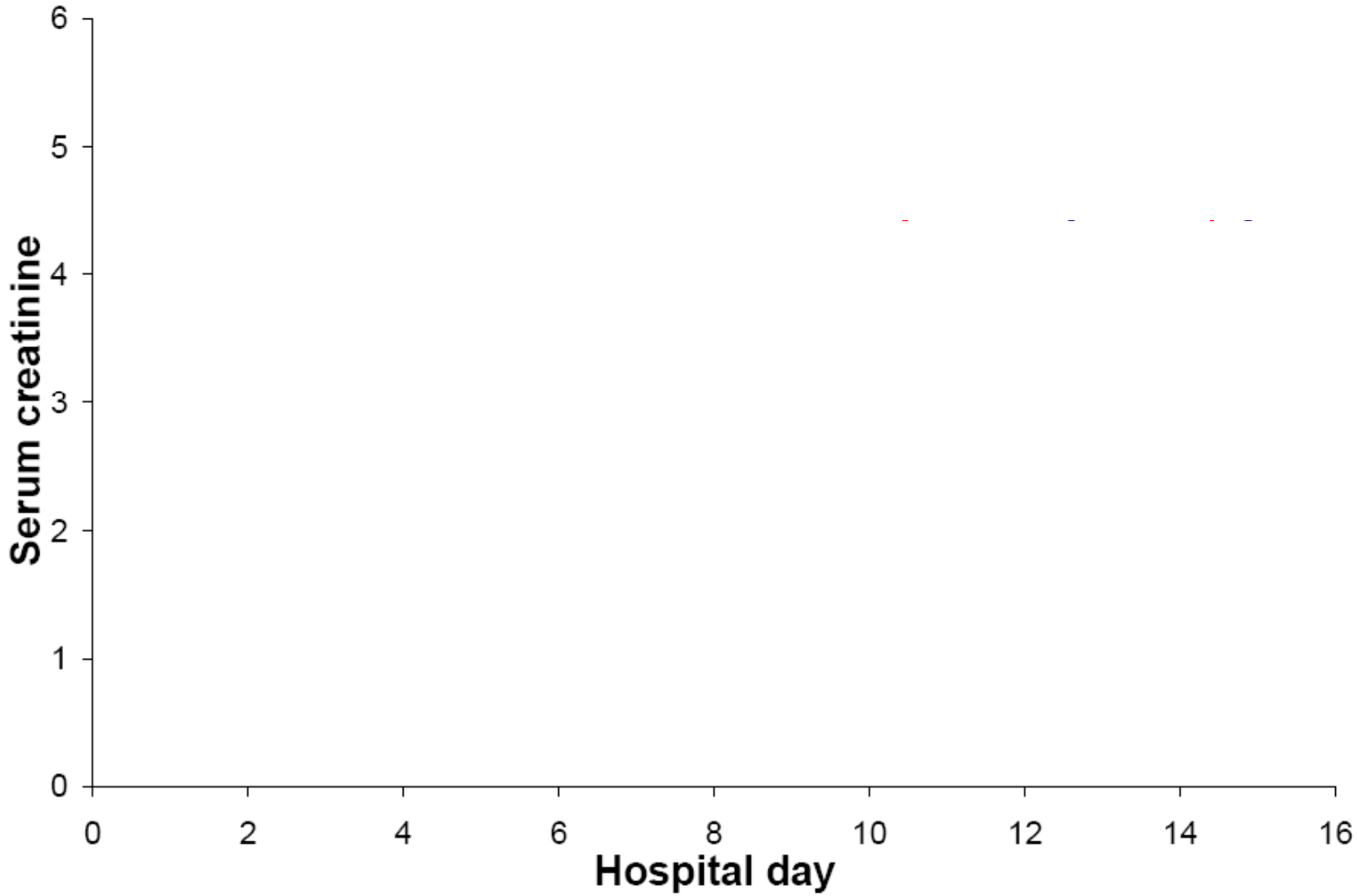
Ms. B's change in SCr



Definition: why does it matter

- Estimating incidence
- Informing patients of their disease, prognosis
- Validation of new biomarkers
- Design of interventional trials

Defining AKI

> 0.3 mg/dL increase

50% increase within 48h

0.5 mg/dL if < 1.9

1.0 mg/dL if 2.0 – 4.9

1.5 mg/dL if > 4.9

1.0 mg/dL increase within 48h

"Sudden" rise of > 2.0 mg/dL

25% increase to at least 2.0 mg/dL within 48h

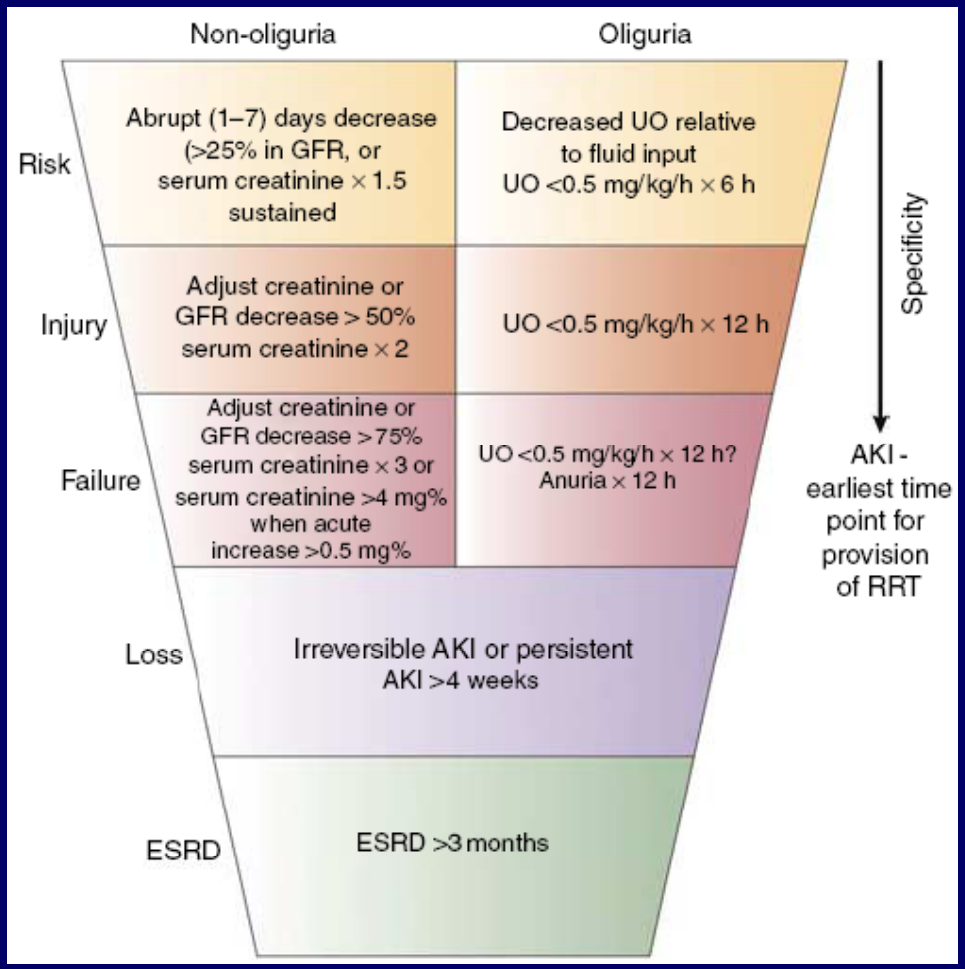
50% increase to at least 1.4 mg/dL

50% increase to at least 2.0 mg/dL

Defining AKI

New proposed definitions

"RIFLE criteria"



Reviewed by Himmelfarb *Kidney Int* 2007

New proposed definitions

AKIN proposed criteria

Stage 1

SCr increase 0.3 or 50%

UO: < 0.5ml/kg/h for > 6h

Stage 2

SCr doubling

UO: < 0.5ml/kg/h for > 12h

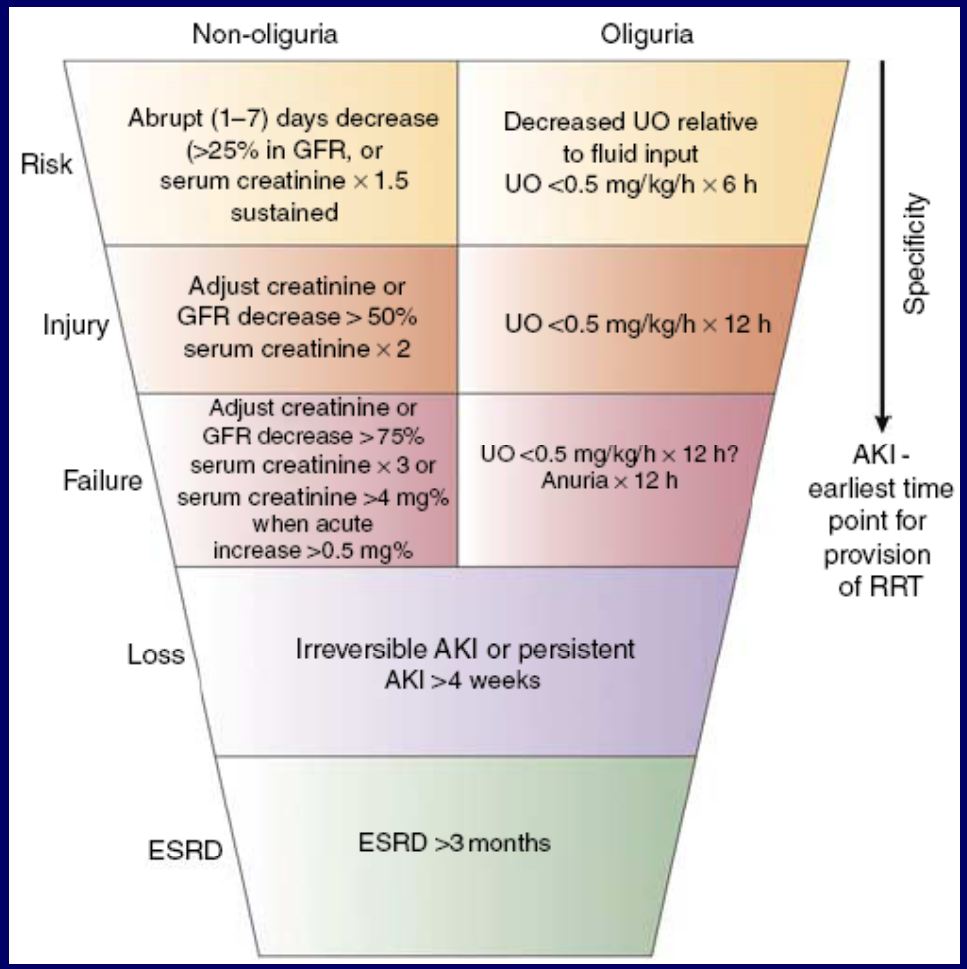
Stage 3

SCr tripling, acute rise 0.5

UO: < 0.3ml/kg/h for > 24h or anuria x 12h

Molitoris *JASN* 2007

"RIFLE criteria"



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New proposed definition

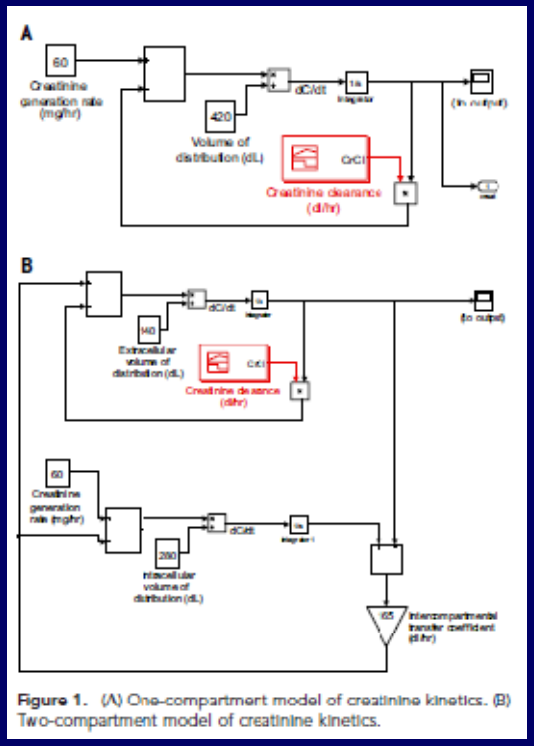


Figure 1. (A) One-compartment model of creatinine kinetics. (B) Two-compartment model of creatinine kinetics.

Stage 1

0.3 mg/dL within 24h

0.5 mg/dL within 48h

Stage 2

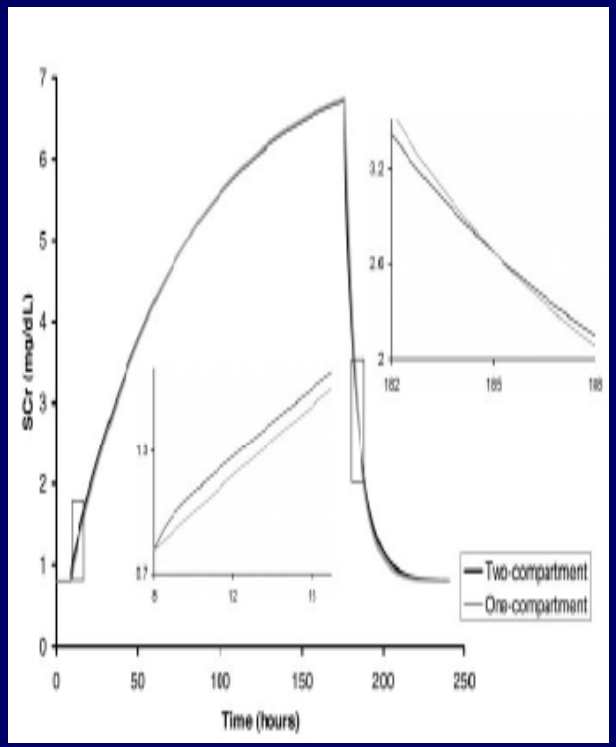
0.5 mg/dL within 24h

1.0 mg/dL within 48h

Stage 3

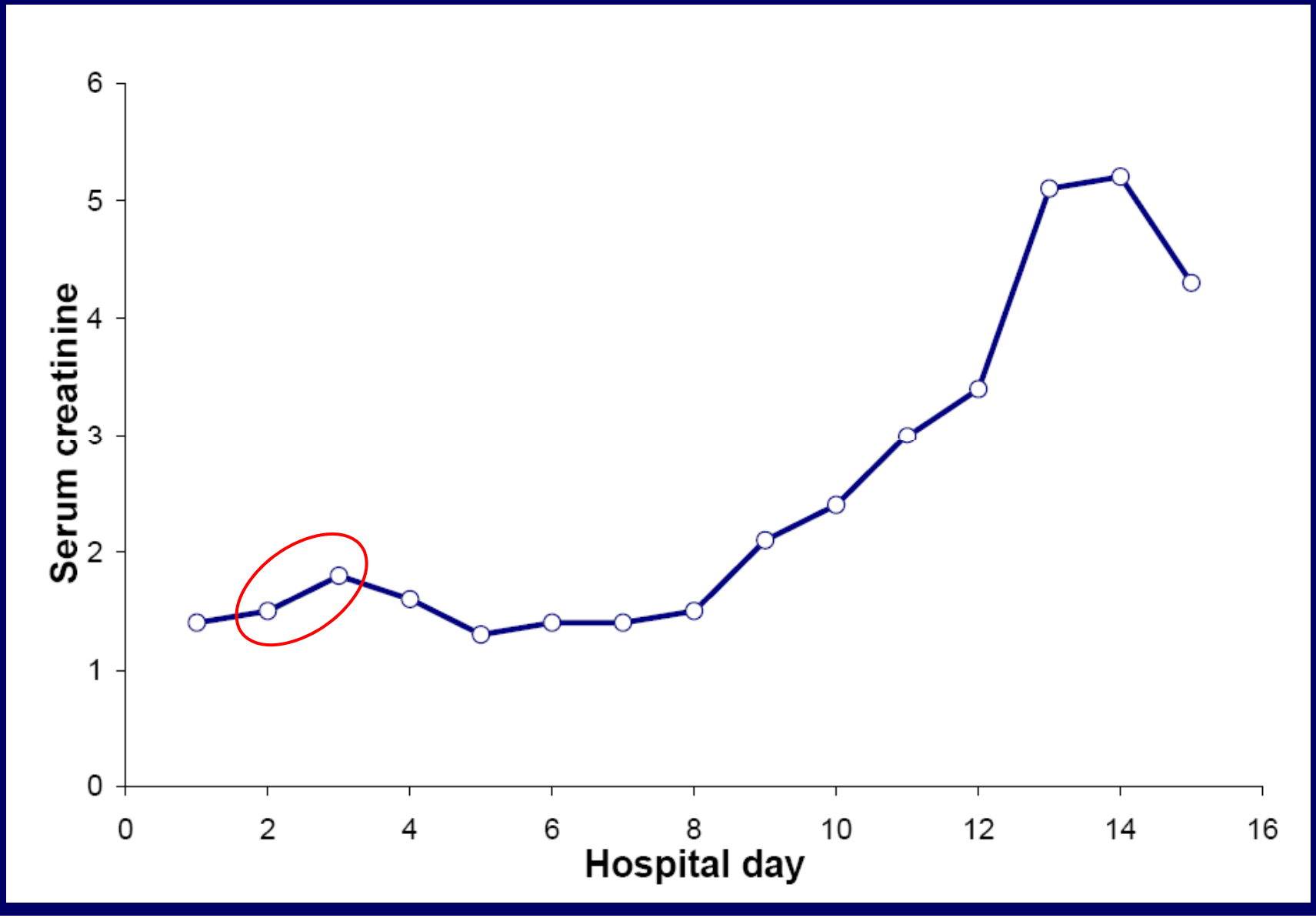
1.0 mg/dL within 24h

1.5 mg/dL within 48h



Waikar & Bonventre, *Creatinine Kinetics and the Definition of AKI,* J Am Soc Nephrol 2009

Ms. B's change in SCr



Studies validating small ΔSCr

- Chertow et al. *JASN* 2005
  - Rise of 0.3 to 0.4: *70% increased risk of death*
- Ricci et al. *Kidney Int* 2008
  - Meta-analysis of 13 studies, 71,000 pts
    - RIFLE "R" (50% increase) = ↑ risk of death
- Lopes et al. *Critical Care* 2008
  - ICU patients
    - AKIN stage 1 (0.3 increase) = 3-fold ↑ risk of death

Definition of AKI

- New focus on smaller changes in SCr
- 0.3 mg/dL rise in SCr
  - ? Time frame
- Controversies?

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Risk factors for AKI

What's been known

Age

Diabetes mellitus

Congestive heart failure

Elevated baseline SCr

Liver disease

Major risk factor: *CKD*

- Well established, intuitive, but incompletely studied

Impact of baseline kidney function

	Cases of AKI-D (N = 1764)	Controls (N = 600,820)
SCr	2.42	1.05
eGFR	43.5	74.2

75% had CKD stage 3 or higher

CKD and AKI summary

- The *dominant* risk factor for AKI is CKD
- Future studies in AKI therapeutics need to enroll CKD patients
- Definitions of AKI need to account for CKD
- Care of the CKD patient

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AKI following general surgery

- Risks for cardiac surgery, cardiac catheterization, sepsis, ICU reasonably well studied

AKI following general surgery

Predictors of Postoperative Acute Renal Failure after Noncardiac Surgery in Patients with Previously Normal Renal Function

Anesthesiology 2007

Sachin Kheterpal, M.D., M.B.A., Kevin K. Tremper, Ph.D., M.D.,† Michael J. Englesbe, M.D.,‡ Michael O'Reilly, M.D.,§ Amy M. Shanks, M.S.,| Douglas M. Fetterman, M.D.,* Andrew L. Rosenberg, M.D.,# Richard D. Swartz, M.D.***

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- > 65,000 general surgery cases ’03 - ’06
- Integrated electronic medical record
  - Including intraop hemodynamics, pressors
- N = 15,102 with preop CrCl > 80
- AKI definition: CrCl < 50 within 7d postop

AKI following general surgery

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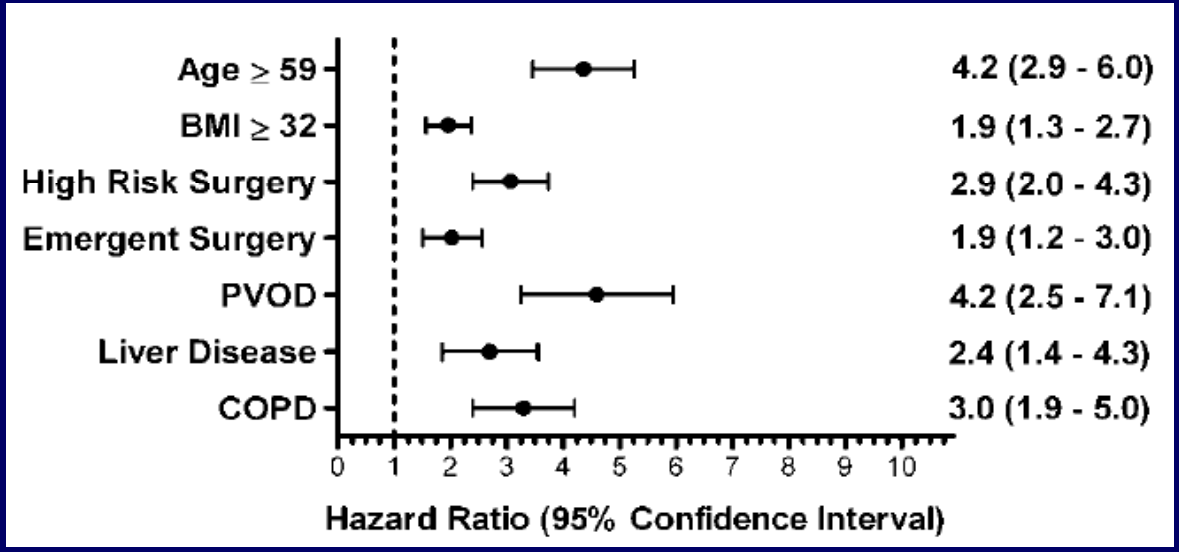
- Incidence 0.8%; AKI-D incidence 0.1%
  - Definition ~ AKIN stage 1 or RIFLE "R"
  - Substantially lower than cardiac surgery (>30%)



Intraoperative

- Vasopressor
- Diuretics

AKI following general surgery

Development and Validation of an Acute Kidney Injury Risk Index for Patients Undergoing General Surgery

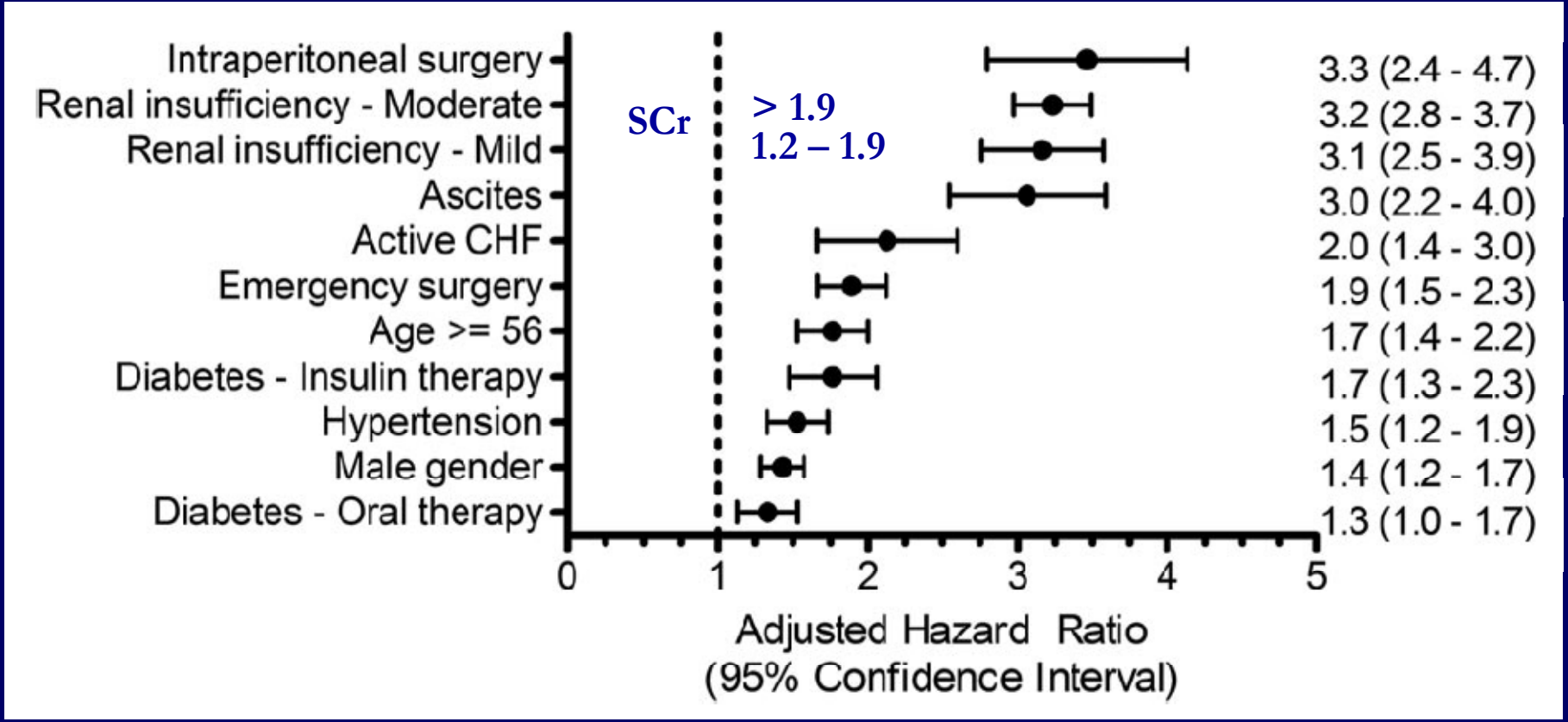
Results from a National Data Set Anesthesiology 2009

Sachin Kheterpal, M.D., M.B.A., Kevin K. Tremper, Ph.D., M.D.,† Michael Heung M.D.,‡ Andrew L. Rosenberg, M.D.,* Michael Englesbe, M.D.,§ Amy M. Shanks, M.S.,‖ Darrell A. Campbell, Jr., M.D.#*

- American College of Surgeons –National Surgical Quality Improvement Program
- Data collection from > 100 hospitals, 75,952 general surgery cases
- “Progressive renal insufficiency” [> 2 mg/dL rise]
- “Acute renal failure necessitating dialysis”

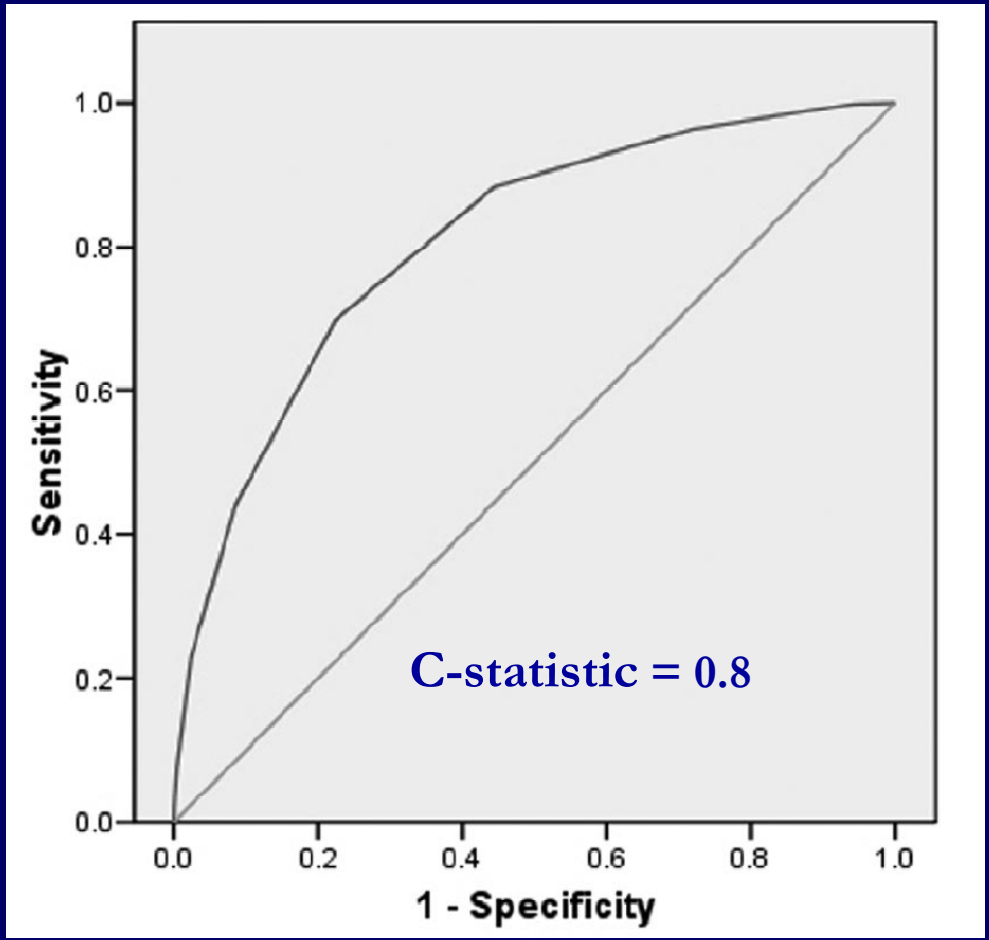
AKI following general surgery

- Incidence 1.0% [using strict AKI criteria comparable to RIFLE I or F]



Kheterpal et al. Anesthesiology 2009

AKI following general surgery



- Age ≥ 56
- Male sex
- CHF
- Ascites
- Hypertension
- Emergency surgery
- Intraperitoneal surgery
- SCr > 1.2
- Diabetes

Kheterpal et al. Anesthesiology 2009

AKI following general surgery

Summary:

- Incidence of significant AKI ~ 1%
- Similar risk factors to cardiac surgery
- *Intraperitoneal* operations
- Risk score for preop stratification, design of renal interventional/biomarker studies

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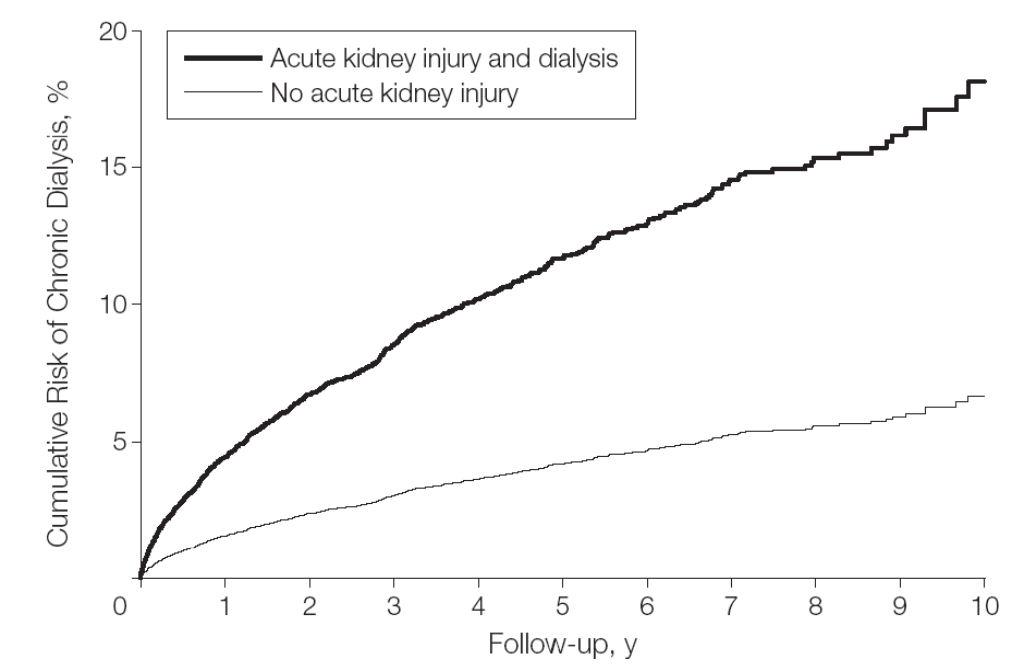
Chronic on acute renal failure

- AKI is a risk factor for renal function decline



Individuals with AKI-D who survived AND recovered renal function following hospitalization

Lo et al. Kidney Int 2009

- 10% risk of ESRD after recovery

Ishani et al. JASN 2009

- 72-fold higher risk than general population
- May account for 3% of ESRD

Amdur et al. Kidney Int 2009

Wald et al. *JAMA* 2009

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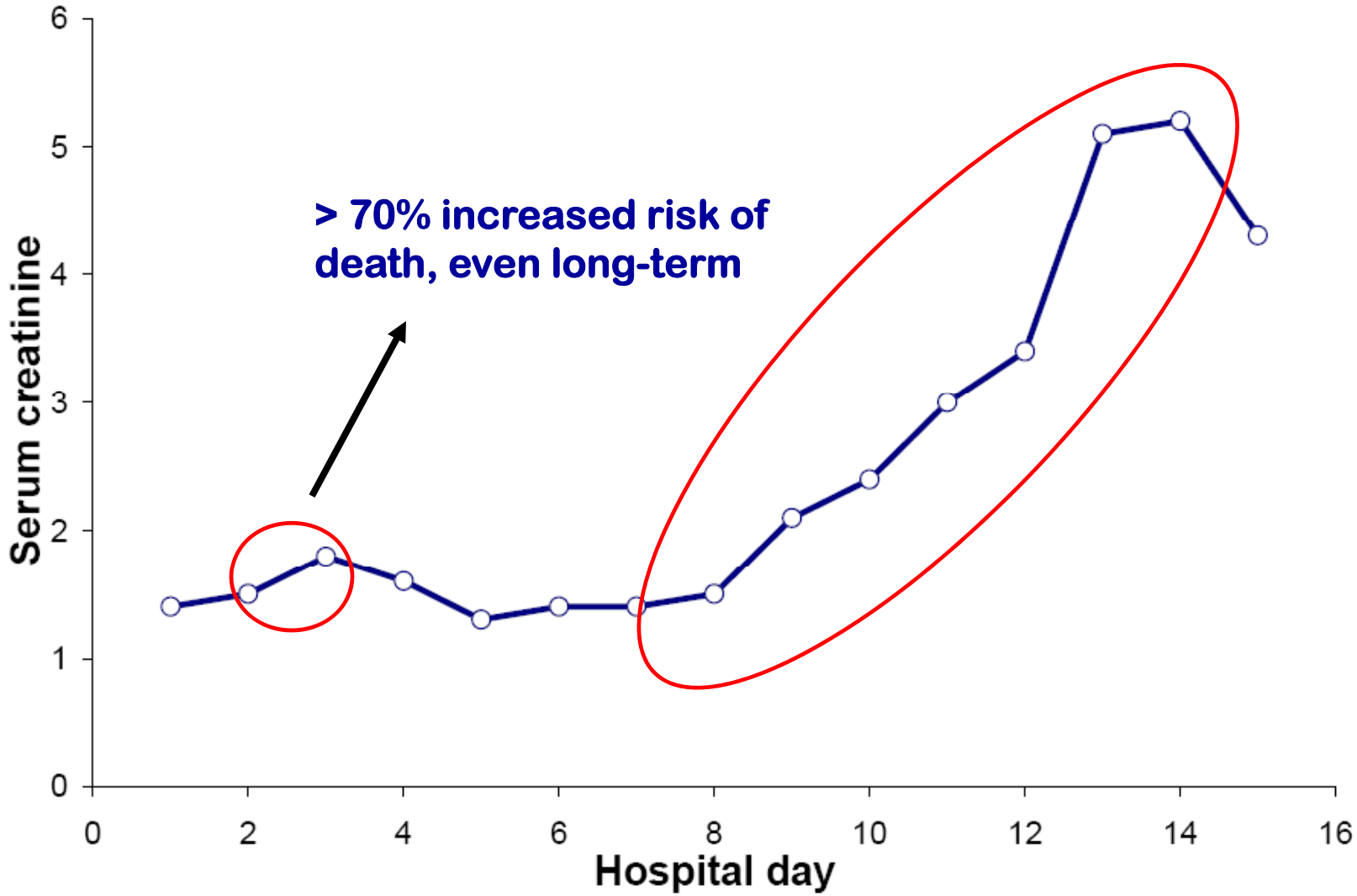
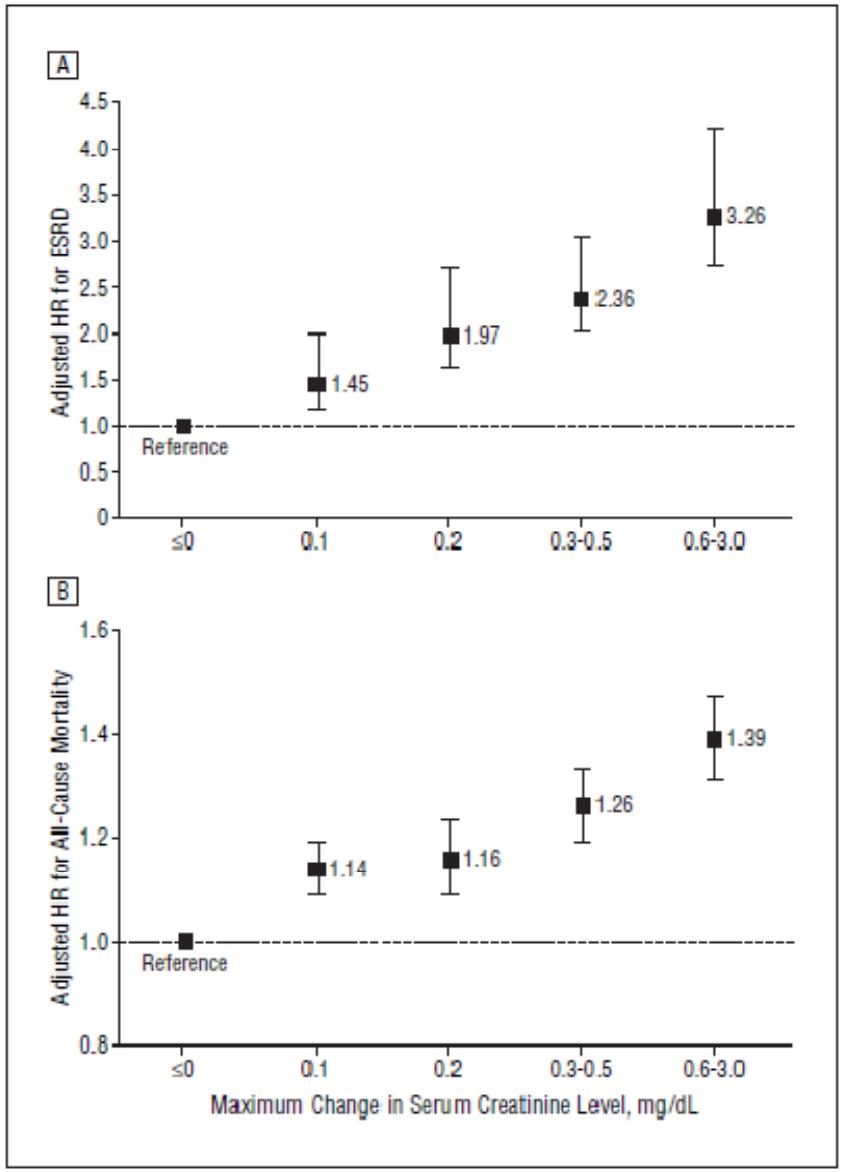


“Validating” an AKI definition

- Is demonstration of an *association* with *death* sufficient to justify a *definition*?
- Rise of 0.3 mg/dL → Increased risk of death
  - But is that enough to DEFINE acute kidney injury

Reductio ad absurdum?

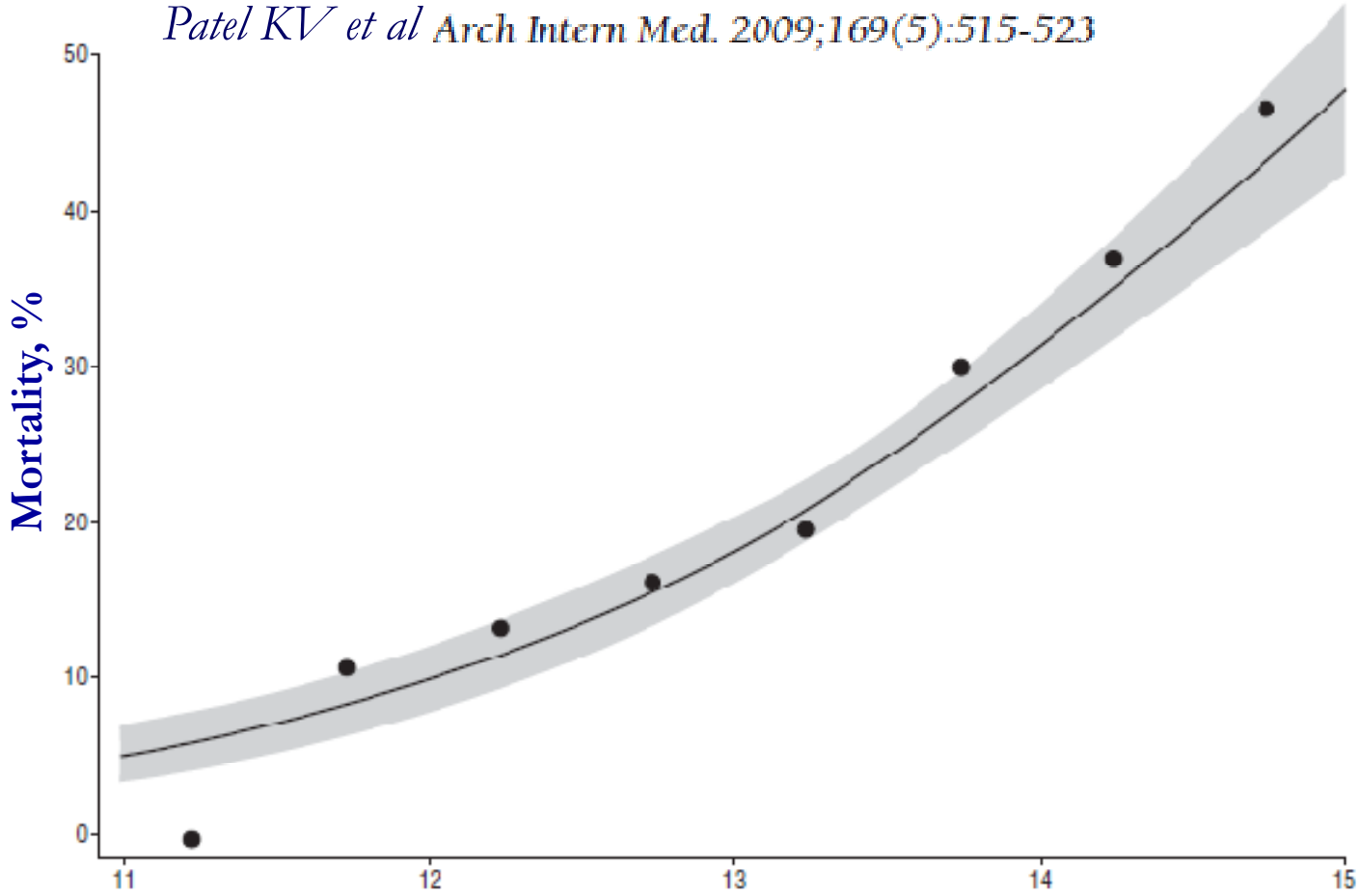


AKI =

any change in SCr?

Newsome BB, Arch Int Med 2009

Perils of relying on epidemiologic associations



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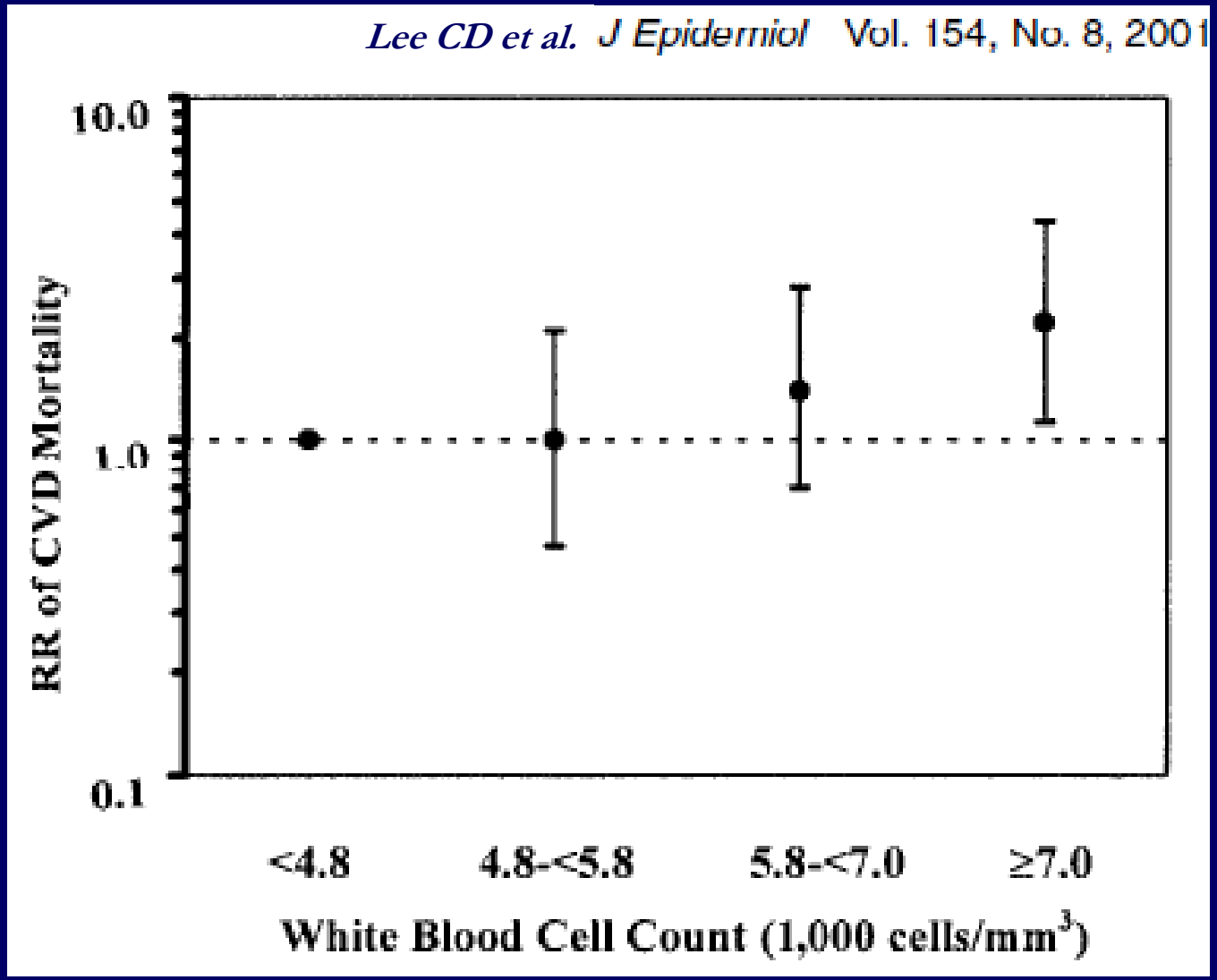

Reasons for skepticism

- Face validity: is a 0.3 mg/dL increase really AKI?
- In CKD, trivial changes in volume status may cause bumps in creatinine
- Imperfect gold standard bias
  - If we use 0.3 as the definition for AKI, we may suffer unintended consequences:
    - Novel injury bimoarkers may appear poorly diagnostic if the gold standard (SCr) is not identifying real injury
    - Interventional studies may be misguided

Disadvantages to expanding "AKI"

- Interventional studies
  - Will preventing a 0.3 mg/dL rise mean anything clinically? *Will it fool the FDA?*
- Makes incidence estimates exquisitively sensitive to definition of "baseline"
- Biomarker studies
  - The imperfect gold standard bias

Imperfect gold standard bias

- If SCr has less than 100% sensitivity and specificity for “true” AKI…

The apparent performance of any biomarker under investigation will be affected

Serum creatinine	New “perfect” marker
sensitivity= 90%	sensitivity= **69%**
specificity= 90%	specificity= **79%**

Summary

- AKI is common, costly, and deadly
- CKD is a major risk factor AND complication
- Definition for eventual interventional studies still a work in progress