

The Prognostic Importance of a Small Acute Decrement in Kidney Function in Hospitalized Patients: A Systematic Review and Meta-Analysis

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Background: Recently, acute kidney injury defined by small changes in serum creatinine levels was associated with worse short-term outcomes; however, the precision and variability of this association was not fully explored.

Study Design: Systematic review and meta-analysis.

Setting & Participants: Hospitalized patients.

Selection Criteria for Studies: MEDLINE and EMBASE databases were searched for observational cohort studies and randomized controlled trials published from 1990 through February 2007 that provided information for small changes in serum creatinine levels.

Predictor: Small acute changes in serum creatinine levels by absolute and percentage of changes in serum creatinine levels (lower threshold for increase in serum creatinine <0.5 mg/dL or <25%).

Outcome: Short-term mortality (≤ 30 days).

Results: Compared with controls, patients with a 10% to 24% increase in creatinine levels had a relative risk (RR) of death of 1.8 (95% confidence interval [CI], 1.3 to 2.5). By comparison, subjects with a 25% to 49% acute change in creatinine levels had an RR of death of 3.0 (95% CI, 1.6 to 5.8), and those with the largest change ($\geq 50\%$) had the greatest RR of death (RR, 6.9; 95% CI, 2.0 to 24.5). Results were similar when absolute changes in creatinine levels were considered and when pooled estimates of adjusted RR were used.

Limitations: Individual patient data were unavailable; thus, only group-level data were pooled for meta-analysis. Results showed a significant degree of statistical heterogeneity that was only partially ameliorated by separating studies into subsets based on clinical setting.

Conclusions: Short-term mortality and acute decreases in renal function are associated through a graded relationship such that even mild changes in serum creatinine levels portend worse outcome in a variety of clinical settings and patient-types.

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INDEX WORDS: Kidney failure, acute; heart failure, congestive; thoracic surgery; critical illness.

Acute kidney injury (AKI), defined in terms of large increases in serum creatinine levels or the need for dialysis therapy, was associated with a marked increase in mortality across several clinical settings.¹⁻⁷ However, recent publications suggested that even small increases in se-

rum creatinine levels may be associated with increased risk of death.⁸⁻¹⁴ Unfortunately, the serum creatinine threshold at which the risk of death increased varied in the literature. Although several studies described a lower threshold for the smallest clinically important increase in serum creatinine levels, the majority did not include an upper threshold in their analysis (eg, AKI defined as serum creatinine level increase > 0.3 mg/dL [$>26 \mu\text{mol/L}$] or >0.5 mg/dL [$>44 \mu\text{mol/L}$]).^{8,13,14} Although this approach does not invalidate the prognostic value of the lower threshold in itself, it obscures the nature of the relationship between change in creatinine level and risk of adverse outcomes. The relationship could be evident at a certain threshold or could be graded or continuously associated.

We performed a systematic review and meta-analysis of all studies published on the prognosis associated with small acute decreases in kidney function. We define “small” as any change be-

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yond that expected by normal variations in laboratory measurements. The objective is to determine the nature of the relationship between various definitions of worsening kidney function and short-term mortality. Finally, we aim to determine whether the association between small changes in renal function and mortality transcends different patient types (eg, cardiac surgical patients, those with congestive heart failure or sepsis).

METHODS

Studies Eligible for Review

Studies were eligible if they provided information about small changes in serum creatinine levels during hospitalization (ie, lower threshold for increase in serum creatinine <0.5 mg/dL [<44 $\mu\text{mol/L}$] or $<25\%$), provided data for short-term mortality (≤ 30 days), and provided comparison data for outcomes for a contemporaneous control group that did not have a change in renal function. Observational cohort studies, including observational comparisons of randomized controlled clinical trials, were included. We excluded studies that analyzed only mortality associated with larger changes in creatinine levels (≥ 0.5 mg/dL [≥ 44 $\mu\text{mol/L}$] or $\geq 25\%$).

Finding Relevant Studies

We performed a systematic search of the MEDLINE and EMBASE bibliographic databases from 1990 through February 2007 to identify published studies evaluating the mortality associated with small acute decreases in renal function. Search strategies combined the medical subject headings (MeSH) terms “kidney failure, acute” or “creatinine blood level” (“creatinine” used instead of “creatinine blood level” as MeSH term for MEDLINE) combined with prognosis (specificity) limited to “humans,” “article” (“journal article” for MEDLINE), and “adult or aged” (“adult” or “middle aged” or “aged” for MEDLINE). We identified potentially relevant studies by using a manual search of references from all eligible studies, review articles, and Science Citation Index Expanded on the Web of Science and searching the top 50 citations for each report through the “related articles” feature of PubMed. Pairs of reviewers independently evaluated the eligibility of each citation, and the full-text article was retrieved if either reviewer considered the citation potentially relevant. Pairs of reviewers independently evaluated the eligibility of the full-text article, with disagreements resolved by a third reviewer.

Quality Assessment

Two independent reviewers assessed study quality according to the guidelines outlined by Hayden et al.¹⁵ We assessed whether each study showed the following 6 characteristics: (1) study sample represented the population of interest, (2) loss to follow-up was not associated with key characteristics and was minimized sufficiently to limit potential bias, (3) the prognostic factor of interest was adequately measured in

study participants to sufficiently limit potential bias, (4) outcomes of interest were adequately measured in study participants, (5) important potential confounders were appropriately accounted for, and (6) statistical analysis was appropriate for design of study. Studies were graded as good quality if they met 5 to 6 criteria, fair if they met 3 to 4 criteria, and poor if they met 2 or fewer criteria.

Data Abstraction Including Renal Function

We abstracted study characteristics, type of patient population and clinical setting, and results from each selected article. One author (S.G.C.) abstracted and a second author (C.R.P.) confirmed these data. Because heterogeneous definitions of AKI were used in the published studies, we contacted the primary investigators, asked them to recategorize the data to meet our definitions of AKI, and obtained raw-group data in 2×2 table format. Definitions were categorized in 2 ways: by percentage of change in serum creatinine levels and by absolute change in serum creatinine levels. Three different gradients for both percentage and absolute decreases in renal function were chosen a priori as definitions for our study. Mild AKI was defined as a change in serum creatinine level of 10% to 24% or 0.3 to 0.4 mg/dL (26 to 35 $\mu\text{mol/L}$). We chose these thresholds because changes greater than 10% or greater than 0.3 mg/dL (>26 $\mu\text{mol/L}$) were just beyond the range of laboratory variation in the measurement of serum creatinine. Moderate AKI was defined as a change in serum creatinine level of 25% to 49% or 0.5 to 0.9 mg/dL (44 to 80 $\mu\text{mol/L}$). Severe AKI was defined as a change in serum creatinine level of 50% or greater or 1.0 mg/dL or greater (≥ 88 $\mu\text{mol/L}$).

Outcome Measures

The primary outcome was unadjusted short-term mortality. The secondary outcome was relative risk (RR) for short-term mortality adjusted for other prognostic factors.

Statistical Analysis

We assessed the mortality observed in patients with increases in serum creatinine levels versus those who had no increases in creatinine levels in stratified 2×2 contingency tables. Six pooled comparisons were made comparing the mortality associated with each stepwise increase in absolute or percentage of change in serum creatinine levels to the referent groups (10% to 24%, 24% to 49%, $\geq 50\%$ change versus $<10\%$ change and 0.3- to 0.4-mg/dL [26- to 35- $\mu\text{mol/L}$], 0.5- to 0.9-mg/dL [44- to 80- $\mu\text{mol/L}$], ≥ 1.0 -mg/dL [≥ 88 - $\mu\text{mol/L}$] change versus <0.3 -mg/dL [<26 - $\mu\text{mol/L}$] change). For this study-level meta-analysis, the Q statistic was used to determine whether between-study heterogeneity was present, with P less than 0.1 considered statistically significant. The I^2 statistic was used to quantify the magnitude of heterogeneity, with values of 0% to 30%, 31% to 50%, and greater than 50% representing mild, moderate, and notable heterogeneity, respectively.¹⁶ Overall results were mathematically pooled using techniques that accounted for within- and between-study heterogeneity (random effects method of DerSimonian and Laird¹⁷). Data were analyzed using the software program Comprehensive Meta Analysis 1.0.25 (Englewood, NJ).

RESULTS

A quality of reporting of meta-analyses flow diagram illustrates the process of identifying and selecting articles (Fig 1). Of 2,339 citations originally identified using our search strategy, 9 studies met our inclusion criteria.^{8,9,11,12,18-22} Seven^{8,9,11,12,18,19,22} of the 9 primary investigators of these studies replied to our request for reanalysis of raw data. In addition, we were able to use data from 1 study²⁰ from an investigator who did not reply to our request because the definitions of AKI used in the report were identical to ours.

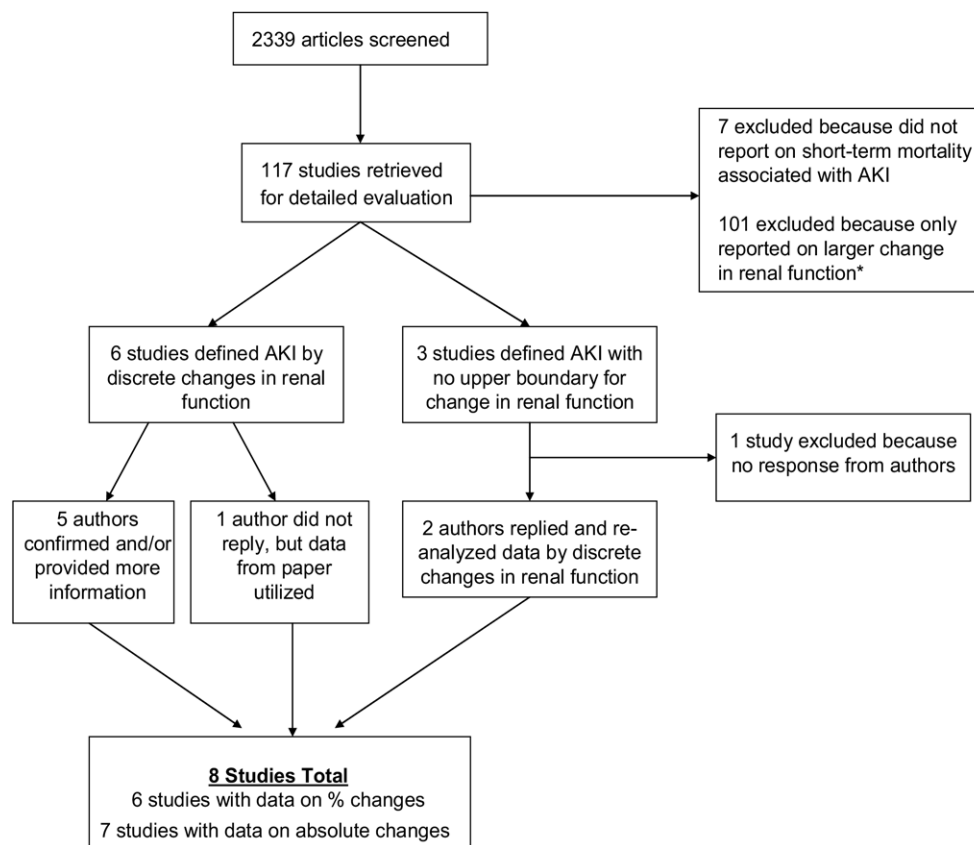
Characteristics of Study Populations

There were 78,855 participants in the 8 studies (Table 1). Seven of the 8 studies were of good method quality (Table 1). Study populations and clinical settings were heterogeneous. Two studies

were conducted in patients after cardiac surgery,^{11,12} 2 studies were conducted in patients admitted for acute decompensated congestive heart failure,^{8,18} 2 studies were of acutely ill patients in the intensive care unit,^{19,20} 1 study was of patients who underwent coronary angiography,²² and 1 study consisted of a broad range of hospitalized patients.⁹ Six were single-center studies. Mean participant age ranged from 53 to 72 years. Three studies were prospective cohort studies,^{8,11,20} 4 studies were retrospective studies of databases or hospital charts,^{9,12,18,22} and 1 study¹⁹ used data combined from 2 randomized controlled trials.^{23,24}

Percentages of Change in Creatinine Versus No Change

There was significant statistical heterogeneity among the primary studies of the risk of short-term mortality associated with mild AKI (10% to



* Change in serum creatinine $\geq 25\%$ or ≥ 0.5 mg/dl (≥ 44 $\mu\text{mol/L}$)

Figure 1. Flow diagram for study selection. Abbreviation: AKI, acute kidney injury.

Table 1. Characteristics of Selected Studies

| Reference | Patient Type | No. of Centers | No. of Patients | Study Type | Increased Serum Creatinine at Baseline (%) | Definition of AKI in Original Publication (change in creatinine) | Referent Group (change in creatinine) | Timing (ascertainment of AKI) | No. of Creatinine Measurements | Length of Follow-up and Cumulative Incidence of Death | Study Quality |
|------------------------------|----------------------|----------------|-----------------|------------|--|--|---------------------------------------|---------------------------------|--|---|---------------|
| Chertow et al ⁹ | Hospitalized | 1 | 9,205 | R | N/A | 0.3 to 0.4 mg/dL; $\geq 25\%$ | ≤ 0.2 mg/dL; $< 25\%$ | Within entire admission | ≥ 2 -9,205 ≥ 3 -7,166 ≥ 4 -5,780 ≥ 5 -4,682 | In hospital 3.1% | Good |
| Forman et al ¹⁸ | CHF | 11 | 1,004 | R | 35.7% (≥ 1.5 mg/dL) | ≥ 0.4 mg/dL | ≤ 0.3 mg/dL | Within entire admission | ≥ 2 | In hospital 2.6% | Good |
| Lassnigg et al ¹¹ | Post-cardiac surgery | 1 | 4,118 | P | 18% (≥ 1.3 mg/dL) | 0.1 to 0.4 mg/dL | -0.3 to 0 mg/dL | Within 48 h of admission to ICU | ≥ 2 | 30 d 5.2% | Good |
| Levy et al ¹⁹ | ICU (severe sepsis) | 236 | 1,036 | RCT* | 60% (≥ 1.2 mg/dL) | 0.1 mg/dL† | Various | Within 24 h of admission to ICU | 2 | 28 d 31.2% | Good |
| Samuels et al ²⁰ | ICU | 1 | 3,795 | P | N/A | 10% to 24% | $< 10\%$ change | Within entire admission | ≥ 2 | In hospital 17.2% | Fair‡ |
| Smith et al ⁸ | CHF | 1 | 412 | P | 25% (> 2.0 mg/dL) | ≥ 0.1 mg/dL§ | Various | Within admission | ≥ 2 | 30 d 15.3% | Good |
| Thakar et al ¹² | Post-cardiac surgery | 1 | 31,677 | R | N/A | 10% to 24%¶ | $< 10\%$ change | Immediate postoperative period | ≥ 2 | In hospital 2.2% | Good |
| Weisbord et al ²² | PCI | 1 | 27,608 | R | 3.2% | 0.25 to 0.5 mg/dL | < 0.25 mg/dL change | Within 3 d of angiography | 2-10,639 3-6,500 4-4,908 | 30 d 1.5% | Good |

Note: To convert serum creatinine in mg/dL to $\mu\text{mol/L}$, multiply by 88.4.

Abbreviations: R, retrospective cohort; P, prospective cohort; RCT, randomized controlled trial; AKI, acute kidney injury; CHF, congestive heart failure; ICU, intensive care unit; PCI, percutaneous coronary intervention; N/A, not available.

*Publication was an analysis of data from 2 randomized controlled trials.

†AKI was defined in several different ways (refer to²² for details).

‡Unable to assess 2 parameters of quality: loss to follow-up and appropriate statistical analysis. One quality parameter was clearly deficient: adjustment for potential confounders.

§Various definitions for AKI starting at creatinine level change of 0.1 mg/dL or greater were analyzed. Creatinine level change of 0.3 mg/dL or greater was the lowest threshold at which increased mortality risk was recognized (19% versus 12%).

¶AKI defined by percentage of change in estimated glomerular filtration rate using the Modification of Diet in Renal Disease Study equation in original publication.

24% increase in serum creatinine; chi-square = 14.6; $P = 0.01$; $I^2 = 66\%$). However, risk estimates were statistically similar; thus, results were mathematically pooled to establish a more precise estimate of the effect. Compared with controls, subjects with mild AKI had a combined unadjusted RR of death of 1.8 (95% confidence interval [CI], 1.3 to 2.5; Fig 2).

There was significant statistical heterogeneity among the primary studies of the risk of short-term mortality from moderate AKI (25% to 49% increase in serum creatinine; chi-square = 68.9; $P < 0.001$; $I^2 = 93\%$). Although we mathematically pooled results to examine a dose-response relationship with acute decreases in kidney function, the precision of these estimates should be viewed with caution given this substantial statistical heterogeneity. Participants with moderate AKI had an unadjusted RR of death of 3.0 (95% CI, 1.6 to 5.8). Participants with the largest increases in serum creatinine levels ($\geq 50\%$) had the greatest unadjusted RR of death (6.9; 95% CI, 2.0 to 24.5), although the high degree of statistical heterogeneity (chi-square = 335.7; $P < 0.001$; $I^2 = 99\%$) limits the validity of the point estimate.

Absolute Changes in Creatinine Versus No Change

Results were similar when absolute changes in creatinine levels were considered. Compared with controls, subjects with a 0.3- to 0.4-mg/dL (26- to 35- $\mu\text{mol/L}$) increase in serum creatinine levels (mild AKI) had a combined unadjusted RR of death of 2.3 (95% CI, 1.8 to 3.0; Fig 3). Subjects with a 0.5- to 0.9-mg/dL (44- to 80- $\mu\text{mol/L}$) increase in serum creatinine levels (moderate AKI) had an unadjusted RR of death of 6.2 (95% CI, 3.2 to 11.7), and those with the largest absolute increases (≥ 1.0 mg/dL [≥ 88 $\mu\text{mol/L}$]) had the greatest unadjusted RR of death (12.4; 95% CI, 4.0 to 38.5). Although there was evidence of a moderate degree of heterogeneity (chi-square = 13.2; $P = 0.04$; $I^2 = 55\%$) for mild AKI, significant heterogeneity also was present for both moderate and severe AKI (chi-square = 92.8; $P < 0.001$; $I^2 = 94\%$; chi-square = 350; $P < 0.001$; $I^2 = 98\%$, respectively).

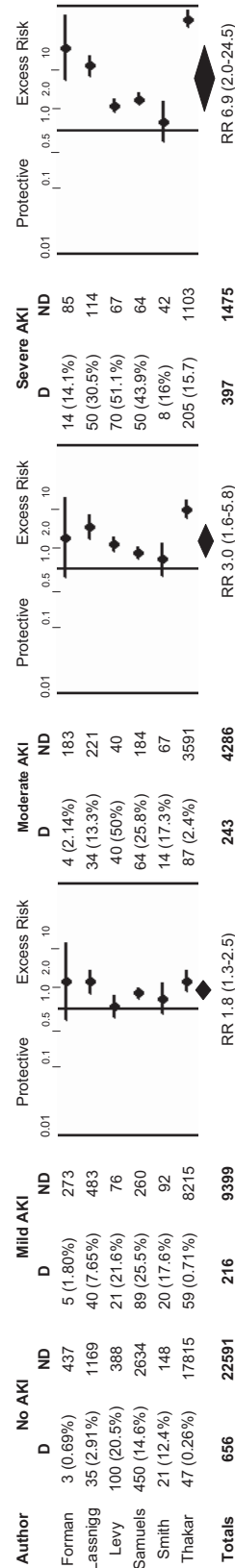


Figure 2. Combined short-term mortality associated with acute increases in serum creatinine levels by percentage of change. Abbreviations: AKI, acute kidney injury; RR, relative risk; D, death; ND, no death.

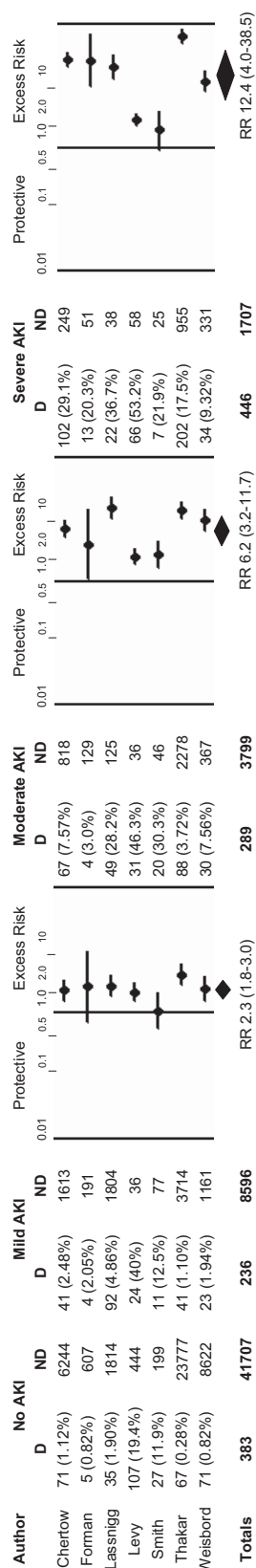


Figure 3. Combined short-term mortality associated with increases in serum creatinine levels by absolute change. Abbreviations: AKI, acute kidney injury; RR, relative risk; D, death; ND, no death.

Adjusted Mortality Risks

Four studies reported mortality risks associated with discrete changes in serum creatinine levels that were adjusted for numerous sociodemographic, clinical, and physiologic covariates.^{9,11,12,22} After adjustment, the most sensitive definition for AKI in the 4 studies was still statistically associated with greater mortality (odds or hazard ratio range, 1.70 to 1.92), with no 95% lower CI overlapping 1.

Subgroup and Sensitivity Analyses

In an effort to explore the potential causes of heterogeneity, we divided the studies into subsets based on clinical setting and reanalyzed the data by sequentially eliminating these subsets. When we reanalyzed the data after excluding the 2 studies of cardiac surgical patients,^{11,12} the degree of heterogeneity was decreased (but still present in a moderate capacity) for 3 of the 6 definitions of AKI (change in creatinine of 10% to 24%, 25% to 49%, and 0.3 to 0.4 mg/dL [26 to 35 μmol/L]). Removal of other types of studies separately (congestive heart failure, intensive care unit) did not decrease the amount of statistical heterogeneity (data not shown).

DISCUSSION

Our review indicates that even very small increases in serum creatinine levels, on the order of 10% to 24% or 0.3 to 0.4 mg/dL (26 to 35 μmol/L), are associated with approximately a 2-fold risk of short-term death (RRs, 1.8 and 2.3, respectively) across a broad spectrum of clinical settings. Furthermore, greater changes in serum creatinine levels of 25% to 49% or 0.5 to 0.9 mg/dL (44 to 80 μmol/L) are associated with a 3- to 5-fold increase in risk of death. The relatively high incidence of AKI in hospitalized patients^{9,25,26} implies that this association with death presents a significant acute health care problem that should be recognized and addressed.

These definitions of AKI involving serum creatinine level changes are much smaller than any used in the “Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease” (RIFLE) classification of AKI proposed by the Acute Dialysis Quality Initiative.²⁷ The first tier

of AKI, Risk, is defined as an increase in creatinine level greater than 50% or a decrease in glomerular filtration rate greater than 25%. The RIFLE criteria have not been widely adopted in clinical practice or research studies to date; however, a few studies showed that the RIFLE classification provided prognostic value in the setting of the intensive care unit and cardiac surgery.²⁸⁻³⁰ The thresholds we used for our definitions for AKI are smaller and connote prognostic significance; therefore, the definitions in our study likely are more sensitive than previous creatinine-based definitions of AKI.

This study hopefully will encourage clinical researchers and epidemiologists to continue to refine and develop a uniform definition for AKI. The lack of significant progress in the prevention and management of AKI can be attributed in part to the failure to identify sensitive, suitable, and uniform definitions for AKI. Several pharmacological strategies that were successful in ameliorating AKI in experimental animals³¹⁻³⁴ failed in humans.³⁵⁻³⁸ Possibly, these interventions would have been successful or novel interventions will be successful if they could be initiated at the onset of AKI, rather than waiting several days for creatinine levels to increase to thresholds that are more dependent on individual preferences of trialists, rather than a rigorously developed definition. Thus, a more sensitive definition of AKI (such as increase in serum creatinine of 10% to 24%) as identified in this meta-analysis to carry prognostic value may enhance the efficacy of future clinical trials of AKI. However, it should be noted that this highly sensitive definition will have low specificity and low positive predictive value for true AKI. Applying interventions to patient groups identified by more versus less sensitive definitions of AKI could affect the risk-benefit ratio of these interventions. Therefore, a highly sensitive creatinine-based definition of AKI (such as 10% to 24% change) could be studied in conjunction with markers of tubular injury (such as the urinary biomarkers interleukin 18, neutrophil gelatinase-associated lipocalin, or kidney injury molecule 1)³⁹⁻⁴¹ to exclude patients with prerenal or postrenal AKI.

Many questions regarding a more sensitive definition of AKI still exist. Should the definition vary depending on the clinical setting? We found that even our most sensitive definition of AKI

(10% to 24% or 0.3- to 0.4-mg/dL [26- to 35- μ mol/L] change in serum creatinine) was associated with increased risk in several clinical settings. However, we still need more data from future studies to determine whether this relationship is stable or varies across clinical settings. Second, is the timing of the increase in creatinine level (eg, early versus later during admission) important? Third, is the duration of the increase important (eg, do short-lived, but marked, increases in creatinine carry more or less risk than prolonged, but less severe, increases in severe creatinine)? Finally, will serum cystatin C or other biomarkers prove superior in terms of their sensitivity to detect varying decreases in renal function compared with serum creatinine level?^{42,43}

Our study has some limitations that should be considered. Although we performed an exhaustive search of the literature for AKI studies, publication bias cannot be ruled out. It is possible that smaller negative studies were not published. We considered formally assessing publication bias through a funnel plot; however, funnel plots cannot be interpreted reliably in the presence of marked heterogeneity.^{44,45} In addition, we were able to obtain only group data, not individual-patient data, and we pooled these group data with meta-analysis. These results confirm a gradient of risk present in several clinical settings. However, the precision of the point estimates provided in this meta-analysis should be interpreted judiciously, particularly results for patients with moderate and severe AKI, because these pooled analyses had high heterogeneity upon formal statistical testing. However, we were able to ameliorate some statistical heterogeneity from the most sensitive definitions of AKI when we excluded studies of patients undergoing cardiac surgery in our sensitivity analyses. The data may also have ascertainment bias. Sicker patients are more likely to have longer hospitalizations and thus have more blood work and assessment of renal function, increasing the probably of detecting a change in serum creatinine levels. However, most of the populations studied were sick populations and routinely had serum creatinine measured daily, along with other routine laboratory tests.

Another limitation is that only 4 studies^{9,11,12,22} provided adjusted RRs for discrete changes in

serum creatinine levels (ie, with an upper limit to the degree of change) that we could effectively pool to create an adjusted estimate of risk for small changes in creatinine levels. However, all 4 studies, involving approximately 72,000 patients, had either adjusted odds or hazard ratios that were very similarly increased (~1.7 to 1.9). Although the investigators controlled for at least 6 and up to 20 covariates in these adjusted analyses, we cannot rule out residual confounding in these individual studies.

Finally, any meta-analysis is also limited by the quality of the primary studies. Fortunately, 7 of the 8 studies were of good quality, as rated by our quality score for prognostic studies. Most primary investigators responded to our requests for additional information, allowing us to reanalyze the data in a uniform fashion.

The priorities in the effort to improve outcomes in patients with AKI are to determine both a standard and meaningful definition for AKI. A consistent definition of AKI will allow physicians to stratify risk, inform clinical decisions, communicate with colleagues, identify targets for intervention, compare results across studies, and make important advances in research. The standard definition of AKI must be associated with increased morbidity or mortality in some or all clinical settings. The definition for AKI must be sensitive so that potentially effective therapies can be applied before full-blown organ failure has developed. This meta-analysis provides an additional impetus for researchers in the AKI field to develop, implement, and validate a new, standard, meaningful, and sensitive definition for AKI, such as the definitions suggested by the studies used for this systematic review.

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