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Chronic Kidney Disease after Acute Kidney Injury: A Systematic Review and Meta-analysis

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Abstract

Acute kidney injury may increase the risk for chronic kidney disease and end-stage renal disease. In an attempt to summarize the literature and provide more compelling evidence, we conducted a systematic review comparing the risk of CKD, ESRD and death in patients with and without AKI. From electronic databases, web search engines, and bibliographies, 13 cohort studies were selected, evaluating long-term renal outcomes and non-renal outcomes in patients with AKI. The pooled incidence of CKD and ESRD were 25.8/100 person-years and 8.6 per 100 person-years, respectively. Patients with AKI had higher risks of developing CKD (pooled adjusted hazard ratio 8.8, 95% CI 3.1-25.5), ESRD (pooled adjusted HR 3.1, 95% CI 1.9-5.0) and mortality (pooled adjusted HR 2.0, 95% CI 1.3-3.1) than patients without AKI. The relationship between AKI and CKD or ESRD was graded depending on the severity of AKI and the effect size was dampened by decreased baseline glomerular filtration rate. Data were limited, but AKI was also independently associated with the risk for cardiovascular disease and congestive heart failure, but not with hospitalization for stroke or all-cause hospitalizations. Meta-regression did not identify any study level factors that were associated with the risk for CKD or ESRD. Our review identifies AKI as an independent risk factor for CKD, ESRD, and death and other important non-renal outcomes.

Introduction

The incidence of acute kidney injury (AKI) has been increasing over time.[1, 2] Concurrently, the prevalence of CKD has also been increasing.[3] AKI has long been thought of as a completely reversible syndrome. However, over the past several years, a plethora of data from experimental animals and humans has been published that indicate that AKI more than likely results in permanent kidney damage (i.e., CKD) and may also result in damage to non-renal organs.[4, 5]

Moreover, the proportion of patients surviving after AKI has also been increasing over time.[1, 6-8] Thus, if AKI indeed heightens the risk for CKD and other organ damage, then it could imply significant public health concerns in regards to the absolute number of persons developing incident CKD, progressive CKD, end-stage renal disease (ESRD), and cardiovascular events.

Non-contemporary long-term follow-up studies of AKI were plagued by lacking follow-up of non-AKI patients, which did not permit the calculation of a relative risk or hazard ratio

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for the outcome of CKD in those with versus those without AKI.[9] However, over the past few years, several studies have attempted to estimate the incidence rate and relative hazards of the development of CKD both in survivors of AKI compared to populations without AKI.

Thus, the goals of this systematic review and meta-analysis were to estimate the risk of CKD, ESRD, death, and other non-renal outcomes in persons with AKI versus those without AKI. We also sought to determine whether pre-existing renal injury (decreased baseline GFR or pre-existing proteinuria) modified these associations.

Results

We identified 618 citations meeting our search criteria. After excluding 582 citations after reviewing the abstracts, 36 articles were selected for further review (Figure 1). Reasons for exclusion are shown in Figure 1. Finally, 13 studies (from 14 articles)[10-22] were selected for inclusion into the systematic review. Study and patient characteristics from the selected articles are listed in Table 1. Eleven of the 13 studies followed more than 3000 patients and all were retrospective. One study included patients with HIV exclusively[12] and two studies included hematopoietic stem cell transplant recipients.[13, 19]

The definitions of AKI varied substantially (Table 2). Maximum length of follow-up ranged from 6 months to 75 months. All 13 studies sufficiently met the quality criteria.

Overall Analyses

The renal outcomes CKD and ESRD were calculated in person years. The pooled rate of CKD was 25.8 per 100 person years (range 3.4-72.2) and ESRD was 8.6 per 100 person years (range 0.63-28.1) (Table 2). The pooled adjusted HR for CKD for AKI vs. no AKI was 8.8 (95% CI 3.1-25.5; Figure 2a) and for ESRD was 3.1 (95% CI 1.9-5.0; Figure 2b). However, heterogeneity was very high ($I^2 > 75\%$). We were not able to reduce statistical heterogeneity to below 75% with deletion of studies from the pooled analyses.

Outcomes by Severity of AKI

The outcomes of CKD and ESRD with varying degrees of AKI were reported in 6 out of 13 studies. The risk for CKD increased in a graded fashion with mild AKI (adjusted HR 2.0, 95% CI 1.4-2.8), moderate AKI (adjusted HR 3.3, 95% CI 1.7-6.2), and severe AKI (adjusted HR 28.2, 95% CI 21.1-37.5) (Table 3). The risk for ESRD also increased in a graded fashion with the severity of AKI: mild AKI (adjusted HR 2.3, 95% CI 1.7-3.3), moderate AKI (adjusted HR 5.0, 95% CI 2.6-9.8), and severe AKI (adjusted HR 8.0, 95% CI 1.3-48.6). However, heterogeneity was still high ($I^2 > 50\%$) for all subgroup analyses except for severe AKI and risk for CKD. Thus, we removed studies one at a time until heterogeneity fell below 25%. Statistical heterogeneity was reduced to 0% for the pooled analyses of moderate and severe AKI and the outcome of CKD, and mild and moderate AKI and the outcome of ESRD. In all cases where these more homogeneous estimates were created, the point estimate did not differ significantly from the inclusive analyses in any qualitative or quantitative fashion (Supplementary Table).

Only one study stratified AKI by recovery status.[12] Choi et al. found that the adjusted risk for ESRD was not present in those with mild AKI that recovered (adjusted HR 0.9, 95% CI 0.6-1.4 vs. HR 2.2, 95% CI 1.5-3.1 in those without recovery) and was markedly attenuated in those with moderate-severe AKI that recovered (adjusted HR 2.5, 95% CI 1.3-4.7 vs. HR 10.6, 95% CI 5.0-22.6 in those without recovery).[12]

Effect Modification by Decreased Baseline GFR and Pre-existing Proteinuria before AKI

The presence of baseline decreased GFR modified the relationship between AKI and both progressive CKD and ESRD. In the 2 studies[11, 16] that reported both the risk for CKD after AKI in those with and without decreased baseline GFR, the risk of CKD was higher in patients without decreased baseline GFR (adjusted HR 38.8, 95% CI 21.9-68.7) than those with decreased baseline GFR (adjusted HR 24.4, 95% CI 15.3-38.9). Similarly, in the 3 studies[12, 17, 20] that reported both the risk for ESRD those with and without decreased baseline GFR, the risk of ESRD was higher in those with AKI and without decreased baseline GFR (adjusted HR 9.1, 95% CI 4.1-20.3) compared to those with decreased baseline GFR (adjusted HR 1.9, 95% CI 1.6-20.3; Table 3)

Two studies compared the association of AKI with either CKD[12] or ESRD[16] in patients with varying degrees of underlying baseline proteinuria. Patients with AKI who had pre-existing proteinuria (and normal baseline GFR) had higher risk of CKD (defined as doubling of creatinine or ESRD) compared to patients without any proteinuria (HR 106.9, 95% CI 76.3-149.8) compared to HR 30.0 (95% CI 24.3-37), respectively.[16] The modifying effect of pre-existing proteinuria was less robust for the outcome of ESRD alone (adjusted HR 3.7, 95% CI 2.4-5.7 with no proteinuria vs. adjusted HR 1.4, 95% CI 0.9-2.2 with proteinuria;[12] Table 3).

AKI and Mortality

The overall post-discharge pooled mortality was 24.2% (3-73.3%). The mortality rate in patients with AKI was 16.8 per 100 person years (range 0.98-43.7). The adjusted risk for death was 2.0 (95% CI 1.3-3.1) for those with AKI compared to those without AKI (Figure 3). When we eliminated the study by James et al. due to a very high risk of death for AKI vs. no AKI, the pooled adjusted HR became 1.6 (95% CI 1.3-2.1),[16] however, this did not reduce statistical heterogeneity.

AKI and Non-renal Outcomes

We also examined the association between AKI and non-renal outcomes, when available (Supplementary Table). Mild AKI was associated with increased occurrence of CHF in two studies (HR 1.4, 95% CI 1.1-1.7, I^2 = 10%) and risk of cardiovascular disease (HR 1.2, 95% CI 0.8-1.8, I^2 = 80%).[12, 23] Moderate-severe AKI was also associated with an increased risk for CHF and cardiovascular disease (HR 2.2, 95% CI 1.6-3.0 for CHF, I^2 = 0%; HR of 1.3, 95% CI 0.9-1.8, I^2 = 0% for cardiovascular disease).[12, 15] In the only study that reported these outcomes, AKI was associated with future hospitalization for AKI (mild AKI HR 2.3, 95% CI 1.7-3.0 and moderate-severe AKI 5.1, 95% CI 3.4-7.6) but was not associated with hospitalization for cerebrovascular accidents (HR 1.2; CI 0.43-3.2) or for other hospitalizations (HR 0.8, 95% CI 0.6-1.1).[23]

Meta-regression

We formally examined the relationship between 5 study level continuous variables and the risk for each of CKD and ESRD via meta-regression. Although there was a trend towards longer length of follow-up being associated with less risk for CKD, and higher proportion of females and older age being associated with greater risk for ESRD, none of the study level variables were statistically associated with the risk for the outcome.

Discussion

This is the first systematic review and meta-analysis summarizing the association of AKI with CKD and ESRD. The data suggest that patients who survive AKI have a greater risk of CKD, ESRD, and other adverse outcomes compared to patients without AKI after

adjustment for several important confounding variables. The relationship between AKI and CKD or ESRD was graded, with a greater risk associated with increasing severity of AKI. The risk for ESRD was modified by baseline GFR and the risk for CKD was modified by pre-existing proteinuria. Recovery of AKI diminished the relationship between AKI and ESRD.

These findings that AKI increases the risk for both CKD and ESRD are not surprising. However, this meta-analysis provides an opportunity to systematically estimate the associated absolute and relative risk of these outcomes after AKI. One finding that is potentially counterintuitive is that patients with normal GFR prior to AKI had a higher relative risk for the development of ESRD compared to those with AKI in the setting of decreased baseline GFR. For example, in the study by Wald et al., the absolute risk for ESRD without AKI and decreased baseline GFR was 9.8% and increased to 18.4% for those with AKI and decreased baseline GFR (approximately 2-fold higher). For those with normal baseline GFR, the absolute risks for ESRD were 4.6% and 0.4% (more than 10-fold) for those with and without AKI, respectively. While the absolute risk for ESRD was lower in those without decreased baseline GFR and AKI than those with AKI and decreased baseline GFR, the relative risk (hazard ratio) for ESRD was *greater* in those with normal GFR because of the extremely low probability (denominator) of ESRD in those without AKI or decreased baseline GFR.

The reasons why AKI would increase the risk of CKD, ESRD, and other adverse outcomes remain unknown. Data from experimental animals suggests that AKI can induce renal fibrosis, and also that it can affect other organs in a deleterious fashion, such as the lungs, heart, and liver.[4, 5, 24] Thus, despite the fact that AKI is typically reversible in nature, by the standard of serum creatinine concentrations, there may be subclinical renal and extra-renal damage that persists and mediates these outcomes.

However, despite all of the fact that all studies performed multivariable adjustments to derive the adjusted point estimates for the hazard ratios via a substantial number of demographic, physiologic and clinical variables, there still remains the possibility that the "independent relationship" between AKI and the outcomes is still biased by residual confounding due to unmeasured variables or imprecise measurement of known confounders. For example, several studies included in this systematic review[11, 14, 16, 17, 20, 22] used ICD-9 codes for ascertainment of important confounders such as CKD, diabetes, hypertension, and heart disease. Administrative codes have been shown to under-report co-morbidities.[25] Furthermore, claims provide nothing in the context of the severity of the co-morbidity (e.g., diet-controlled type 2 diabetes vs. severe type 2 diabetes requiring high doses of insulin with or without adequate glycemic control). Thus, in the absence of a randomized, controlled trial of an intervention that reduces AKI which in turn reduces the incidence of CKD, ESRD, or any other of the outcomes potentially related to AKI, then it is challenging to deduce causality with absolute confidence.

The strengths of this systematic review are the following: adequate length of follow-up in the studies (most over 2 years), all studies reported parameter estimates of the hazard ratio adjusted for confounders, four studies examined outcomes associated with differing severities of AKI. The limitations include a high-degree of statistical heterogeneity among the primary analyses which may limit the validity of the point estimates and confidence intervals. However, we were able to demonstrate stable associations when more homogeneous studies were pooled. Part of the heterogeneity was related to different definitions of AKI (and of CKD). However, the outcomes of ESRD and death are less prone to bias.

Since this review demonstrates an unequivocal association between AKI and CKD in a number of large, well-performed studies, we would encourage the medical community to focus efforts on determining whether this relationship is modifiable or simply a prognostic factor that serves as a barometer and predictor of ongoing and future risk. Only elegant studies in experimental animals and randomized trials in humans of interventions to prevent AKI prior to its occurrence or given after AKI to ameliorate the severity and duration of injury or interfere with subsequent organ injury will be able to address this question.

Methods

This study was performed in accordance with published guidelines for systematic review, analysis, and reporting for meta-analyses of observational studies.

Studies Eligible for Review

A study published from January 1985 onward was eligible for inclusion if it conducted at least 6 months of follow-up of patients after a defined episode of AKI and reported the incidence of at least 1 of the following outcomes: (1) End stage renal disease (ESRD), (2) CKD or (3) progression of CKD. We excluded studies that contained fewer than 50 participants in the initial cohort and studies that exclusively focused on “AKI syndromes” (e.g., rapidly progressive glomerulonephritis, hemolytic-uremic syndrome, hepato-renal syndrome) and studies that reported only mortality. Studies were required to include a control group without AKI.

Literature Review and Study Selection

We searched the MEDLINE and EMBASE (January 1985 to February 2011) databases using the following terms: acute renal insufficiency, acute kidney injury, acute kidney failure, chronic kidney disease, chronic renal failure, chronic renal insufficiency, End stage renal disease; progression (explode), treatment outcome, risk. An additional search was performed through the Scopus and references of all selected articles were reviewed to identify any eligible studies. The search was restricted to humans only. Each article chosen by the primary reviewer (SS) was reviewed by a second reviewer to confirm eligibility (SGC).

Data Collection

Two reviewers (SS and SGC) extracted data by using a standardized data extraction form. The reviewers extracted data about characteristics of participants (number, age, and sex), clinical setting, type of study (prospective versus retrospective), dates of enrollment, definition and severity of AKI, definition of CKD, and incidence of the outcomes in participants with and without AKI. Severity of AKI was grouped in the “mild”, “moderate” and “severe”, when possible. Mild AKI roughly represented the equivalent of Stage 1 AKIN or RIFLE R AKI. Moderate AKI roughly represented Stage 2 AKIN or RIFLE I AKI. Severe AKI roughly represented AKIN Stage 3 or RIFLE F AKI or dialysis-requiring AKI. Incident CKD was defined as per the study investigators, representing stage 4 CKD in 2 studies,[11, 22] CKD stage 3,[19] doubling of creatinine or ESRD,[16] and GFR decline > 4 ml/min/year.[15] Progressive CKD was defined as having pre-existing decreased GFR (eGFR < 60 ml/min) prior to AKI and meeting the definition of stage 4 CKD[11] or doubling in creatinine/ESRD.[16] Method quality was assessed by using criteria adapted from Hayden et al.[26] Any discrepancies about data extraction or quality score were resolved by a third reviewer.

Outcome Measures

Primary outcome measures were the adjusted hazard ratios (HR) for incident or progressive CKD, and ESRD in survivors of AKI compared to those without AKI. Progressive CKD was only evaluated in a subgroup analysis of the 2 studies[11, 16] that reported this outcome separately for those with and without decreased baseline GFR. The adjusted HR for long-term mortality, cardiovascular events, and hospitalizations were secondary outcomes. We also assessed unadjusted incidence rates for each of these end points, defined by the number of events in survivors beyond hospitalization or other relevant short-term period (28 or 30 days) divided by patient-years of follow-up. We assessed method quality of the studies by using the criteria of Hayden et al.: 1) representative study sample; 2) lack of study attrition; 3) adequate measurement of prognostic factor of interest (AKI); 4) adequate measurement of study outcome; 5) accounted for important potential confounders; 6) utilized appropriate statistical analyses.[26]

Statistical Analysis

Random effects meta-analysis was conducted to estimate the magnitude of risk associated with AKI for each outcome, as measured by the combined adjusted HRs with 95% confidence intervals. Adjusted risk estimates included those published in final multivariate models for each study, which considered confounding from sociodemographic and clinical covariates, such as age, gender, race, co-morbidities, medications, and laboratory values. Inverse variance-weighted averages of logarithmic HRs were calculated for each of the endpoints. We formally assessed heterogeneity of effects between studies with the Cochran Q and the I^2 statistic. We evaluated the association of AKI with the outcomes in the following pre-specified subgroups: 1. Dose response by severity of AKI; 2. Presence of decreased baseline GFR; 3. Presence of pre-existing proteinuria. All pooled analyses were conducted using Review Manager 5.0.25 (Cochrane Collaboration, Copenhagen). We also performed meta-regression using SAS 9.1 (Cary, NC) on 5 study-level variables (duration of follow-up, year of publication, overall mortality rate, proportion of males, and mean age) to determine the relationship between these variables expressed continuously and the natural log of the relative risk of CKD and ESRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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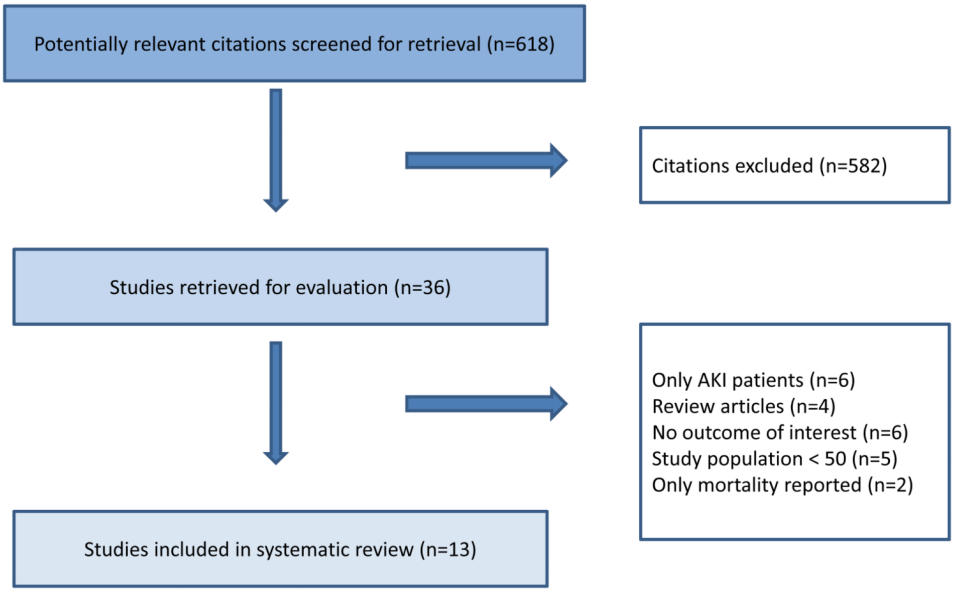

Figure 1. Selection of Studies

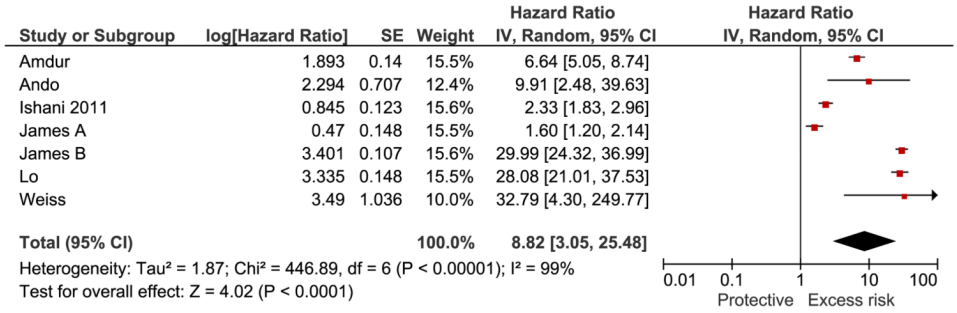

Figure 2a. Pooled Adjusted Hazard Ratios for CKD after AKI

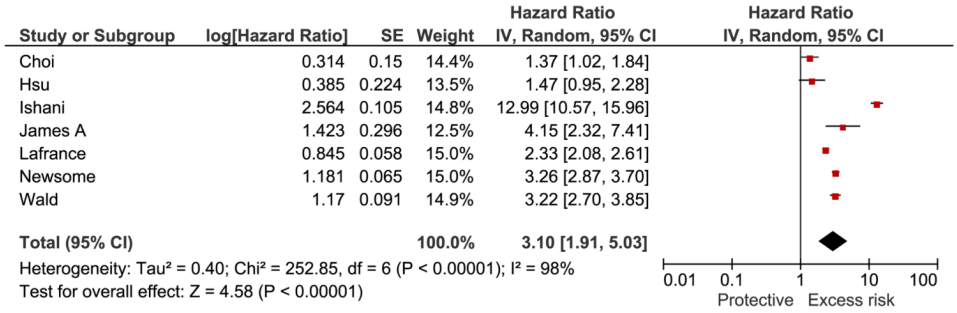

Figure 2b. Pooled Adjusted Hazard Ratios for ESRD after AKI

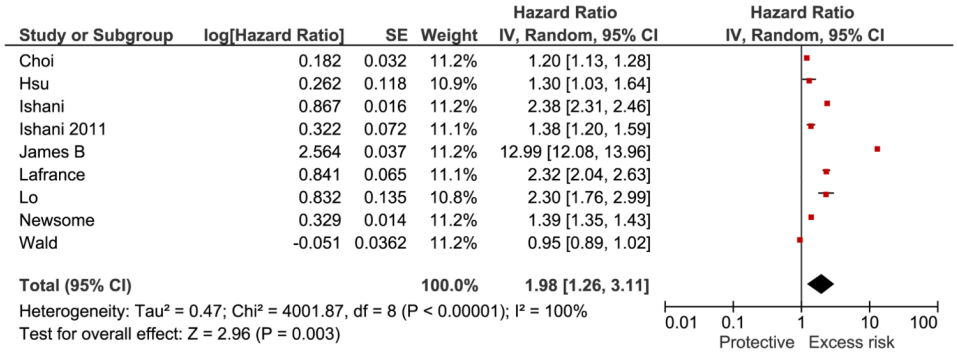

Figure 3. Pooled Adjusted Hazard Ratios for Mortality after AKI

Table 1

Characteristics of Included Studies

First author, year of publication	Clinical Setting	No of pts	Years of enrollment	Mean age	Male (%)	White (%)	CKD	CKD progression	ESRD	Mortality
Hsu, 2009[10]	Hospitalized	39805	1996-2003	66.6	56.6	73			✓	✓
Lo, 2009[11]	Hospitalized	3773	1996-2003	63.5	61	66.6	✓	✓		✓
Choi, 2010[12]	HIV	17325	1975-1995	44	98	28			✓	✓
Weiss, 2006[13]	HCT	174	2002	54	67	83	✓	✓		
Newsome, 2008[14]	MI	87094	1994-1995	77.1	51.5	87			✓	✓
James(A), 2010[15, 23]*	Coronary Angiography	11249	2004	63.6	69.6	NR	✓	✓	✓	✓
Wald, 2009[17]	ICU	8855	2006	62	60	NR			✓	✓
Lafrance, 2010[18]	CKD	6862	2002	69.8	54	NR			✓	✓
Ando, 2010[19]	HCT	158	1987	31	61.3	NR	✓	✓		
James(B), 2010[16]	Hospitalized and Non-Hospitalized	920985	2002	61	65	NR		✓	✓	✓
Ishani, 2009[20]	Hospitalized	233803	2000	79.2	38.8	89			✓	✓
Amdur, 2009[22]	Hospitalized	113272	1999-2005	70.8	97.8	74	✓	✓		✓
Ishani, 2011[21]	Cardiac Surgery	29388	1999-2005	65.4	98.8	84.4	✓	✓		✓

Abbreviations: HIV-Human immunodeficiency Virus, HCT-Hematopoietic stem cell transplant, VA-Veterans affairs, NR-Not reported ICU-Intensive care unit, MI-Myocardial infarction, CKD-Chronic kidney disease, ESRD- end stage renal disease; Y- Yes, N-No CKD definition was variable in different studies-It was CKD stage 4 in Lo[11], Amdur[22] and decrease in GFR>4 ml/min/year in James A[15], decrease in GFR of at least 25% from baseline in Weiss[13]

*Data is ascertained from two different manuscripts that referred to the same study population

Table 2

AKI definitions and Outcomes

First author, year of publication	AKI Definition Severity	Method of Ascertainment of AKI	Follow-up (mean or median in months)	Post-Discharge Mortality Overall (%)	Mortality Rate in AKI patients (per 100 person-yrs)†	Renal Outcomes In AKI patient (per 100 person-yrs)†	
						CKD Rate	ESRD Rate
Hsu, 2009[10]	RRT	Labs and code for RRT	6	19.7	43.7	…	28.1
Lo, 2009[11]	RRT	Labs and code for RRT	32.9	13.3	4.9	47.9	…
Choi, 2010[12]	RIFLE	Labs	68.4	48.5	9.9	…	0.6-5.6
Weiss, 2006[13]	> 2 fold increase in Cr	Labs	12	17.2	…	72.2	…
Newsome, 2008[14]	Cr ↑0.3-0.5; 0.6-3.0	Labs	49.2	73.3	19.4	…	0.6
James A, 2010[15, 23]	AKIN	Labs	21.8	5.7	12.7-31.5	4.6-8.6†	1.6-4.2†
Wald, 2009[17]	RRT	Diagnostic codes	36	34.8	10.1	…	2.6
Lafrance, 2010[18]	↓ eGFR 25% & ≥5 ml/min	Labs	19.4	15.3	9.4	…	12.1
Ando, 2010[19]	>2 fold increase in Cr	Labs	73.8			4.1	…
James B, 2010[16]	ARF	Diagnostic codes	35	3	1.0-12.4†	0.03-15.8†	…
Ishani, 2009[20]	ARF	Diagnostic codes	24	64	28.8	…	2.5
Amdur, 2009[22]	ARF & ATN	Diagnostic codes	75	44.7	7.8	22	…
Ishani, 2011[21]	Class 1-4	Labs	61.2	23.1	4.1-6.6†	6.6-10.5†	…

Abbreviations: AKI- acute kidney injury; RRT- renal replacement therapy; RIFLE- Risk Injury Failure Loss End Stage Renal Disease classification; Cr- creatinine; eGFR- estimated glomerular filtration rate; AKIN- Acute Kidney Injury Network classification; ARF- acute renal failure; ATN- acute tubular necrosis

†Range of rates is provided for studies that examined outcomes by differing severity of AKI.

Ishani[21]-AKI definition-Percent increase in creatinine post operatively for Class 1(1%-24% rise in creatinine), class 2(25%-49%), class 3(50%-99%), class 4(>100%)

Choi[12]-The rate of ESRD was 0.6/100 person years for those with mild AKI and 5.6/100 person years for those with moderate –severe AKI.

James A[15]-The rate of incident CKD was 4.6/100 person-years and ESRD was 1.6/100 person years for those with mild AKI and 8.6/100 person-years and 4.2/100 person years respectively for those with moderate-severe AKI. The mortality rate was 12.7 and 31.5/100 person years respectively for those with mild AKI and with moderate-severe AKI.

James B[16]-The rate of CKD progression was 0.03/100 person years and mortality was 0.98/100person years for those with mild AKI and it was 15.8/100person years and 12.4/100 person years respectively for those with moderate-severe AKI.

Ishani[21]-The rate of incident CKD was 6.6/100 person years and mortality was 4.1/100 person years for those with mild AKI and 10.5/100 person years and 6.6/100 person years respectively for those with moderate-severe AKI.

Table 3

Pooled HR for Outcomes of CKD and ESRD by Severity of AKI, Decreased Baseline GFR, and Pre-AKI Proteinuria

Grouping	Comparison	Outcome	# Studies	References	HR	CI	I^2
Overall	AKI vs. No AKI	CKD	7	11, 13, 15, 16, 19, 21, 22	8.8	3-25.5	99%
	AKI vs. No AKI	ESRD	7	10, 12, 14, 15, 17, 18, 20	3.1	1.9-5.0	98%
Dose response	Mild AKI vs. No AKI	CKD	2	15, 21	2.0	1.4-2.8	74%
	Moderate AKI vs. No AKI		3	13, 15, 21	3.3	1.7-6.2	63%
	Severe AKI vs. No AKI		2	11, 13	28.2	21.1-37.5	0%
	Mild AKI vs. No AKI	ESRD	4	12, 14, 15, 18	2.3	1.7-3.3	84%
	Moderate AKI vs. No AKI		3	12, 14, 15	5.0	2.6-9.8	88%
	Severe AKI vs. No AKI		2	12, 17	8.0	1.3-48.6	98%
Effect modification by decreased baseline GFR	AKI on decreased GFR vs. No AKI and decreased GFR	CKD	2	11, 16	24.4	15.3-38.9	89%
	AKI on normal GFR vs. No AKI and normal GFR		2	11, 16	38.8	21.9-68.9	81%
	AKI on decreased GFR vs. No AKI and decreased GFR	ESRD	3	12, 17, 20	1.9	1.6-2.3	0%
	AKI on normal GFR vs. No AKI and normal GFR		3	12, 17, 20	9.2	4.1-20.3	93%
Effect modification by pre-existing proteinuria	AKI with proteinuria vs. No AKI and proteinuria	CKD	1	16	106.9	76.3-149.8	NA
	AKI without proteinuria vs. No AKI without proteinuria		1	16	30	24.3-37	NA
	AKI with proteinuria vs. No AKI with proteinuria	ESRD	1	12	1.4	0.9-2.2	NA
	AKI without proteinuria vs. No AKI without proteinuria		1	12	3.7	2.4-5.7	NA

Abbreviations: AKI- acute kidney injury; CKD- chronic kidney disease; ESRD- end stage renal disease; HR- hazards ratio; CI- confidence interval