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The growth of acute kidney injury: a rising tide or just closer attention to detail?

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Acute kidney injury (AKI), previously termed acute renal failure, is associated with increased mortality, prolonged hospital stay, and accelerated chronic kidney disease (CKD). Over the past 2 decades, dramatic rises in the incidences of AKI have been reported, particularly within the United States. The question arises as to whether these changes reflect actual increases in disease incidence, or are potentially explained by the introduction of consensus definitions that rely on small standardized changes in serum creatinine, changes in coding and reimbursement, or increasingly available and more liberal use of dialysis. In this review, we explore the secular trends in AKI incidence in North America and Western Europe and its potential contributors.

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Throughout the medical literature, classic descriptions of acute kidney injury (AKI) have detailed its devastating effects on individual patients.[1–3] However, similar efforts to characterize the impact of AKI at a population level have been lacking until recently. Over the past two decades, the increased availability of electronic health records and large prospective cohorts of patients with AKI have facilitated the study of this disease in different settings. Rapid increases in the incidence of AKI have been reported, highlighting a growing contribution to the public health burden of advanced kidney disease.[4–15] Collectively, these observations have led to calls for greater resources to be directed toward its treatment and prevention.[12,16–18] However, residual concerns exist over the potential inflating effects of using administrative codes and increasingly sensitive laboratory definitions for reporting disease incidence.[19] Furthermore, if the growth observed is indeed 'real,' then the factors responsible remain poorly characterized. Here, we review these trends and explore potential explanations for these observations.

GROWTH IN THE INCIDENCE OF AKI: IS IT REAL?

Changes in the incidence of AKI using administrative codes

Most data illustrating a growth in hospitalized AKI have used administrative codes that rely on health-care providers to document that AKI has occurred. Xue *et al.*[6] evaluated the growth of AKI between 1992 and 2001 among elderly Medicare beneficiaries. Medicare is the US government program designed to provide health-care coverage for people aged $\geqslant$65 years and those with end-stage renal disease. By sampling 5 million hospitalizations, they found an increase in the standardized rates of acute renal failure (ARF) from 14.6/1000 discharges to 36.4/1000 discharges using diagnostic codes for ARF (11%/year) (Figure 1a). The rises in rates occurred whether ARF was coded as a principal or secondary diagnosis, arguing against the 'adding-on' of these diagnoses to maximize reimbursement as a major determinant of these changes. Furthermore, the steady nature of the rise in this and other studies would not necessarily be expected from, for example, an abrupt change in reimbursement policies. Nevertheless, this study was limited by reporting of hospital-based incidences that can be affected by temporal variation in admission practices and case-mix.

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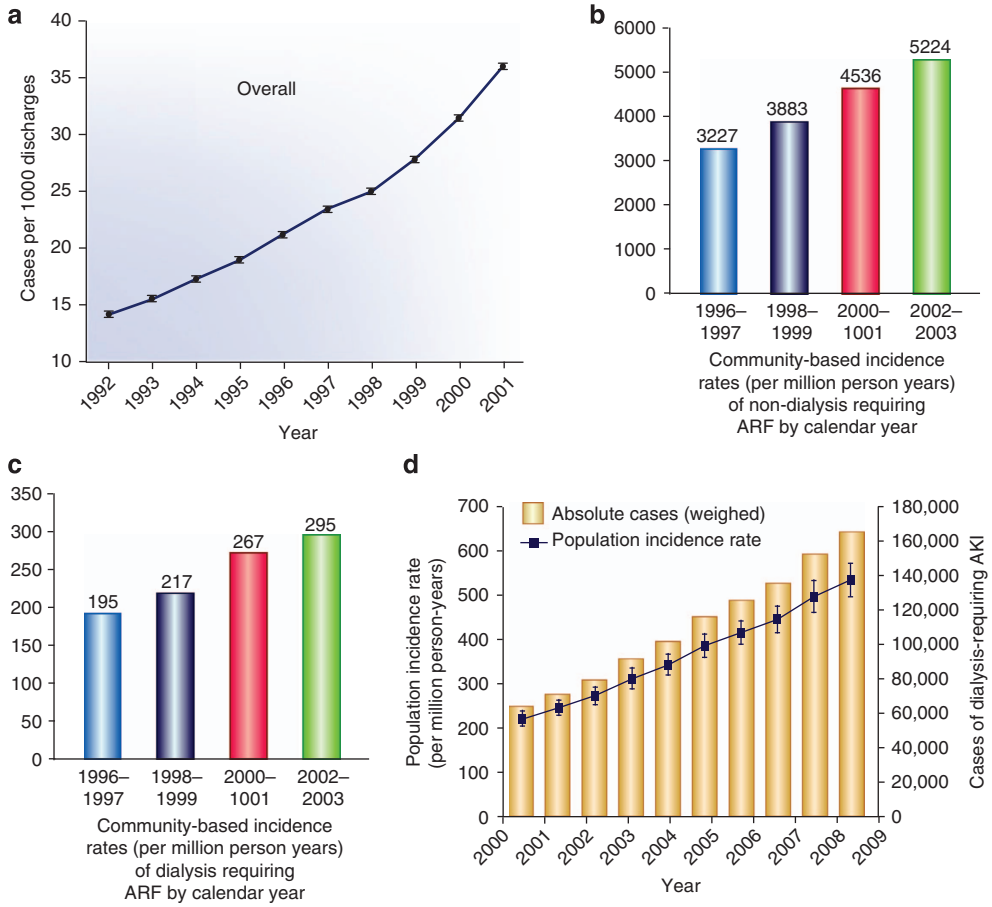

Figure 1 | Temporal trends in the hospital-based and population-based incidence of acute kidney injury (AKI). (**a**) Hospital-based incidence in AKI among elderly (aged >65 years) Medicare beneficiaries using administrative codes (USA).[6] (**b**, **c**) Community-based incidence of nondialysis- and dialysis-requiring AKI in Northern California (USA) using administrative codes and creatinine-based definitions,[9] respectively. (**d**) Population incidence of dialysis-requiring AKI using the Nationwide Inpatient Sample and US Census data.[32] ARF, acute renal failure.

Using both administrative codes and US census data, Waikar *et al.*[7] examined the *population-based* incidence of AKI within a nationally representative data set of hospitalizations between 1988 and 2002. The Nationwide Inpatient Sample (NIS) captures patient-level data from a 20% stratified probability sample of teaching and nonteaching hospitals across the United States. During this pre-RIFLE time period, the population-based incidence of ARF rose from 610 to 2880 cases per million per year. As with the Medicare study, increases were seen using either primary or secondary ARF codes.

The decision to enter a discharge code of ARF is influenced by multiple factors including whether the event is deemed clinically significant or as part of health-care reimbursement. Therefore, it is important to understand how increasing awareness or other external factors may affect coding practices. Although difficult to measure directly, some insight can be gained by examining change in the performance of administrative codes over time against a known reference standard (for example, serum creatinine change). Increasing awareness among medical providers might manifest by either gains in the sensitivity for AKI codes or loss of specificity (that is, increase in false positives). Using a doubling of serum creatinine between nadir and peak hospital values, the authors detected improvement in the diagnostic sensitivity of the major International Classification of Diseases, Clinical Modification diagnosis codes for ARF, Ninth Revision, between 1994 (17.4% of cases) and 2002 (29.3% of cases).[7] However, the degree of improvement in the sensitivity observed was determined to be insufficient (70% needed in 2002) to account for the majority of growth observed.

Hwang *et al.*[20] examined the validity of the International Classification of Diseases, Tenth Revision (implemented in Canada since 2000) codes for acute kidney failure among elderly patients in Canada. Compared with the period examined in an earlier report (1994–2002), this later study encompassed years following publication of the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney Disease) criteria (2003–2010). Using a doubling of serum creatinine (prehospital to peak within 48 h), investigators reported a substantially higher diagnostic sensitivity of 61.6% (95% confidence interval: 57.5–65.5). Even when a milder

injury standard was used (that is, a 50% increase in serum creatinine), the same diagnostic codes were still almost twice as sensitive at 56.4% (95% confidence interval: 53.2–59.7) than those observed in the earlier US study. Specificities in this and the study of Waikar *et al.*[7] remained >95%, arguing against a large number of false positives contributing to these reported increases. Although geographical variation in practice and coding patterns make accurate comparisons between these two studies impossible, the higher sensitivities observed in the later time periods do suggest a trend toward increased AKI reporting.

More recently, Grams *et al.*[21] evaluated the performance of discharge billing codes for AKI in hospitalized patients from the ARIC (Atherosclerosis Risk in Communities) cohort between 1996 and 2008 using KDIGO (Kidney Disease: Improving Global Outcomes) criteria as the reference standard. The sensitivity of billing code–identified AKI improved from 9.7% (1996–2002) to 24.4% (2002–2008), with specificity remaining high in both time eras. Collectively, these findings indicate that the sensitivity of administrative codes for AKI vary by region, and have increased over time. Thus, studies relying *exclusively* on coding to examine changes in AKI incidence or its related outcomes should be interpreted with caution.

Changes in the incidence of AKI using laboratory-based criteria

Despite these observations, several lines of evidence suggest that growth in AKI is occurring. Hou *et al.*[22] and Nash *et al.*[23] described early changes in incidence and risk factors for AKI between two tertiary care hospitals. They applied the same set of graded changes in serum creatinine during hospitalization and observed an increase in the hospital-based incidence of AKI from 4.9% in 1979 to 7.2% in 1996. However, these studies were conducted in two different medical centers where regional differences in admission practices may have contributed.

A decade ago, studies uncovering associations between incremental changes in serum creatinine and mortality led to the development of the first consensus definition for AKI.[14,24] Known as the RIFLE criteria,[25] this classification scheme introduced a consistent approach for defining and staging AKI, allowing for more standardized comparisons between settings. Numerous validation studies have since confirmed a dose-dependent relationship between the severity of AKI and poor outcomes, prompting even more sensitive iterations of these criteria in recent years (Acute Kidney Injury Network (AKIN)/KDIGO) (Table 1).[26,27]

Although the usefulness of these newer criteria to clinical practice remain to be defined, their application within research settings has resulted in large increases in the reported incidence of AKI, driven largely by the inclusion of less severe AKI (Table 2a–c). Another important consideration is that creatinine-based definitions of AKI require quantifying acute changes from a so-called 'baseline' value. Ideally, this value would reflect a given patient's steady-state kidney function just before the AKI insult. However, information on prehospital kidney function is often lacking, prompting the use of various surrogate estimates. These may include inpatient values (for example, admission, nadir) or the imputation of values such as back-calculating a baseline creatinine using estimated glomerular filtration rate (eGFR) of 75 ml/min per 1.73 m^2 (eGFR 75) in patients with missing data.[25] However, this approach can inflate or reduce the reported incidence of AKI and its prognosis.[28,29] In one study of 4863 hospitalized adults, the use of eGFR 75 approach or the minimum inpatient serum creatinine increased the incidence of AKI from 25.5% to 38.3% or 35.9%, respectively, compared with when AKI was measured using a known outpatient baseline value.[28] These increases were likely owing, in part, to erroneously identifying patients with stable chronic kidney disease (CKD) as having AKI. The use of minimum inpatient creatinine also appeared to overestimate AKI incidence. Although the reasons are not clear, potential explanations include changes in serum creatinine resulting from volume depletion on admission, followed by active rehydration protocols that further lower nadir serum creatinine values, leading to overreporting of AKI. Conversely, the use of the first admission serum creatinine value as a baseline led to an underreporting of AKI incidence at 13.7%, possibly because of unrecognized community-acquired AKI. As the misclassifying effects of surrogate baselines can be pronounced when applied to a large portion of the study population, interpreting epidemiologic studies of AKI that liberally apply these surrogates should be made with these limitations in mind. It also highlights the importance of providing the best estimate of baseline kidney function possible using available clinical information (see 'Limitations of serum creatinine as a biomarker of AKI' under the section 'Future Directions').

The strongest evidence supporting the growth of non-dialysis-requiring AKI comes from studies applying a fixed definition sequentially over time. Hsu *et al.* leveraged an integrated health-care system within Northern California (USA) to examine the population incidence of AKI between 1996 and 2003. Using previous criteria described by Hou *et al.*,[22] AKI was defined by an increase in serum creatinine level of 0.5 mg/dl for patients with a baseline serum creatinine level of ⩽1.9 mg/dl, 1.0 mg/dl for patients with a baseline level of 2.0–4.9 mg/dl, and 1.5 mg/dl for patients with a baseline level of ⩾5.0 mg/dl. In addition to improving sensitivity, this approach likely reduced other potential sources of bias. For example, a recent study suggests that clinicians may be more likely to code for AKI among CKD patients, possibly because their absolute baseline creatinine levels are already elevated.[20] Furthermore, given the nonlinear relationship between GFR and serum creatinine, patients with CKD require a smaller loss in kidney function to be classified as having AKI when applying a 0.3 mg/dl threshold for change than in patients with preserved kidney function. Thus, an increase in the hospital prevalence of patients with CKD over time may make it 'easier' for a

Table 1 | Evolution of consensus definitions for AKI

Criteria	RIFLE[25]	AKIN[26]	KDIGO[27,92]
Date of release	2004	2007	2012
Baseline	Not specifically defined. If not available, back-calculate a serum creatinine using an eGFR of 75 ml/min/1.73 m^2 using the MDRD equation	48-h window	Not specifically defined. If not available, use lowest serum creatinine during hospitalization, or calculate SCr using MDRD assuming baseline eGFR 75 ml/min/1.73 m^2 when there is no evidence of CKD
Time interval	Diagnosis and staging: within 1–7 days and sustained more than 24 h	Diagnosis: within 48 h Staging: 1 week	Diagnosis: 50% increase in SCr within 7 days or 0.3 mg/dl (26.5 μmol/l) within 48 h

Criteria		Creatinine	Urine output		Creatinine (urine output criteria same)		Creatinine (urine output criteria same)
Stage	Risk	Increased SCr 1.5–1.9 times baseline or GFR decrease >25%	<0.5 ml/kg/h for 6–12 h	1	Increased SCr 1.5–1.9 times baseline *OR* ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	1	Increased SCr 1.5–1.9 times baseline (7 days) *OR* ⩾0.3 mg/dl (⩾26.5 μmol/l) increase (48 h)
	Injury	2.0–2.9 times baseline or GFR decrease >50%	<0.5 ml/kg/h for ⩾12 h	2	Same as RIFLE minus eGFR criteria	2	same as AKIN
	Failure	3.0 times baseline, GFR decrease >75%, or SCr ⩾4.0 mg/dl (354 μmol/l) with an acute rise of ⩾0.5 mg/dl (44 μmol/l)	<0.3 ml/kg/h for ⩾24 h *OR* Anuria for ⩾12 h	3	Same as RIFLE or on RRT. eGFR criteria removed	3	3.0 times baseline, *OR* Increase in SCr ⩾4.0 mg/dl (354 μmol/l) *OR* Initiation of renal replacement therapy *OR* For <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2
	Loss	Persistent ARF = complete loss of kidney function (need for dialysis) >4 weeks			Notable differences: (1) Addition of 0.3 mg/dl absolute change in SCr to increase diagnostic sensitivity (2) eGFR criteria removed (3) 48-h time window to ensure acuity (also allows for inpatient baseline values) (4) Exclusion of Loss/ESKD categories as diagnostic criteria		Notable differences: (1) Time frame differences for absolute versus relative changes in serum creatinine (2) 0.5 mg/dl increase for those with SCr ⩾4.0 mg/dl (354 μmol/l) no longer required if minimum AKI threshold met (3) Inclusion of eGFR criteria for children
	ESKD	End-stage kidney disease (>3 months)					

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ARF, acute renal failure; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; MDRD, Modification of Diet in Renal Disease; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, and End-stage Kidney Disease; SCr, serum creatinine.

Table 2a | Hospital-based incidence rates of AKI for cardiac surgery before and after RIFLE/AKIN/KDIGO

Study	Era			Country	Enrollment	Setting	Definition of AKI	Incidence
Chertow *et al.*[134]	Before			USA (Veterans Affairs)	1987–1994	Cardiac surgery	RRT	1.1%
Mangano *et al.*[135]	RIFLE	AKIN	KDIGO	USA	1991–1993	Cardiac surgery	Postoperative serum creatinine >2 mg/dl with at least a 0.7 mg/dl increase from preoperative levels.	7.7%
Lenihan *et al.*[75]				USA (National Hospital Discharge Survey)	1999–2008	Cardiac surgery	ICD-9 Codes for ARF	7.7%
Hobson *et al.*[136]	After			USA (Florida)	1992–2002	Cardiothoracic surgery	RIFLE	43%
Dasta *et al.*[137]	RIFLE	AKIN	KDIGO	USA (Pittsburgh)	1998–2002	Cardiac surgery (CABG)	RIFLE	6.9%
Kuitunen *et al.*[138]				Finland (Helsinki)	2003	Cardiac surgery	RIFLE	19.3%

greater proportion of patients to be classified as having AKI. Requiring progressively larger increases in serum creatinine to meet diagnostic criteria as the baseline rises as in the above criteria reduces this potential for bias. Using these criteria, Hsu *et al.* reported that the community-based incidence of non-dialysis AKI increased from 3227 to 5224 per million

Table 2b | Hospital-based incidence rates of AKI before and after RIFLE/AKIN/KDIGO

Study	Era	Country	Enrollment	Setting	Definition used	Incidence
Hou *et al.*[22]	Before	USA (Chicago)	1979	Hospitalized (single center)	Increase in serum creatinine by 0.5 mg/dl if baseline ⩽1.9 mg/dl, 1.0 mg/dl if baseline 2.0–4.9 mg/dl, and 1.5 mg/dl if baseline ⩾5 mg/dl	4.9%
Nash *et al.*[23]	RIFLE AKIN KDIGO	USA (Boston)	1996	Hospitalized (single center)	Increase in serum creatinine by 0.5 mg/dl if baseline ⩽1.9 mg/dl, 1.0 mg/dl if baseline 2.0-4.9 mg/dl, and 1.5 mg/dl if baseline ⩾5 mg/dl	7.2%
Liano *et al.*[139]		Spain (Madrid)	1991–1992	Hospitalized (multicenter)	Increase in serum creatinine 2 mg/dl in normal renal function or 50% increase if CKD	AKI: 209/million/year (95% CI: 195–223) ATN: 88/million/year (95% CI:79–97)
Hsu *et al.*[9]		USA (California)	1996–2003	Hospitalized (multicenter)	Increase in serum creatinine by 0.5 mg/dl if baseline⩽1.9 mg/dl, 1.0 mg/dl if baseline 2.0–4.9 mg/dl, and 1.5 mg/dl if baseline ⩾5 mg/dl	Nondialysis-requiring AKI: 3227 to 5224 per million person-years Dialysis-requiring AKI: 195 to 295 per million person-years
Liangos *et al.*[139]		USA (National Hospital Discharge Survey)	2001	Hospitalized patients (multicenter)	ICD-9-CM codes for acute renal failure	1.9%
Uchino *et al.*[140]	After	Australia (Melbourne)	2000–2002	Hospitalized (single center)	RIFLE	18%
Ali *et al.*[141]	RIFLE AKIN KDIGO	United Kingdom (Scotland)	2003	Hospitalized patients (multicenter)	RIFLE	1811/million/year (AKI) 336/million/year (ACRF)
Porter *et al.*[142]		United Kingdom (Nottingham)	2011–2013	Hospitalized patients (multicenter)	AKIN + RIFLE	10.7%

Table 2c | ICU-based incidences rates of AKI before and after RIFLE/AKIN/KDIGO

Study	Era	Country	Enrollment	Setting	Definition used	Incidence
Brivet *et al.*[143]	Before	France	1991	ICU	Increase in serum creatinine to >3.5 mg/dl or BUN >100 mg dl in non-CKD or 100% above baseline levels if CKD	7%
Uchino *et al.*[4]	RIFLE AKIN KDIGO	Global	2000–2001	ICU	Severe AKI: urine output <200 ml per 12 h or BUN >84 mg/dl + RRT	5.7% (95% CI: 5.5–6.0%)
Hoste *et al.*[144]	After	USA (Pittsburgh)	2000–2001	ICU (single center)	RIFLE	67%
Osterman *et al.*[145]	RIFLE AKIN KDIGO	United Kingdom and Germany	1988–1999	ICU (multicenter)	RIFLE	35.8%
Bagshaw *et al.*[146,147]		Australia/New Zealand	2000–2005	ICU (multicenter)	RIFLE on admission AKIN on admission	36.1% 37.1%
Bagshaw *et al.*[148]		Australia/New Zealand	2000–2005	ICU patients with sepsis (multicenter)	RIFLE on admission	42.1%
Cruz *et al.*[149]		Italy	2003	ICU (multicenter)	RIFLE	10.8% (95% CI: 9.5–12.1)
Nisula *et al.*[150]		Finland (Helsinki)	2011–2012	ICU (multicenter)	KDIGO	39.3% (95% CI: 37.5–41.1)

Abbreviations: ACRF, acute on chronic renal failure; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ARF, acute renal failure; ATN, acute tubular necrosis; BUN, blood urea nitrogen; CABG, coronary artery bypass surgery; CI, confidence interval; CKD, chronic kidney disease; ICD-9-CM, International Classification of Diseases, Clinical Modification; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, and End-stage Kidney Disease; RRT, renal replacement therapy.

Table 3 | Studies reporting the population-based incidence of dialysis-requiring acute kidney injury (AKI)

Study	Country	Enrollment years	Population-based incidence per million per year
Feest *et al.*[151]	UK (England)	1986–1990	22
Waikar *et al.*[7] [a]	USA (National)	1988	40
Khan *et al.*[152]	UK (Scotland)	1989–1990	50
Liano *et al.*[153]	Spain (Madrid)	1991	57
Korkeila *et al.*[154]	Finland (Kuopio)	1992–1993	80
Stevens *et al.*[155]	UK (East Kent)	1996	83
Cole *et al.*[156]	Australia (Victoria)	1996	134
Hsu(CY) *et al.*[9] [a]	USA (California)	1996	195
Robertson *et al.*[157]	UK (Scotland)	1994–2000	187
Metcalfe *et al.*[31]	UK (Scotland—Grampian/Tayside)	2000	203
Hsu(RK) *et al.*[32] [a]	USA (National)	2000	222
Waikar *et al.*[7] [a]	USA (National)	2002	270
Prescott *et al.*[158]	UK (Scotland—entire)	2002	286
Hsu(CY) *et al.*[9] [a]	USA (California)	2002	295
Hsu(RK) *et al.*[32] [a]	USA (National)	2009	533

[a]Data from multiple years presented from single studies.

patient-years (Figure 1b), confirming observations that growth is occurring and reminding us that the number of patients with AKI is substantially larger than captured by administrative data alone.

Changes in the incidence of dialysis-requiring AKI

There has also been a parallel increase in observed rates of AKI requiring renal replacement therapy (RRT). As RRT is a procedure tightly linked to reimbursement, it is less susceptible to variations in coding practices. One study found a high sensitivity (90.3%) and specificity (93.8%) using procedure codes for RRT linked to major AKI codes when using chart review as a diagnostic standard.[30] Using the same approach to interrogate the NIS, the incidence of AKI requiring RRT within the United States increased by sixfold from 40 to 270 patients per million population between 1988 and 2002. Hsu *et al.*[9] observed a remarkably similar increase in the rates of AKI requiring RRT from 195 to 295 per million person-years between 1996 and 2003 using an integrated health-care system database in California (USA) (Figure 1c). Similar growth has been reported in other countries (Table 3). For example, Metcalfe *et al.*[31] estimated the population-based incidence of AKI requiring RRT in Scotland (United Kingdom) at 203 cases per million in the year 2000, a rate mirroring the US estimate from the same year (222 cases per million population).[32] A subsequent prospective study using data encompassing all hospitals within Scotland estimated that the population-based incidence of AKI requiring RRT grew to 286 (95% confidence interval: 269–302) cases per million in 2002.[31] Concurrent growth within the United States also occurred with a similar population incidence of 270 per million population in 2002.[7] A recent update using the NIS database by Hsu *et al.*[32] reported continued increases by up to 10%/year between 2000 and 2009, with a near tripling in the absolute number of annual cases (Figure 1d). However, the extent to which these increases reflect changes in underlying patient characteristics, provider practices, or increased availability of RRT over time is not yet known (see the section 'Potential reasons for growth in AKI' below).

In conclusion, studies have demonstrated a growing incidence of AKI among hospitalized patients. However, interpreting trends in AKI and its outcomes should be interpreted with potential increases in reporting and the inclusion of less severe AKI in mind. Nevertheless, population-based studies using more 'objective' creatinine-based criteria coupled with a rapidly growing incidence of AKI requiring dialysis suggest that increases in AKI are indeed occurring and that the numbers of patients experiencing AKI are larger than those indicated by administrative data alone.

POTENTIAL REASONS FOR THE GROWTH IN AKI

Earlier and more liberal use of dialysis

One possible explanation for the increasing incidence of AKI requiring RRT is more liberal application of dialytic support. However, between 1988 and 2002, Waikar *et al.*[7] observed increases in the comorbidity burden and illness severity of patients receiving acute dialysis in the United States. For example, the proportion of AKI patients receiving dialysis with at least 3 comorbidities rose from 16.9 to 24.6% between the first and last third of the study. Furthermore, the proportion of those requiring mechanical ventilation also increased from 18.0% in 1988 to 32.4% in 2002. Although 'code-creep' may have partially contributed to the former, the rise in mechanical ventilation is less likely to be affected by coding and do not support more liberal application of acute dialysis to less sick patients as the primary reason for these increases.

Other possibilities include increasing availability of RRT and earlier or lower thresholds for initiation, a trend observed with the initiation of chronic dialysis.[33,34] Although observational data do suggest potential benefit for earlier initiation in AKI,[35,36] few studies have examined secular trends in the timing of dialysis initiation during AKI. Table 4 lists the serum creatinine and blood urea nitrogen levels at the time of RRT initiation within major observational studies and clinical trials within the past two decades. We have also included a few selected studies from the more distant past for comparison. Although it is clear that the timing of initiation has evolved since the 'early days' of dialytic therapy, more recent data do not suggest an obvious trend toward earlier initiation over the past two decades using these criteria alone. However, as most studies included are clinical trials with specific criteria for RRT initiation, these findings may not mimic changes in real-world practice patterns. Furthermore, recent practice surveys suggest that nephrologists are more likely to initiate RRT based on more 'imminent' indications such as hypervolemia, acidosis, or electrolyte disturbances rather than the degree of azotemia alone, particularly as severity of illness increases.[37,38] For example, attention to prognostic significance of fluid overload in critically ill patients with and without AKI has

Table 4 | Mean/median serum BUN and creatinine at initiation of RRT in observational studies and clinical trials

Study	Type	Location (country)	Study enrollment	Mean serum creatinine at initiation (mg/dl)[a]	Mean BUN at initiation (mg/dl)
Early					
Parsons *et al.*[159]	Historical comparison	UK	1956–1958	—	Early 120–150 Late 200
Fischer *et al.*[160]	Historical comparison				Early 152 Late 231
Kleinknecht *et al.*[161]	Historical comparison	France	1966–1970	—	Early threshold 93 Late 164
Contemporary					
Gettings *et al.*[162]	Observational	Scotland	1989–1997	3.3 ± 1.8	73.2 ± 39.6
Mehta *et al.*[163]	RCT (modality study)	USA	1991–1995	4.4, 4.6	78.5, 87.1
Schiffl *et al.*[164]	RCT (dose of IHD)	Germany	1993–1998	4.9 ± 1.4 4.6 ± 1.0	91 ± 13 88 ± 16
Ronco *et al.*[165]	RCT (dose of CRRT)	Italy	1994–1999	3.5 ± 1.5 3.7 ± 1.6 3.6 ± 2.1	51.0 ± 12.1 50.1 ± 10.9 54.1 ± 12.1
Bouman *et al.*[166]	RCT (early vs. late)	Netherlands	1998–2000		Early 45.7 (38.4–57.7) Late 104.7(61.6–116.0)
Cho *et al.*[167]	Observational (PICARD)	USA	1999–2001	4.0, 5.1 (by modality)	77, 95 (by modality)
Vinsonneau *et al.*[168]	RCT (modality study) (Hemodiafe)	France	1999–2003	4.8 (95% CI: 4.6–5.2) 4.9 (95% CI: 4.3–5.3)	86.8 (95% CI: 81.2–92.4) 81.2 (95% CI: 72.9–86.8)
Uchino *et al.*[169]	Observational (BEST study)	Global	2000–2001	Median (IQR) 3.3 (2.2–4.8)	not reported
Carl *et al.*[170]	Observational (early vs. late)	USA	2000–2004	Early 5.0 ± 2.1 Late 5.8 ± 3.4	Early: 66.0 ± 20.2 Late: 137 ± 28.4
Prescott *et al.*[171]	Observational	UK	2002	Median (range) 4.2 (0.55–26.9), 5.8 (0.77–19.8) (by CKD status)	Median (range) 72.8 (11.2–263) 100.8 (25.2–308.1) (by CKD status)
Palvesky *et al.*[172]	RCT (dose of RRT) (ATN Study)	USA	2003–2007	4.1 ± 2.3 4.1 ± 2.0	65.9 ± 30.2 66.7 ± 35.2
Bellomo *et al.*[173]	RCT (dose of CRRT) (ANZICS)	Australia/New Zealand	2005–2008	3.8 ± 2.2 3.7 ± 2.2	67.8 ± 37.3 63.9 ± 34.2

Abbreviations: ATN, acute tubular necrosis; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; IQR, interquartile range; RCT, randomized controlled trial; RRT, renal replacement therapy.
[a]If data were from RCT, means ± s.d. were presented for each arm (if available).

also increased in recent years, although its impact on acute dialysis practice is not yet known.[39–42] However, one study examining secular trends in dialysis-requiring AKI following elective major surgery within Ontario, Canada, found that the timing of dialysis postoperatively shrank from a median of 5 days (interquartile range: 3–9) in 1995 to 2 days (interquartile range: 1–6) in 2009.[10] Further studies are required to determine whether and why more aggressive dialysis initiation is occurring and whether this strategy is yielding significant benefit. Nevertheless, it should be emphasized that AKI requiring dialysis still represents a small fraction of patients experiencing AKI.

Increases in comorbidity burden that affect susceptibility to AKI

Another potential contributor to the growth in AKI is an increase in the number of patients hospitalized who are susceptible to this disease. As the absolute number of hospital deaths associated with AKI requiring dialysis has increased, the case–fatality ratio appears to be decreasing. The previously described study by Waikar *et al.*[7] revealed declining mortality from as high as 41.3% in 1988 down to 28.1% in 2002, a decrease not entirely attributable by increased discharges to ongoing care facilities. The mortality associated with dialysis-requiring AKI has since decreased further to 23.5% in 2009 in a similar study by Hsu *et al.*[32] Although improving therapies for diseases including myocardial infarction, sepsis, and acute lung injury may be contributing, similar progress for treatment of AKI itself has not occurred. The latter prompts the question over whether some of these improvements may be due to an increasing number of patients who require a less severe insult that prompts the need for RRT. For example, as CKD is the predominant premorbid risk factor for AKI,[43,44] an increase in the hospital prevalence of CKD would be a plausible explanation for both the increasing earlier initiation and the lower associated mortality rates observed. Although it has been pointed out that only modest increases in the population-based prevalence of CKD have occurred,[16,45,46] it is not clear whether the same holds true for hospitalized populations. A recent Canadian study found a near tripling in the prevalence of patients with CKD being considered

for major surgery from 2.0% in 1995–1997 to 5.5% in 2006–2009.[47] Unfortunately, diagnostic codes have been shown to be relatively insensitive for capturing CKD with sensitivities ranging between 26.6 and 42.4% and may also be subject to 'code-creep' over time.[48–50] One study examining the secular trends of renal dysfunction in patients hospitalized with heart failure found that the mean admission eGFR of patients admitted to Mayo Clinic hospitals between 1987 and 2002 decreased from 73 ± 31 to 55 ± 25 ml/min per 1.73 m^2.[51] Although likely reflecting some increase in AKI, some of this trend may also be attributable to an increasing prevalence of CKD among patients with heart failure. Of importance, as heart failure hospitalizations continue to rise (Figure 2b),[52] it is worth noting that nearly one-third of patients hospitalized for heart failure within the United States and more than half of the patients in the French intensive care units have admission creatinine values of >2 mg/dl.[53]

In addition to lower eGFR, other risk factors that confer susceptibility to AKI may also be increasing in prevalence. For example, proteinuria has been identified to have a dose-dependent association with the risk of developing AKI.[54–56] The hypothesis that this may also be contributing is supported by analyses of the NIS data set indicating that the prevalence of diabetes among hospitalized patients was as high as 19.4% in 2008.[57] Similarly, obesity itself has recently been identified to be an independent risk factor for AKI, an effect potentially mediated by increases in the burden of oxidative stress.[58] Parallel increases in the prevalence of obesity among hospitalized patients are also being observed.[59] Last, one of the fastest growing group of patients experiencing AKI is the elderly,[8] a group that constitutes ~35% of hospitalizations within the United States.[60] In addition to being most likely to experience critical illnesses,[61,62] age-related structural and functional changes in the kidney including sclerosis, vascular rarefaction, and loss of GFR and autoregulatory capacity all combine to increase the risk for AKI in this growing population.[63]

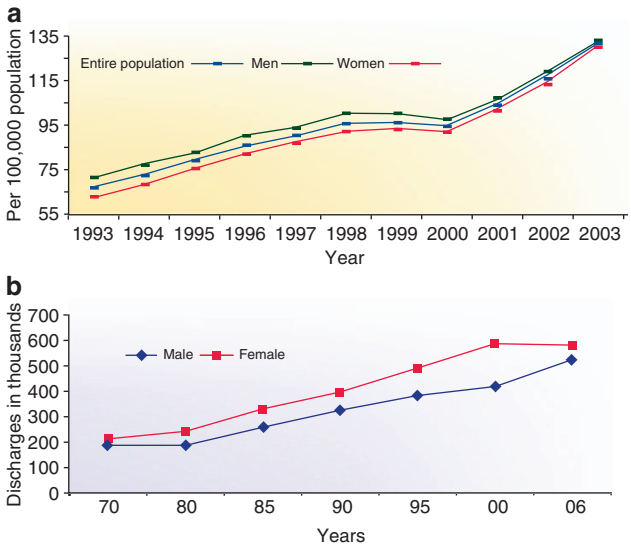

Figure 2 | Temporal trends in sepsis and heart failure hospitalizations. National US trends of hospital discharges for (**a**) sepsis using the Nationwide Inpatient Sample (USA)[66] and (**b**) congestive heart failure using the National Hospital Discharge Survey (USA).[52]

Other changes in case-mix

Acute and chronic conditions associated with AKI. Another possibility that might explain the reported growth in AKI includes increases in its underlying precipitants.[4] For example, increases in hospitalizations for sepsis have paralleled growth in AKI,[64–66] recently surpassing acute myocardial infarction and stroke for frequency of emergency medical service encounters (Figure 2a). Two studies examining the population-based incidence of sepsis in the United States reported age-adjusted increases in sepsis-related hospitalization of ~8% per year.[65,66] Among the elderly, rates of hospitalization with pneumonia also increased by 20% between 1988 and 2002, with an accompanying increase in patients admitted with ⩾3 comorbid diagnoses including a higher prevalence of CKD.[67] These changes have also been characterized by increasing illness severity, with severe sepsis accounting for nearly half of the sepsis-related hospitalizations, as well as increases in accompanying organ failure, with the lung and kidney being most commonly involved.

Another increasingly common condition associated with the development of AKI is acute decompensated heart failure (ADHF). ADHF remains a leading cause of Medicare-associated hospitalizations, constituting ~1 million admissions per year.[52] Impaired kidney function is extremely common among patients hospitalized with ADHF, and it is one of the most potent predictors of mortality.[68,69] Approximately 64% of patients with serum creatinine values on admission have an eGFR of <60 ml/min per 1.73 m^2,[68,69] with worsening of renal function during hospitalization occurring in up to 37% of hospitalized patients with ADHF.[70,71] Hospitalization rates for ADHF have increased by nearly 150% over the past two decades[52] (Figure 2b), a number projected to rise with the advancing age of the population and improved survival in patients with cardiovascular disease.

A higher frequency of invasive procedures over time has also been suggested as a part of the changing casemix of AKI.[16,23] Hassan *et al.*[72] demonstrated that rates of angioplasty in Canada more than doubled between 1994 and 2005, whereas rates of coronary bypass surgery remained relatively stable, resulting in an increase in percutaneous coronary intervention to coronary artery bypass surgery ratio. However, despite this increasing frequency of percutaneous coronary intervention, rates of AKI have actually declined for patients associated with acute myocardial infarction, particularly among those requiring cardiac catheterization.[73] By analyzing 33,249 hospitalizations from the electronic medical record data set of 56 hospitals across the United States between 2000 and 2008, Amin *et al.*[73] found a decrease in the adjusted rates of AKI by 4.4% a year during this time interval

(5.5% in those treated with cardiac catheterization; Figure 3a). These findings persisted even when more severe definitions of AKI were used (that is, doubling of serum creatinine) and after adjusting for a potential increase in the frequency of monitoring of kidney function.[74]

One result of the increasing application of minimally invasive procedures including percutaneous coronary intervention and laparoscopic surgeries may be an increasing complexity of cases referred for major surgery. A recent study of patients undergoing major elective surgery in Ontario, Canada, between 1995 and 2009 found that patients were increasingly older (increasing proportion of age $\geqslant$65 years from 39.5 to 50.6%) and sicker (proportion with $\geqslant$2 comorbidities increasing from 10.2 to 18.4%) over time.[10] Patients hospitalized with an underlying diagnosis of CKD, hypertension, congestive heart failure, liver disease, and diabetes were at a higher independent risk for dialysis-requiring AKI, the incidence of which increased threefold during this time frame. This increase was experienced primarily by those undergoing cardiac (1 in 390 to 1 in 80) and vascular (1 in 230 to 1 in 85) surgeries (Figure 3b). This trend has also been confirmed among cardiac surgery patients within the United States.[75] As data from randomized controlled trials continue to favor coronary artery bypass surgery for patients with advanced coronary artery disease or complex lesions, this population may reflect an important expanding subgroup of patients at risk for developing AKI.[76,77]

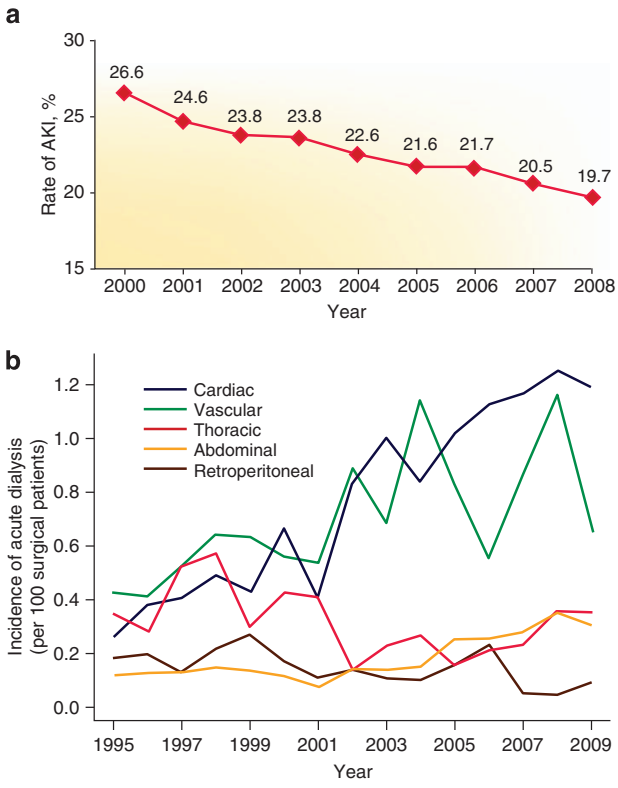

Figure 3 | Temporal trends in MI and surgery associated acute kidney injury (AKI). Temporal trends in the incidence of dialysis-requiring AKI during hospitalization for (**a**) acute myocardial infarction in the United States[73] and (**b**) major surgery in Ontario, Canada.[10]

In an attempt to quantify the potential impact of some of the above-mentioned factors, Hsu *et al.*[32] used regression modeling to potentially explain the continued growth of dialysis-requiring AKI. Adjusting for demographics, as well as hospitalizations involving sepsis, mechanical ventilation, congestive heart failure, and cardiac catheterization, the authors found that increases in these types of hospitalizations accounted for only 30% of the observed growth. Even considering potential shifts in inpatient case-mix to more complicated procedures such as major surgery, one would potentially expect these to be also captured by mechanical ventilation records, suggesting the importance of other contributors.

One increasingly recognized contributor includes patients with cancer.[78–80] Improvements in the prevention, diagnosis, and treatment of malignancy have reduced cancer-related mortality by 20% over the past two decades.[81] As patients with malignancy largely include the elderly with high comorbidity burden, this improved survival may also be increasing the number of survivors at risk for developing AKI. In addition, these welcome advances also carry inherent risks that can contribute to AKI. Recent data using creatinine-based definitions suggest that the incidence of AKI among hospitalized patients with cancer may be as high as 12%.[82] The etiology of AKI varies widely in this population, but includes traditional risk factors such as volume depletion from vomiting and diarrhea, sepsis from immunosuppression, attendant antibiotic use (prophylaxis and treatment), and serial imaging. In addition, disease-associated factors including renal cancers, cast nephropathy, tumor lysis syndrome, hypercalcemia and hyperuricemia, glomerular disease, and obstruction are also important contributors. Finally, the spectrum of potentially nephrotoxic chemotherapies and myeloablative protocols have grown drastically, including, but not limited to, platinum-based therapies, methotrexate, calcineurin inhibitors, gemcitabine, cytokine therapies (for example, interleukin-2), and anti–vascular endothelial growth factor agents, and are detailed elsewhere.[83] Enhancing our understanding of these adverse sequelae and their management (that is, 'Onco-nephrology') has been recently recognized by the American Society of Nephrology as a growing area of need.[78]

Medications

Early single-center studies were among the first to suggest an expanding role of medications in the changing epidemiology of AKI. In the previous series of studies by Hou *et al.*[22] and Nash *et al.*,[23] the contribution of medications grew from 7 to 16% over a 17-year span between two centers. This increase in prominence was marked by increases in the repertoire of potential nephrotoxic drugs available. In 1979, aminoglycosides accounted for 82% of AKI caused by drugs; however, by 1996, they accounted for only 29% of drug-related AKI.

Large observational studies of critically ill patients estimate that medications now contribute to almost one-fifth of severe AKI in adults.[84] Even among children, nephrotoxin exposures (16% of cases) have supplanted primary renal disease (7% of cases) as a leading cause of AKI.[85] A recent matched case–control study in 2008 found that most (>80%) of all hospitalized children with and without AKI were exposed to at least one potentially nephrotoxic medication, with a median number of at least two (range: 0–8) for children who developed AKI.[86]

In addition to newer chemotherapeutic agents, nephrotoxins are becoming increasingly varied with an ever-expanding repertoire of antimicrobial agents.[87] Recent attention has also been directed to commonly used interventions previously considered to be benign. These include a critical reexamination of certain intravenous fluid formulations including hydroxyethyl starches[88–90] and, more recently, chloride-rich solutions.[91] The former have been associated with a higher incidence of AKI and RRT in recently conducted trials in critically ill patients, and no longer recommended for initial volume expansion.[92,93] Chloride-rich solutions have also been demonstrated to associate with an increased risk for AKI and RRT in a recent open-label sequential period study;[91] however, these findings remain to be validated in randomized trials. As secular trends in the growth in use of chloride-rich solutions are difficult to quantify, their contribution to the increasing rates of AKI observed remain uncertain. However, increasing emphasis on early and aggressive fluid resuscitation as a component of standard therapy in diseases such as sepsis have occurred over the past decade.[94,95] These data compel us to examine the safety of intravenous solutions with the same level of scrutiny as other pharmacotherapeutics.

Even outside of hospitalization, an increasing spectrum of medications commonly administered in a chronic stable setting is becoming recognized for their nephrotoxic potential (Table 5). Nonsteroidal anti-inflammatory drug exposure, in particular, continues to be problematic in patients at risk for AKI, including those with hypertension, congestive heart failure, and CKD, and it is one of the five areas recently identified by the American Society of Nephrology Quality and Patient Safety Task Force 'most open' to improvement.[96,97] In addition to nonsteroidal anti-inflammatory drugs, proton-pump inhibitors and phosphate-based purgatives have been implicated in AKI, many of which do not require a prescription and therefore more difficult to study.

Aside from an increasing variety of nephrotoxic medications, growth in AKI over the past two decades has also occurred on a background of increasingly aggressive blood pressure control. This is particularly true among patients with CKD, the group identified to be at the highest risk for developing AKI.[43,44] Peralta *et al.*[98] observed that nearly one-third of hypertensive patients with CKD were on $\geqslant 3$ antihypertensive drugs, including 50% on diuretics and 58% on renin–angiotensin–aldosterone system (RAAS) inhibition. Increasing efforts to improve blood pressure control typically increases the number of medications prescribed, leading to a wider pulse pressure and a lowering of diastolic blood pressure. Even in the absence of frank hypotension, a fall in blood pressure in patients with impaired renal autoregulation, particularly those with CKD, hypertension, and the elderly, may lead to increased risk of AKI.[99]

One component of the above strategy has included widespread adoption of RAAS inhibitors. No other class of medications has been so widely integrated into treatment for multiple chronic conditions, including proteinuric and nonproteinuric CKD, diabetes, coronary artery disease, systolic heart failure, and hypertension.[100–105] Simultaneously, efforts to improve CKD awareness, including increased electronic reporting, have potentially increased their use.[106–108] However, although the renal benefits of lowering intraglomerular pressure are well established, it is also known to come at the expense of blunting regional hemodynamic autoregulation that may lower the threshold for developing or worsening AKI in circumstances that 'stress the kidney' *in susceptible individuals*. One recent study observed that RAAS inhibition was among the most common medication classes associated with adverse drug events among patients hospitalized with AKI, including exacerbation of hypotension or AKI itself.[109] RAAS inhibition has also been associated with AKI in other conditions such as cardiac surgery and contrast exposure.[110,111] Analyses from the ONTARGET and the VA NEPHRON-D studies, two randomized studies comparing single versus dual RAAS blockade, found the latter to be associated with a greater loss of kidney function over time, a finding largely driven by increases in AKI.[112,113] Not surprisingly, the use of a triple therapy combination, of angiotensin-converting enzyme inhibitors, diuretics, and nonsteroidal anti-inflammatory drugs, was also recently reported to be associated with a 31% increased risk for AKI.[114] In aggregate, these findings suggest that the changing pharmacoepidemiology of AKI is an important and emerging area of investigation.

FUTURE DIRECTIONS

Limitations of serum creatinine as a biomarker of AKI

As the potential contributors to AKI become more varied and common, a premium will be placed upon the ability to extend AKI phenotyping beyond describing the clinical setting in which the injury occurs. Most studies predominantly use changes in serum creatinine to stage AKI. In addition to how the choice of baseline creatinine can affect the reported incidence of AKI, a few important biological and measurement considerations of creatinine potentially limit accuracy in diagnosing AKI. Leaving aside the inherent difficulties in interpreting small changes in serum creatinine in neonates and infants, serum creatinine depends equally upon both creatinine generation and excretion. Creatinine generation can be influenced by multiple factors, and can be reduced in AKI. Whether changes in production rate is similar in all types of AKI is unknown, as intuitive differences between sepsis-associated AKI and drug-induced AKI, for

Table 5 | Medications that associate with AKI at a population level

Study	Design/setting	Medication	AKI definition	Risk of AKI
Leonard *et al.*[174] (1987–2002)	Nested case–control in a National General Practitioner data set, London, UK	Proton-pump inhibitor	Acute interstitial nephritis (diagnosis codes, free text)	Adjusted OR 3.2 (95% CI: 0.80–12.79)
Dormuth *et al.*[175] (1997–2008)	Nested case–control of new users aged >40 years, Canada + UK + USA	High-potency statins	Hospitalization for AKI using a validated coding algorithm	Fixed effect rate ratio: non-CKD 1.34 (95% CI: 1.25–1.43) CKD 1.1 (95% CI: 0.99–1.23)
Bird *et al.*[176] (2001–2011)	Nested case–control study of men aged 45–80 years within a Health Plan Claims Database, United States	Fluoroquinolones	Hospitalization with a primary discharge diagnosis of ARF (ICD-9-CM)	RR 2.18 (95% CI: 1.74–2.73)
Hurst *et al.*[177] (2002–2006)	Retrospective Cohort, Department of Defense EMR	Phosphate-based purgatives (USA)	50% Increase in serum creatinine	Adjusted OR 2.35 (95% CI: 1.51–3.66)
Zhao *et al.*[178] (2004–2008)	Population-based cohort study of elderly adults, Ontario, Canada	Fibric acid derivatives	Hospitalization for increase in serum creatinine code (ICD-10) within 90 days of prescription	Adjusted OR 2.4 (95% CI: 1.7–3.3)
Schneider *et al.*[179] (2006)	Nested case–control study of elderly patients in Quebec, Canada	NSAIDs/COX-2 inhibitors	Hospitalization with ICD-9 discharge diagnoses of acute renal failure within 30 days of prescription	RR 2.05 (95% CI: 1.61–2.60)
Wikman *et al.*[180] (2008–2011)	Prospective cohort of 271 consecutively treated HIV patients	HAART therapy (Madrid/ Spain)	RIFLE/AKIN	7 episodes/100 patient-years
Gandhi *et al.*[181] (2003–2012)	Population-based retrospective cohort of elderly adults in Ontario, Canada	Calcium-channel blocker + clarithromycin	Hospitalization with ICD-9 discharge diagnoses of acute renal failure within 30 days of prescription	OR 1.98 (95% CI: 1.68–2.34) compared with azithromycin

Abbreviations: AKI, acute kidney injury; ARF, acute renal failure; CI, confidence interval; CKD, chronic kidney disease; COX-2, cyclooxygenase-2; EMR, electronic medical record; HAART, highly active antiretroviral therapy; ICD-9-CM, International Classification of Diseases, Clinical Modification; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; RR, relative risk.

example, likely exist.[115] In addition, creatinine generation or release will also depend upon hepatic creatine synthesis, which will be reduced in liver disease, and affected by other endocrine disorders.[116] Finally, it must also be recognized that serum creatinine is measured as a concentration and thus affected by variations in volume status, particularly among patients with congestive heart failure, one of the growing populations experiencing AKI discussed in this review. Recent attempts to quantify the impact of fluid accumulation on the characterization of AKI suggest that it can hinder a timely diagnosis or mask less severe injury.[40,117] In a *post hoc* analysis of the Fluid and Catheter Treatment Trial (FACTT), Liu *et al.*[40] found that AKI was potentially misclassified in up to 18% of patients after adjusting serum creatinine values for net fluid balance and estimated total body water. Most cases were patients in whom the diagnosis of AKI would have otherwise been 'missed' without adjustment. These patients experienced mortality rates similar to those with AKI that persisted before and after adjustment. These data suggest that the incidence of AKI may actually be underestimated in some patients and that the impact of fluid accumulation in its diagnoses and staging is not trivial.

Conversely, modest increases in serum creatinine may not necessarily reflect parenchymal injury and may even be associated with improved prognosis in some circumstances. For example, Coca *et al.*[118] recently demonstrated that preoperative use of angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker before cardiac surgery associates with AKI using serum creatinine–based definitions but not with significant elevations in tubular injury markers compared with non-AKI patients. Testani *et al.*[119,120] observed that the indices of hemoconcentration associated strongly with worsening renal function (that is, increases in serum creatinine) yet also with reduced mortality during treatment of decompensated heart failure. Collectively, these examples highlight the need to allow for complementary information regarding ongoing parenchymal damage to be added to observed functional changes. The ability to segregate tissue injury from changes in function is a knowledge gap that novel tissue injury biomarkers propose to fill.[121–123] Figure 4 illustrates the conceptual framework proposed by the Acute Dialysis Quality Initiative (ADQI) that describes how AKI might be classified using a combination of both functional (for example, serum creatinine, urine output) markers and damage (for example, tubular injury) biomarkers. This expands upon the current paradigm that infers injury by the presence of functional changes alone. The potential for enhanced phenotyping with newer injury markers might allow for the characterization of 'subclinical' injury (upper right quadrant) that may eventually be accompanied by functional loss but still associate with worse outcomes, patients with loss of function who may be at risk for damage, and those with both ongoing damage and loss of function (lower right quadrant).[123] In addition to facilitating a timely and accurate diagnosis of ongoing parenchymal damage, recent studies suggest that these markers may potentially provide additional diagnostic and prognostic information that complement serum creatinine.[124–126]

In the interim, future studies that use administrative codes alone to examine trends in the incidence of AKI and its associated outcomes should be interpreted in light of

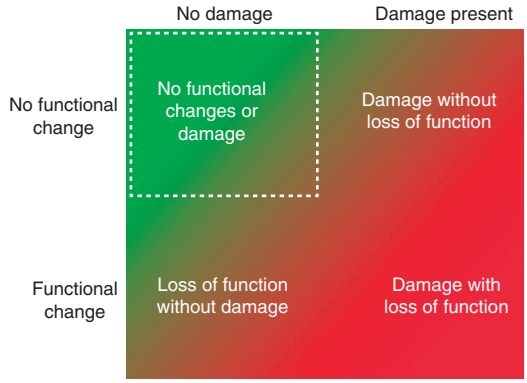

Figure 4 | Proposed framework by the Acute Dialysis Quality Initiative (ADQI) for evaluating acute kidney injury (AKI) using both functional and damage markers simultaneously.[121,123]

potential increases in reporting over time that includes less severe AKI. Whenever possible, the magnitude of these effects should be estimated by consistently applying a single laboratory-based definition throughout the survey period in at least a subset of patients. Greater emphasis should also be placed on providing population-based, rather than hospital-based, incidence rates to reduce the impact of variation in admission practices in disease reporting.[127] Attention to premorbid information on baseline kidney function is also essential to minimize potential bias and to anchor the study of the long-term effects of AKI.[128] If information on premorbid kidney function is not available, estimates of baseline kidney function should make use of clinical data available and sensitivity analyses performed.[129] Regardless of the further refinements in the diagnostic approach to this disease, it is important to remember that each iterative definition has demonstrated a dose-dependent association between increasingly severe AKI and poor outcomes.[13,130,131] Refinements to standardized definitions for other acute conditions such as acute myocardial infarction that also once heavily relied on coding but continue to incorporate newer and improved diagnostics along with robust validation efforts highlight an important path for investigators of AKI to follow.[132,133] Last, with data sources currently available, continued efforts should be undertaken to pinpoint the reasons for this observed growth, including identifying subgroups experiencing the most rapid increases in AKI and modifiable risk factors that can attenuate this growth.

SUMMARY

The hospital- and population-based reported incidences of AKI have increased in North America and Europe. Although evidence suggests some increases in the diagnostic sensitivity of administrative codes, studies applying consistent creatinine-based definitions over time indicate that 'true' increases in AKI are occurring. The incidence of dialysis-requiring AKI is also increasing, although the reasons for this growth and the effect of changes in how this treatment is being applied remains to be studied. Contributors to the growth of AKI include increases in the known precipitants of AKI such as sepsis, major surgery, and congestive heart failure, higher age and comorbidity burden of patients that increase the risk of AKI including CKD, proteinuria, diabetes, and obesity, and the broadening repertoire of medications that either are directly nephrotoxic or may lower the threshold for sustaining AKI.

In conclusion, the important work accomplished in this field within a relatively short time frame has uncovered that AKI is a growing problem. The parallel increase in workload, related patient outcomes, and escalating health-care costs associated with this disease highlight important and growing challenges for the medical community. Reducing the burden of AKI will require identifying those experiencing the fastest growth in AKI and its complications, refinements to how we approach the diagnosis of AKI, including the development and validation of biomarkers that can complement the limitations of serum creatinine, and research that identifies modifiable targets to prevent, treat, and reduce the impact of this disease.

DISCLOSURE

EDS reports a previous consulting agreement with Abbvie and Alere. AD declared no competing interests.

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