ACUTE KIDNEY INJURY: IT'S NOT JUST ACUTE, AND IT'S NOT JUST THE KIDNEYS

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TABLE 2 | Continued

<table>
<tr><th>References</th><th>Validated Measure</th><th>Study Population</th><th>N</th><th>Administrative Health Data Source</th><th>Reference Standard</th><th>Study Findings</th><th>Limitations</th></tr>
<tr><td>Tomlinson et al. (50)</td><td>AKI</td><td>Adults without ESRD hospitalized in England in 2005 and 2010</td><td>121 (58 in 2005, 63 in 2010)</td><td>Discharge billing codes, including ICD-10 diagnostic code for AKI</td><td>Standardized review of selected medical charts using KDIGO AKI definition (using SCr criteria)</td><td>
<table>
<tr><th></th><th>Sensitivity-% (CI)</th><th>Specificity-% (CI)</th><th>PPV-% (CI)</th><th>NPV-% (CI)</th></tr>
<tr><td>AKI</td><td>NR</td><td>NR</td><td>95 (91–99)</td><td>NR</td></tr>
<tr><td>AKI, 2005 Only</td><td>NR</td><td>NR</td><td>95 (89–100)</td><td>NR</td></tr>
<tr><td>AKI, 2010 Only</td><td>NR</td><td>NR</td><td>94 (88–100)</td><td>NR</td></tr>
</table>
</td><td>- Small sample size, single-center data may limit generalizability
- One diagnostic code examined only
- Sensitivity, specificity, and NPV could not be reported</td></tr>
<tr><td>Grams et al. (51)</td><td>AKI</td><td>Adults without ESRD hospitalized in the US between 1996 and 2008, Atherosclerosis Risk in Communities (ARIC) study participants</td><td>10,056</td><td>Discharge billing codes, including ICD-9 diagnostic and procedure codes for AKI</td><td>Standardized review of selected medical charts using KDIGO AKI definition (using SCr criteria)
Standardized review of electronic medical record using KDIGO AKI definition (using SCr or UO criteria)</td><td>
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<tr><th></th><th>Sensitivity-% (CI)</th><th>Specificity-% (CI)</th><th>PPV-% (CI)</th><th>NPV-% (CI)</th></tr>
<tr><td>AKI (vs. Chart Review)</td><td>17.4 (11.6–23.1)</td><td>99.6 (99.3–99.9)</td><td>92.0 (85.9–98.2)</td><td>81.8 (76.5–87.2)</td></tr>
<tr><td>Stage 2 or 3 AKI (vs. Chart Review)</td><td>40.3 (CI NR)</td><td>NR</td><td>NR</td><td>99.9 (CI NR)</td></tr>
<tr><td>Stage 3 AKI (vs. Chart Review)</td><td>36.5 (CI NR)</td><td>99.9 (CI NR)</td><td>NR</td><td>NR</td></tr>
<tr><td>AKI (vs. Electronic Medical Record)</td><td>11.7 (8.8–14.5)</td><td>98.9 (98.2–99.5)</td><td>83.5 (75.4–91.7)</td><td>69.3 (66.9–71.7)</td></tr>
</table>
</td><td>- Cohort admitted between 1996 and 2008; nearly 50% of hospitalizations used for chart review were between 1996 and 2002. Sensitivity significantly increased when comparing hospitalizations between 1996 and 2002 vs. 2002 and 2008; age <65 vs. ≥65 years. This may reflect increased AKI awareness
- Electronic medical record data is from one center, which may limit generalizability</td></tr>
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TABLE 2 | Continued

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<tr><td>Maass et al. (52)</td><td>ARF</td><td>Adults, aged 65 years or older, hospitalized in Germany between May-December 2010</td><td>3000 (of which 1500 were post-operative)</td><td>Discharge billing codes, including ICD-10 diagnostic and procedure codes for ARF</td><td>Standardized review of selected medical charts for ARF</td><td><table>
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<tr><td>ARF</td><td>17.6 (12.7–24.1)</td><td>99.2 (98.7–99.4)</td><td>56.6 (CI NR)</td><td>NR</td></tr>
</table></td><td>- KDIGO criteria not applied</td></tr>
<tr><td>D'Arienzo et al. (53)</td><td>AKI</td><td>Children (aged 0–18 years) without ESRD admitted to pediatric ICU in Canada between 2003 and 2005</td><td>2051 (355 cardiac surgery, 1696 non-cardiac surgery)</td><td>Provincial health care administrative database using ICD-9 primary and secondary diagnostic and dialysis procedure codes</td><td>Standardized chart review using KDIGO AKI definition (using SCr or UO criteria) and severity</td><td><table>
<tr><th></th><th>Sensitivity-% (CI)</th><th>Specificity-% (CI)</th><th>PPV-% (CI)</th><th>NPV-% (CI)</th></tr>
<tr><td>Cardiac Surgery, Any AKI</td><td>5.9 (4.7–7.6)</td><td>100 (99.2–100)</td><td>100 (88.2–100)</td><td>49.4 (47.5–51.4)</td></tr>
<tr><td>Cardiac Surgery, Stage 2 or Worse AKI</td><td>14.1 (10.8–18.2)</td><td>99.3 (98.7–99.7)</td><td>81.8 (67.4–91.2)</td><td>84.0 (82.5–85.4)</td></tr>
<tr><td>Cardiac Surgery, Stage 3 AKI</td><td>14.3 (9.7–20.5)</td><td>98.1 (97.3–98.7)</td><td>45.5 (31.7–59.8)</td><td>91.3 (90.0–92.4)</td></tr>
<tr><td>Non-Cardiac, Any AKI</td><td>13.8 (12.6–15.1)</td><td>99.1 (98.9–99.3)</td><td>82.4 (78.2–85.8)</td><td>78.5 (77.8–79.2)</td></tr>
<tr><td>Non-Cardiac, Stage 2 or Worse AKI</td><td>23.6 (21.3–26.1)</td><td>98.3 (98.0–98.5)</td><td>61.8 (57.0–66.3)</td><td>91.7 (91.1–92.1)</td></tr>
<tr><td>Non-Cardiac, Stage 3 AKI</td><td>42.2 (38.0–46.5)</td><td>98.0 (97.7–98.2)</td><td>51.5 (46.7–56.2)</td><td>97.1 (96.7–97.3)</td></tr>
</table></td><td>- Small sample size for cardiac surgery cohort
- Center-specific practices may limit generalizability
- Cohort admitted between 2003 and 2005; higher sensitivity may be apparent based on more current practices and increased AKI awareness</td></tr>
<tr><td>Etzioni et al. (54)</td><td>ARF</td><td>Adults hospitalized for surgical operations across 8 hospitals in USA between 2013 and 2015</td><td>41,432 surgical hospitalizations (37% general surgery, 20% orthopedic)</td><td>Intra-hospital administrative data using ICD-9 codes diagnostic and dialysis procedure codes</td><td>ACS' NSQIP administrative data, including patient information, treatment, and complications</td><td>Concordance (Cohen Kappa value) between administrative and ACS NSQIP data for ARF: 0.10.
Hospital-specific concordance was not statistically significant ($P = 0.19$), suggestive of significant inter-hospital heterogeneity for ARF</td><td>- Absence of a "gold standard," Reference standard did not use chart reviewed data and confirm AKI using SCr or UO data
- Significant inter-hospital variability is likely contributory to poor concordance</td></tr>
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TABLE 2 | Continued

References	Validated Measure	Study Population	N	Administrative Health Data Source	Reference Standard	Study Findings	Sensitivity-% (CI)	Specificity-% (CI)	PPV-% (CI)	NPV-% (CI)	Limitations
Garland et al. (55)	AKI-RRT	Adults (aged 40 years or older), requiring life support, admitted to 11 adult ICUs in Canada between 2007 and 2012	20,764 hospitalizations involving 17,624 unique individuals	Intra-hospital administrative database using ICD-10 diagnostic and procedure codes. For RRT, codes representing intermittent or continuous HD, excluding PD, were used	Clinical data from combined Winnipeg ICU database and Manitoba dialysis registry	HD Codes	92.2 (90.2–93.8)	96.6 (96.3–96.9)	55.4 (52.8–57.9)	99.6 (99.5–99.7)	- Single-center data may limit generalizability - Absence of a "gold standard," Reference standard did not use chart reviewed data and confirm AKI using SCr or UO data
						Above + HD Catheter Codes	92.3 (90.3–93.9)	96.2 (96.0–96.5)	52.8 (50.3–55.3)	99.6 (99.5–99.7)	
						Above + ARF Diagnostic Codes	94.5 (92.8–95.9)	86.7 (86.2–87.1)	24.4 (23.0–25.9)	99.7 (99.6–99.8)	

ACS' NSQIP, American College of Surgeons' National Surgical Quality Improvement Program; AKI, acute kidney injury; AKI-RRT, AKI receiving renal replacement therapy; AMI, acute myocardial infarction; ARF, acute renal failure; CABG, coronary artery bypass graft; CI, confidence interval; CRRT, continuous renal replacement therapy; ESRD, end-stage renal disease; HD, hemodialysis; ICD-9, International Classification of Disease, Ninth Revision; ICD-10, International Classification of Disease, Tenth Revision; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; NHDS, National Hospital Discharge Survey; NIS, Nationwide Inpatient Sample; NPV, negative predictive value; NR, not reported; PD, peritoneal dialysis; PPV, positive predictive value; SCr, serum creatinine; UO, urine output.

did not improve sensitivity of administrative health care data, relative to chart review, using creatinine only (sensitivity 11.7 vs. 17.4%) (51). Of note, the authors used KDIGO criteria for creatinine, but a more stringent definition for urine output, to improve sensitivity. In another study of children admitted to ICU, sensitivity was also not improved when using creatinine or urine output criteria, relative to creatinine alone (53). However, urine output criteria alone, relative to creatinine alone, had higher sensitivity for detecting any AKI (13.7 vs. 5.9%) and for detecting stage 2 or worse AKI (18.2 vs. 14.1%). NPV was more variable (49.4–99.7%), but most reported an NPV of >80%. PPV was more variable (24.4–100%), but most reported PPV of >50%. These results are consistent with those published in an earlier systematic review (47).

There are a number of limitations when validating administrative data for AKI. The most significant problems are related to the fact that the definition of AKI has changed significantly in the past 15 years, which is certainly a source of misclassification bias of AKI outcomes (16). Although oliguria has been associated with increased mortality in ICU populations and is an important component of the KDIGO definition (3, 63), urine output data are also difficult to extract from administrative databases and even chart review (51). Most validation studies have used creatinine criteria alone. Further validation studies are required to validate the use of billing codes using KDIGO criteria, different stages of severity, and inclusion of serum creatinine and/or urine output criteria for use in administrative health research.

There are additional challenges with validity when interpreting data based on physician billing codes. Physician billing practices change as our understanding of the significant morbidity and mortality associated with AKI evolves over time. For example, it is unclear whether practice changes are responsible for the increasing incidence of AKI observed from administrative health studies; however, the only study comparing administrative data at different time periods (2005 vs. 2010) did not show any significant change in PPV over time (50). Many administrative databases report only a limited number of billing codes; therefore, patients with milder AKI may be underrepresented. As well, billing codes have continued and will continue to change over time, requiring repeated validation of newer codes (16, 64). However, one study comparing administrative data derived from *ICD-9* vs. *ICD-10* billing codes showed no change in sensitivity (80.0%) and only a small decrease in specificity (98.3 vs. 95.5%), respectively (59).

Another major issue is limited generalizability, or external validity, given the significant heterogeneity of these studies (16). For example, the study by D'Arienzo et al. suggests that sensitivity may be lower in pediatric patients with milder AKI and/or post–cardiac surgery (53). The study by Schaffzin et al. suggests that sensitivity is lower in pediatric patients with nephrotoxin-related AKI (49). These results reflect the significant heterogeneity in the populations studied, including age, disease severity, and etiology of AKI. Furthermore, practice standards are highly variable for the recognition and management of AKI, and this may be different across countries or academic vs. community centers. The reference standard is usually based on standardized chart review at one to two academic centers; these results may not be generalizable to nationwide practice for patients with AKI. Finally, administrative databases may not capture certain segments of the population in countries where there is both universal public and private health care systems and/or large uninsured populations (16).

In summary, these validation studies continue to be limited by variable definitions for AKI, significant heterogeneity of data sources and population studies, and reduced generalizability. Future studies are needed to further validate subpopulations, particularly in the pediatric population; as well, standardized guidelines for defining AKI using discharge billing codes will be essential in improving the applicability of administrative data to AKI health research (19).

EPIDEMIOLOGY AND OUTCOMES OF AKI

Administrative health research has served as an important methodological source for a number of observational epidemiology studies, which have fundamentally changed our understanding of AKI. This section will focus on studies in AKI conducted using administrative health data in the past 5 years.

Incidence

AKI is common in hospitalized patients with particularly high incidence rates seen in critically ill, post–cardiac surgery, oncology, and nephrotoxin-exposed adults and children (1, 3, 62, 65, 66). However, there have been conflicting results regarding the changing temporal trends in AKI and AKI receiving KRT. One of the first studies used a national database to identify cases of AKI receiving KRT using *ICD-9* codes and found that from 2000 to 2009, the incidence had increased by an average of 10% per year (67). Another study identified more than 18,000 adult patients with AKI receiving KRT using *ICD-10* codes between 2000 and 2012 (68). The authors found that the crude incidence rate of AKI receiving KRT increased nearly 3-fold from 2000 to 2006; although the rate of growth remained stable between 2006 and 2012, the use of continuous renal replacement therapy (CRRT) increased throughout this period and especially in patients >75 years with high comorbid disease. In children, a similar trend of dialysis receiving AKI has been reported (69). Our group found an increasing trend in the incidence of AKI, as well as use of hemodialysis and CRRT among hospitalized children (1 month to 18 years) in Ontario, Canada (69). However, another large study, which compared the annual AKI incidence rate using data from an electronic health record surveillance tool and administrative data (70), found no difference in AKI incidence between 2006 and 2014 when adjusted for age and sex using either data source.

Short-Term Outcomes

Health administrative databases have improved our understanding that AKI is independently associated with increased hospital mortality and morbidity, including length of hospital and ICU stay, and increased health care costs. One study in Japan across more than 280 hospitals showed a decreasing trend in crude in-hospital mortality from 45% in 2007 to 36% in 2016 (71). An Italian study showed in-hospital mortality rate of nearly 30% with the highest risk being in patients with AKI receiving KRT [odds ratio, 2.7; 95% confidence interval (CI), 2.7–2.8] (72). Finally, another Canadian study showed mortality rates between 30 and 40% for adult patients with AKI receiving KRT, but no association with increased mortality in centers who manage a lower volume of patients requiring KRT (73). The Canadian study in children with AKI receiving KRT also examined 30-day mortality, finding an increased rate from 14 to 25% between 1996 and 2009, although this rate subsequently decreased to 19% by 2015 (69). Another study in Japan included pediatric patients (>12 years) and reported 50% in-hospital mortality rate for patients treated with CRRT (74).

Several studies have also described rates of renal recovery, as well as the recurrence risk after AKI, both of which reflect a growing appreciation for AKI as a dynamic process (75–78). A study of critically ill children in Canada showed that children with stage 3 AKI were more than 3-fold likely to have elevated serum creatinine at discharge (>1.5× baseline), relative to those without stage 3 AKI (79). A small study examined children who received ventricular assist devices (VADs) for heart failure and subsequently went on to undergo heart transplant (80). Those children without renal recovery (serum creatinine ≥1.5× baseline) 7 days after VAD implantation, relative to children who had full recovery, were not at increased risk for CKD at 1 year following heart transplant; however, those with reduced estimated glomerular filtration rate 1 month after VAD implantation were at increased risk for CKD.

There is also increased interest in the relative cost and burden associated with AKI. One study in Alberta, Canada, estimated the incremental cost of AKI to be more than Canadian $200 million per year (81). Patients with AKI receiving KRT had prolonged length of stay by more than 7 days and increased cost by up to $20,000, relative to patients without AKI. Another large study of adults from Alberta, Canada, undergoing cardiac surgery also showed increased length of stay and costs associated with increased AKI severity (82).

Risk Factors

Risk factors for AKI in hospitalized patients include extremes of age, underlying illness (i.e., sepsis, cardiovascular disease with or without bypass surgery, oncologic disease), nephrotoxin exposure, inflammatory mediators (i.e., cytokine release), and disease severity (62, 75, 83–89). A large study in the United States of 3.6 million postsurgical patients found that AKI was common postoperatively, affecting more than 10% of hospitalized patients (86). AKI in patients with CKD is also an important risk factor for subsequent progression to ESKD (88). One study highlighted that patients who progressed from stage 3 to stage 4 CKD also had a high risk for AKI (89). Other subpopulations noted to be at increased risk for AKI-related morbidity and mortality include adults with decompensated liver disease (90) and stroke (91).

A number of studies have examined the impact of nephrotoxic medications using administrative health data (92–98). One study in hospitalized children across six of the largest children's hospitals in the United States found that combined use of vancomycin with piperacillin/tazobactam conferred more than 3-fold increased risk for antibiotic-associated AKI, relative to vancomycin with another antipseudomonal antibiotic (93). Other nephrotoxins examined include non-steroidal anti-inflammatory drugs in young, healthy adults (94), brands and dosing of immunoglobulin products (95), and statin use in elderly patients (96), all of which showed modest associations with AKI. Administrative data were also used to develop an evidence-based nephrotoxin medication list that could be used as part of a screening program for AKI in children (98).

Long-Term Outcomes

AKI is associated with increased risk for development of cardiovascular disease, CKD, and ESKD in adults (1, 75, 78, 83, 99). A study in Northern California, including more than 43,000 patients, showed that AKI in adults is independently associated with HTN as early as 6 months after initial event (99). Another large study of more than 100,000 patients in the United States showed that more than 30% of hospitalized adults with AKI went on to develop CKD at 1-year follow-up (78).

The risks of long-term kidney and cardiovascular sequelae after pediatric AKI remain uncertain, at least partially due to the fact that studies have lacked comparator cohorts, have had high losses to follow-up, and/or have had short follow-up periods. Recent prospective cohort studies have conflicting results; TRIBE-AKI, FRAIL-AKI, and ASSESS-AKI all found that cardiac surgery–associated AKI survivors have similar 4–7-year kidney outcomes vs. children without AKI (24–26), whereas Benisty et al. found higher long-term risks of CKD and HTN among survivors of ICU-associated AKI (27). Although there is a clear signal of increased CKD risk among pediatric AKI survivors in other cohort studies (6, 13, 28–30), the long-term outcomes after episodes of dialysis-receiving AKI remain uncertain.

Health administrative databases provide a unique opportunity to follow children many years after an episode of AKI, even after the age of 18 years, to study their long-term outcomes. Moreover, CKD and HTN-related cardiovascular changes start early in life; therefore, it is essential to understand the timing and magnitude of the onset of these events after an episode of AKI, so that appropriate treatment can be initiated in time to address these risk factors and avoid or delay future cardiovascular disease (100). Current AKI guidelines in neonates and children do not provide recommendations for long-term follow-up, primarily due to a lack of studies with robust data.

Several studies have examined long-term outcomes in hospitalized children with AKI. A recent study from Ontario using administrative health data with median 10-year follow-up compared children surviving AKI receiving KRT with hospital-matched controls (101). The authors found that these children had significantly increased hazard for major adverse kidney events (composite outcome of kidney failure and all-cause mortality) [adjusted hazard ratio (HR), 4.97; 95% CI, 4.04–6.10], CKD (adjusted HR, 8.70; 95% CI, 6.68–11.34), and HTN (adjusted HR, 3.35; 95% CI, 2.59–4.33). Another cohort of critically ill children with AKI in Quebec was also found to have increased risk for mortality 5–7 years following hospital discharge, relative to children without AKI (adjusted HR, 3.1; 95% CI, 1.5–6.6) (6). Health care utilization was also increased for critically ill children with AKI, relative to children without AKI, including increased hospitalizations and physician visits at 5 years following hospital discharge (7). This cohort also had increased risk for HTN (adjusted HR, 2.19; 95% CI, 1.47–3.26) (9) and CKD (adjusted HR, 2.2; 95% CI, 1.1–4.5) (8) at 5-year follow-up, defined using administrative health care data. Another study following critically ill children with congenital heart disease showed that those who developed AKI within 5 days of cardiac surgery were at significantly increased risk for CKD at 5 years, relative to those who did not develop AKI (HR, 3.8; 95% CI, 1.4–10.4) (102). We have also previously reported that, among children who underwent cardiac surgery for congenital heart disease, those who received dialysis for AKI during their index cardiac surgery admission were at a 5-fold higher risk of ESKD (crude HR, 5.0; 95% CI, 2.0–12.6) compared with those who did not receive dialysis during their cardiac surgery admission (103).

CONCLUSION

Our understanding of AKI has undergone a significant transformation over the past 15 years partly due to methodological advances in which AKI has been studied by epidemiologists (1). Hand-in-hand with a veritable explosion of research demonstrating the morbidity and mortality related to AKI in adults and children, there has been significant attention paid to "big data" (18, 25, 37). Registries containing administrative health care data are readily available, efficient, and large (14, 19). Validation studies have been shown that administrative health care data are highly specific, despite having modest sensitivity, for the diagnosis of AKI. There are important limitations as well, including heterogeneity of data sources and inconsistent reporting on specific outcome measures (i.e., quality of life, patient-reported outcomes). The statements from the ADQI consensus conference recognized many strategies by which administrative health data could be applied to AKI-specific research studies and address knowledge gaps in the field (18–23).

Studies using administrative health care data have expanded our understanding of the incidence, risk factors, and outcomes of AKI in both adults and children. Importantly, we have demonstrated that these clinically relevant findings have been supported by results from traditional data sources. Continued progress in the application of large data sources to epidemiological studies will continue to further our understanding of important patient-related outcomes of adults and children with AKI.

AUTHOR CONTRIBUTIONS

EU drafted the manuscript, prepared the figures, and reviewed and revised the manuscript. GS also contributed to the manuscript and reviewed and revised the manuscript. RC supervised the manuscript preparation and reviewed and revised the manuscript for intellectual content. MZ reviewed and revised the manuscript for intellectual content. All authors approved the final manuscript as submitted.

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