Temporal trends in acute kidney injury in a cohort of hospitalized Albertan patients

by

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Abstract:

Introduction: Acute kidney injury (AKI) is associated with significant morbidity and mortality. It affects approximately 4 to 7% of hospitalizations each year with a reported annual increase of 10% in incidence. Many studies have relied on administrative diagnostic codes to describe temporal trends in AKI, which have poor sensitivity in identifying AKI. Furthermore, few studies have shown demographic trends in AKI using serum creatinine-based definitions (KDIGO AKI).

Objective: We aimed to identify trends in AKI using diagnostic codes and KDIGO AKI and associated severity, mortality, and demographic changes over a 10-year study period. We also aimed to identify change in recognition of AKI through diagnostic codes during the study period.

Design, setting, and participants: The retrospective cohort was composed of adult patients admitted to hospital in Alberta, Canada from 2009 to 2018 using the Alberta Kidney Disease Network database.

Exposure/Measure: AKI was assessed using validated KDIGO AKI definitions and AKI diagnostic codes. AKI associated in-hospital acute dialysis, in-hospital all-cause mortality, and 90-day post discharge all-cause mortality were assessed. We used generalized linear models with a Gaussian family to determine the absolute rates of AKI and mortality by year of incidence. We determined the sensitivity and specificity of AKI diagnostic codes using KDIGO AKI definitions as the standard of reference.

Results: Between January 2009 and December 2018, we identified 348, 242 hospitalizations with an episode of AKI (12.3%). An increase in rates of AKI was seen using both AKI diagnostic codes and KDIGO AKI definitions with an unadjusted mean rate increase of 14.2/1000 hospitalizations [95% CI 12.7,15.6, $p < 0.01$] noted in the latter. Stage 1 AKI was the most common (unadjusted mean rate 88.6/1000 hospitalizations [95% CI 88.2,89.0]). There was an overall decrease in in-hospital mortality across all stages of AKI with the greatest decrease noted in stage 3 AKI (unadjusted rate difference -80.8/1000 AKI Stage 3 hospitalizations [95% CI -

94.9, -66.8]). Similar trends were identified in 90-day mortality. AKI diagnostic codes showed low sensitivity (24.6%), but high specificity (99%) with an improvement noted in AKI recognition over time (17.5% to 33%).

Conclusion: Overall, there has been an increase in rates of AKI in hospitalized patients, largely driven by mild forms of AKI. Despite the increasing rates of AKI, there has been a decrease in mortality, especially in the most severe forms of AKI. In combination with the trends in diagnostic coding, our findings suggest there has been better recognition and, likely as a result, better management of AKI over time.

Preface:

This thesis is an original work by Anita Dahiya. Ethics approval was obtained and the requirement for participant consent was waived by the institutional review boards at the University of Alberta (Pro00053469) and Calgary (REB16-1575). The study is based in part by Alberta Health and Alberta Health Services; however, the interpretation and conclusions of contained are those of the researchers and do not represent the views of the Government of Alberta or Alberta Health Services. There are no competing interests to declare.

The dataset (Alberta Kidney Disease Network database) is not available to researchers due to a contractual agreement with Alberta Health; however, a similar dataset can be obtained from https://absporu.ca/research-services/service-application/. The study was funded through an operating grant from the Canadian Institutes of Health Research held by the project supervisor, Dr. Neesh Pannu.

The thesis was drafted by Anita Dahiya; however, statistical analysis was conducted by a professional statistician, Natasha Wiebe. The thesis was critically reviewed and revised by the project supervisor, statistician, and supervisory committee prior to submission. Part of this manuscript was accepted for poster presentation at the 28th International Conference on Advances in Critical Care Nephrology: AKI & CRRT 2023.

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List of Abbreviations:

ACEi Angiotensin converting enzyme inhibitor

ADQI Acute Disease Quality Initiative

AH Alberta Health

AKDN Acute kidney disease networks

AKI Acute kidney injury

AKIN Acute Kidney Injury Network

ARB Angiotensin II receptor blocker

BMI Body mass index

DIN Drug identification number

eGFR Estimated glomerular filtration rate

ICD AKI Acute kidney injury as defined by ICD diagnostic/administrative codes

ICU Intensive care unit

KDIGO Kidney Disease Improving Global Outcomes

KDIGO AKI Acute kidney injury as defined by KDIGO criteria

KRT Kidney replacement therapy

NHS National Health Service

NPV Negative predictive value

NSAID Non-steroidal anti-inflammatory drug

PIN Pharmaceutical information network

PPV Positive predictive value

RIFLE Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease

RRT Renal replacement therapy

SCr Serum creatinine

US United States

Introduction:

Acute kidney injury (AKI) is a syndrome which involves a sudden decrease in kidney function as a result of functional impairment or direct structural damage. Evidence of injury is typically apparent before clinical manifestations of kidney failure. Unfortunately, AKI is common, especially in the hospitalized population, and is associated with significant morbidity and mortality. Therefore, it is important to accurately identify the population affected by AKI over time in hopes of reducing the burden of this syndrome.

Definition of AKI

The definition of acute kidney injury (AKI) has evolved over time. In 1802, William Heberden had first documented "ischuria renalis" in reference to AKI in his "Commentaries on the History and Cure of Diseases"[1]. In the early twentieth century, there were descriptions of kidney injury secondary to toxins, trauma, pregnancy, and direct surgical interventions[2]. This was followed by the first descriptions of acute tubular necrosis (ATN) in reference to crush injuries sustained by soldiers during wartimes[3]. It was not until 1951 that Homer Smith, in his textbook "The kidney-structure and function in health and disease", introduced the term "acute renal failure". However, for the years that followed, there was no consistent biochemical definition of AKI and so, there was significant variability in the reporting of incidence, prevalence, and outcome.

In 2002, The Acute Dialysis Quality Initiative (ADQI) developed the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End stage kidney disease definition), which not only used a combination of serum creatinine (SCr) values and urine output to account for the severity of injury, but also discussed the timing of injury[4]. The use of the RIFLE criteria introduced the concept of "acute kidney injury" and subsequent use of this criteria showed significant mortality associated with AKI even in the absence of kidney replacement therapy (KRT)[5-8]. Subsequently, the Acute Kidney Injury Network (AKIN) refined the RIFLE criteria to account for smaller changes in the serum creatinine values[9]. Finally, these definitions were further refined to increase sensitivity and specificity to the now more commonly used Kidney Diseases Improving Global Outcomes (KDIGO) criteria[10].

KDIGO definition of AKI

To address the growing prevalence of kidney disease, the KDIGO foundation was established in 2003 with the mandate "to improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement practice guidelines". It was noted that the RIFLE and AKIN criteria, although validated criteria to identify AKI, identified slightly different populations. A study conducted by Joannidis et al showed that the RIFLE criteria failed to detect 9% of cases identified by the AKIN criteria, the majority of which were stage 1 AKI[11]. Stage 1 AKI was found to be associated with a nearly two-fold increase in mortality when compared to cases without AKI. The AKIN criteria failed to identify 26.9% of the cases identified by RIFLE. This study highlighted the need for refinement in the AKI diagnostic criteria. To address this need, the KDIGO criteria was created in 2012 (Table 1) and subsequently validated against the RIFLE criteria in a prospective study, which demonstrated higher sensitivity of the KDIGO criteria[12].

Despite the availability of a consensus criteria, AKI can be challenging to diagnose as clinical suspicion must first prompt either the measurement of serum creatine and/or urine output. Changes in serum creatinine and urine output are late markers of kidney injury, especially in patients without underlying chronic kidney disease[13,14]. Furthermore, the use of changes in serum creatinine to identify AKI rely on the availability of previous creatinine measurements, which may not always be readily available. Lastly, the current KDIGO definition of AKI was derived predominantly from patients admitted to the ICU. There are novel biomarkers available that at high levels suggest renal injury in the absence of changes in serum creatinine; however, there is limited use of these biomarkers in clinical practice due to issues with specificity and limited information on clinical outcomes[14-18]. Finally, there is no defined gold standard for the identification of AKI, but many would consider the KDIGO criteria to be the current reference standard.

Epidemiology of AKI

AKI is a global issue affecting both the community and hospitalized population. In a 2013 meta-analysis of 154 studies that used KDIGO equivalent definitions of AKI, the pooled incidence rates of AKI were 21.6% with 2.3% requiring dialysis[19]. In Canada, greater than 7% of hospitalization are

complicated by AKI, affecting more than 180000 patients annually[20]. Hospitalized patients that are older, male, and more comorbid, especially with pre-existing chronic kidney disease (CKD), are more likely to be affected by AKI[21-24]. Furthermore, a significant proportion of AKI events are diagnosed at the time of admission, suggesting that pre-hospital factors play an important role in the development of AKI[25]. The most common cause of AKI across various settings is hypotension (40.2%) followed by dehydration (38.2%)[26]. However, it is important to recognize that AKI can have several different pathophysiologic etiologies depending on the exposure precipitating the kidney injury.

Unfortunately, the recent studies have also reported annualized increase in AKI incidence. In the few studies that have used serum creatinine-based definitions of AKI, this increase seems to be largely driven by increases in stage 1 AKI[27-29]. It is felt that this increase is attributed to increasing age and comorbidity of patients in combination with increased use of nephrotoxic medications and complex procedures[30]. Given the poor outcomes associated with AKI, there is a call to action to reduce the global incidence of AKI and its associated complications[31-33].

Outcomes associated with AKI

Short term outcomes

AKI is associated with significant morbidity and mortality. In the acute period, a decline in renal function can result in disturbances in acid-base and electrolyte homeostasis and hypervolemia. Hypervolemia is associated with both morbidity and mortality. Studies have shown reduced 90-day survival in patients with AKI complicated by hypervolemia and increased mortality in patients initiated on KRT with a positive fluid balance (odds ratio 2.3, 95% CI 1.2-4.5)[34,35]. Furthermore, AKI is associated with an increased length of stay and increased in-hospital mortality[36-38]. An episode of AKI puts patients at risk of further episodes of AKI (up to 31%), which is associated with progression to CKD[39]. Ninety day follow-up after non-dialysis requiring AKI in critically ill patients showed progression to stage 3,4, and 5 CKD, which was associated with increased mortality correlated with increased severity of CKD[40].

Long-term outcomes

AKI is also associated with poor long-term outcomes. AKI is associated with an increased risk of progression to CKD (pooled adjusted hazard ratio of 8.8) and requirement for KRT[41]. A prospective observation study of 226 patients with AKI requiring dialysis with apparent recovery prior to discharge showed 14% progression to CKD at the end of a 5-year follow up period[42]. Furthermore, 5 to 12.5% of patients after an episode of AKI requiring dialysis require long-term KRT after 10-year follow-up[42,43]. There is a strong association between AKI and poor cardiovascular outcomes.

Twenty percent of patients who have an AKI event during hospitalization will be readmitted within 30 days with heart failure and AKI survivors have 86% increase in death from any cardiovascular cause[44-46]. Even outside of the ICU and corrected for patient age and comorbidities, AKI is associated with high mortality rates[19,47,48]. Studies have shown that there is a graded relationship between AKI severity and mortality[6,49]. This higher risk of mortality relative to hospitalized patients without AKI remains significant even 1-year post AKI event[25,38]. Therefore, accurate identification and awareness of the incidence of AKI is important to optimize the care of patients affected by AKI. Fortunately, recent studies have demonstrated decreasing rates in AKI associated mortality[29,32,33,49,50].

Temporal trends in AKI

With the evolution in definitions of AKI over the past century, there is difficulty comparing the incidence and prevalence of AKI. To simplify large-scale analyses, many studies characterizing trends in AKI have relied on the use of International Classification of Disease (ICD) diagnostic codes. Studies using ICD coding have shown up to a 10-fold increase in the incidence of AKI[51,52]. Furthermore, despite decreasing mortality rates, these studies have shown an increase in dialysis requiring AKI[30]. The use of ICD codes is influenced by changes in diagnostic criteria and awareness of AKI, which may distort the true changes in AKI incidence. To investigate the validity of the use of ICD codes in identifying AKI, Grams et al compared the use of diagnostic codes to KDIGO AKI criteria in 10, 056 patients hospitalized between 1996 and 2008[53]. Unfortunately, ICD codes demonstrated poor sensitivity (17.2%), but high specificity (98%), which questions the validity in using ICD codes to capture trends in AKI incidence.

With the introduction of KDIGO and equivalent criteria, there has been improved standardization in reporting of AKI, especially in the hospitalized population. however, these studies have reported variable changes in AKI incidence, often included a limited patient population, and have not evaluated demographics trends in patients with AKI.

Table 1. KDIGO AKI Criteria

Stage	Change in Serum Creatinine	Urine Output
1	1.5–1.9 times baseline OR Increase of ≥ 0.3 mg/dl (≥ 26.5 mmol/l)	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase of ≥ 4.0 mg/dl (≥ 353.6 mmol/l) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2	< 0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Thesis Objectives

The poor outcomes associated with AKI, have significant implications for health resource utilization and health care costs. It is therefore important for health systems to have an accurate understanding of AKI incidence, the affected patient population as well as temporal trends. In this study, using data collected from a publicly funded, population-based database, we aimed to determine the following using a cohort of hospitalized patients in Alberta, Canada from 2009 to 2018:

1. The trends in AKI incidence using both AKI diagnostic codes (ICD AKI) and KDIGO serum creatinine-based definitions (KDIGO AKI). The use of diagnostic codes is included to compare our results with the current literature and assess the performance of diagnostic codes in reference to the current standard (KDIGO AKI).
2. The demographic changes of patients affected by AKI
3. The change in severity of AKI
4. The change in mortality associated with AKI

Methods:

Data source for the cohort

The cohort was designed using the Alberta Kidney Disease Network database (AKDN) (Figure 1)[54]. This database collects information on physician claims, hospitalizations, ambulatory care visits, and outpatient prescriptions for all adults registered with Alberta Health (AH); this data is subsequently linked to provincial clinical laboratories and renal programs. Additional information on this database has been described elsewhere. In this study, we focused on hospitalized patients who are registered in the database because 1. Most studies conducted on temporal trends have used the hospitalized populations and so this would allow for better comparison. 2. There is a greater number of serum creatinine values drawn in hospital which would increase the likelihood of identifying AKI. 3. There is more information available regarding ICD diagnostic codes in the inpatient population. The cohort included all adult patients (≥18 years) hospitalized between January 1, 2009, and December 31, 2018. The dates were chosen to cover at least a ten-year period. Patients were excluded if they developed end stage kidney disease (ESKD) during the study. ESKD was defined as the initiation of chronic kidney replacement therapy, receipt of a kidney transplant, or development of an estimated glomerular filtration rate (eGFR) <15 mL/min per 1.73m^2. This exclusion criteria were applied as the validity of AKI definitions has not been established in this population.

Characterization of patient demographics and hospitalizations

Patient age, biological sex, and residence were identified using administrative data. Visible minorities were identified using a combination of postal code and 2016 Canadian census data. The Pampalon index of material deprivation was also included to identify socioeconomic inequalities in health care services at the postal code level[55].

Patient morbidities were defined using previously validated algorithms that use a combination of physician claims, hospitalizations, and ambulatory care data[56-59]. Comorbidities included atrial fibrillation, alcohol misuse, asthma, cancer (lymphoma, all metastatic cancers, non-metastatic breast, cervical, colorectal, pulmonary, and prostate cancer), chronic heart failure, chronic pain, chronic obstructive pulmonary disease, chronic liver disease (viral hepatitis B, cirrhosis), severe constipation, dementia, depression, diabetes, epilepsy, gout, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, myocardial infarction, Parkinson's disease, peptic ulcer disease, peripheral artery disease, psoriasis, osteoporosis, rheumatoid arthritis, schizophrenia and stroke or transient ischemic attack. Severe chronic kidney disease was defined as a

sustained eGFR <30 mL/min per 1.73m^2. Data lookback extended as far as April 1994 where records were available as most of the AKDN datasets begin around that time.

Prescriptions included angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and oral non-steroidal anti-inflammatory drugs. A new prescription within 120 days prior to hospitalization was classified as baseline use. Prescription data was collected from the pharmaceutical information network (PIN) which collects patient outpatient medication files for all adults registered in Alberta Health. All drug identification numbers (DINs) were searched on the Health Canada Drug Database. DINs before 1994 have been deactivated and archived and so were not included in the dataset. Table 2 shows a list of drugs included in the analysis (Table 2).

Hospitalizations were characterized by whether time was spent in an intensive care unit or not and by primary diagnosis. Primary diagnosis was categorized as the following: cancer, cardiovascular, gastrointestinal, genitourinary, hematologic, infection, injury, orthopedic, respiratory and other. The primary diagnosis was determined using the first/admission ICD-10 CA diagnostic code found in the discharge abstract database/hospitalization documentation.

Acute kidney injury and mortality

AKI was defined using serum creatinine KDIGO criteria (KDIGO AKI) and AKI diagnostic codes (ICD AKI) (Table 3)[10]. Using serum creatinine values, AKI was defined as an increase in serum creatinine ≥26.5 μmol/L from baseline or an increase >50% of baseline. Baseline serum creatinine was determined using the lowest, most recent outpatient value in the 7 to 365 days prior to hospitalization. If this was not available, the lowest serum creatinine value between 7 days prior to hospitalization and the end of the hospitalization was used. If serum creatinine values were unavailable prior to or during the hospitalization, AKI could not be determined, and the participant was excluded. Urine output information was not included in the determination of AKI. The severity of AKI was determined based on KDIGO staging. ICD AKI was defined using hospital diagnoses related to AKI. Participants were excluded if they have a hospital diagnosis of AKI but did not meet serum creatinine criteria for AKI. AKI requiring dialysis was determined using a combination of procedural codes for dialysis in combination with an AKI diagnostic code. In-hospital mortality was defined using discharge codes. Ninety day mortality was defined as any in-hospital death plus any death that occurred within 90 days of hospitalization, which is identified using Vital Statistics data. The last potential follow-up for participants was December 31, 2018.

Table 2. Names of drugs included in the analysis

Drug Category	Drug Name	Unique DIN, N
ACEi	BENAZEPRIL	15
	CAPTOPRIL	87
	CILAZAPRIL	39
	ENALAPRIL	120
	FOSINOPRIL	42
	LISINOPRIL	174
	PERINDOPRIL	96
	QUINAPRIL	43
	RAMIPRIL	223
	TRANDOLAPRIL	41
ARB	AZILSARTAN	5
	CANDESARTAN	154
	EPROSARTAN	4
	IRBESARTAN	155
	LOSARTAN	134
	OLMESARTAN	74
	TELMISARTAN	94
	VALSARTAN	143
Diuretics	Drug	DIN, N

	ACETAZOLAMIDE	12
	AMILORIDE	3
	BENDROFLUMETHIAZIDE	4
	BUMETANIDE	4
	CHLORTHALIDONE	30
	EPLERENONE	8
	ETHACRYNIC	6
	FUROSEMIDE	80
	HYDROCHLOROTHIAZIDE	407
	HYDROCHLOROTHIAZIDE;AMILORIDE	10
	HYDROCHLOROTHIAZIDE;ENALAPRIL	7
	HYDROCHLOROTHIAZIDE;IRBESARTAN	67
	HYDROCHLOROTHIAZIDE;TRIAMTERENE	10
	INDAPAMIDE	60
	METHYCLOTHIAZIDE	2
	METOLAZONE	6
	SPIRONOLACTONE	9
	SPIRONOLACTONE;HYDROCHLOROTHIAZIDE	5
	TORSEMIDE	5
	TRIAMTERENE	5
NSAIDs	ACETYLSALICYLIC	365

	ACETYLSALICYLIC;METHOCARBAMOL	29
	ACETYLSALICYLIC;ORPHENADRINE	2
	BENZYDAMINE	11
	CARISOPRODOL	1
	CELECOXIB	67
	CHLORZOXAZONE	8
	CYCLOBENZAPRINE	23
	DESMOPRESSIN	26
	DICLOFENAC	114
	DIFLUNISAL	10
	ETODOLAC	18
	ETOPROFEN;KETOPROFEN	44
	FENOPROFEN	2
	FLOCTAFENINE	8
	FLURBIPROFEN	20
	GLUCOSAMINE	1
	IBUPROFEN	190
	IBUPROFEN;METHOCARBAMOL	14
	INDOMETHACIN	36
	KETOROLAC	32
	LUMIRACOXIB	1

	MECLOFENAMATE	0
	MEFENAMIC	7
	MELOXICAM	34
	MEPERIDINE	32
	METHOCARBAMOL	52
	METOCLOPRAMIDE	34
	NABUMETONE	15
	NAPROXEN	150
	ORPHENADRINE	9
	OXAPROZIN	3
	OXYPHENBUTAZONE	2
	PENTAZOCINE	8
	PHENYLBUTAZONE	18
	PIROXICAM	39
	ROFECOXIB	3
	SULINDAC	14
	TENOXICAM	6
	TETRAHYDROCANNABINOL	1
	TIAPROFENIC	26
	TOLMETIN	4
	VALDECOXIB	2

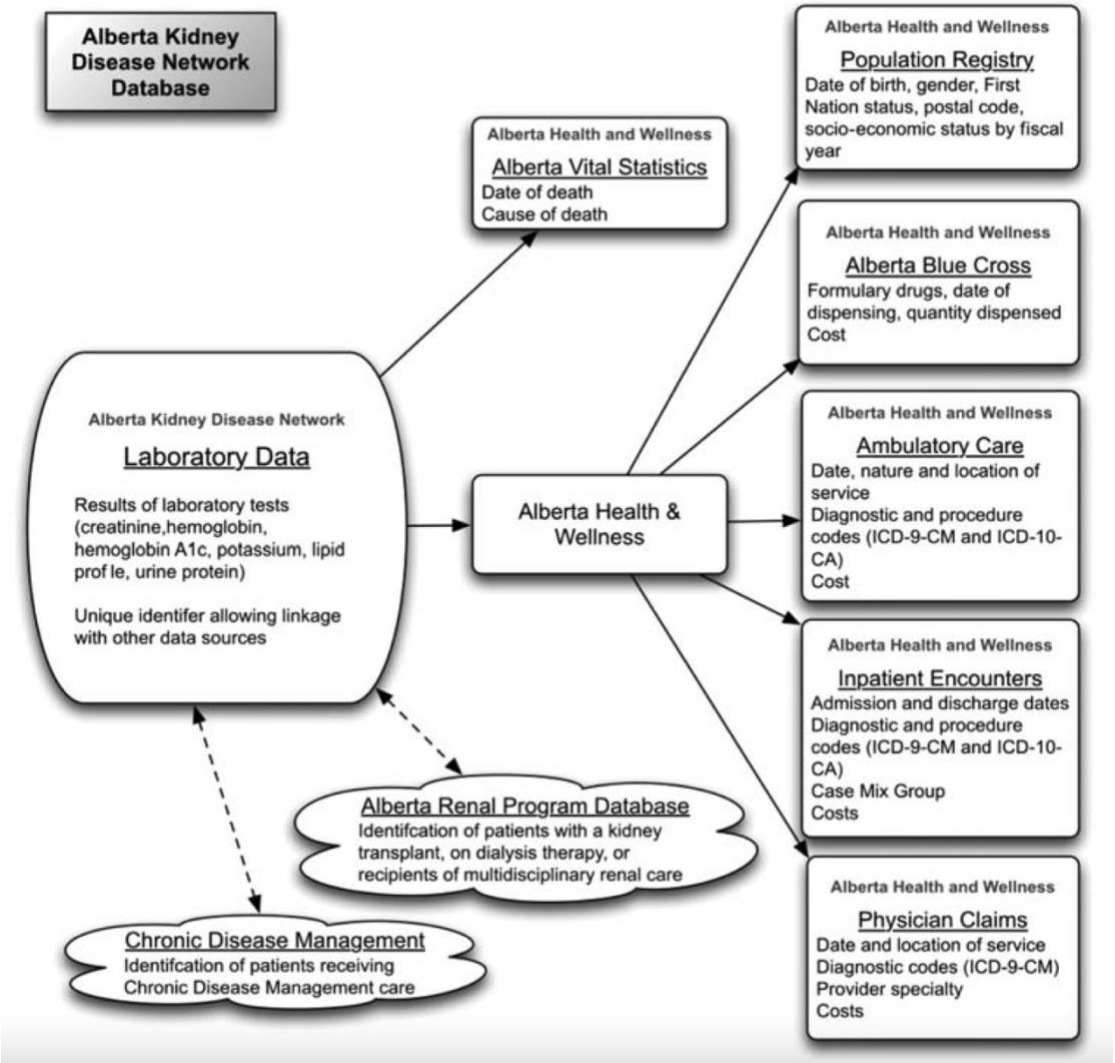

Figure 1. Data source and variables linked to AKDN laboratory database (adapted from Hemmelgarn et al[54]).

Table 3. International diagnostic code data dictionary

Variable	Label	Definition	Value Range
akdnid	De-identified akdn id	Unique id	4 - 5385730
event_date	Hospitalization date	Date of event	Date9.
event_end_date	Discharge date	Date of discharge	Date9.
aki_all_dx	AKI all diagnosis	AKI all diagnosis	1
aki_all_dx_code	AKI all diagnosis code	ICD code ICD 9 CM: 584, 584.5, 584.6, 584.7, 584.8, 584.9 ICD 10 CA: N17, N17.0, N17.1, N17.2, N17.8, N17.9	string
aki_all_dx_codeid	AKI all diagnosis code type	ICD type: ICD 9CM, ICD 10CA	string
aki_rrt	AKI requiring dialysis	AKI requiring dialysis	1
aki_rrt_code	AKI requiring dialysis code	ICD code ICD 9 CM: 584, 584.5, 584.6, 584.7, 584.8, 584.9 With one of: ICD 9 CM procedure: 39.95 ICD 9 CM: V451, V560, V561 ICD 10 CA: N17, N17.0, N17.1, N17.2, N17.8, N17.9 With one of: ICD 10 CA: Z992 Z491 Z490 CCI: 1PZ21HQBR, 1PZ21HQBS, 1JQ53, 1JT53	string
aki_rrt_codeid	AKI requiring dialysis code type	ICD type: ICD 9CM, ICD 9CM procedure, ICD 10CA, CCI	string
aki_mr	AKI most responsible	AKI most responsible	1

Variable	Label	Definition	Value Range
aki_mr_code	AKI most responsible code	ICD code ICD 9 CM: 584, 584.5, 584.6, 584.7, 584.8, 584.9 ICD 10 CA: N17, N17.0, N17.1, N17.2, N17.8, N17.9	string
aki_mr_codeid	AKI most responsible code type	ICD type: ICD 9CM, ICD 10CA	string
rhab	Rhabdomyolysis	Rhabdomyolysis	1
rhab_code	Rhabdomyolysis code	ICD code ICD 9 CM: 728.88 ICD 10 CA: M628.9, T796	string
rhab_codeid	Rhabdomyolysis code type	ICD type: ICD 9CM, ICD 10CA	string

Statistical analyses

The statistical analysis was done in Stata MP 17.0 (www.stata.com). The baseline descriptive statistics were reported as counts and percentages, or medians and inter-quartile limits, as appropriate. To estimate the difference between hospitalization associated with AKI and those without, a generalized estimating equation was used. The data was fit to a binomial distribution. The participant was considered the panel variable and an exchangeable working correlation matrix was used. A panel variable was used as a single participant can have more than one hospitalization. To determine differences in patient characteristics over the calendar years, a generalized estimating equation was used, except with a Gaussian distribution. Again, the participant was used as a panel variable. Changes in patient comorbidities over time were depicted using bar and line graphs. There were missing values in the material deprivation quintile (10.9%) and rural dwelling (1.7%); in these cases, missingness was represented using indicator variables.

The absolute rates of AKI and in-hospital mortality by year of incidence was determined using generalized linear models. The indicator variable in this case was each calendar year. To account for non-independence within participants, robust estimates of standard error were performed. The data was presented as rates per 1000 hospitalizations with 95% confidence intervals. Fully adjusted data represents the rates per 1000 hospitalizations that were adjusted for patient demographics, including age, biological sex, rural residence, and material deprivation, and patient comorbidities. To

determine trends in the rates, the data was fit to a linear model using the continuous version of the calendar year and differences in rates were estimated using the same. The threshold *p* for statistical significance was <0.05.

Calibration and discrimination for AKI diagnostic codes were determined over the study period. Agreement, kappa, prevalence, C statistics, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) were calculated using the KDIGO AKI definition as the reference standard. The data was further stratified by age and sex. To determine the performance of ICD codes for each stage of AKI, the number of AKI events identified by ICD codes was divided by the number of AKI events identified by each stage of AKI identified using KDIGO criteria for each calendar year.

Results:

Cohort characteristics

To generate the cohort, patients were included if they were hospitalized during the study period; this resulted in 4, 475, 847 patients between January 2009 and December 2018 that were initially assessed. Of this, 3, 173, 434 were excluded because they were never hospitalized (3, 155, 965 patients), they had evidence of ESKD and required KRT (7, 321 patients), and/or had an eGFR <15 mL/min per 1.73m^2 (8, 160 patients) (Figure 2). 2, 828, 940 hospitalizations (involving 1, 300, 413 patients) met the inclusion criteria (Table 4). This included 1, 112, 165 hospitalizations for 493, 890 male patients (39.1 and 38.0 %, respectively) and 1, 716, 775 hospitalizations for 806, 523 female patients (60.9 and 62.0%, respectively) (Table 4). We identified 348,242 hospitalizations in 226, 913 patients with an episode of AKI as defined by KDIGO criteria (12.3%). Demographic characteristics of hospitalizations with and without AKI are provided in Table 5. In general, patients with AKI were older (median 70 vs 51 years), more likely to be male (55.3 vs 37.1%), and had more comorbidities (median of 4 vs 2, p value <0.01). Patients with AKI were more likely to have all comorbidities assessed in comparison to patients without AKI. Specifically, patients with AKI were more likely to have diagnosis of hypertension and diabetes when compared to patients without AKI (69.4 vs. 37.8% and 35.3 vs. 15.8%, respectively). The baseline eGFR was lower in patients with AKI (median 70 vs 86 mL/min/1.73m^2, respectively). Patients with AKI were more likely to be prescribed ACEi/ARBs and diuretics (48.7% and 44.8%, respectively) prior to their hospitalization compared to patients without AKI (25.6 and 18.9%, respectively). In comparison, patients without AKI were more likely to be prescribed NSAIDs prior to their hospitalization (15.3 vs 11.2%). The most common primary admitting diagnosis for patients experiencing an AKI event was related to a cardiovascular diagnosis (18.9%); patients without AKI were mostly likely to be admitted for a gastrointestinal diagnosis (9.7%). Patients with AKI were more likely to be admitted to the ICU when compared to patients without AKI (18.8 vs. 5.2%).

Table 4. Inclusion criteria applied to generate the study cohort

Inclusion Criteria	
	Age >18
	No history of ESKD or requirement of chronic KRT
	eGFR >15 mL/min per 1.73m^2
	Hospitalized
	Have serum creatinine data available

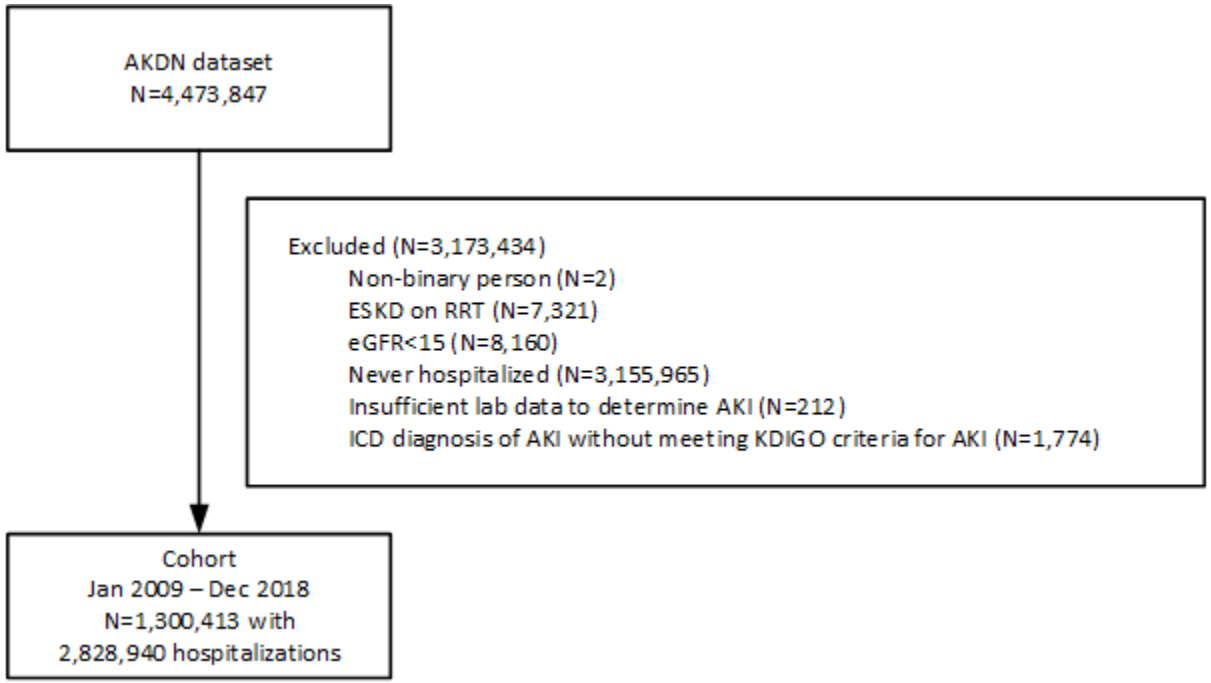

Figure 2. Participant flow for study cohort generation.

Figure 2 Legend: There were 4, 473, 847 hospitalizations from 2009 to 2018 in the province of Alberta. Of which, 2, 828, 940 met all study inclusion and exclusion criteria and were included in the study cohort

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Table 5. Characterization of hospitalizations with and without AKI in the province of Alberta from 2009 to 2018

		AKI	No AKI	Total Population
N (%)		348,242 (12.3)	2,480,698 (87.7)	2,828,940
Age median (Q1, Q3)		70 (56, 82)	51 (32, 69)	54 (33, 72)
Male Sex n (%)		192,718 (55.3)	919,447 (37.1)	1,112,165 (39.3)
Visible minority median (Q1, Q3)		23 (13, 39)	22 (13, 40)	22 (13, 39)
Rural n (%)		49,441 (14.8)	351,879 (14.4)	401,320 (14.4)
Baseline kidney function	**Serum creatinine (μmol/L) median (Q1, Q3)**	84 (64,111)	72 (59, 88)	73 (60, 90)
	Estimated glomerular filtration rate (mL/min/1.73 m^2) median (Q1, Q3)	70 (47, 93)	86 (68,106)	85 (65,104)
Number of comorbidities median (Q1, Q3)		4 (2, 6)	2 (0, 4)	2 (0,4)
Baseline comorbidities n (%)				
	Severe chronic kidney disease	9,753 (2.8)	7,970 (0.3)	17,723 (0.6)
	Hypertension	241,771 (69.4)	938,455 (37.8)	1,180,226 (41.7)
	Diabetes mellitus	122,999 (35.3)	392,527 (15.8)	515,526 (18.2)
	Myocardial infarction	30,118 (8.6)	90,579 (3.7)	120,697 (4.3)
	Heart failure	90,238 (25.9)	216,878 (8.7)	307,116 (10.9)
	Peripheral arterial disease	21,716 (6.2)	60,351 (2.4)	82,067 (2.9)

	Stroke	70,657 (20.3)	251,956 (10.2)	322,613 (11.4)
	Pulmonary disease	117,984 (33.9)	447,736 (18.0)	565,720 (20.0)
	Asthma	25,329 (7.3)	129,613 (5.2)	154,942 (5.5)
	Liver disease	9,099 (2.6)	24,009 (1.0)	33,108 (1.2)
	Peptic ulcer disease	3,310 (1.0)	9,965 (0.4)	13,275 (0.5)
	Cancer	39,296 (11.3)	180,208 (7.3)	219,504 (7.8)
	Pain	78,364 (22.5)	510,683 (20.6)	589,047 (20.8)
Outpatient prescription n (%)				
	ACEi/ARB	169,642 (48.7)	634,414 (25.6)	804,056 (28.4)
	Diuretic	155,906 (44.8)	469,607 (18.9)	625,513 (22.1)
	NSAID	39,030 (11.2)	378,533 (15.3)	417,563 (14.8)
Admission diagnosis n (%)				
	Cardiovascular	65,946 (18.9)	204,118 (8.2)	270,064 (9.5)
	Respiratory	39,905 (11.5)	146,258 (5.9)	186,163 (6.6)
	Gastrointestinal	40,097 (11.5)	240,480 (9.7)	280,577 (9.9)
	Hematologic	18,454 (5.3)	50,029 (2.0)	64,483 (2.4)
	Cancer	23,230 (6.7)	154,999 (6.2)	178,229 (6.3)
	Infection	19,570 (5.6)	34,210 (1.4)	53,780 (1.9)
	Genitourinary	31,610 (9.1)	143,291 (5.8)	174,901 (6.2)
	Orthopedic	11,622 (3.3)	170,933 (6.9)	182,555 (6.5)
	Injury	31,944 (9.2)	229,211 (9.2)	261,155 (9.2)
	Other	65,864 (18.9)	1,107,169 (44.6)	1,173,033 (41.5)
Admission to ICU n (%)		65,594 (18.8)	128,658 (5.2)	194,252 (6.9)

Trends in characteristics of patients with AKI

Over the study period, there was slight, but statistically significant increase in age and the proportion of males and patients from a rural location with AKI (Table 6). There was a statistically significant increase in the number and percentage of comorbidities assessed, apart from chronic pain (Figure 3). Hypertension, followed by diabetes, remained the most common diagnoses throughout the study period. There was an increase in the prescription of ACEi/ARB over time. An increase in AKI in admissions related to respiratory, genitourinary, hematologic, and infectious disease was noted over time with a decrease noted in cardiovascular admissions. There was a decrease in the proportion of patients with AKI who received ICU care (20.1 in 2009 to 18.8% in 2018, $p < 0.01$).

Trends in AKI incidence

Between 2009 and 2018, KDIGO AKI rates increased from 113.4/1000 hospitalizations to 125.9/1000 hospitalizations (unadjusted mean rate increase of 14.2/1000 hospitalizations [95%CI 12.7,15.6], $p < 0.01$) (Figure 4). Over the same period, in comparison to KDIGO AKI, AKI rates defined by ICD diagnostic codes (ICD AKI) demonstrated a greater rate increase, on average, by 22.5/1000 hospitalizations (unadjusted, [95%CI 21.8, 23.3], $p < 0.01$) When adjusted for age, sex, and comorbidities, no statistically significant change is noted in KDIGO AKI rates; however, ICD AKI rates increased on average by 17.9 [95% CI 17.2,18.6, $p < 0.01$].

Trends in AKI incidence by age and sex

KDIGO AKI rates increased with age ($p<0.01$), ranging from a mean rate of 35.3/1000 hospitalizations [95%CI 34.8,35.8] in patients aged 18 to 39 to a mean rate of 251.4/1000 [95%CI 249.8-253.1] hospitalizations

Table 6. Temporal trends in demographic characteristics of patients hospitalized with AKI in Alberta from 2009 to 2018

		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
N		28, 742	29, 849	32, 434	34, 065	34, 755	36, 759	38, 026	37, 501	37, 627	38, 484
Age median (Q1, Q3)		71 (56, 81)	70 (56, 81)	70 (56, 82)	71 (56, 82)	70 (56, 82)	70 (56, 82)	69 (55, 81)	69 (56, 81)	70 (56, 81)	69 (56, 81)
Sex n (%)	**Male**	15, 653 (54.5)	16, 612 (55.7)	17, 836 (55.0)	18, 560 (54.5)	18, 950 (54.5)	20, 125 (54.7)	20, 980 (55.2)	20, 990 (56.0)	21, 106 (56.1)	21, 906 (56.9)
Visible Minority median (Q1, Q3)		23 (13, 38)	22 (13, 37)	23 (13, 38)	22 (13, 38)	22 (13, 38)	23 (13, 39)	23 (13, 39)	23 (13, 38)	23 (13, 40)	23 (13, 40)
Rural n (%)		3, 756 (13.6)	4, 080 (14.3)	4,308 (13.8)	4,345 (13.3)	4,852 (14.5)	4,881 (13.8)	5,003 (13.7)	5,085 (14.1)	6,385 (17.6)	6,746 (18.2)
Baseline kidney function	**Serum creatinine (μmol/L) median (Q1, Q3)**	84 (65, 111)	85 (65, 111)	83 (64, 110)	83 (63, 110)	82 (62, 109)	83 (63, 110)	82 (62, 109)	85 (65, 113)	86 (66, 114)	86 (66, 114)
Number of comorbidities median (Q1, Q3)		3 (2, 5)	3 (2, 5)	4 (2, 6)	4 (2, 6)	4 (2, 6)	4 (2, 6)	4 (2, 6)	4 (2, 6)	4 (2, 6)	4 (2, 6)
Baseline comorbidities n (%)											
	Severe chronic kidney disease	697 (2.4)	709 (2.4)	790 (2.4)	922 (2.7)	907 (2.6)	1,177 (3.2)	1,107 (2.9)	1,111 (3.0)	1,123 (3.0)	1,210 (3.1)

	Hypertension	19,183 (66.7)	20,185 (67.6)	22,283 (68.7)	23,742 (69.7)	24,161 (69.5)	25,712 (69.9)	26, 462 (69.6)	26, 275 (70.1)	26, 590 (70.7)	27, 178 (70.6)
	Diabetes mellitus	9,124 (31.7)	9,760 (32.7)	10,794 (33.3)	11,829 (34.7)	11,925 (34.3)	13,192 (35.9)	13,567 (35.7)	13,886 (37.0)	14,149 (37.6)	14,773 (38.4)
	Myocardial infarction	2,366 (8.2)	2,542 (8.5)	2,654 (8.2)	2,844 (8.3)	3,023 (8.7)	3,127 (8.5)	3,257 (8.6)	3,265 (8.7)	3,445 (9.2)	3,595 (9.3)
	Heart failure	7,438 (25.9)	7,816 (26.2)	8,437 (26.0)	8,836 (25.9)	9,066 (26.1)	9,524 (25.9)	9,704 (25.5)	9,588 (25.6)	9,865 (26.2)	9,964 (25.9)
	Peripheral arterial disease	1,619 (5.6)	1,768 (5.9)	1,903 (5.9)	2,076 (6.1)	2,167 (6.2)	2,355 (6.4)	2,308 (6.1)	2,476 (6.6)	2,461 (6.5)	2,583 (6.7)
	Stroke	5,312 (18.5)	5,752 (19.3)	6,494 (20.0)	6,907 (20.3)	7,097 (20.4)	7,595 (20.7)	7,836 (20.6)	7,906 (21.1)	7,711 (20.5)	8,047 (20.9)
	Pulmonary disease	9,410 (32.7)	9,722 (32.6)	10,981 (33.9)	11,618 (34.1)	11,872 (34.2)	12,542 (34.1)	12,941 (34.0)	12,759 (34.0)	13,058 (34.7)	13,081 (34.0)
	Asthma	2,175 (7.6)	2,208 (7.4)	2,480 (7.6)	2,587 (7.6)	2,592 (7.5)	2,754 (7.5)	2,771 (7.5)	2,624 (7.0)	2,645 (7.0)	2,493 (6.5)
	Liver disease	595 (2.1)	691 (2.3)	720 (2.2)	794 (2.3)	886 (2.5)	952 (2.6)	1093 (2.9)	1075 (2.9)	1124 (3.0)	1169 (3.0)
	Peptic ulcer disease	318 (1.1)	343 (1.1)	319 (1.0)	351 (1.0)	321 (0.9)	333 (0.9)	338 (0.9)	347 (0.9)	345 (0.9)	295 (0.8)
	Cancer	3,125 (10.9)	3,342 (11.2)	3,495 (10.8)	3,918 (11.5)	3,981 (11.5)	3,964 (10.8)	4,271 (11.2)	4,250 (11.3)	4,386 (11.7)	4,564 (11.9)
	Pain	6,470 (22.5)	6,836 (22.9)	7,108 (21.9)	7,432 (21.8)	7,916 (22.8)	8,278 (22.5)	8,590 (22.6)	8,737 (23.3)	8,509 (22.6)	8,488 (22.1)
Outpatient Prescription n (%)											

	ACEi/ARB	13,402 (46.6)	14,374 (48.2)	16,081 (49.6)	16,981 (49.8)	17,396 (50.1)	18,114 (49.3)	18,322 (48.2)	18,048 (48.1)	18,179 (48.3)	18,745 (48.7)
	Diuretic	12,536 (43.6)	13,236 (44.3)	14,984 (46.2)	15,795 (46.4)	15,901 (45.8)	16,645 (45.3)	16,770 (44.1)	16,393 (43.7)	16,646 (44.2)	17,000 (44.2)
	NSAID	3,280 (11.4)	3,490 (11.7)	3,901 (12.0)	4,063 (11.9)	4,068 (11.7)	4,179 (11.4)	4,275 (11.2)	3,913 (10.4)	3,910 (10.4)	3,951 (10.3)
Admission diagnosis n (%)											
	Cardiovascular	5,846 (20.3)	5,846 (19.6)	6,235 (19.2)	6,502 (19.1)	6,519 (18.8)	7,078 (19.3)	7,063 (18.6)	6,868 (18.3)	6,796 (18.1)	7,193 (18.7)
	Respiratory	3,285 (11.4)	3,143 (10.5)	3,610 (11.1)	3,842 (11.3)	3,944 (11.3)	4,389 (11.9)	4,343 (11.4)	4,421 (11.8)	4,598 (12.2)	4,330 (11.3)
	Gastrointestinal	3,278 (11.4)	3,581 (12.0)	3,663 (11.3)	3,859 (11.3)	3,937 (11.3)	4,155 (11.3)	4,417 (11.6)	4,303 (11.5)	4,470 (11.9)	4,434 (11.5)
	Hematologic	1,508 (5.2)	1,631 (5.5)	1,680 (5.2)	1,788 (5.2)	1,798 (5.2)	1,905 (5.2)	1,985 (5.2)	2,032 (5.4)	2,039 (5.4)	2,088 (5.4)
	Cancer	2,124 (7.4)	2,154 (7.2)	2,254 (6.9)	2,269 (6.7)	2,244 (6.5)	2,380 (6.5)	2,470 (6.5)	2,415 (6.4)	2,425 (6.4)	2,495 (6.5)
	Infection	1,359 (4.7)	1,606 (5.4)	1,850 (5.7)	2,091 (6.1)	2,035 (5.9)	2,121 (5.8)	2,162 (5.7)	2,080 (5.6)	2,000 (5.3)	2,266 (5.9)
	Genitourinary	2,252 (7.8)	2,433 (8.2)	2,729 (8.4)	2,952 (8.7)	3,259 (9.4)	3,428 (9.3)	3,568 (9.4)	3,680 (9.8)	3,610 (9.6)	3,699 (9.6)
	Orthopedic	970 (3.4)	1,039 (3.5)	1,180 (3.6)	1,230 (3.6)	1,117 (3.2)	1,175 (3.2)	1,379 (3.6)	1,149 (3.1)	1,196 (3.2)	1,187 (3.1)
	Injury	2,610 (9.1)	2,763 (9.3)	2,919 (9.0)	2,977 (8.7)	3,276 (9.4)	3,307 (9.0)	3,486 (9.2)	3,511 (9.4)	3,552 (9.4)	3,543 (9.2)

	Other	5,510 (19.2)	5,653 (18.9)	6,314 (19.5)	6,555 (19.2)	6,626 (19.1)	6,821 (18.6)	7,153 (18.8)	7,042 (18.8)	6,941 (18.4)	7,249 (18.8)
Admission to ICU n (%)		5,787 (20.1)	5,893 (19.7)	6,172 (19.0)	6,466 (19.0)	6,604 (19.0)	6,774 (18.4)	6,921 (18.2)	6,831 (18.2)	6,806 (18.1)	7,340 (19.1)

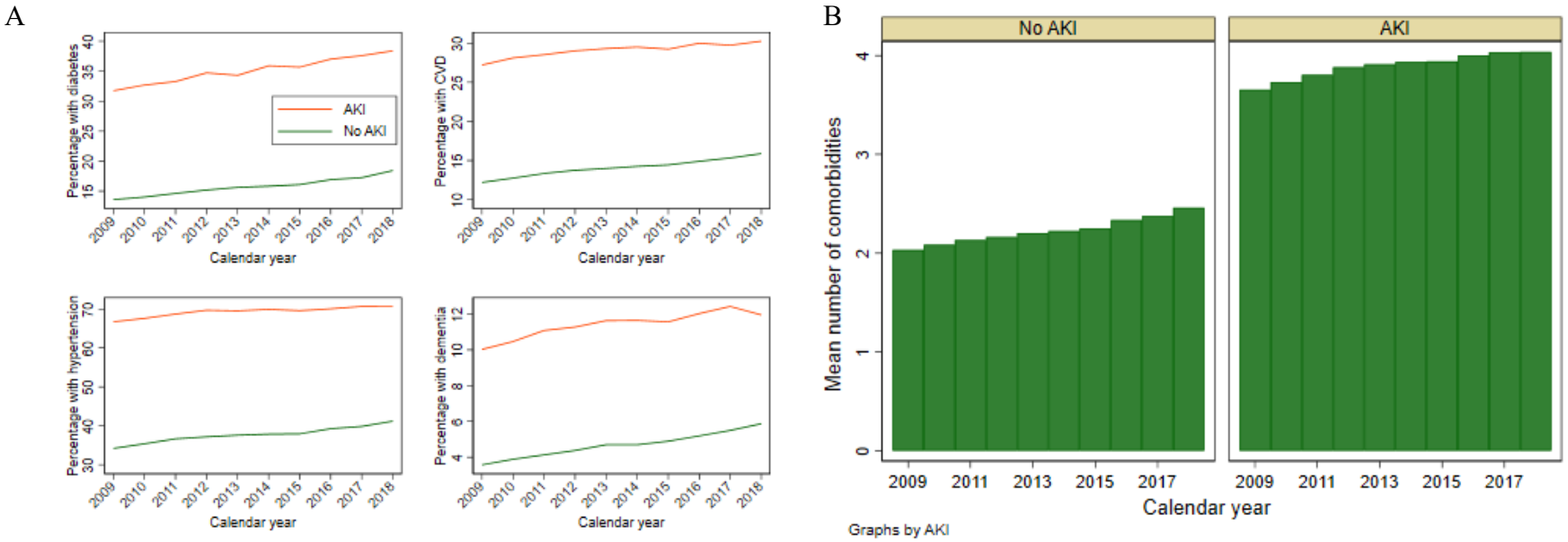

Figure 3. Temporal trends in comorbidities of patients hospitalized with AKI between 2009 and 2018

Figure 3 Legend: Panel A. The percentage of patients with diabetes and hypertension in hospitalized patients with and without AKI admitted between 2009 and 2018. Panel B. The number of comorbidities reported in patients hospitalized with and without AKI between 2009 and 2018.

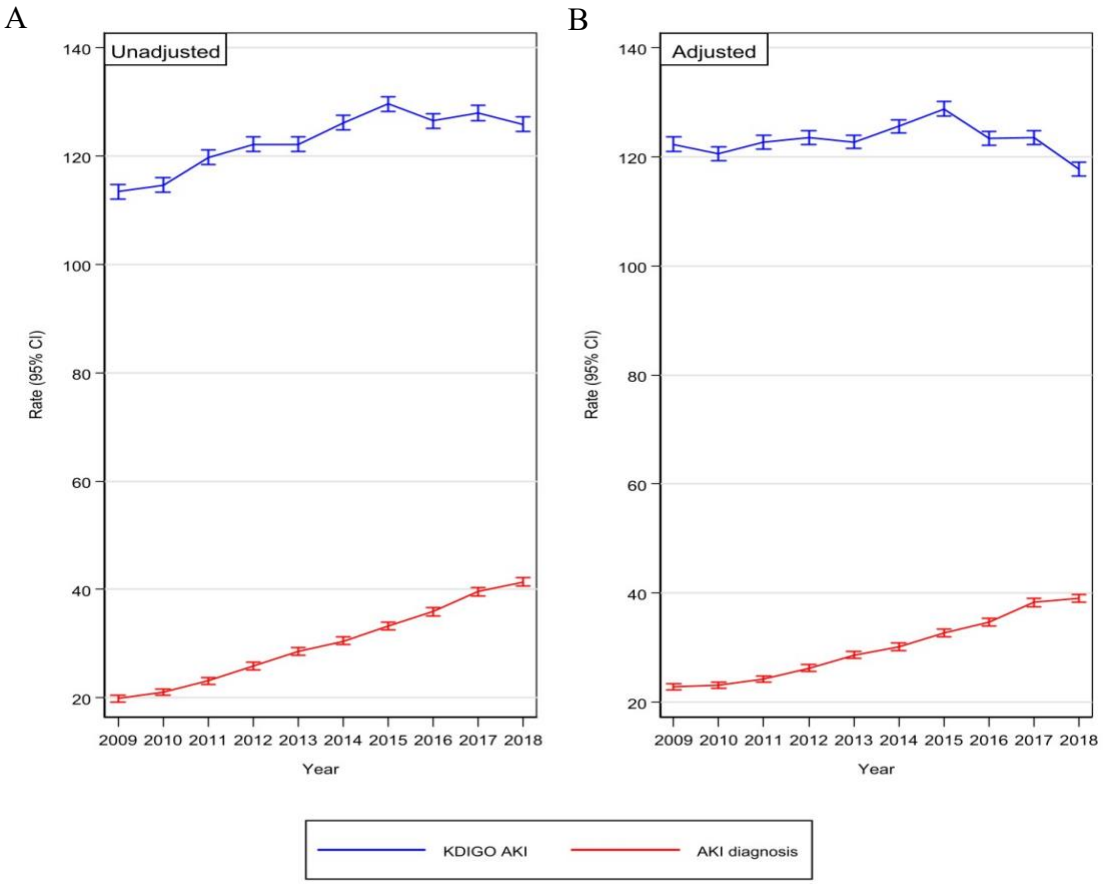

Figure 4. Rates of AKI (per 1000 hospitalizations) in the province of Alberta identified by KDIGO and ICD codes from 2009 to 2018.

Figure 4 Legend: Panel A: Unadjusted rates of AKI per 1000 hospitalizations between 2009 and 2018. Panel B: Adjusted rates of AKI per 1000 hospitalizations between 2009 and 2018 (adjusted for age, sex, rural residence, material deprivation, and comorbidities)

in patients aged 80 year or greater (Figure 5A). ICD AKI rates also increased ($p<0.01$) when stratified by age, ranging from a mean rate of 5.5/1000 hospitalizations [95%CI 5.3,5.7] in patients aged 18 to 39 to a mean rate of 68.0/1000 [95%CI 67.1,69.0] hospitalizations in patients aged 80 or greater (Figure 6A). In patients, aged 18 to 39 and 40 to 59, with KDIGO AKI, an increase in rate of AKI was seen by 7.0 [95%CI 5.6,8.4] and 7.4 [95%CI 6.0,8.8]. A similar increase was seen in patients aged 60 to 79 and greater than 80. Again, the rate difference was statistically insignificant when fully adjusted. An increase in rates of ICD AKI was also seen in all age categories; however, in comparison to KDIGO AKI, a greater rate increase was noted in all age categories (unadjusted rate difference of 20.4 [95% CI 19.7,21.2] in patients aged 18 to 39 to 20.7 [95% CI 20.0,21.4] in patients 80 and older). The increase in rates of ICD AKI remained statistically significant when fully adjusted.

When stratified by sex, the rates of KDIGO AKI increased in both males (unadjusted rate difference 12.5 episodes per 1000 hospitalizations [95%CI 10.7,13.6]) and females (unadjusted rate difference 12.2 episodes per 1000 hospitalizations [95%CI 11.1,14.0]) over the study period (Figure 5B). Males had greater overall rates of AKI (mean rate difference of 82.6/1000 hospitalizations [95%CI 81.6,83.8]). Rates of ICD-AKI also increased in both males and females; (males, unadjusted rate difference 22.0 episodes per 1000 hospitalizations [95%CI 21.4,22.8], females, unadjusted rate difference, 22.1 episodes per 1000 hospitalizations [95%CI 21.3,22.7]) (Figure 5B). Like KDIGO AKI trends when stratified by age, statistical significance was lost when fully adjusted. However, statistical significance in the increase of ICD AKI rates was maintained when fully adjusted.

Trends in AKI severity

In hospitalizations complicated by KDIGO AKI, stage 1 AKI was most common (unadjusted mean rate, 88.6/1000 hospitalizations [95%CI 88.2,89.0]) (Figure 7A). The rates of all stages of AKI severity increased over the study period; however, the greatest increase in rate was seen in stage 1 AKI, which increased by 11.5/1000 hospitalizations [95% CI: 10.0,12.7]. Stage 2 AKI increased by 0.9/1000 hospitalizations [95%CI 0.4,1.4] and stage 3 AKI increased by 1.7/1000 hospitalizations [95%CI 1.3,2.2]. When fully adjusted, the increase in rates of AKI in stages 1 and 3 lost statistical significance (Figure 7B). Interestingly, when fully adjusted, there was a slight, but statistically significant decrease in rates of stage 2 AKI (rate difference of -1.2 [95% CI -1.7,-0.7). The rates of AKI requiring KRT remained stable during the study period (unadjusted rate difference, 0.04/1000 hospitalizations [95%CI -0.01,-0.2], ($p= 0.56$). This did not change when the data was fully adjusted.

Trends in AKI-related mortality

In-hospital mortality increased with severity of AKI (unadjusted mean rate, 93.0/1000 AKI stage 1 hospitalizations vs 308.4/1000 AKI stage 3 hospitalizations; P<0.001) (Figure 8). The greatest decrease was noted in stage 3 AKI (unadjusted rate difference -80.8/1000 AKI stage 3 hospitalizations [95%CI -94.9,-66.8]). Even when fully adjusted, statistically significant decreases in mortality were noted across all stages of AKI. When using ICD AKI, lower rates of mortality were noted; however the trend towards decreasing mortality was preserved (unadjusted rate decrease of -3.4/1000 hospitalizations with AKI [95% CI: -4,-2.7]) (Figure 9).

Similarly, 90-day mortality increased with severity of AKI (unadjusted median rates, stage 1 AKI, 170.6/1000 AKI stage 1 hospitalizations vs 400.0/1000 AKI stage 3 hospitalizations) (Figure 8). Mortality decreased across all stages of AKI with the greatest decrease noted in Stage 3 AKI (unadjusted rate difference -85.7/1000 AKI stage 3 hospitalizations [95%CI -101.3,-70.1]). Again, a decrease in mortality was also noted in 90 day mortality associated with ICD AKI (unadjusted rate difference -2.0 [95% CI: -3.2,-0.8]).

Trends in the performance of coding KDIGO AKI with ICD diagnostic codes

Over time, the sensitivity of coding KDIGO AKI with ICD diagnostic codes has increased from 17.5 to 33.1% (Table 7) and the specificity has decreased from 99.4 to 98.1%. Sensitivity increased with increasing age (26.9% in patients 80 years or more vs. 15.9% in patients 18 to 39 years); however, a specificity was increased in younger patients (99.8% in patients 18 to 39 years and 97.2% in patients 80 years or more). Performance of ICD coding was similar in men and women. An increase in recognition of AKI was noted in all KDIGO stages of AKI with the largest increase noted in stage 1 AKI (Table 8).

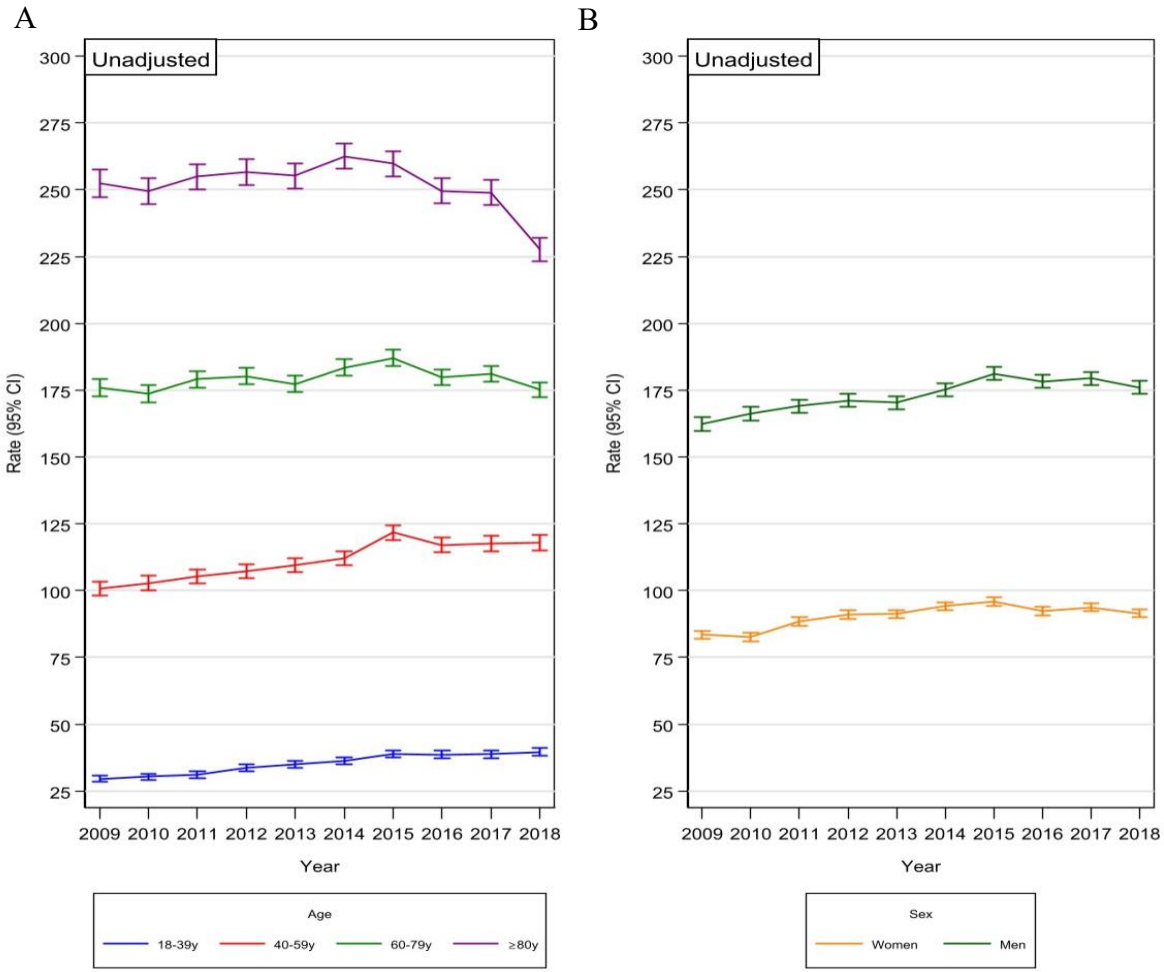

Figure 5. Rates of AKI (per 1000 hospitalizations) identified using KDIGO criteria

Figure 5 Legend: Panel A: Unadjusted rates of AKI per 1000 hospitalizations between 2009 and 2018 stratified by age. Panel B: Unadjusted rates of AKI per 1000 hospitalizations between 2009 and 2018 stratified by sex

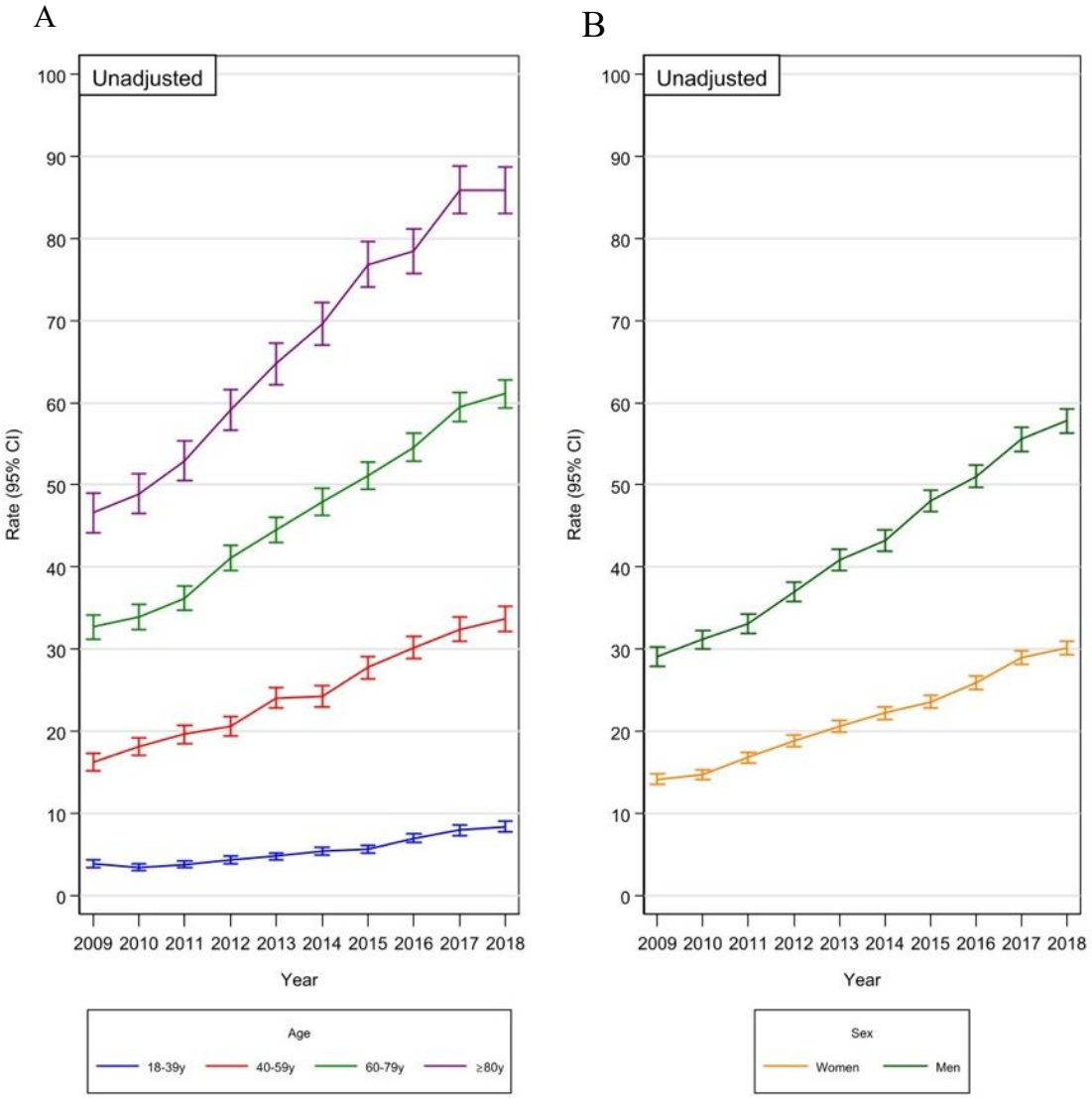

Figure 6. Rates of AKI (per 1000 hospitalizations) identified using ICD codes

Figure 6 Legend: Panel A: Unadjusted rates of AKI per 1000 hospitalizations stratified by age group Panel B: Unadjusted rates of AKI per 1000 hospitalizations stratified by sex

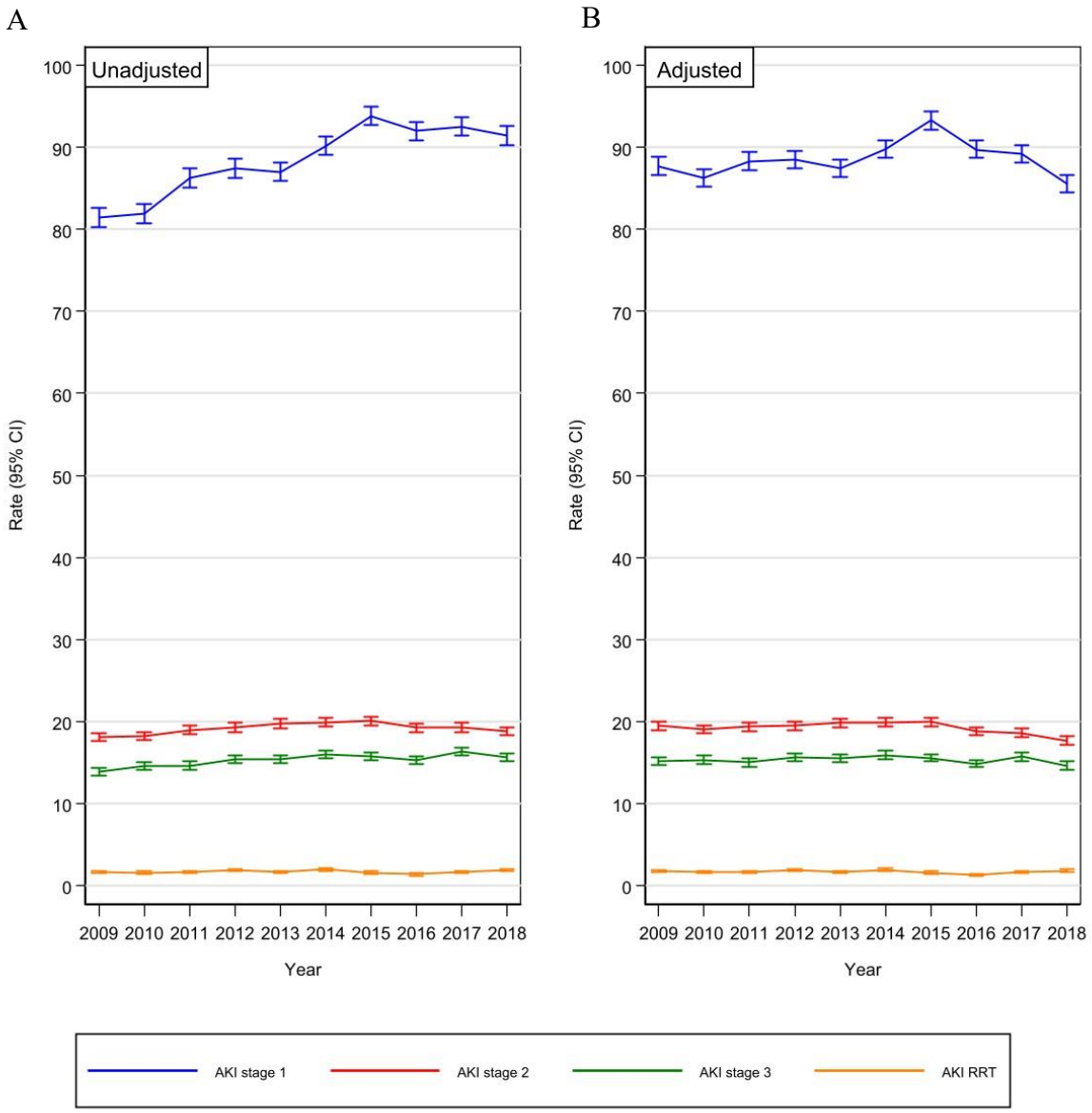

Figure 7. Rates of AKI (per 1000 hospitalizations) stratified by KDIGO severity stage and requirement of renal replacement therapy in the province of Alberta between 2009 and 2018

Figure 7 Legend: Panel A: Unadjusted rates of AKI per 1000 hospitalizations between 2009 and 2018 Panel B: Adjusted rates of AKI per 1000 hospitalizations between 2009 and 2018 stratified by KDIGO severity stage (adjusted for age, sex, rural residence, material deprivation, comorbidities)

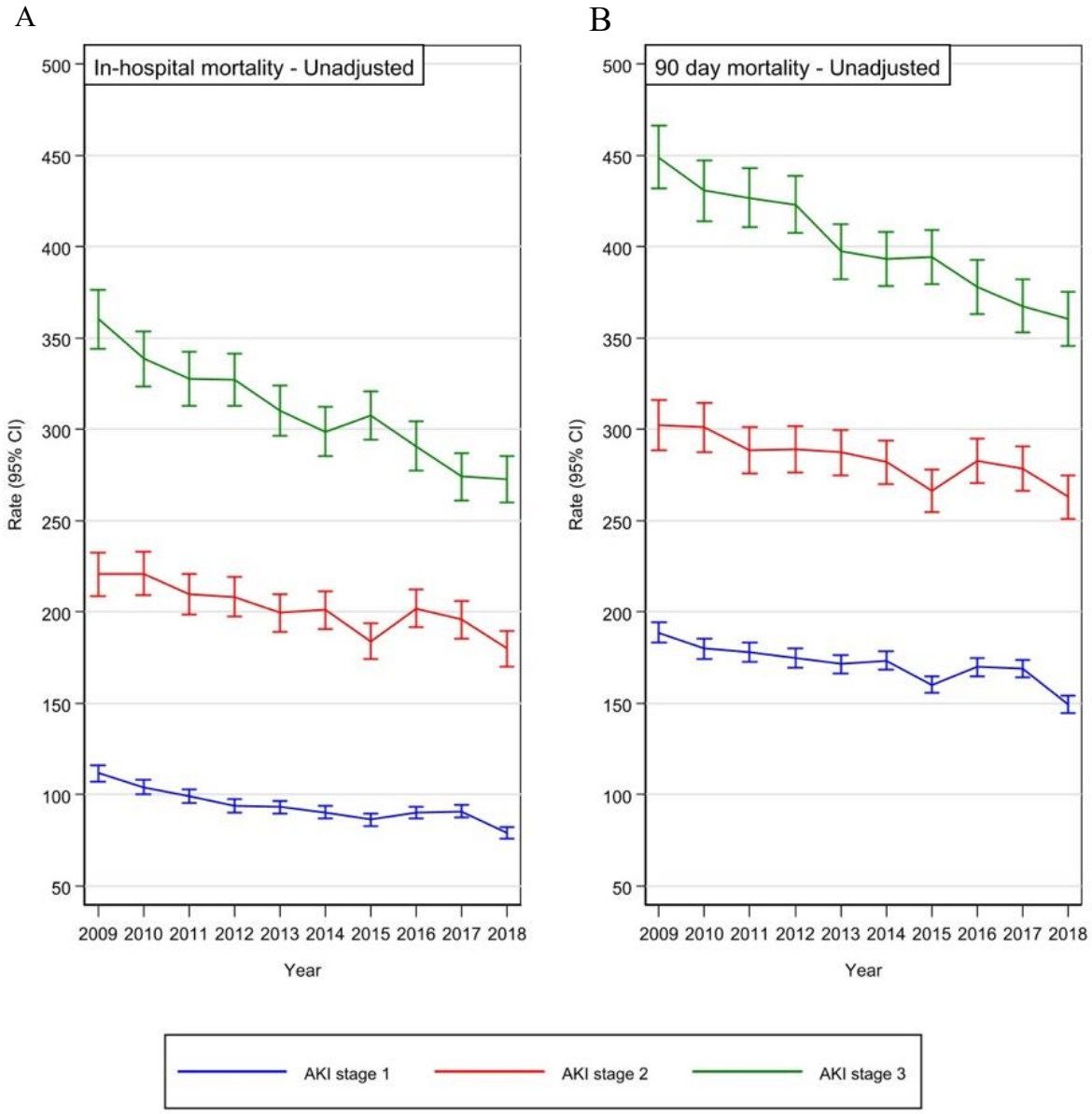

Figure 8. Rates of in-hospital and 90-day mortality (per 1000 stage 1, 2 or 3 AKI hospitalizations) associated with KDIGO AKI

Figure 8 Legend. Panel A: Unadjusted in-hospital mortality rates stratified by severity of AKI in hospitalizations from 2009 to 2018. Panel B: Unadjusted 90-day mortality rates stratified by severity of AKI in hospitalizations from 2009 to 2018

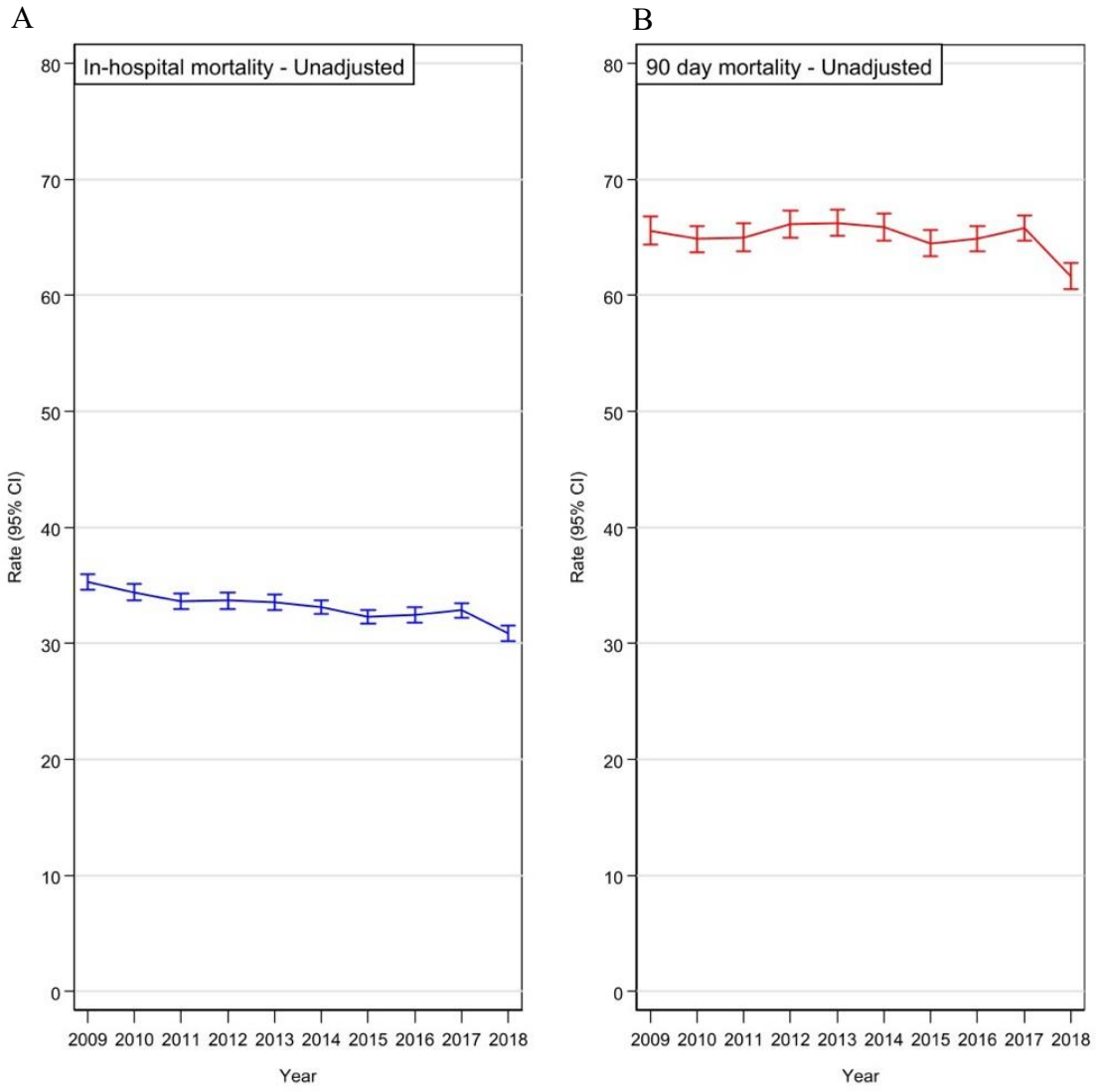

Figure 9. Rates of in-hospital and 90-day mortality (per 1000 hospitalizations) associated with ICD AKI

Figure 9 Legend: Panel A. Unadjusted rates of in-hospital mortality per 1000 hospitalizations from 2009 to 2018 Panel B. Unadjusted rates of 90-day mortality per 1000 hospitalizations from 2009 to 2018

Table 7. Calibration and discrimination for AKI diagnostic codes with KDIGO defined AKI as the reference standard

Characteristic	Agreement	Kappa	Prevalence	C-statistic	Sensitivity	Specificity	PPV	NPV
Overall	0.850	0.322	0.186	0.62	0.246	0.988	0.830	0.852
Year								
2018	0.864	0.403	0.180	0.66	0.329	0.982	0.799	0.869
2017	0.857	0.383	0.186	0.65	0.309	0.983	0.804	0.862
2016	0.855	0.359	0.185	0.63	0.284	0.985	0.810	0.858
2015	0.846	0.330	0.194	0.62	0.256	0.987	0.829	0.847
2014	0.847	0.316	0.190	0.62	0.242	0.989	0.833	0.848
2013	0.850	0.311	0.185	0.61	0.234	0.990	0.844	0.850
2012	0.846	0.286	0.187	0.60	0.212	0.991	0.850	0.845
2011	0.845	0.266	0.185	0.59	0.193	0.993	0.864	0.844
2010	0.846	0.256	0.182	0.59	0.183	0.994	0.872	0.845
2009	0.844	0.245	0.184	0.58	0.175	0.994	0.875	0.843
Age, y								
18-39	0.916	0.242	0.098	0.58	0.155	0.998	0.881	0.916
40-59	0.877	0.313	0.152	0.61	0.223	0.994	0.877	0.877
60-79	0.833	0.333	0.211	0.62	0.263	0.986	0.838	0.833
≥80	0.782	0.306	0.271	0.62	0.271	0.972	0.784	0.782

Biological sex								
Women	0.868	0.322	0.162	0.62	0.241	0.990	0.819	0.870
Men	0.832	0.320	0.211	0.62	0.250	0.987	0.838	0.832

The reference standard is KDIGO defined AKI. The statistics presented above do not account for non-independence; participants can have more than one AKI-related hospitalization within one given calendar year

Table 8. Temporal trends of diagnostic coding of AKI by KDIGO stage

Year	Stage 3	Stage 2	Stage 1	No AKI
2018	0.729	0.449	0.236	0.982
2017	0.682	0.410	0.223	0.983
2016	0.661	0.386	0.199	0.985
2015	0.650	0.342	0.172	0.987
2014	0.631	0.316	0.156	0.989
2013	0.610	0.307	0.150	0.990
2012	0.583	0.283	0.130	0.991
2011	0.566	0.259	0.115	0.993
2010	0.556	0.238	0.105	0.994
2009	0.558	0.224	0.098	0.994

Discussion:

In this population-based study of temporal trends in AKI in a cohort of hospitalized Albertan patients over a ten-year period, we have shown that 12.3% of hospitalizations are complicated by an episode of AKI. Furthermore, we have shown that these rates are increasing using both diagnostic codes and KDIGO criteria. Based on our study, this increase in AKI is largely driven by stage 1 AKI; however, an increase was also noted in stage 3 AKI. There has been a demographic shift in patients experiencing AKI with an increase in comorbidity. Incidence of AKI is also increasing in all age groups and sexes; although, older and male patients continue to be the most likely population to experience AKI in hospital. Absolute mortality in AKI remains high; however, despite this increase in patient comorbidity, there has been a decrease in AKI associated mortality with the greatest decline in mortality noted in stage 3 AKI.

The incidence of AKI among hospitalized patient was 12.3% in our study. This result, although high, is on the lower end of rates when compared to previous studies which have shown rates of AKI from 0.6 to 41.2% (Table 9)[27-29,32,33,50,60]. Using KDIGO serum creatinine-based definitions of AKI, we noted a 14.2/1000 hospitalizations increase in KDIGO AKI over the study period. Given the variability in reporting of incidence of AKI in the literature, it is difficult to compare our findings directly with other studies; however, a similar increase was noted by Long et al. Like findings made by Sohaney et al, this increase was largely driven by stage 1 AKI[27]. Furthermore, when the data is adjusted for age, sex, and comorbidities, the statistical significance in the increase in incidence is lost, which would suggest that the increase in AKI incidence is influenced by increasing age and comorbidity. This result is similar to findings made in previous studies[49,60]. Despite the increase in unadjusted rates of AKI, including stage 3 AKI, the rates of KRT have remained stable (unadjusted rate difference, 0.04/1000 hospitalizations [95%CI -0.01-0.2], (p= 0.56). Previous studies evaluating the incidence of AKI requiring dialysis treatment have shown conflicting results, perhaps due to differences in health systems, the prescription of dialysis treatment, and the identification of AKI[27,32,50,61]. Our findings suggest that there has not been a significant shift in the prescription of dialysis for AKI.

Table 9. Summary of current studies in temporal trends in rates of acute kidney injury and associated mortality

Author/Year of publication	Location of study	Study years	Study population	Number of hospitalizations/Patients with AKI in the study (total population)	Definition of AKI used in the study	Temporal trends in rates of AKI	Demographic trends in population with AKI	Mortality trends		
								Time period assessed	Overall rate	Temporal trend
Sohaney 2022	US	2008 to 2017	Patients admitted to Veterans Health Administration acute care facilities	548, 782 hospitalizations (2, 689, 093 hospitalizations) (20.4%)	AKI diagnostic codes Serum creatinine KDIGO definition	Stable rate (not explicitly discussed)	N/A	In hospital mortality 1 year mortality	6% 28%	Decrease (6.1 to 4.9%?) Stable (?)
Sohaney 2021	US	2008 to 2017	Patients admitted to Veterans Health Administration acute care facilities	920, 938 hospitalizations (4, 263, 600 hospitalizations) (21.6%)	AKI diagnostic codes Serum creatinine KDIGO definition	Stable rate	N/A	N/A	N/A	N/A

Stack 2020	Ireland	2003 to 2014	Hospitalized and community patients Data collected using the National Kidney Disease Surveillance System	40, 786 patients (451 646 patients) (9.0%)	Serum creatinine KDIGO definition	Increase by 2 fold (5.48 to 12.39 per 100 patient years)	Increase observed in all age and sex categories	N/A	N/A	N/A
Harding 2020	US	2000 to 2015	Hospitalized patients requiring dialysis Data collected using the National Inpatient Sample	N/A	AKI diagnostic codes	Increase of 55.7% (26.4 to 41.1 per 100000 persons)	Increase in all age and sex categories 5 times higher rates noted in patient with diabetes	In-hospital mortality	N/A	Decrease from 34.4 to 28.7 per 100 persons
Kashani 2017	US	2006 to 2014	Hospitalized patients Data collected using US Census Bureau	1, 740 patients in ICU (10, 283 patients) (17.0%) 2, 811 patients in general ward (41, 847 patients) (6.7%)	AKI diagnostic codes “Sniffer” AKI diagnosis	Stable rate (475 to 497 per 100000 person years)	Increase noted in patients with higher BMI	N/A	N/A	N/A

			data from a single tertiary care center							
Kolhe 2016	England	1998 to 2013	Hospitalized patients not requiring dialysis Data collected using the Hospital Episode Statistics dataset	1, 139, 167 hospitalizations (194, 157, 726 hospitalizations) (0.6%)	AKI diagnostic codes	Increase from 317 to 3995 per million people (15, 463 to 213,700 cases)	Increase noted in all ages Slight decrease in males	In hospital mortality	N/A	Decrease from 43.5 to 24.1%
Long 2016	Iceland	1993 to 2013	Hospitalized patients Data collected from a single tertiary care center	10, 419 patients (25 274 patients) (41.2%)	Serum creatinine KDIGO definition	Increase from 18.6 to 29.9/1000 hospitalizations	N/A	Overall	N/A	Decrease from 53 to 46%
Kolhe 2015	England	1998 to 2013	Hospitalized patients requiring dialysis	65, 937 patients (194, 157, 726 hospitalizations)	AKI diagnostic codes	Increase from 15.9 to 208.7 per million people (774 cases to 11, 164 cases)	Increase in patients >85 years (2.8 to 5.5%)	In-hospital	N/A	Increase from 30.3 to 41.1%

			Data extracted using Hospital Episode Statistics of every NHS hospital admission				Decrease in patients <65 (45.1 to 39.5%)	Overall		Increase from 24.5 to 46.8%
Hsu 2013	US	2000 to 2009	Hospitalized patients admitted to the ICU requiring dialysis Data collected from the Nationwide Inpatient Sample	1, 095, 000 hospitalizations (N/A)	AKI diagnostic codes	Increase from 222 to 533 per million person years (63000 to 164000 cases)	N/A	In patient	N/A?	Decrease from 29.1% to 23.5%

Until more recently, studies evaluating temporal trends in AKI have relied on the use of diagnostic codes, largely because of convenience. However, previous studies have shown that there is limited sensitivity of diagnostic codes as they rely heavily on physician recognition. Our study supports the poor sensitivity of the use of diagnostic codes in identifying AKI using KDIGO AKI rates as the reference standard. Over the study period, the sensitivity improved from 17.5 to 32.9%. Of note, this increase is affected by an increase in prevalence of AKI; however, similar trends were noted in trends of kappa, which would suggest this increase is not solely driven by prevalence. This increase in sensitivity is likely partially driven by better coding of milder forms of AKI as the highest fold increase in recognition (2.4 fold) was noted in stage 1 AKI. Based on our results, stage 3 AKI had the greatest recognition and coding for AKI. In contrast, AKI diagnostic codes have a high specificity (99%). Similar to a study done by Sohaney et al, in contrast to KDIGO AKI, a greater increase was noted in ICD AKI[27]. Furthermore, unlike KDIGO AKI, when fully adjusted, the incidence of ICD AKI was still increasing. In combination with the calibration results, this would suggest that there has been an increase in the use of AKI diagnostic codes, but also better recognition of AKI over time.

Over our study period, there has been an increase in comorbidity in hospitalized patients with AKI, especially hypertension and diabetes. The greatest increase in AKI was noted in the elderly population. This is consistent with previous studies which have largely shown increase in AKI in the elderly population[28,32,62]. Although males have higher rates of AKI overall, the rates of AKI are increasing in both sexes at similar rates.

Despite an increase in age and comorbidity, there has been a decrease in in-hospital and 90-day mortality associated with AKI. A similar result was found in a recent UK study[63]. This decrease is mortality despite increasing rates of AKI is likely a reflection of a large proportion of stage 1 AKI patients. Other studies have shown a greater reduction in mortality, ranging from 16 to 50%, however, many of these studies relied on AKI diagnostic codes and likely reflect a different patient population. In our study cohort, the largest decrease in mortality was noted in the most severe stages of AKI, which has been previously reported in a smaller cohort[49]. When the data was fully adjusted, this decrease in mortality remained statistically significant, which would suggest that the treatment and management of AKI has improved over time, especially in the most severe forms of AKI. Furthermore, this decrease is noted despite stable rates of renal KRT and decreasing rates of ICU admission, which would reinforce improvement in the treatment and management of AKI over time.

The primary strength of this paper is that it involves a large cohort of patients from a diverse population, thus is easily generalizable to most populations in North America. However, our study does have some limitations. Although every effort to identify baseline serum creatinine for the patients was made, 212 patients had insufficient data to determine AKI; however, as this is a small number relative to the cohort, it is unlikely to have influenced the results significantly. This study was conducted on hospitalized patients and so may not generalizable to people who are in the community. Furthermore, we had limited racial data available and so it is

difficult to generalize based on racial background. Although multiple comorbidities were accounted for when determining rates of mortality, potential cofounding factors cannot completely be accounted for. Finally, sensitivity and specificity of ICD codes are affected by the increasing prevalence of KDIGO AKI; however, the increase in prevalence is unlikely to explain the improvement in Kappa.

Conclusion:

In conclusion, there has been an increase in rates of AKI in hospitalized patients, largely driven by mild forms of AKI; this is likely because of increasing age and comorbidity in the hospitalized population. There has been concurrent improvement in the recognition of AKI over time, especially of milder forms of AKI. Despite increasing age and comorbidity in hospitalized patients, there has been an overall decrease in mortality, especially in the most severe forms of AKI. This may be influences by better recognition and therefore management of AKI. Despite this improvement, mortality associated with even mild forms of AKI remains high.

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