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Health outcomes according to severity of acute kidney injury at ICU admission: a population-based cohort study

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Abstract

Purpose: The presence and severity of acute kidney injury (AKI) upon ICU admission provides important short- and long-term prognostic information. Existing reports have been limited by inadequate baseline kidney function assessment, incomplete outcome capture, limited adjustment for illness severity, and small sample sizes.

Methods: We conducted a population-level study of all adult (≥ 18 years) Ontario, Canada residents with available outpatient baseline creatinine measurements admitted to the ICU from 2009–2021. AKI at the time of ICU admission was determined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Outcomes included death and kidney replacement therapy (KRT). Multivariable logistic regression modeling was used to estimate adjusted odds ratios (aOR).

Results: The study cohort included 484,956 adults (43% female) admitted to the ICU. Mean (SD) age and baseline eGFR were 68 (15) years and 77 (25) mL/min/1.73 m^2, respectively. AKI was present in 105,671 (22%). Relative to no AKI, stage 1 AKI was associated with approximately twofold higher odds for 90-day mortality (aOR 1.89 [95% CI 1.85–1.93]) while stages 2 and 3 AKI were associated with approximately 2.5-fold higher odds (stage 2 aOR 2.64 [95% CI 2.54–2.73], stage 3 aOR 2.54 [95% CI 2.45–2.63]). Relative to no AKI, there was a progressively increased risk for KRT dependence at 90 days: stage 1 (aOR 2.05 [95% CI 1.79–2.34]), stage 2 (aOR 4.28 [95% CI 3.40–5.40]), and stage 3 (aOR 8.61 [95% CI 7.71–9.62]).

Conclusion: The presence and severity of AKI at the time of ICU admission are strongly associated with adverse health outcomes. Stage 2 and 3 AKI portend a similarly high risk of mortality.

Keywords: Intensive care unit, ICU, Acute kidney injury, AKI, Kidney, Renal, Mortality, End-stage kidney disease, ESKD

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Introduction

Acute kidney injury (AKI) is a common and serious complication of critical illness. Patients admitted to the intensive care unit (ICU) are particularly vulnerable to AKI due to a multitude of factors, including infection, major surgery, hemodynamic instability, nephrotoxic medications, and multi-organ failure [1]. Prior prevalence estimates of AKI in the ICU range from 20 to 50%, with variation by region, ICU type, and AKI definition [2–6]. The occurrence of AKI in critical illness is associated with increased risks for mortality, morbidity (specifically end-stage kidney disease [ESKD]), and reduced quality of life [6–10]. This link between AKI and adverse health outcomes is due to AKI not only being a marker of illness severity, but also a contributing factor to clinical deterioration [1].

Prior studies on health outcomes following AKI in the ICU have been limited by several factors. First, they often do not include a comprehensive capture of baseline outpatient kidney function, which is necessary to accurately identify the presence and severity of AKI [11]. Second, they often are limited to a single centre or a group of academic centres, and may fail to reliably capture longer-term outcomes that occur outside of those specific settings. Third, many have included relatively small sample sizes, resulting in measures of association with a large amount of uncertainty. Furthermore, most prior studies have defined AKI severity as the worst severity achieved at any time during ICU stay, making their results difficult to apply to patients at or during their ICU admission (rather than afterwards, when the worst AKI stage can be known for all patients). We argue that AKI severity at the time of ICU admission (a uniform index time for inter-individual comparison and adjustment according to severity of illness at that timepoint) may be more directly relevant for health risk prognostication, goals of care discussions, resource allocation, health policy, quality initiatives, and clinical trial design. In particular, adjustment for the severity of illness at the time of AKI staging allows for better determination of the impact of AKI on clinical outcomes beyond AKI being a marker of illness severity itself.

To directly address these limitations of prior studies, we conducted a population-based cohort study across all adult patients with available baseline kidney function measurements who were admitted to ICUs across Ontario, Canada, to measure the association between AKI severity at ICU admission and health outcomes. All Ontario residents receive universal health care coverage, which allows for comprehensive capture of laboratory data and health outcomes within provincial health care administrative databases.

Take-home message

This population-level study included 484,956 critically ill adults with accurate measures of baseline kidney function. We found a strong association between acute kidney injury at the time of ICU admission and outcomes, including death, end-stage kidney disease, and length of stay. A doubling of serum creatinine from baseline (Stage 2 AKI) at ICU admission portended a similar mortality risk to stage 3 AKI. These results will inform risk prognostication, goals of care discussions, resource allocation, health policy, quality initiatives, and clinical trial design

Methods

Study design and setting

This was a population-level, observational cohort study of adult (≥ 18 years) residents of Ontario, Canada, using linked databases held at ICES (formerly, Institute for Clinical Evaluative Sciences). Ontario is Canada's most populous province with > 16 million residents. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board. The reporting of this study follows guidelines for observational studies (Electronic Supplementary Table S1) [12].

Data sources

Baseline characteristics and outcome data were ascertained from de-identified, linked databases housed at ICES. Demographic and vital status information was obtained from the Ontario Registered Persons Database. Diagnostic and procedural information from all hospitalizations was collected using the Canadian Institute for Health Information Discharge Abstract Database (DAD). Diagnostic information from emergency room and day surgery visits was determined using the National Ambulatory Care Reporting System. Information was also obtained from the Ontario Health Insurance Plan (OHIP) database, which contains all health claims for inpatient and outpatient physician services. Dialysis and kidney transplant information was obtained from the Canadian Organ Replacement Registry. Laboratory information is contained in the Ontario Laboratory Information System (OLIS), which captures laboratory tests for all patients in Ontario. ICU-specific information (including serum creatinine and severity of illness at time of ICU admission) was collected using the Critical Care Information System (CCIS). Definitions for patient characteristics and clinical variables are listed in Electronic Supplementary Table S2. These datasets were linked using unique

encoded identifiers and analyzed at ICES. The databases were complete for all variables used except for rural residence and neighborhood income quintile, which were missing in < 0.5% of individuals. The only reason for lost follow-up was emigration from the province, which occurs in < 0.5% of Ontario residents annually [13].

Cohort definition

All Ontario residents ≥ 18 years of age admitted to the ICU between January 1, 2009, and February 28, 2021, were included. If an individual had multiple ICU admissions during this time period, only the initial ICU admission was included. The date of ICU admission served as the study index date. Individuals were excluded if they had no serum creatinine available at the time of ICU admission, were on maintenance dialysis prior to admission, had a prior kidney transplant, or had no available baseline creatinine value (defined as a single outpatient measurement collected −7 to −365 days prior to admission with use of the measurement closest to admission when multiple measurements were available) [14].

Exposure

Individuals were classified based on the severity of AKI at the time of ICU admission. This classification was determined according to the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine-based AKI criteria by comparing the serum creatinine drawn closest to the time of ICU admission (including using values drawn prior to ICU admission when they were closest to the time of ICU admission) to the baseline creatinine value, or requirement of kidney replacement therapy (KRT) on the date of ICU admission [11]. Urine output data were not available to determine AKI stage according to KDIGO urine output criteria.

Outcomes

The primary outcomes were mortality at three time points: during ICU admission, during hospital admission, and at 90 days post-index. Secondary outcomes included KRT requirement during ICU admission, KRT dependence at 90 days among survivors, length of ICU stay among survivors, and length of hospital stay among survivors.

Statistical analysis

Baseline characteristics were described overall and by AKI stage. Continuous variables were presented as means (standard deviation [SD]) or medians (25th–75th percentile interquartile range [IQR]), as appropriate. Categorical variables were presented as number (%). Kaplan–Meier curves were produced to display survival probability by AKI stage up to 90 days. Crude and multivariable logistic regression modeling were used to measure the associations between AKI stage and mortality/KRT outcomes. Model variables were selected a priori based upon clinical knowledge, previous literature, and availability within ICES: age, sex, baseline estimated glomerular filtration rate (eGFR) (calculated using the 2021 CKD-EPI equation [15]), rural residence, neighborhood income quintile, comorbidities (coronary artery disease, myocardial infarction, congestive heart failure, arrhythmia, stroke, hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease, cancer, osteoarthritis, osteoporosis, dementia, mood disorder, and other mental health conditions), ICU level, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to the Multiple Organ Dysfunction Score (MODS) on ICU admission but subtracting the contribution of the MODS renal component (determined according to serum creatinine), and sepsis. MODS is an ICU severity of illness score, which evaluates six organ systems (respiratory, renal, hepatic, cardiovascular, hematologic, and neurologic) on a 0 (normal) to 4 (severe dysfunction) scale, which is uniformly captured upon ICU admission for all patients in Ontario [16]. Sepsis was determined using a validation definition for identification within administrative health data [17, 18]. Statistical differences for length of stay were determined by one-way ANOVA testing for means and Kruskal–Wallis testing for medians. A sensitivity analysis was conducted where individuals with a baseline eGFR < 15 mL/min/1.73 m^2 were excluded as some of these individuals may be considered to have progressed from advanced chronic kidney disease (CKD) to ESKD rather than having developed AKI. A separate sensitivity analysis was conducted where those individuals with no available outpatient serum creatinine measurements between −7 to −365 days prior to admission were included and assigned an imputed baseline eGFR of 75 mL/min/1.73 m^2 (with back-calculation of baseline serum creatinine), an accepted approach for estimating missing baseline kidney function [19]. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). 95% confidence intervals (CI) that did not overlap with 1.0 and two-sided p values < 0.05 were treated as statistically significant.

Results

Baseline characteristics

Among the 845,322 Ontario residents admitted to the ICU within the accrual period, 484,956 met the inclusion criteria and were included in the analytic cohort (Fig. 1). The cohort consisted of 379,285 (78%) individuals without AKI, 66,718 (14%) with stage 1 AKI, 17,714 (4%) with stage 2 AKI, and 21,239 (4%) with stage 3 AKI

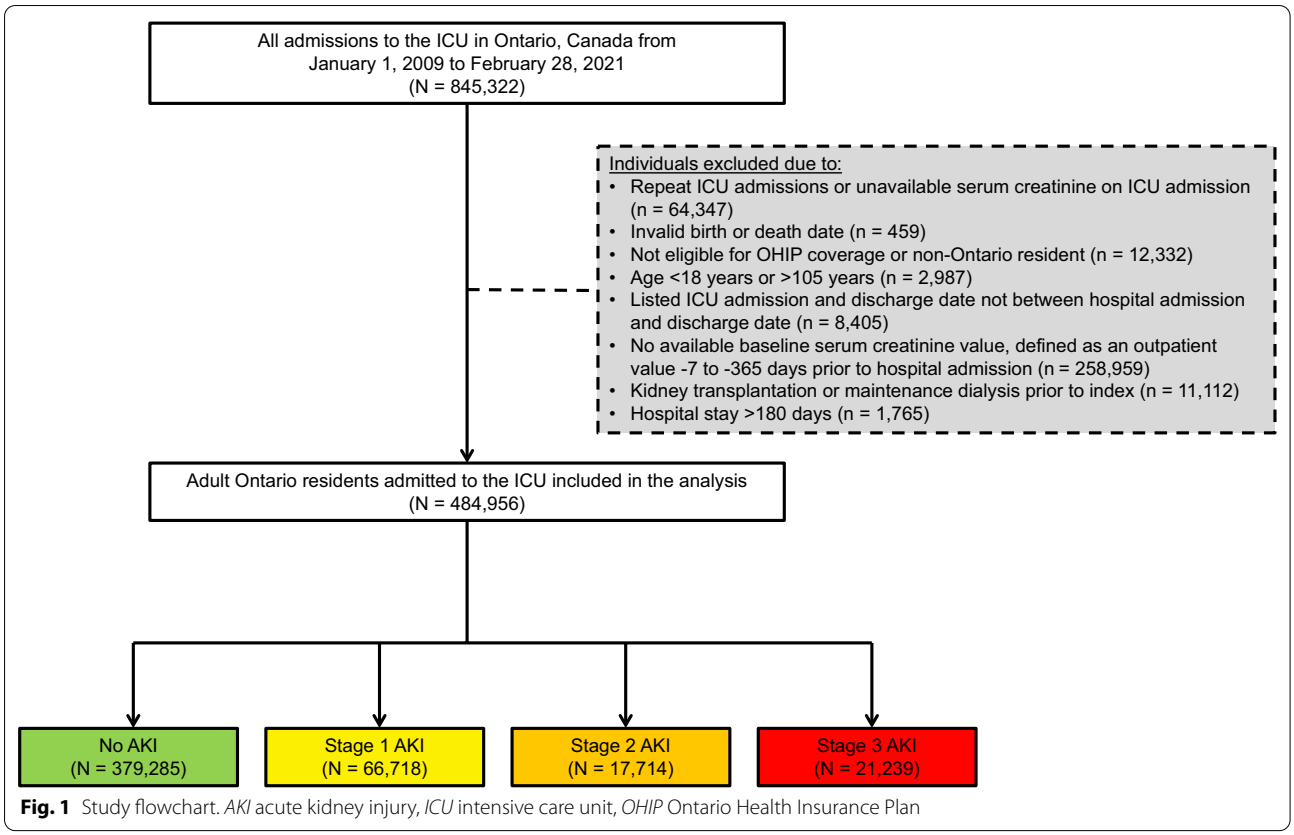

Fig. 1 Study flowchart. *AKI* acute kidney injury, *ICU* intensive care unit, *OHIP* Ontario Health Insurance Plan

at the time of ICU admission (Table 1). Among individuals with stage 3 AKI, 4,873 (23%) were defined as stage 3 AKI according to receiving KRT within 24 h of ICU admission. The mean (SD) age of the cohort was 68 (15) years. Females comprised 43% of the cohort. Mean (SD) baseline eGFR was 77 (25) mL/min/1.73 m^2.

Mortality

Figure 2A, B displays Kaplan–Meier curves of survival probability up to 90 days according to the presence of AKI and by AKI stage. Figure 3A–C display the absolute percentages of death during ICU stay, during hospitalization, and within 90 days by AKI stage. Across all time frames, individuals with no AKI had the lowest mortality, followed by stage 1 AKI, while stages 2 and 3 AKI had the highest mortality percentages of similar magnitude. Figure 3D displays the crude and adjusted odds ratios (OR) for the associations between AKI stage and mortality outcomes. For all mortality outcomes in multivariable adjusted models and relative to no AKI, all stages of AKI were associated with increased odds of death. The highest odds of death were found in individuals with stages 2 and 3 AKI, which were of similar magnitude. For instance, relative to no AKI, stage 1 AKI was associated with approximately 1.9-fold higher odds for death within 90 days (OR 1.89 [95% CI 1.85–1.93]) while stages 2 and 3 AKI were associated with approximately 2.5-fold higher odds (stage 2 AKI OR 2.64 [95% CI 2.54–2.73], stage 3 AKI OR 2.54 [95% CI 2.45–2.63]). Similar patterns were seen for death during ICU stay and death during hospitalization.

Kidney replacement therapy

Figure 4A, B display the absolute percentages of KRT initiation during ICU stay and KRT dependence at 90 days among survivors. KRT dependence at 90 days increased by AKI stage at ICU admission as follows: no AKI (0.3%), stage 1 AKI (0.8%), stage 2 AKI (0.9%), and stage 3 AKI (12.0%). Figure 4C displays the crude and adjusted ORs for the associations between AKI stage and KRT outcomes. In multivariable models and relative to no AKI, there was a progressively increased risk for KRT initiation in the ICU as follows: stage 1 AKI (OR 3.07 [95% CI 2.87–3.29]), stage 2 AKI (OR 5.70 [95% CI 5.23–6.20]), and stage 3 AKI (OR 42.7 [95% CI 40.3–45.2]). Relative to no AKI, there was also a progressively increased risk for KRT dependence at 90 days as follows: stage 1 AKI (OR 2.05 [95% CI 1.79–2.34]), stage 2 AKI (OR 4.28 [95% CI 3.40–5.40]), and stage 3 AKI (OR 8.61 [95% CI 7.71–9.62]).

Table 1 Baseline characteristics of the study cohort

Characteristic	Total	No AKI	Stage 1 AKI	Stage 2 AKI	Stage 3 AKI
N (%)	484,956	379,285 (78)	66,718 (14)	17,714 (4)	21,239 (4)
Age, years, mean (SD)	68 (15)	67 (15)	70 (15)	67 (15)	67 (14)
Sex, *N* (%)					
Female	207,609 (43)	160,707 (42)	28,643 (43)	9008 (51)	9251 (44)
Male	277,347 (57)	218,578 (58)	38,075 (57)	8706 (49)	11,988 (56)
Baseline kidney characteristics					
Creatinine, µmol/L, mean (SD)	92 (47)	89 (40)	99 (42)	80 (26)	139 (117)
eGFR, mL/min/1.73 m^2, mean (SD)[a]	77 (25)	79 (24)	71 (27)	83 (24)	66 (34)
eGFR category, *N* (%)					
≥ 60 mL/min/1.73 m^2	365,802 (75)	297,337 (78)	42,370 (64)	13,972 (79)	12,123 (57)
45–59 mL/min/1.73 m^2	61,183 (13)	45,572 (12)	10,932 (16)	2490 (14)	2189 (10)
30–44 mL/min/1.73 m^2	37,854 (8)	25,265 (7)	9150 (14)	1189 (7)	2250 (11)
15–29 mL/min/1.73 m^2	16,855 (3)	9623 (3)	4177 (6)	63 (0)	2992 (14)
< 15 mL/min/1.73 m^2	3262 (1)	1488 (0)	89 (0)	0 (0)	1685 (8)
Outpatient nephrology visit within prior 1 year, *N* (%)	30,916 (6)	18,089 (5)	6458 (10)	1204 (7)	5165 (24)
Neighborhood income quintile, *N* (%)[b]					
Quintile 1 (lowest)	109,021 (23)	82,938 (22)	16,002 (24)	4520 (26)	5561 (26)
Quintile 2	101,813 (21)	79,104 (21)	14,305 (22)	3794 (22)	4610 (22)
Quintile 3	95,487 (20)	74,953 (20)	13,047 (20)	3349 (19)	4138 (20)
Quintile 4	90,244 (19)	71,508 (19)	11,982 (18)	3096 (18)	3658 (17)
Quintile 5 (highest)	86,649 (18)	69,475 (18)	11,115 (17)	2875 (16)	3184 (15)
Rural residence, *N* (%)[c]	69,789 (14)	55,736 (15)	9058 (14)	2301 (13)	2694 (13)
Comorbidities, *N* (%)					
Coronary artery disease	107,632 (22)	90,771 (24)	11,684 (18)	1914 (11)	3263 (15)
Myocardial infarction	48,453 (10)	37,810 (10)	7328 (11)	1296 (7)	2019 (10)
Congestive heart failure	77,991 (16)	53,383 (14)	16,123 (24)	3352 (19)	5133 (24)
Arrhythmia	50,154 (10)	38,395 (10)	8093 (12)	1664 (9)	2002 (9)
Stroke	17,248 (4)	13,876 (4)	2275 (3)	526 (3)	571 (3)
Hypertension	227,613 (47)	177,045 (47)	32,515 (49)	7594 (43)	10,459 (49)
Diabetes mellitus	163,462 (34)	117,609 (31)	28,267 (42)	7381 (42)	10,205 (48)
Asthma	20,767 (4)	16,208 (4)	2958 (4)	788 (4)	813 (4)
COPD	52,972 (11)	39,318 (10)	9042 (14)	2208 (12)	2404 (11)
Cancer, *N* (%)	147,531 (30)	117,355 (31)	19,742 (30)	4961 (28)	5473 (26)
Osteoarthritis, *N* (%)	106,197 (22)	83,050 (22)	14,614 (22)	3896 (22)	4637 (22)
Osteoporosis, *N* (%)	8538 (2)	6841 (2)	1059 (2)	318 (2)	320 (2)
Dementia, *N* (%)	25,410 (5)	17,794 (5)	4929 (7)	1416 (8)	1271 (6)
Mood disorder, *N* (%)	84,049 (17)	66,108 (17)	10,940 (16)	3315 (19)	3686 (17)
Other mental health condition, *N* (%)	46,606 (10)	34,750 (9)	6837 (10)	2284 (13)	2735 (13)
Charlson comorbidity index category, *N* (%)					
≤ 2	297,406 (61)	245,534 (65)	33,472 (50)	9261 (52)	9139 (43)
3–4	114,757 (24)	83,788 (22)	19,359 (29)	4934 (28)	6676 (31)
≥ 5	72,793 (15)	49,963 (13)	13,887 (21)	3519 (20)	5424 (26)
ICU admission characteristics					
ICU level, *N* (%)					
Level 2	170,162 (35)	139,261 (37)	21,754 (33)	4393 (25)	4754 (22)
Level 3	314,794 (65)	240,024 (63)	44,964 (67)	13,321 (75)	16,485 (78)
Multiple organ dysfunction score (MODS), median (IQR)	2 (0–5)	1 (0–4)	3 (1–6)	5 (2–7)	6 (4–8)
Sepsis, *N* (%)	35,090 (7)	14,503 (4)	9607 (14)	5077 (29)	5903 (28)
Use of vasopressors, *N* (%)	130,230 (27)	92,981 (25)	21,155 (32)	7489 (42)	8605 (41)
Mechanical ventilation, *N* (%)	331,937 (68)	257,103 (68)	47,606 (71)	13,246 (75)	13,982 (66)

Table 1 (continued)

AKI acute kidney injury, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *ICU* intensive care unit, *IQR* 25th–75th percentile interquartile range, *SD* standard deviation

[a] Calculated using the 2021 creatinine-based CKD-EPI equation [15]

[b] Neighborhood income quintile missing in 1,742 individuals (0.4% of cohort)

[c] Rural defined as residing in a location with population < 10,000, missing in 958 individuals (0.2% of cohort)

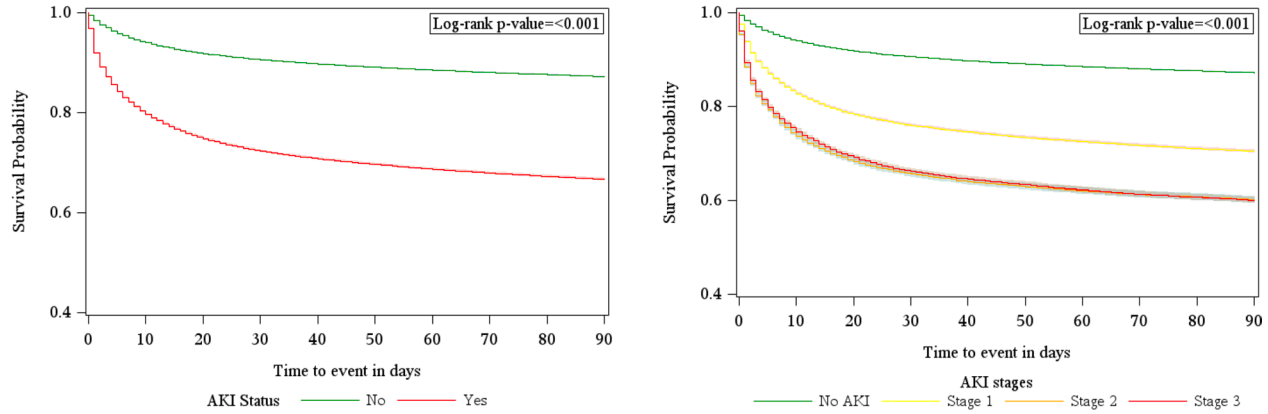

Fig. 2 Kaplan–Meier curves for survival probability by AKI stage to 90 days. **A** KM curve for time to death by AKI status 90 days post-index for primary cohort. **B** KM curve by AKI stages 90 days post-index for primary cohort. *AKI* acute kidney injury, *KM* Kaplan–Meier

Length of stay

Electronic Supplementary Table S3 displays the mean and median lengths of stay among survivors by AKI stage. Length of stay increased progressively by AKI stage. The median (25th-75th percentile interquartile range) hospital length of stay increased as follows: no AKI 8 (5–14) days, stage 1 AKI 10 (6–19) days, stage 2 AKI 12 (7–24) days, and stage 3 AKI 15 (8–28) days; $P < 0.001$.

Sensitivity analyses

Sensitivity analyses excluding individuals with baseline eGFR < 15 mL/min/1.73 m^2 (Electronic Supplementary Figures S1–S2 and Table S4) and including individuals with no available outpatient baseline serum creatinine measurements who were assigned an imputed baseline eGFR of 75 mL/min/1.73 m^2 with back calculation of baseline serum creatinine (Electronic Supplementary Figures S3-S4 and Tables S5–S7) yielded similar results to the primary analyses.

Discussion

In this large, population-based cohort study of critically ill adults with available baseline kidney function measurements, we found that 22% had AKI at the time of ICU admission. This included 14% with stage 1 AKI, 4% with stage 2 AKI, and 4% with stage 3 AKI. Furthermore, AKI was strongly associated with 90-day mortality, including approximately twofold higher odds for stage 1 AKI, and approximately 2.5-fold higher odds for stages 2–3 AKI, compared to no AKI. AKI was also strongly associated with ESKD (defined as persistent KRT dependence at 90 days) among survivors. This relationship increased progressively from twofold higher odds for stage 1 AKI, to fourfold higher odds for stage 2 AKI, to over eightfold higher odds for stage 3 AKI, compared to no AKI. The presence and severity of AKI was also associated with a greater length of ICU and hospital stay.

These findings extend the results of prior work examining the epidemiology of AKI in the ICU. This study, including nearly half a million adults admitted to the ICU in Ontario, Canada, represents the largest cohort to date on this topic. The prevalence estimate for AKI in the ICU of 22% fits within the lower range of the 20–50% range reported in prior studies [2–6]. This may relate to several factors. To begin, we examined AKI at the time of ICU admission (rather than anytime during ICU admission) to establish a uniform index date for inter-individual comparison. Moreover, we only included patients with available outpatient baseline creatinine measurements within 7 to 365 days prior to hospital admission (an established and recommended definition for baseline kidney function [14]) in order to accurately capture AKI according to KDIGO criteria [11]. This is in contrast to many prior studies, which have used the first serum creatinine

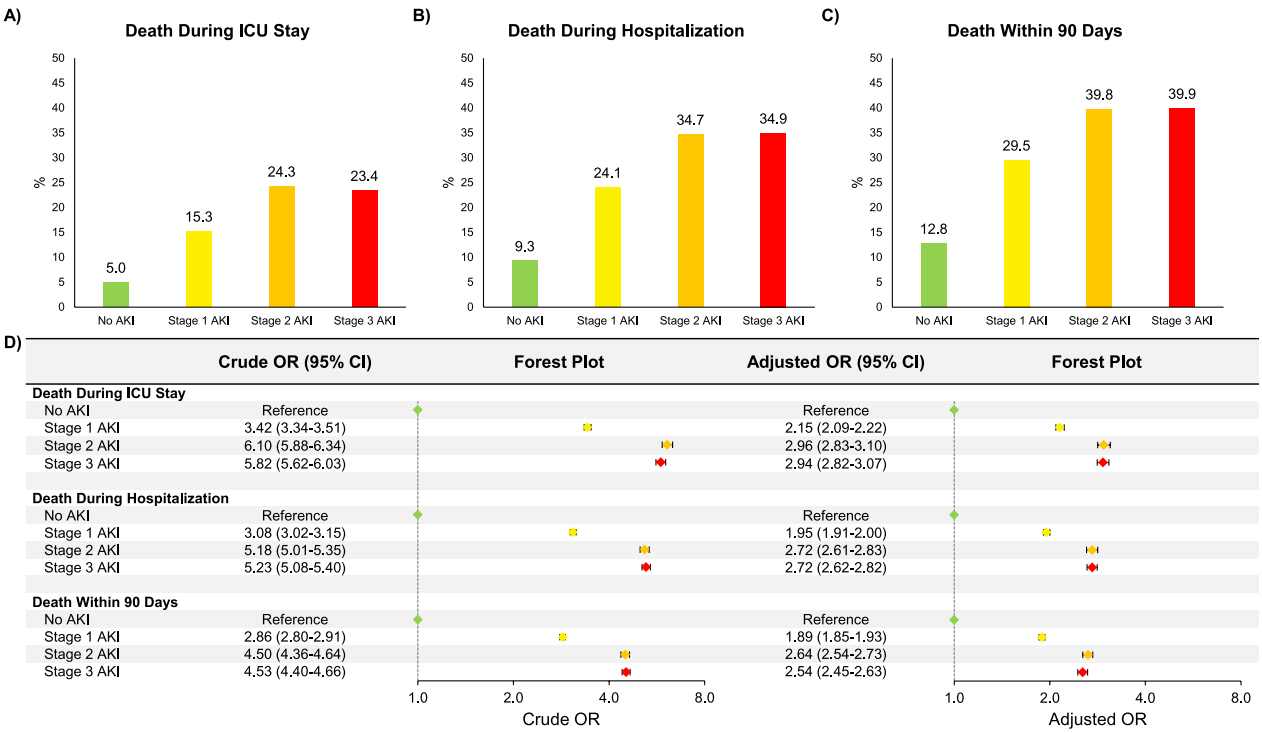

Fig. 3 Mortality during ICU stay, during hospitalization, and within 90 days following AKI at ICU admission. **A** Absolute percentage of death during ICU stay. **B** Absolute percentage of death during hospitalization. **C** Absolute percentage of death within 90 days. **D** Crude and adjusted ORs (95% CIs) for the association between AKI severity and death. Adjusted models included the following additional variables: age, sex, baseline eGFR, rural residence, neighborhood income quintile, comorbidities (coronary artery disease, myocardial infarction, congestive heart failure, arrhythmia, stroke, hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease, cancer, osteoarthritis, osteoporosis, dementia, mood disorder, and other mental health conditions), ICU level, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to MODS (but subtracting the MODS renal component), and sepsis. *AKI* acute kidney injury, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *ICU* intensive care unit, *MODS* multiple organ dysfunction score, *OR* odds ratio

on admission to hospital (i.e., in the setting of acute illness), which can result in misclassification of AKI status and severity [20]. Finally, our population-level design included both academic and non-academic centres, which differs from most prior studies, which focused exclusively on academic centres. Varying rates of illness severity between academic and non-academic centres may contribute to AKI prevalence, and our approach may be more generalizable across all ICU settings.

Consistent with prior studies, we found that the presence and severity of AKI in the ICU are strongly associated with increased mortality [4–6]. We found that the odds for mortality within three separate time frames (during ICU stay, during hospitalization, and within 90 days) showed a progressive increase from no AKI through stage 1 and 2 AKI. However, unique to our study, we found that the odds of death were nearly identical between stages 2 and 3 AKI. The large sample size afforded by this population-based cohort design allowed for more accurate measurement of ORs than prior work, which may explain this finding. For instance, the AKI-EPI study reported a progressively increased mortality risk by AKI severity, including an increased risk going from stage 2 to stage 3 AKI [6]. Given the much smaller sample size from the AKI-EPI study, the 95% CIs for the ORs were wide and overlapped substantially between AKI stages. Since serum creatinine is slow to change in response to rapid changes in kidney function, this finding may also reflect that serum creatinine-based AKI staging utilizes arbitrary cutoffs and eGFR estimates are inaccurate in the context of acute changes in kidney function. For example, some severely ill patients with a dilutional reduction in serum creatinine might have had more severe AKI than was determined using serum-creatinine-based AKI criteria alone. Additionally, some of the 23% of patients classified as having stage 3 AKI due to receipt of RRT might have started RRT earlier than necessary for their degree of kidney dysfunction, leading to better-than-anticipated outcomes. This could also be expected for a small percentage of patients who received RRT for an intoxication rather than AKI. Furthermore, high mortality rates prior to ICU admission (or non-admission to

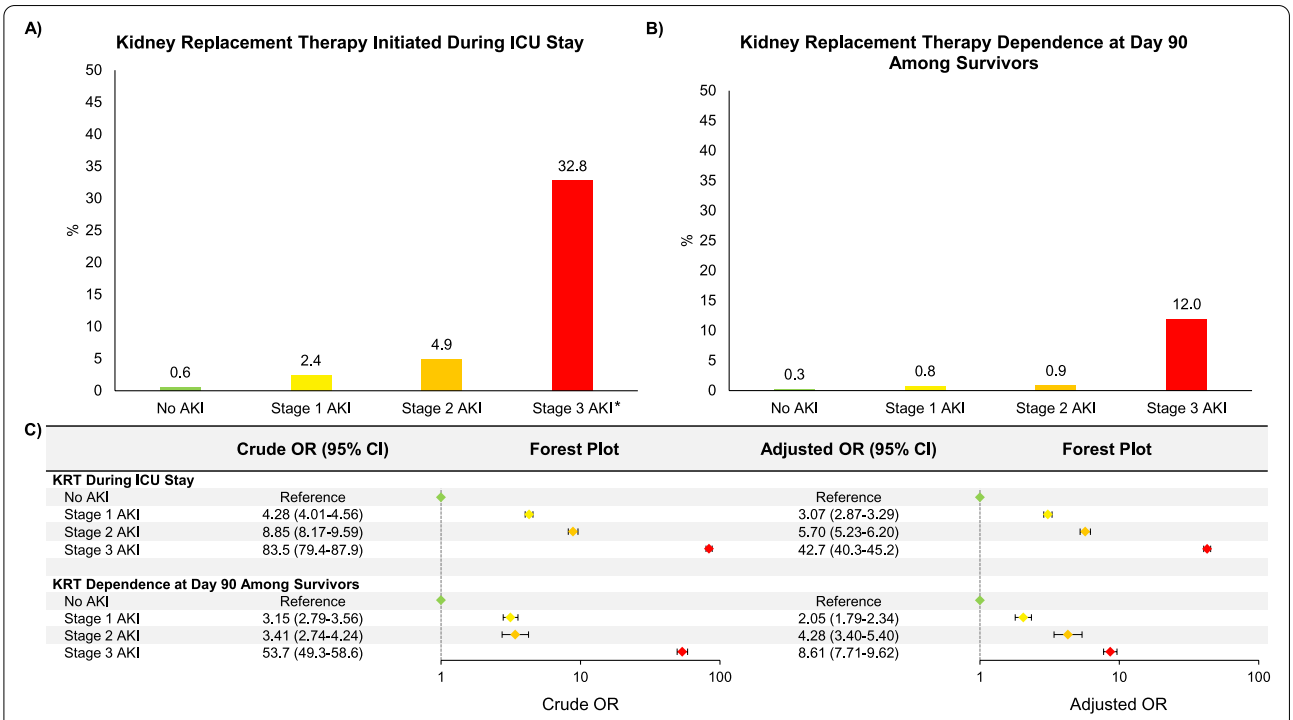

Fig. 4 Kidney replacement therapy initiation during ICU stay and dependence at 90 days following AKI at ICU admission. *This includes 6957 patients of whom 4873 (70%) were defined as stage 3 AKI due to receipt of KRT within 24 h of ICU admission. This additionally includes 2084 patients (30%) who were defined as stage 3 AKI due to creatinine-based criteria and received KRT > 24 h after ICU admission. The latter represents 12.7% of all those with stage 3 AKI due to creatinine-based criteria only (16,366 patients), at ICU admission. **A** Absolute percentage of kidney replacement therapy initiation during ICU stay. **B** Absolute percentage of kidney replacement therapy dependence at day 90 among survivors. **C** Crude and adjusted ORs (95% CIs) for the association between AKI severity and kidney replacement therapy outcomes. Adjusted models included the following additional variables: age, sex, baseline eGFR, rural residence, neighborhood income quintile, comorbidities (coronary artery disease, myocardial infarction, congestive heart failure, arrhythmia, stroke, hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease, cancer, osteoarthritis, osteoporosis, dementia, mood disorder, and other mental health conditions), ICU level, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to MODS (but subtracting the MODS renal component), and sepsis. *AKI* acute kidney injury, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *ICU* intensive care unit, *KRT* kidney replacement therapy, *MODS* multiple organ dysfunction score, *OR* odds ratio

ICU due to perceived futility) of a more co-morbid stage 3 AKI population could have led to relatively better outcomes for those patients who were admitted to ICU with stage 3 AKI. Nonetheless, the focus of this study was on patients at the time of their ICU admission and involved a thorough adjustment for severity of illness at that time-point. As such, our results strongly suggest that clinicians should be alert to the increased risk portended by a doubling of serum creatinine from baseline (Stage 2 AKI) at ICU admission.

This study, along with prior literature, also emphasizes that AKI in the ICU is strongly associated with non-recovery of kidney function [21–24]. KRT dependence over 90 days, which was one of our study outcomes, is a well-accepted definition for ESKD [25–27]. Our findings of steep and progressively increased risk for ESKD following AKI in the ICU are highly consistent with prior work. For instance, a systematic review and meta-analysis found that, compared to no AKI, stage 1, stage 2, and stage 3 AKI were associated with a 2.3-, 4.0-, and 8.0-fold higher risk of ESKD, respectively [24]. Similarly, we found that the odds of ESKD approximately doubled with every stepwise increase in AKI severity stage.

These results also provide the strongest evidence to date on the relationship between AKI at the time of ICU admission and length of stay. While prior studies have linked AKI to prolonged length of stay [28–31], the large sample size in this cohort uniquely allowed for precise measurement by AKI stage, revealing a clear stepwise increase in length of stay by AKI severity amongst survivors.

The strengths and novelty of this study include a large population-based cohort well-powered to accurately and precisely quantify associations, comprehensive capture of baseline outpatient kidney function allowing accurate classification of the presence and severity of AKI, complete capture of outcome events using provincial data registries, and inclusion of both academic

and non-academic centres. However, the findings must be interpreted within the context and limitations of the study design. First, the observational study design allowed for the evaluation of association but not causation. The statistical models accounted for numerous known potential confounders, including demographics, comorbidities, and severity of illness, to reduce observed confounding; however, unobserved confounding may still have occurred. Second, while the use of a large administrative health care dataset provided sufficient power to measure associations between ICU-related AKI severity stages and the study outcomes, this also limited the granularity of certain variables at the individual level, such as urine output in the ICU. KDIGO includes both serum creatinine and urine output criteria by which to define both the presence and severity of AKI. There is no clear consensus regarding the best choice of baseline creatinine for determining AKI severity for hospitalized patients [32]. The risks of misclassification, according to a 26.5 μmol/L cutoff, using our approach (most recent serum creatinine from 7 to 365 days prior to admission), have been shown to be minor compared to using a mean value of all serum creatinine results from 7 to 365 days prior to admission (13.7% vs 11.1%) [14]. At the same time, our approach improves generalizability to settings where care may be more fragmented and it increases clinical applicability by avoiding the need for the calculation of a mean value. Given the lack of urine output data, our results should only be interpreted in the context of KDIGO serum creatinine-based AKI criteria and not its urine output-based criteria. However, the reliability of using urine output criteria to diagnose AKI has also been criticized as overly sensitive, prone to misclassification, lacking prospective validation, and confounded by factors such as fluid status and diuretic use [33, 34]. Furthermore, accurate urine output data is not typically available preceding ICU admission, the time point of interest for this study. Third, the administrative databases utilized did not define the exact reason for ICU admission or etiology of AKI on a case-by-case basis. However, we accounted for related factors, such as comorbidities, mechanical ventilation, vasopressor use, sepsis, and a validated severity of illness measure (MODS) [16]. Fourth, as this was a population-based study of patients admitted to the ICU, it included both individuals from level 2 and level 3 ICUs. This differs from many prior studies, which only included level 3 ICUs. While this makes these results more generalizable to all ICU settings, it may also contribute to why we found an ICU AKI rate on the lower end of the range previously reported in the literature [2–6]. Nonetheless, as above, we did adjust for variables, such as vasopressor use, mechanical ventilation, sepsis, and MODS score, which would account for some of the key differences across levels of ICU care. Finally, KRT dependence at 90 days was included as a study outcome as it is a well-accepted definition for ESKD [25–27]. As this represents a dichotomous outcome over a pre-specified time point, it does not allow for a competing risk analysis. However, as we restricted this analysis to individuals who survived to 90 days (who we believe this outcome is most clinically meaningful for), there was no competing risk for death.

In summary, this population-based observational cohort study represents the largest study to date comprehensively detailing the magnitude of associations between both the presence and severity of AKI at ICU admission, and adverse health outcomes, including mortality, ESKD, and prolonged length of stay. Clinicians should be aware that a doubling of serum creatinine from baseline (Stage 2 AKI) at ICU admission portends a similar mortality risk to stage 3 AKI. Overall, these results will inform prognostication surrounding goals of care discussions with patients admitted to the ICU, and their families, while also informing health policy, resource allocation, quality initiatives, and clinical trial design.

Supplementary Information

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Author contributions

GLH and EGC conceived and designed the study, interpreted the data, and drafted the manuscript. AYD acquired and analyzed the data. GAK, RW, SAS, OGR, SMF, MH, AB, MMS, LLTNP, DF, and TR contributed to result interpretation and critically revised the manuscript. All authors have read and approved the final version of the manuscript for publication.

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Data availability
The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Declarations

Conflicts of interest
RW has received speaker and consulting fees from Vantive. SAS has received speaking fees and an unrestricted educational grant from Vantive. OGR has received speaking fees and an investigator initiated research grant from Vantive. MMS has received consultancy fees from Astrazeneca.

Ethical approval
The use of data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board.

Consent to participate
ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and management.

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