Epidemiology of acute kidney injury in Canadian critical care units: a prospective cohort study

Épidémiologie des lésions rénales aiguës dans les unités de soins intensifs au Canada: étude prospective de cohorte

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Abstract

Purpose We undertook this study to characterize the epidemiology of acute kidney injury (AKI) in Canadian critical care units. We aimed to identify predictors of mortality for patients diagnosed with AKI.

Author contributions All of the authors made substantial contributions to the design of the study and to the acquisition and interpretation of the data. All of the authors made material contributions to drafting the article and the revisions for important intellectual content and approved the final version to be published. Rahim Moineddin was responsible for the statistical analysis.

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Methods We conducted a prospective cohort study of consecutive patients admitted to critical care units at five Canadian hospitals over a 30-day period. Each patient was followed until hospital discharge or for a maximum of 30 days. The serum creatinine criteria for the Acute Kidney Injury Network (AKIN-SCr) system were used to identify, classify, and characterize patients who developed AKI. We used multivariable logistic regression to predict 30-day mortality among patients with AKI.

Results We identified 603 patients, 161 (26.7%) of whom developed AKI. Compared to patients without AKI, those with AKI were more likely to die (29.2% vs 8.6%, $P < 0.001$). The risk of death increased with increasing AKIN-SCr stage ($P < 0.001$). In all, 19 patients (11.8% of those with AKI) commenced dialysis a median of one day

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(interquartile range, one to two days) after AKI diagnosis. At AKI diagnosis, the blood urea nitrogen (BUN) level (adjusted odds ratio [OR] 1.68, 95% confidence interval [CI] 1.01 to 2.79/10 mmol·L⁻¹) and serum bicarbonate (adjusted OR 0.88, 95% CI 0.81 to 0.95/1 mmol·L⁻¹) were associated with 30-day mortality and predicted death with an area under the receiver-operating characteristic curve of 0.79 (95% CI 0.71 to 0.86).

Conclusions Acute kidney injury is a common complication of critical illness in Canada. The development of even the mildest stage of AKI is associated with a substantially higher risk of death. At AKI diagnosis, routine clinical data may be helpful for predicting adverse outcomes.

Résumé

Objectif Nous avons entrepris cette étude pour établir l'épidémiologie des lésions rénales aiguës (LRA) dans les unités de soins intensifs au Canada. Nous avons cherché à identifier les éléments prédictifs de mortalité chez les patients ayant un diagnostic de LRA.

Méthode Nous avons mené une étude prospective de cohorte sur des patients consécutifs hospitalisés dans les unités de soins intensifs de cinq hôpitaux canadiens, au cours d'une période de 30 jours. Chaque patient a été suivi jusqu'à sa sortie de l'hôpital ou pendant une période maximum de 30 jours. Les critères de créatinine sérique du Réseau des lésions rénales aiguës (AKIN-SCr) ont été utilisés pour identifier, classer et définir les patients qui ont développé des LRA. Nous avons utilisé un modèle de régression logistique multifactorielle pour prédire la mortalité à 30 jours parmi les patients ayant une LRA.

Résultats Nous avons identifié 603 patients, parmi lesquels 161 (26,7 %) ont développé une LRA. Comparativement aux patients sans LRA, ceux qui en étaient atteints avaient un plus grand risque de décès (29,2 % contre 8,6 %, $P < 0,001$). Le risque de décès a augmenté parallèlement au stade AKIN-SCr ($P < 0,001$). Globalement, 19 patients (11,8 % des patients ayant une LRA) ont commencé une dialyse dans un délai médian d'une journée (plage interquartile, 1 à 2 jours) après le diagnostic de LRA. Au moment du diagnostic de LRA, le taux d'urée sanguine (rapport de cotes ajusté [RC]: 1,68; intervalle de confiance à 95 % [IC]: 1,01 à 2,79/10 mmol·L⁻¹) et de bicarbonates sériques (RC ajusté: 0,88; IC à 95 %: 0,81 à 0,95/1 mmol·L⁻¹) ont été associés à la mortalité et au taux de décès théorique à 30 jours avec une aire sous la courbe ROC (receiver-operating characteristic) de 0,79 (IC à 95 %: 0,71 à 0,86).

Conclusions Une lésion rénale aiguë est une complication fréquente des maladies graves au Canada. Le développement d'un stade même mineur de LRA est associé à une élévation substantielle du risque de décès. Au moment du diagnostic de

LRA, les données cliniques habituelles peuvent contribuer à prédire une évolution préjudiciable.

Acute kidney injury (AKI) is a common complication of critical illness and is associated with a heightened risk of adverse outcomes.^{1,2} Despite technical advancements in the management of AKI, the mortality rate among these patients frequently exceeds 30%.³ Recent guidelines⁴ have provided a framework for diagnosing AKI in its earliest of stages, but clinicians have limited ability to prognosticate with respect to the progression of AKI, including the subsequent requirement for renal replacement therapy (hereafter referred to as “dialysis”) and death. It has been suggested that the development of effective therapeutic maneuvers for the prevention or early treatment of AKI have been impeded by late diagnosis of this disorder.⁵

We undertook a multicentre cohort study to characterize the incidence and outcomes of AKI in an unselected cohort of patients admitted to Canadian intensive care units (ICUs). Among the patients with AKI, we sought to identify clinical predictors of mortality at the time of AKI diagnosis. The ability to identify patients with AKI who might experience adverse outcomes may enable clinicians to target therapies, such as the earlier initiation of dialysis^{6,7} to those who would derive the greatest benefit.

Methods

Subjects

We prospectively collected data on consecutive patients admitted to medical and surgical ICUs during a 30-day period at five Canadian centers, including three in Toronto, [Mount Sinai Hospital (June 23, 2008 to July 22, 2008), St. Michael's Hospital (June 1, 2008 to June 30, 2008), Sunnybrook Health Sciences Centre (June 23, 2008 to July 23, 2008)], and two in Saskatoon [St. Paul's Hospital and Royal University Hospital March 9, 2009 to April 8, 2009)]. The three Toronto hospitals operated independently, with no cross appointment of nephrologists or intensivists between sites. The same group of nephrologists and intensivists served the two Saskatoon sites. The initiation and prescription of dialysis at study centers were at the discretion of nephrologists in coordination with intensivists. In the event of multiple ICU admissions for a given patient, only data pertaining to the first ICU admission were considered. Because patients at risk of AKI were the focus of this study, we excluded individuals undergoing chronic dialysis. The primary outcome was the development of AKI, and the secondary outcome was mortality at 30 days.

Table 1 AKIN classification scheme

AKIN stage	Change in serum creatinine from baseline*	Urine output
1	$\geq 26.4 \mu\text{mol}\cdot\text{L}^{-1}$ or 150–200% (1.5- to 2.0-fold)	$< 0.5 \text{ mL}\cdot\text{kg}^{-1}$ for 6–12 hr
2	200–300% (> 2 - to 3-fold)	$< 0.5 \text{ mL}\cdot\text{kg}^{-1}$ for at least 12 hr
3	$> 300\%$ (> 3 -fold) or serum creatinine $\geq 354 \mu\text{mol}\cdot\text{L}^{-1}$ with an acute increase of at least $44 \mu\text{mol}\cdot\text{L}^{-1}$ or application of acute renal replacement therapy (dialysis)	$< 0.3 \text{ mL}\cdot\text{kg}^{-1}$ for 24 hr or anuria for 12 hr

Only the serum creatinine criteria were considered for this study

*In the current study, the baseline serum creatinine level was the value obtained most closely following the patient's hospital admission. AKIN = Acute Kidney Injury Network

Research ethics boards at Mount Sinai Hospital, St. Michael's Hospital, Sunnybrook Health Sciences Centre, St. Paul's Hospital, and Royal University Hospital approved the study in June 2008 and waived the requirement for patient consent.

Identification of patients with AKI

Acute kidney injury was defined according to the Acute Kidney Injury Network (AKIN) staging system,⁴ with the first creatinine value obtained after hospital admission considered the baseline. Acute kidney injury was diagnosed on the first day on which a $27 \mu\text{mol}\cdot\text{L}^{-1}$ ($0.3 \text{ mg}\cdot\text{dL}^{-1}$) or a 50% rise in creatinine from baseline was observed. Patients were further classified by the serum creatinine criteria of the AKIN system (AKIN-SCr) as stages 1, 2, or 3 based on the highest creatinine recorded over the course of the 30-day follow-up period (Table 1). The AKIN urine output criteria were not used to diagnose or classify AKI in this study. This approach has been taken in other large epidemiological studies due to the difficulty of ascertaining hourly urine output, which is required to apply the AKIN urine criteria.¹ Furthermore, urine output is unreliably collected or missing in non-ICU settings, thereby limiting its use in identifying patients with AKI prior to ICU admission. Among patients with AKI, we documented nephrology consultations and dialysis initiation and recorded the patients' characteristics on the day these events took place.

Data collection and follow-up

Demographic, clinical, and laboratory data from hospital charts were recorded on the day of ICU admission and, when applicable, on the day of AKI diagnosis. Patients were followed until hospital discharge, death, or for a maximum of 30 days. Patients who were discharged from hospital prior to 30 days of follow-up were assumed to be alive on day 30. Standardized case report forms were utilized at all study sites. The data collectors (A.O., A.M., A.Z., B.R.), trained by the lead investigators (R.W., M.H), abstracted data prospectively from hospital charts and recorded them on standardized case report forms using criteria delineated in a

study operations manual. Randomly selected case report forms were then reviewed retrospectively by the lead investigators to confirm the integrity of the data collection.

Statistical analysis

All two-group comparisons (AKI vs no AKI) were performed using the two-sample *t*-test (normally distributed continuous data), the Mann-Whitney U-test (nonnormally distributed continuous data), or the Chi-square test (categorical data). Multigroup comparisons were analyzed using one-way analysis of variance (normally distributed continuous data), the Kruskal-Wallis test (nonnormally distributed continuous data) and the Chi-square test (categorical data). The 30-day follow-up period was selected because available research personnel could collect data for this time period. Similarly, the sample size was based on a convenience sample and was intended to provide a comprehensive glimpse of all ICU admissions during the selected period of study.

Among patients with AKI, we sought to evaluate patient characteristics available on the day of AKI diagnosis that might predict 30-day mortality. Multivariable logistic regression was performed using clinical, biochemical, and hematological data, all obtained on the day of AKI diagnosis, to identify independent predictors of 30-day mortality. We first selected potential predictors through univariate analysis and clinical relevance and subsequently used automated search procedures to streamline the number of predictors. These automatic procedures included backward elimination, forward selection, and stepwise selection. Each of the automated approaches yielded the same variables. When the urine output data were not available, they were categorized as "missing" so urine output could be included in the regression analyses without excluding a large proportion of patients. Model calibration was evaluated with the Hosmer-Lemeshow test, and model discrimination was described as the area under the receiver-operating characteristic curve (AUC). The model was further adjusted for baseline characteristics including age, sex, and number of preexisting co-morbidities. All tests were two-sided, and statistical significance was defined as

$P < 0.05$. Statistical analyses were performed using SPSS software (version 16.0; SPSS, Chicago, IL, USA) and SAS software (version 9.2; SAS Institute, Cary NC, USA).

Results

Overview of the cohort

During the period of observation, 603 eligible patients were admitted to the ICUs being studied. A total of 263 were admitted to St. Michael's Hospital, 170 to Sunnybrook Health Sciences Centre, 76 to Mount Sinai Hospital, and 94 to the Saskatoon hospitals. Most patients were admitted with a surgical diagnosis (63%); the remainder had a primary medical diagnosis. Of the 161 (26.6%) patients who developed AKI, 99 (61.5%), 29 (18.0%), and 33 (20.5%)

reached AKIN-SCr stages 1, 2, and 3, respectively. Acute kidney injury preceded ICU admission in 11 (1.8%) patients. A total of 38 patients (23.6% of those with AKI) underwent a nephrology consultation, and 19 patients (11.8% of those with AKI) commenced dialysis.

Compared to patients without AKI, those with AKI were older (64.7 ± 15.6 vs 59.0 ± 18.2 yr, $P = 0.001$) and were more likely to be male (71.4% vs 61.1%, $P = 0.019$) (Table 2). Preexisting hypertension, diabetes mellitus, and coronary disease were more frequent among patients with AKI. At ICU admission, individuals with preexisting or subsequent AKI were more likely to be undergoing mechanical ventilation and taking vasopressors. Serum creatinine and BUN levels and the white blood cell count were higher in these individuals, whereas the pH, serum bicarbonate, and hemoglobin levels were significantly lower.

Table 2 Baseline characteristics of the patient cohort

Variable	AKI ($n = 161$)	No AKI ($n = 442$)	P
Male	115 (71%)	270 (61.1%)	0.0194
Age (yr)	64.7(15.6)	59.0(18.2)	0.0005
Preexisting illnesses			
Diabetes mellitus	52 (32%)	88 (20%)	0.0014
Hypertension	89 (55%)	180 (41%)	0.0015
Coronary artery disease	77 (48%)	160 (36%)	0.0097
Cerebrovascular disease	18 (11%)	30 (7%)	0.0779
Reasons for ICU admission			
Cardiovascular	80 (50%)	164 (37%)	0.01
Neurological	10 (6%)	88 (20%)	
Pulmonary	19 (11%)	53 (12%)	
Trauma	10 (6%)	62 (14%)	
Infection	16 (10%)	19 (4%)	
Gastrointestinal	12 (8%)	21 (5%)	
Other	14 (9%)	35 (8%)	
Serum creatinine on hospital admission ($\mu\text{mol}\cdot\text{L}^{-1}$)	128.3 (111.7)	93.2 (72.8)	< 0.0001
Characteristics on admission to ICU			
Mechanical ventilation	145 (90%)	309 (70%)	< 0.0001
Receipt of vasopressors	86 (53%)	145 (33%)	< 0.0001
Laboratory data on admission to ICU			
Serum creatinine ($\mu\text{mol}\cdot\text{L}^{-1}$)	149.3 (113.9)	84.0 (59.6)	< 0.0001
Blood urea nitrogen ($\text{mmol}\cdot\text{L}^{-1}$)	12.1 (11.8)	6.1 (5.3)	< 0.0001
pH	7.3 (0.1)	7.4 (0.1)	0.0002
Bicarbonate ($\text{mmol}\cdot\text{L}^{-1}$)	20.2 (5.0)	22.8 (4.7)	< 0.00001
Potassium ($\text{mol}\cdot\text{L}^{-1}$)	4.3 (0.8)	4.2 (2.3)	0.7294
Hemoglobin ($\text{g}\cdot\text{L}^{-1}$)	102.6 (23.9)	108.5 (24.4)	0.0091
White blood cell count ($\times 10^9\cdot\text{L}^{-1}$)	16.6 (16.8)	13.2 (14.8)	0.0191
Platelets ($\times 10^9\cdot\text{L}^{-1}$)	200.8 (113.6)	205.8 (109.4)	0.6234

Categorical variables are expressed as number of patients (%) and continuous variables as the mean (SD). Data were missing for the following variables (number of patients): serum creatinine at ICU admission (1), blood urea nitrogen (2), pH (133), bicarbonate (6), potassium (2), hemoglobin (5), platelets (5), white blood cells (5). AKI = acute kidney injury; GI = gastrointestinal; ICU = intensive care unit

Patient characteristics on the date of AKI diagnosis

The characteristics of the 161 patients with AKI, stratified by the peak AKIN-SCr stage that they would achieve, are described in Table 3. On the day of the AKI diagnosis, mechanical ventilation was associated with the peak AKIN-SCr stage, and urine output was inversely related to the peak AKIN-SCr stage (1670 ± 1231 , 1841 ± 2309 , and 766 ± 808 mL for stages 1, 2, and 3, respectively). Serum creatinine and BUN levels were highest in individuals who would ultimately peak at AKIN-SCr stage 3. No other laboratory variables were associated with the ultimate AKIN-SCr stage attained.

Overview of 30-day outcomes

By 30 days following ICU admission, 85 (14.1%) patients had died, 75 (12.4%) were alive and still in hospital, and 443 (73.5%) had been discharged. Altogether, 79.0% patients without AKI were discharged alive within 30 days; and 71.7%, 44.8%, and 30.3% of patients reaching AKIN-SCr stages 1, 2, and 3, respectively, were discharged within 30 days. The median length of stay in the ICU was significantly longer among patients with AKI (3 days [interquartile range {IQR} 1-5 days vs 1 day {IQR} 1-3 days] among patients with no AKI, $P < 0.001$). The length of stay in the ICU was incrementally prolonged at ascending AKI stages (2 days [IQR 1-4 days] vs 3 days [IQR 1-9 days] vs 6.5 days [IQR 3-17 days] for AKIN-SCr stages 1, 2, and 3, respectively; $P < 0.001$).

Figure (A – Top graph) 30-Day mortality, by the Acute Kidney Injury Network (AKIN) serum creatinine (SCr) stage. $P < 0.001$ for the gradient in mortality. (B – Bottom graph) 30-Day mortality, by the AKIN-SCr stage and by the reason for intensive care unit (ICU) admission. Clear bars = surgical reasons; dark bars = medical reasons

Compared to patients without AKI, those with any stage of AKI were significantly more likely to die in hospital: 47 (29.2%) vs 38 (8.6%, $P < 0.001$) (Figure). We observed a

Table 3 Patients with AKI stratified by peak AKIN-SCr stage: characteristics on the day of AKI diagnosis

Parameter	AKIN-SCr I ($n = 99$)	AKIN-SCr II ($n = 29$)	AKIN-SCr III ($n = 33$)	P
No. of days from hospital admission to AKI (IQR)	1.0 (0-4.0)	1.0 (0-2.0)	1.0 (0-5.0)	0.0581
No. of days from ICU admission to AKI (IQR)	1.0 (0-3.0)	0.5 (0-2.0)	0.5 (0-1.5)	0.4024
Mechanical ventilation	56 (57%)	18 (62%)	27 (82%)	0.0341
Receipt of vasopressors	35 (35%)	15 (52%)	18 (55%)	0.0804
Urine output	1669.8 (1230.9)	1841.0 (2308.8)	766.3 (808.0)	0.0269
Laboratory data on day of AKI diagnosis				
Serum creatinine ($\mu\text{mol}\cdot\text{L}^{-1}$)	155.6 (77.4)	165.5 (73.1)	261.2 (192.3)	< 0.0001
Blood urea nitrogen ($\text{mmol}\cdot\text{L}^{-1}$)	11.3 (6.4)	9.6 (5.3)	16.9 (12.2)	0.0005
pH	7.2 (1.0)	7.3 (0.1)	7.3 (0.1)	0.6875
Bicarbonate ($\text{mmol}\cdot\text{L}^{-1}$)	21.3 (5.2)	20.5 (6.9)	20.4 (6.9)	0.6661
Potassium ($\text{mmol}\cdot\text{L}^{-1}$)	4.6 (2.6)	4.1 (0.9)	4.4 (1.0)	0.4657
Hemoglobin ($\text{g}\cdot\text{L}^{-1}$)	98.9 (22.1)	106.8 (26.1)	99.9 (27.2)	0.3088
Platelets ($\times 10^9\cdot\text{L}^{-1}$)	210.7 (118.4)	221.8 (150.3)	177.5 (143.8)	0.3539
White blood cell count ($\times 10^9\cdot\text{L}^{-1}$)	14.0 (6.1)	10.9 (5.6)	13.5 (10.4)	0.1340

Categorical variables are expressed as number of patients (%). Continuous variables are expressed as the mean (SD) or median (IQR), as appropriate. Data were missing for the following variables (number of patients): urine output (73), blood urea nitrogen (14), pH (53), bicarbonate (17), potassium (15), hemoglobin (13), platelets (13), white blood cells (13)

AKI = acute kidney injury; IQR = interquartile range

Table 4 30-Day mortality among patients with AKI according to AKIN-SCr stage

AKIN-SCr stage	Proportion of patients who reached stage	30-Day mortality* (%)
I	61.5	19.2
II	18.0	37.9
III	20.5	51.5

* $P < 0.001$ for the trend in mortality with ascending AKIN-SCr stages. AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; SCr = serum creatinine

significant gradient in the likelihood of death with increasing AKIN-SCr stage ($P < 0.001$) (Figure and Table 4).

Clinical features on the day of AKI diagnosis and subsequent mortality

The characteristics of the 161 AKI patients at the time of AKI diagnosis, stratified by subsequent mortality during the 30-day follow-up period, are described in Table 5. Among the patients with AKI, those admitted to the ICU with a medical diagnosis were more likely to die than those admitted with a surgical diagnosis [36 (22.4%) vs 11 (6.8%), $P < 0.001$]. In a logistic regression model that considered all clinical variables on the day of AKI diagnosis, only BUN—adjusted odds ratio (OR) 1.81, 95% confidence interval (CI) 1.10 to 2.98 per 10 mmol·L⁻¹ increase—and serum bicarbonate (adjusted OR 0.89, 95% CI 0.80 to 0.95 per 1 mmol·L⁻¹ increase) were significantly associated with 30-day mortality, with an AUC of 0.72 (95% CI 0.58 to 0.85). The Hosmer-Lemeshow statistic for the model was 4.94 ($P = 0.76$), indicating good

calibration. After adjustment for baseline characteristics, including age, sex, and number of preexisting co-morbidities, BUN (adjusted OR 1.68, 95% CI 1.01 to 2.79 per 10 mmol·L⁻¹ increase) and serum bicarbonate (adjusted OR 0.88, 95% CI, 0.81 to 0.95 per 1 mmol·L⁻¹ increase) were significantly associated with 30-day mortality, with an AUC of 0.79 (95% CI, 0.71 to 0.86). The Hosmer-Lemeshow statistic for the model was 13.48 ($P = 0.10$), indicating good calibration.

Discussion

Acute kidney injury is a common complication of critical illness, occurring in more than one-quarter of patients admitted to ICUs in five Canadian centres in our study. Using the AKIN-SCr staging system, higher AKI stage was associated with a graded increase in 30-day mortality. Importantly, even stage 1 AKI was associated with a mortality risk of about 20%, which is more than double that of critically ill patients with no AKI. At the time AKI was first identified, higher BUN and lower serum bicarbonate levels were independently associated with 30-day mortality.

The advent of standardized criteria for the diagnosis and classification of AKI has led to a reevaluation of the epidemiology of this condition. A multicentre retrospective observational study reported that AKI, as defined by the AKIN criteria, occurred in 22% of all patients admitted to ICUs in Veterans Affairs hospitals in the United States.¹ Our data indicated a similar rate of 27%, recognizing that interstudy differences may be due to a number of factors. Our study was conducted exclusively at tertiary care

Table 5 Characteristics at AKI diagnosis stratified by vital status at 30 days

Parameter	Alive at 30 days (<i>n</i> = 114)	Death within 30 days (<i>n</i> = 47)	<i>P</i>
Characteristics on day of AKI diagnosis			
Mechanical ventilation	62 (54%)	39 (83%)	0.001
Receipt of vasopressors	39 (34%)	29 (62%)	0.001
Urine output (mL·24 hr)	1857.6 (1655.9)	856.1 (922.5)	< 0.0001
Laboratory data on day of AKI diagnosis			
Serum creatinine (μmol·L ⁻¹)	170.5 (108.4)	199.8 (135.7)	0.151
Blood urea nitrogen (mmol·L ⁻¹)	11.1 (7.2)	14.9 (9.9)	0.010
pH	7.2 (0.9)	7.3 (0.2)	0.896
Bicarbonate (mmol·L ⁻¹)	22.0 (4.9)	18.5 (7.3)	0.005
Potassium (mmol·L ⁻¹)	4.5 (2.4)	4.3 (1.0)	0.604
Hemoglobin (g·L ⁻¹)	98.7 (22.9)	105.3 (26.6)	0.132
Platelets (× 10 ⁹ ·L ⁻¹)	215.6 (137.2)	181.4 (112.7)	0.147
White blood cell count (× 10 ⁹ ·L ⁻¹)	13.0 (6.2)	13.8 (9.3)	0.529

Categorical variables are expressed as number (%) of patients. Continuous variables are expressed as the mean (SD). Data were missing for the following variables (number of patients): urine output (73), blood urea nitrogen (14), pH (53), bicarbonate (17), potassium (15), hemoglobin (13), platelets (13), white blood cells (13). AKI = acute kidney injury

centres, whereas the aforementioned study was performed at a wider range of hospital types where ICU illness acuity may have been lower. Furthermore, they used the serum creatinine level at the time of ICU admission as the baseline from which AKI was identified and evaluated. As the kidney function of these patients might have already deteriorated significantly by the time of their ICU admission, it may have led to underestimation of the true frequency of AKI in their cohort.

Recognizing that the time of admission to the ICU is variable, our study chose to use the creatinine level at hospital admission as the baseline. This approach is also imperfect as it does not account for fluxes in kidney function that may have occurred prior to hospital admission. In a study where preadmission values were considered, AKI occurred in 67% of critically ill patients.⁸ For individuals whose preadmission values were missing, the “baseline” creatinine was back-calculated based on an estimated glomerular filtration rate (GFR) of $75 \text{ mL} \cdot \text{min}^{-1} / 1.73 \text{ m}^{-2}$. However, the assumption of virtually normal baseline kidney function is inconsistent with modern cohorts of AKI patients of whom up to one-third have demonstrated a background of chronic kidney disease.⁹ Furthermore, depending on the severity and duration of the patient’s illness, substantial changes in the serum creatinine concentration may have already occurred by the time of hospital presentation. These studies highlight the difficulties inherent in ascertaining baseline kidney function, which represents a major challenge when studying AKI.^{10–12}

Timely diagnosis of AKI requires accurate estimation of the GFR in the context of acutely changing renal function. The AKIN criteria base the diagnosis of AKI primarily on changes in serum creatinine as an indicator of the GFR. Even the lowest categories (i.e., modest changes in serum creatinine) are associated with significantly increased morbidity and mortality.¹³ It should be noted that changes in the serum creatinine level may lag behind acute changes in the GFR and severely interfere with an early diagnosis of AKI.

Recently, a series of renal biomarkers have emerged that may diagnose AKI earlier and facilitate prognostication and intervention. Cystatin C (CysC) is a novel biomarker that may be a more accurate surrogate than creatinine for indicating an acutely changing GFR as it does not undergo nonglomerular clearance. Also, its volume of distribution is smaller than that of creatinine, thereby facilitating its accumulation in the intravascular space.¹⁴ In a mixed cohort of patients from medical and surgical ICUs, CysC identified patients with AKI in its earliest stages up to 1.5 days earlier than serum creatinine with an AUC of 0.82.¹⁵ In a prospective cohort study of unselected ICU patients, admission serum CysC in the third and fourth quartile was significantly associated with all-cause mortality (hazard ratios 1.23 and 1.41, respectively) even after

adjustment for age, ICU diagnosis, AKI diagnosis by the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score.¹⁶ Likewise, elevated urinary interleukin (IL)-18 can identify AKI 24 and 48 hours prior to serum creatinine with AUCs of 0.73 and 0.65, respectively.¹⁷

To enhance the accuracy of biomarkers in predicting a diagnosis of AKI or its outcome (e.g., dialysis requirement, mortality), it is possible to evaluate several biomarkers collectively. In patients with cardiopulmonary bypass-associated AKI, for example, the combination of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and *N*-acetyl- β -(D)-glucosaminidase (NAG) demonstrated modest predictive value for identifying AKI immediately following surgery and three hours post-operatively (AUCs 0.75 and 0.78, respectively).¹⁸ Among hospitalized patients who underwent nephrology consultations for AKI, the combination of urinary NAG activity, urinary KIM-1 levels, and the APACHE II score provided the best discriminatory capacity for the outcome of dialysis or death (AUC 0.83) in comparison to other clinical variables.¹⁹ In contrast, a multicenter study of patients hospitalized with pneumonia who subsequently developed severe AKI (corresponding to “failure” in the similar RIFLE²⁰ classification system) examined clinical predictors of “renal nonrecovery,” defined as a need for dialysis, in-hospital mortality, or persistent RIFLE–failure at hospital discharge.²¹ Age, the initial serum creatinine level, the pneumonia severity index, and the nonrenal Sequential Organ Failure Assessment (SOFA) score²² predicted renal nonrecovery with an AUC of 0.78. The addition of plasma NGAL to the model improved the AUC only marginally to 0.80. Further study is therefore necessary to identify the most effective approach for incorporating novel biomarkers into the diagnosis and management of AKI.

The ability to identify patients who are likely to die shortly after a diagnosis of AKI is also an important clinical endeavor as it may permit the timely administration of therapeutic strategies to improve the clinical outcome. As an example, recent meta-analyses suggested that earlier institution of dialysis in patients with AKI might be associated with improved survival.^{6,7} In comparison to studies focusing on prognostic factors later in the course of AKI,^{19,21} we aimed to identify clinical predictors of death on the day of AKI diagnosis, a clinically relevant time point if early interventions are to be initiated. Although novel biomarkers may assist with the earlier diagnosis and risk stratification of patients with AKI,^{15,17–19} we demonstrated that the BUN and bicarbonate concentrations, two routinely determined clinical variables, have reasonable prognostic significance even after adjusting for baseline patient characteristics.

This is the first characterization of the epidemiology of AKI in Canadian ICUs using contemporary criteria for defining and staging AKI. We included consecutive patients with a diversity of medical problems at five hospitals, and our data therefore provide a comprehensive profile of patients admitted to Canadian ICUs. In addition to highlighting the prognostic importance of even stage 1 AKI, our work provides clinicians with useful tools to identify patients with AKI who are at higher risk of an adverse outcome.

Our study also has some important limitations. First, using the serum creatinine level determined at the time of hospital admission as the baseline for a diagnosis of AKI may have underestimated the frequency of AKI. Whereas the AKIN staging system for AKI incorporates a parallel set of criteria based on the severity and duration of oliguria, we relied on creatinine changes alone to diagnose and stage AKI. Other large epidemiological studies have taken this approach as well because of the inherent challenges of collecting the hour-to-hour urine output data needed for the AKIN and RIFLE classification schemes.¹ Second, our study is limited by its reliance on serum creatinine as a surrogate marker for the GFR, particularly given its dependence on muscle mass and the numerous nonglomerular factors that affect accumulation of creatinine in the intravascular space. However, in clinical practice, serum creatinine remains the gold standard for monitoring kidney function, notwithstanding its limitations. Third, although we ascertained outcomes at 30 days, we could not confirm the vital status of individuals discharged from hospital prior to the 30-day endpoint. The assumption that these people were alive may have led to some misclassification. Because patients with AKI are more likely to die following discharge, such misclassification likely underestimated mortality among patients with AKI. Finally, our prognostic model was derived from an unselected cohort of patients admitted to the ICU and should be validated in various populations of patients with AKI.

In conclusion, kidney injury is a common feature of critical illness in Canadian ICUs, and even mild AKI is associated with a substantial risk of death. The highest AKI stage achieved was closely correlated with ICU length of stay and in-hospital mortality, confirming the relevance of this classification system in Canadian patients. Selected routine laboratory parameters at the time of AKI diagnosis were associated with 30-day mortality. However, their ability to identify those patients who will die is modest.

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