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Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study

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Take-home message: In this first multinational cross-sectional study on the epidemiology of AKI in ICU patients using the complete KDIGO criteria. AKI occurred in more than half of ICU patients and was associated with mortality and worse renal function. Adjusted risks for mortality were similar across different continents and regions.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-3934-7) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* Current reports on acute kidney injury (AKI) in the intensive care unit (ICU) show wide variation in occurrence rate and are limited by study biases such as use of incomplete AKI definition, selected cohorts, or retrospective design. Our aim was to prospectively investigate the occurrence and outcomes of AKI in ICU patients. *Methods:* The Acute Kidney Injury–Epidemiologic Prospective Investigation (AKI-EPI) study was an international cross-sectional study performed in 97 centers on patients during the first week of ICU admission. We measured AKI by Kidney Disease: Improving Global Outcomes (KDIGO) criteria, and outcomes at hospital discharge. *Results:* A total of 1032 ICU patients out of 1802 [57.3 %; 95 % confidence interval (CI) 55.0–59.6] had AKI. Increasing AKI severity was associated with hospital mortality when adjusted for other variables; odds ratio of stage 1 = 1.679 (95 % CI 0.890–3.169; $p = 0.109$), stage 2 = 2.945 (95 % CI 1.382–6.276; $p = 0.005$), and stage 3 = 6.884 (95 % CI 3.876–12.228; $p < 0.001$). Risk-adjusted rates of AKI and mortality were similar across the world. Patients developing AKI had worse kidney function at hospital discharge with estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 in 47.7 % (95 % CI 43.6–51.7) versus 14.8 % (95 % CI 11.9–18.2) in those without AKI, $p < 0.001$. *Conclusions:* This is the first multinational cross-sectional study on the epidemiology of AKI in ICU patients using the complete KDIGO criteria. We found that AKI occurred in more than half of ICU patients. Increasing AKI severity was associated with increased mortality, and AKI patients had worse renal function at the time of hospital discharge. Adjusted risks for AKI and mortality were similar across different continents and regions.

Keywords Acute kidney injury · Critically ill · Renal replacement therapy · Epidemiology · Kidney function · Hospital mortality

Introduction

Over the past decades there was an increasing incidence of acute kidney injury (AKI), and given the adverse outcomes especially in the long term, AKI is now a growing concern for health care worldwide [1, 2]. AKI is a frequent complication in patients admitted to the intensive care unit (ICU) and is associated with adverse outcomes including increased length of ICU and hospital stay, development of chronic kidney disease (CKD), and increased short- and long-term mortality risk [3–6].

Since the publication of the RIFLE consensus classification for AKI, and the modifications by the Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO), these definitions have been used in the majority of studies reporting on AKI [7–9]. Establishing an accurate event rate for AKI is important for health policy, quality initiatives, and for

design of clinical trials. However, analyzing AKI in the ICU setting from existing databases is often limited by missing data elements needed for application of these definitions (e.g., inclusion of urine output, selection of baseline serum creatinine, etc.). Administrative databases are limited, as billing codes do not capture many cases of AKI [10]. Together with differences in patients' baseline characteristics, this may explain the wide variation in the occurrence of AKI reported in ICU patients, with an average reported occurrence of 30–40 % [2]. Further, there is no information on the worldwide patterns of AKI using current definitions.

The objective of the Acute Kidney Injury–Epidemiologic Prospective Investigation (AKI-EPI) study was to prospectively investigate the epidemiology of AKI in ICUs worldwide using the latest consensus definition for AKI and a standardized data collection instrument.

Methods

The AKI-EPI study is a multicenter international cross-sectional study on the epidemiology of AKI in ICU patients. A convenience sample of investigators was asked to record AKI during the first week of admission in ten or more consecutively admitted ICU patients. When a hospital had several ICUs, the investigators were encouraged to record these as individual cohorts. Investigators were recruited after announcement of the study by the principal investigators at international critical care meetings.

This manuscript reports results according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [11].

Participants

Patients who were 18 years or older and admitted to the ICU were included. Exclusion criteria were chronic renal replacement therapy (RRT), kidney transplantation within 3 months before ICU admission, anticipated alive ICU discharge within 24 h, and readmission to the ICU during the same hospitalization episode. The number of cases recorded by the investigators determined the sample size of the study.

In order to reduce the risk of information bias, we excluded units that recorded less than 10 patients, and units were allowed to record a maximum of 65 patients.

Data collection

Data were anonymously recorded via a specific password-protected website. The website was opened from 1 April 2009 until 31 December 2010. The data collection included both serum creatinine and urine output details for diagnosis of AKI and assessment of AKI severity. AKI was diagnosed and classified on the basis of the worst serum creatinine or urine output criteria according to the KDIGO classification [9]. For this a reference serum creatinine concentration was recorded. This reference serum creatinine value was defined as a concentration obtained within a 3-month period before ICU admission and considered to be representative of the baseline kidney function according to the judgment of the treating physician. If this reference value was not available, we used the minimum of either serum creatinine at the time of admission to the ICU, or in patients without CKD, a calculated serum creatinine concentration using the MDRD equation as recommended by the Acute Dialysis Quality Initiative (ADQI) [7, 9, 12]. When used, modality of RRT was also recorded.

The Simplified Acute Physiology Score (SAPS) 3 score was used for assessment of severity of illness at the time of ICU admission, and the Sequential Organ Failure Assessment (SOFA) score for organ dysfunction at the time of diagnosis of AKI [13, 14]. Glomerular filtration rate was estimated with the CKD-EPI equation (eGFR), and patients with eGFR less than 60 mL/min/1.73 m^2 were classified as CKD class 3 or higher [15]. Outcomes were measured at the time of ICU and hospital discharge and included mortality and the renal outcomes serum creatinine, eGFR, and RRT.

In order to establish eGFR, the investigators scored race and ethnicity of the participants (Caucasian, black, Asian, Hispanic, or other).

We used five different methods to group countries: continents, according to latitude, world zones according to the United Nations geo-scheme classification, according to the World Bank's classification of income of countries, and to the proportion of the global domestic product (GDP) spend for country health expenditure as reported by the World Health Organization [16–18].

Local ethics committees approved the study according to the local regulations.

Statistical analysis

Data are presented as median and interquartile range (IQR; 25th and 75th percent quartile) or proportion [95 % confidence interval (CI)]. Comparison of categorical variables was performed with the Chi-square or the Fisher exact test, and continuous variables were compared with the Mann–Whitney *U* test. In case of missing data that are essential for assessment of AKI, patients were excluded. In case of data missing completely at random, the number of observations included in the analysis is reported. We planned a sensitivity analysis of the occurrence rate of AKI in patients with known reference serum creatinine value.

Multivariate logistic regression analysis was conducted to investigate risk factors for mortality and AKI. A three-level hierarchical logistic regression model was applied using proc glimmix. Variables selected for inclusion in the regression model were those with biological or plausible rationale and a p value of 0.25 or less in bivariate analysis of AKI and no-AKI patients, and survivors and non-survivors. In the three models we used the random effects variables country and center.

The logistic regression model for mortality was used to calculate predicted mortality. Calibration of the models was assessed by the Hosmer–Lemeshow goodness of fit test. The Hosmer–Lemeshow statistic, however, explicitly assumes that all of the observations are independent, and it is not clear if this test is robust when this assumption may be violated, as in this data set. Therefore, the goodness of fit was tested on a non-hierarchical logistic regression model in which we included all fixed covariates and also country. The area under the receiver operating characteristic curve assessed discrimination (c statistic).

Statistical significance was accepted when the p value was less than 0.05 (double sided). Statistical analysis was performed with the software packages SPSS statistics version 22 (IBM Corporation and others, NY, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA); 95 % CI for proportions were calculated in Excel (Microsoft Corporation, USA) [19].

Results

A total of 139 ICUs were registered on the website. After exclusions, the final study cohort consisted of 97 ICUs that reported on 1802 patients, originating from 33 different countries (15 European, 5 South American, 5 Asian, 4 North American, 2 African, Australia and New Zealand) (study flow chart and unit characteristics are in Fig. 1 and Table 1 in the electronic supplementary material).

The median age of the patients included in the study was 63 years, 64.4 % were male (95 % CI 62.2–66.6), and 68.1 % were Caucasian (95 % CI 66.0–70.3) (Table 1). AKI occurred in 1032 ICU patients (57.3 %; 95 % CI 55.0–59.6) at day 1 (1, 2) of ICU stay. In 630 patients (35.0 %; 95 % CI 32.8–37.2) baseline creatinine information was not available, and the reference serum creatinine concentration was estimated on the basis of the MDRD equation ($n = 169$), or serum creatinine at ICU admission ($n = 461$). When these patients were excluded, the occurrence of AKI was higher (62.5 %; 95 % CI 59.7–65.3; $p = 0.005$). Comorbidities such as cancer, hypertension, chronic heart failure, cirrhosis, AIDS, chronic obstructive pulmonary disease (COPD), or diabetes mellitus were present in 71.5 % of patients (95 % CI 69.4–73.5). Two or more co-morbidities were present in 37.6 % of patients (95 % CI 35.4–39.8). The majority of patients had an unplanned ICU admission, coming from the emergency department, operating room, or a hospital ward, and 48.1 % of the patients had surgery before admission (95 % CI 45.8–50.4).

Sepsis and hypovolemia were the most frequent reported aetiologies for AKI (Table 2). Nephrotoxic drugs were reported as the aetiology for AKI in 14.4 % (95 % CI 12.0–17.3) of patients. At the time of AKI diagnosis, one-third of patients were treated with diuretics and 11.9 % with non-steroidal anti-inflammatory drugs (95 % CI 9.6–14.5). Aminoglycosides, glycopeptides, and contrast media were administered in less than 10 % of AKI patients. Half of AKI patients were treated with vasoactive therapy at the time of AKI diagnosis, and one-third were mechanically ventilated. A SOFA score of 2 or more for the liver or coagulation component was present in one-fifth of patients.

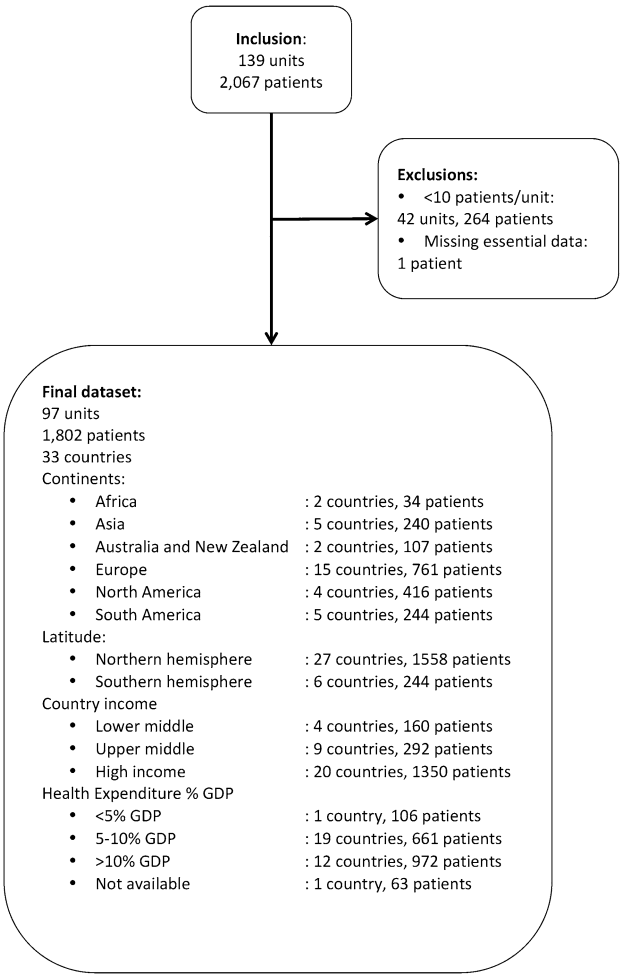

Fig. 1 Patients flow chart

Table 1 Baseline characteristics, outcomes, and adjusted odds ratios for acute kidney injury

	All patients	No AKI	AKI	*p*
Baseline characteristics				
Number of patients	1802 (100 %)	770 (42.7 %)	1032 (57.3 %)	
Age (years)	63 (52, 73)	61 (49, 70)	65 (54, 75)	<0.001
Male	1161 (64.4 %)	511 (66.4 %)	650 (63.0 %)	0.138
Race, ethnicity				<0.001
Caucasian	1228 (68.1 %)	496 (64.4 %)	732 (70.9 %)	
Black	100 (5.5 %)	44 (5.7 %)	56 (5.4 %)	
Asian	246 (13.7 %)	131 (17.0 %)	115 (11.1 %)	
Hispanic	156 (8.7 %)	77 (10.0 %)	79 (7.7 %)	
Other	72 (4.0 %)	22 (2.9 %)	50 (4.8 %)	
Continent				<0.001
Australia and New Zealand	107 (6.0 %)	33 (4.3 %)	74 (7.2 %)	
Africa	34 (1.9 %)	4 (0.5 %)	30 (2.9 %)	
Asia	230 (12.8 %)	128 (16.7 %)	102 (10.0 %)	
Europe	761 (42.5 %)	304 (39.6 %)	457 (44.6 %)	
North America	416 (23.2 %)	185 (24.1 %)	231 (22.6 %)	
South America	244 (13.6 %	114 (14.8 %)	130 (12.7 %)	
Type of hospital				0.265
Academic	1300 (72.1 %)	545 (70.8 %)	755 (73.2 %)	
Non-academic	502 (27.9 %)	225 (29.2 %)	277 (26.8 %)	
Number of hospital beds	600 (300, 850)	560 (300, 850)	600 (300, 850)	0.159
Number of ICU beds	19 (12, 23)	19 (12, 23)	19 (12, 23)	0.058
Number of ICU beds per nurse				
Day	2 (2, 2)	2 (2, 2)	2 (2, 2)	0.929
Night	4 (3, 6)	4 (3, 6)	4 (3, 6)	0.575
ICU organization				0.390
Closed ICU	1534 (85.1 %)	650 (84.4 %)	884 (85.7 %)	
Open ICU	216 (12.0 %)	93 (12.1 %)	25 (11.9 %)	
Unknown	52 (2.9 %)	27 (3.5 %)	25 (2.4 %)	
Comorbidities				
Cancer	357 (19.8 %)	145 (18.8 %)	212 (20.5 %)	0.367
Heart failure (NYHA class IV)	101 (5.6 %)	28 (3.6 %)	73 (7.1 %)	0.002
Cirrhosis	83 (4.6 %)	23 (3.0 %)	60 (5.8 %)	0.005
Hypertension	858 (47.6 %)	303 (39.4 %)	555 (53.8 %)	<0.001
COPD	288 (16 %)	124 (16.1 %)	164 (15.9 %)	0.903
Diabetes ($n = 1520$)	384 (25.3 %)	115 (17.5 %)	269 (31.2 %)	<0.001
Reason for ICU admission ($n = 1799$)				
Unplanned ICU admission	1282 (71.3 %)	517 (67.2 %)	765 (74.3 %)	0.001
Cardiovascular	624 (34.6 %)	193 (25.1 %)	431 (41.8 %)	<0.001
Hypovolemic shock	152 (8.4 %)	46 (6.0 %)	106 (10.3 %)	0.001
Septic shock	279 (15.5 %)	62 (8.1 %)	217 (21.0 %)	<0.001
Liver failure	71 (3.9 %)	15 (1.9 %)	56 (5.4 %)	<0.001
Acute abdomen, other	146 (8.1 %)	47 (6.1 %)	99 (9.6 %)	0.007
Neurologic	466 (25.9 %)	214 (27.8 %)	252 (24.4 %)	0.106
Surgical status at admission ($n = 1539$)				<0.001
Scheduled surgery	500 (32.5 %)	241 (37.1 %)	259 (29.1 %)	
Emergency surgery	240 (15.6 %)	105 (16.2 %)	135 (15.2 %)	
No surgery	799 (51.9 %)	304 (46.8 %)	495 (55.7 %)	
Anatomical site of surgery				
Transplantation surgery	15 (0.8 %)	3 (0.4 %)	12 (1.2 %)	0.074
Cardiac surgery	190 (10.5 %)	84 (10.9 %)	106 (10.3 %)	0.663
Neurosurgery	83 (4.6 %)	60 (7.8 %)	23 (2.2 %)	<0.001
Other surgery	483 (26.8 %)	211 (27.4 %)	272 (26.4 %)	0.620
In-hospital location before ICU admission ($n = 1638$)				<0.001
Other ward	354 (21.6 %)	270 (38.1 %)	317 (34.1 %)	
Emergency room	587 (35.8 %)	240 (33.9 %)	257 (27.6 %)	
Operation room	497 (30.3 %)	126 (17.8 %)	228 (24.5 %)	
Other ICU	106 (6.5 %)	34 (4.8 %)	72 (7.7 %)	
None	94 (5.7 %)	38 (5.4 %)	56 (6.0 %)	
SAPS 3 score	53 (42, 66)	48 (39, 59)	58 (46, 70)	<0.001
Serum creatinine at ICU admission (mg/dL)	1.10 (0.80, 1.70)	0.90 (0.70, 1.18)	1.40 (0.96, 2.39)	<0.001
Reference serum creatinine (mg/dL)	0.95 (0.78, 1.19)	0.90 (0.70, 1.10)	1.00 (0.80, 1.26)	<0.001
Reference serum creatinine based upon				<0.001

Table 1 continued

	All patients	No AKI	AKI	*p*
History	1171 (65 %)	439 (57.0 %)	732 (70.9 %)	
ICU admission value	461 (25.6 %)	283 (36.8 %)	178 (17.2 %)	
MDRD recalculated value	169 (9.4 %)	48 (6.2 %)	121 (11.7 %)	
eGFR (mL/min/1.73 m^2)	81 (60, 96)	85 (70, 101)	76 (53, 93)	<0.001
eGFR <60 mL/min/1.73 m^2	446 (24.8 %)	118 (15.3 %)	328 (31.8 %)	<0.001
Vasoactive drugs before ICU admission	318 (17.6 %)	100 (13.0 %)	218 (21.1 %)	<0.001
Infection	272 (15.1 %)	92 (11.9 %)	180 (17.4 %)	0.001
Outcomes				
ICU outcomes				
Length of stay ICU (days)	5 (3, 9)	4 (3, 6)	6 (4, 12)	<0.001
$Creatinine_{discharge}$ (mg/dL) ($n = 1165$)	0.9 (0.7, 1.4)	0.8 (0.6, 1.0)	1.2 (0.8, 2.0)	<0.001
RRT at discharge ($n = 1693$)	118 (7.0 %)	1 (0.1 %)	117 (12.1 %)	<0.001
eGFR (mL/min/1.73 m^2)	80 (46, 104)	95 (75, 110)	57 (29, 89)	<0.001
eGFR <60 mL/min/1.73 m^2	400 (34.3 %)	70 (13.2 %)	330 (52.0 %)	<0.001
Death	266 (15.7 %)	34 (4.7 %)	232 (24.0 %)	<0.001
Hospital outcomes				
Length of stay (days)	14 (8, 26)	12 (7, 22)	15 (9, 29)	<0.001
$Creatinine_{discharge}$ (mg/dL) ($n = 1057$)	0.9 (0.7, 1.3)	0.8 (0.7, 1.0)	1.1 (0.8, 1.8)	<0.001
RRT at discharge ($n = 1694$)	44 (2.6 %)	0 (0 %)	44 (4.5 %)	<0.001
eGFR (mL/min/1.73 m^2)	79 (50, 103)	94 (72, 110)	61 (33.5, 90)	<0.001
eGFR <60 mL/min/1.73 m^2	346 (32.7 %)	71 (14.8 %)	275 (47.7 %)	<0.001
Death	312 (18.4 %)	52 (7.2 %)	260 (26.9 %)	<0.001

	Odds ratio	95 % Confidence interval	*p*
Adjusted odds ratios for acute kidney injury			
Age (/year)	1.006	0.995, 1.018	0.303
Gender			
Male	Reference		
Female	0.993	0.736, 1.340	0.965
Race, ethnicity			
Caucasian	Reference		
Black	0.835	0.454, 1.536	0.562
Asian	1.000	0.327, 3.063	1.000
Hispanic	0.683	0.359, 1.299	0.245
Other	0.941	0.410, 2.157	0.885
Number of ICU beds	0.998	0.990, 1.005	0.509
Continent			
Australia and New Zealand	Reference		
Africa	1.598	0.186, 13.753	0.665
Asia	0.296	0.056, 1.555	0.146
Europe	0.457	0.131, 1.597	0.203
North America	0.462	0.099, 2.159	0.291
South America	0.428	0.107, 1.722	0.218
Comorbidities			
Heart failure (NYHA class IV)	0.974	0.489, 1.942	0.941
Cirrhosis	1.084	0.470, 2.502	0.850
Hypertension	1.770	1.291, 2.427	<0.001
Diabetes	1.767	1.261, 2.477	0.001
Reason(s) for ICU admission			
Unplanned ICU admission	Reference		
Planned ICU admission	1.232	0.713, 2.128	0.455
Cardiovascular	1.665	1.150, 2.411	0.007
Liver failure	2.075	0.797, 5.405	0.135
Acute abdomen, other	1.619	0.929, 2.821	0.089
Surgical status at admission			
Scheduled surgery	Reference		
Emergency surgery	1.077	0.579, 2.002	0.815
No surgery	1.012	0.546, 1.876	0.969
Transplantation surgery	4.944	0.786, 31.091	0.088
Neurosurgery	0.324	0.154, 0.680	0.003
In-hospital location before ICU admission			
Other ward	Reference		
Emergency room	0.815	0.543, 1.222	0.321
Operation room	0.962	0.589, 1.573	0.878

Table 1 continued

	Odds ratio	95 % Confidence interval	*p*
Other ICU	1.029	0.520, 2.038	0.934
None	1.188	0.560, 2.519	0.653
SAPS 3 score	1.028	1.014, 1.042	<0.001
eGFR (mL/min/1.73 m^2)	0.995	0.989, 1.001	0.114
Vasoactive drugs before ICU admission	1.406	0.968, 2.042	0.074
Infection	0.821	0.532, 1.265	0.371

Values are presented as *n* (proportion) or median (interquartile range)
Adjusted odds ratios were generated by a multivariable model for acute kidney injury with random effects variables country and center Multivariate model: calibration was assessed by the Hosmer–Lemeshow goodness of fit test, $\chi^2 = 6.233$, $df = 8$, $p = 0.621$. Discrimination assessed by the area under the receiver operating characteristic curve for the model for occurrence of acute kidney injury = 0.728 (95 % CI 0.700–0.756), $p = 0.014$. Patients included in the analysis, $n = 1479$
AKI acute kidney injury, *OR* odds ratio, *CI* confidence interval, *NYHA* New York Heart Association functional classification of heart failure, *COPD* chronic obstructive pulmonary disease, *AIDS* acquired immune deficiency syndrome, *COPD* chronic obstructive lung disease, *ICU* intensive care unit, *SAPS 3* Simplified Acute Physiology Score 3, *eGFR* estimated glomerular filtration rate

Table 2 Variables at the time of acute kidney injury ($n = 666$)

Etiology of AKI	
Sepsis	271 (40.7 %)
Hypovolemia	227 (34.1 %)
Drug related	96 (14.4 %)
Cardiogenic shock	88 (13.2 %)
Hepatorenal syndrome	21 (3.2 %)
Obstruction of the urine outflow tract	9 (1.4 %)
Predisposing factors for AKI	
Diuretic treatment	216 (32.4 %)
NSAID administration	79 (11.9 %)
Aminoglycoside administration	45 (6.8 %)
Glycopeptide administration	9 (1.4 %)
Amphotericin administration	0 (0 %)
Radiocontrast media administration	14 (2.1 %)
Organ dysfunction at time of AKI	
Mechanical ventilation	
Invasive	185 (27.8 %)
Non-invasive	33 (5.0 %)
FiO_2	0.4 (0.3, 0.6)
PaO_2	90 (471, 114)
PaO_2/FiO_2	227 (142, 314)
Vasoactive therapy	325 (48.8 %)
Norepinephrine	242 (36.3 %)
Dose (μg/kg/min)	0.26 (0.10, 0.60)
Epinephrine	24 (3.6 %)
Dose (μg/kg/min)	0.25 (0.10, 0.48)
Dopamine	78 (10.4 %)
Dose (μg/kg/min)	6.6 (5.0, 10.0)
Dopamine ≤4 μg/kg/min	16 (2.4 %)
Dobutamine	69 (10.4 %)
Dose (μg/kg/min)	5.0 (3.2, 7.5)
Glasgow coma score	14.5 (10, 15)
Bilirubin (mg/dL)	0.9 (0.5, 1.8)
SOFA score for liver ≥2 (bilirubin ≥2mg/dL)	122 (21.3 %)
Platelets ($\times 10^3$/μL)	170 (111, 235)
SOFA score for platelets ≥2 (platelets <100 × 10^3/μL)	135 (21.2 %)
Urine output (mL/24 h)	955 (450, 1680)

Data are presented as *n* (%) or median (interquartile range)
AKI acute kidney injury, *NSAID* non-steroidal anti-inflammatory drug, *FiO_2* fraction of inspired oxygen, *PaO_2* arterial oxygen concentration, *SOFA score* Sequential Organ Failure Assessment score

Comparison of patients who had AKI and patients without AKI

Patients who developed AKI were older, more often Caucasian, more severely ill at the time of ICU admission as illustrated by a higher SAPS 3 score, and had worse kidney function at baseline and at the time of ICU admission (Table 1). A greater proportion of AKI patients were admitted from another hospital ward or ICU, had a medical reason for ICU admission, and had comorbidities such as heart failure, hypertension, diabetes, and cirrhosis. Also, a greater proportion of AKI patients had hypovolemic or septic shock, and were already treated with vasopressor agents at the time of ICU admission. Further, more AKI patients had, at the time of ICU admission, liver failure or acute abdomen.

After adjustment, hypertension, diabetes, cardiovascular cause of admission, neurosurgery, and SAPS 3 score were associated with occurrence of AKI. AKI patients had longer lengths of stay in the ICU and hospital, and worse renal outcomes indicated by a higher serum creatinine concentration, lower eGFR, more patients with CKD stage 3 or greater, and a greater proportion of patients who were treated with RRT (non-recovery of renal function) at the time of ICU and hospital discharge (Table 1).

Occurrence rate and mortality of AKI

A maximum AKI severity of KDIGO stage 1 occurred in 331 patients (18.4 %; 95 % CI 16.7–20.2), KDIGO stage 2 in 161 patients (8.9 %; 95 % CI 7.7–10.3), and KDIGO stage 3 in 540 patients (30.0 %; 95 % CI 27.9–32.1).

There was a stepwise increase in mortality with increasing AKI severity [KDIGO stage 1: odds ratio (OR) 2.19; 95 % CI 1.44–3.35, KDIGO stage 2: OR 3.88; 95 %

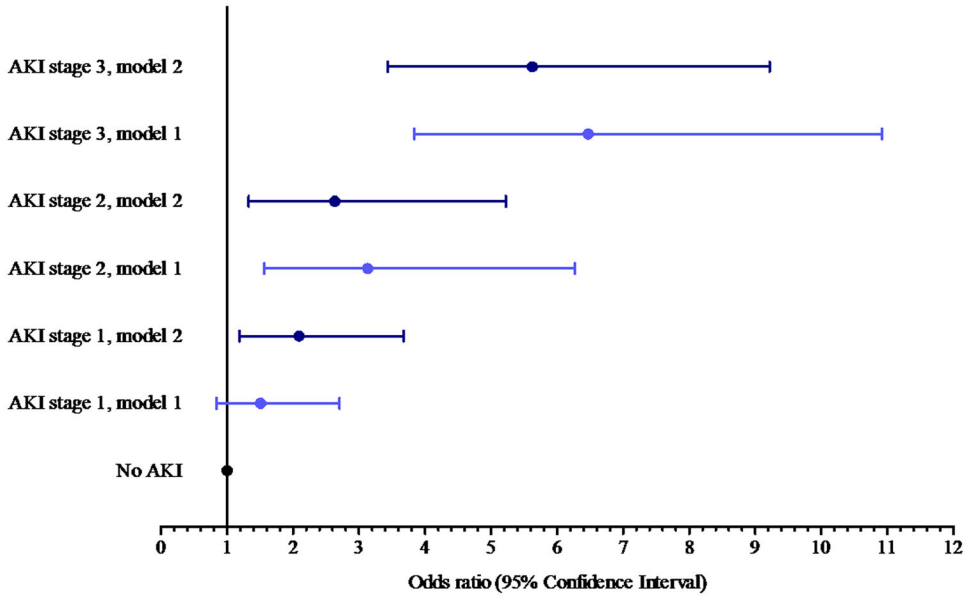

Fig. 2 Adjusted odds ratio for mortality per AKI severity grade. The association of severity of AKI and hospital mortality was explored and adjusted in two three-level hierarchical logistic regression models. Variables included in the first model were country and center (random effects), and a set of fixed predictors. Variables included in the first model were country and center (random effects) and a set of fixed predictors (model 1). The second model was similar to model 1, but without the variables serum creatinine at time of ICU admission and location before ICU admission (model 2). The full models for mortality are reported in the Table 3 in the electronic supplementary material. Model 1: Calibration assessed by the Hosmer–Lemeshow goodness of fit test, $\chi^2 = 4.266$, $df = 8$, $p = 0.832$. Discrimination assessed by the area under the receiver operating characteristic curve for the model for occurrence of hospital death = 0.847 (95 % CI 0.819–0.875), $p < 0.001$. Patients included in the analysis, $n = 1232$. Model 2: Calibration assessed by the Hosmer–Lemeshow goodness of fit test, $\chi^2 = 7.873$, $df = 8$, $p = 0.446$. Discrimination assessed by the area under the receiver operating characteristic curve for the model for occurrence of hospital death = 0.840 (95 % CI 0.814–0.866), $p < 0.001$. *AKI* acute kidney injury

CI 2.42–6.21, and KDIGO stage 3: OR 7.18; 95 % CI 5.13–10.04]. When adjusted for other variables that may explain mortality, KDIGO stage 2 (OR 2.945; 95 % CI 1.382–6.276; $p = 0.005$) and KDIGO stage 3 (OR 6.884; 95 % CI 3.876–12.228; $p < 0.001$) were still associated with increased in-hospital mortality (Fig. 2) (comparison alive and death in Table 2 in the electronic supplementary material; adjusted mortality models in Tables 3 and 4 in the electronic supplementary material). This was similar in two sensitivity analyses, one including countries that included 30 or more patients, and another excluding patients where baseline serum creatinine was unknown and assessed by the MDRD equation (data not shown). A third sensitivity analysis of patients without missing variables showed a significant association of AKI stage 1 with mortality (OR 2.09; 95 % CI 1.19–3.67; $p = 0.010$) (Fig. 2).

We found a significant difference in the occurrence of AKI and in mortality for patients with AKI between continents and world zones (Fig. 1 in the electronic supplementary material). However, adjusted rates for AKI and mortality were quite similar across different continents (Table 1; Fig. 3). When countries were grouped according to income, proportion of GDP spend for health expenditure, or latitude, the rates of AKI and mortality associated with AKI were also similar (Fig. 1 in the electronic supplementary material).

Renal replacement therapy

During the whole 1-week study period, a total of 243 patients were treated with RRT (13.5 % of all patients; 95 % CI 12.0–15.1, and 23.5 % of AKI patients; 95 % CI 21.1–26.2). The majority of RRT procedures were with a continuous modality (CRRT); CRRT in 615 sessions (75.2 %; 95 % CI 72.1–78.0), intermittent hemodialysis in 197 sessions (24.1 %; 95 % CI 21.3–27.1), and peritoneal dialysis in six sessions (0.7 %; 95 % CI 0.3–1.6).

Discussion

This is the first cross-sectional study to evaluate the occurrence of AKI defined by the complete KDIGO classification in ICUs worldwide. As such it provides, a decade after the BEST Kidney study, a contemporary update on the occurrence rate and mortality of AKI [20]. We found that AKI was a frequent finding, occurring in

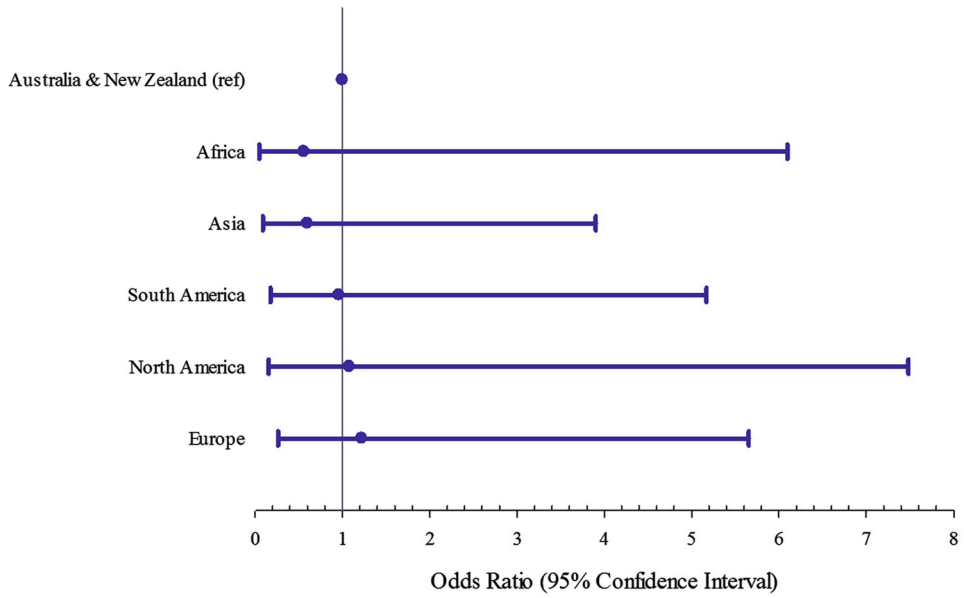

Fig. 3 Adjusted association of continent and mortality of AKI patients. The association of continent and risk for mortality was explored and adjusted in a three-level hierarchical logistic regression model. Variables included in the model were country and center (random effects) and a set of fixed predictors. The full models for mortality are reported in Table 4 in electronic supplementary material. Calibration assessed by the Hosmer–Lemeshow goodness of fit test, $\chi^2 = 10.080$, $df = 8$, $p = 0.259$. Discrimination assessed by the area under the receiver operating characteristic curve for the model for mortality = 0.800 (95 % CI 0.763–0.837), $p < 0.001$. Patients included in the analysis, $n = 703$

over half of ICU patients. Occurrence of AKI and crude mortality from AKI showed significant variation across countries and regions of the world. However, after adjusting for baseline risk, rates of AKI and mortality for patients with AKI were actually quite similar in different continents. Although we were unable to ensure that sites were truly representative of a given country or region, our results suggest that at least for large academic institutions AKI imposes a similar burden on patients worldwide. This finding adds strength to the estimates of AKI rates and outcomes and demonstrates generalizability of our results. Prior studies have found wide variation in the rates of AKI in ICU patients, likely due to variation in the application of AKI criteria (use of urine output, estimates of baseline creatinine, etc.) [5]. While clinicians, researchers, industry, and policy makers require robust estimates of AKI incidence to guide decision-making. These results also have important implications for health care delivery around the world. Indeed they suggest that the level of health care does not influence rate and mortality of AKI. Alternatively, the results may suggest that current strategies to reduce AKI in developed countries are ineffective or have not been implemented in any large-scale way. This may be illustrated by recent findings from the UK that revealed delays in diagnosis and poor assessment of risk in 43 % of AKI cases [21].

We found a greater use of RRT in ICU patients compared to a previous international multicenter study (13.5 vs. 4.3 %) [20]. This may be explained by an increased occurrence of severe AKI during the last decade or by more liberal criteria for initiation of RRT [2].

AKI developed in patients who had hypertension or diabetes, were admitted for a cardiovascular reason, and who were more severely ill on admission. Similar to others, we found that AKI was associated with higher mortality, but also with increased length of stay, greater rates of renal non-recovery, and higher serum creatinine at discharge [12, 22, 23]. These outcomes suggest the important economic and social impact of AKI in this patient population [1, 2, 6]. Even after adjusting for a large number of possible confounders, we found that AKI defined by KDIGO was strongly associated with mortality. It is difficult to determine whether mortality can be attributed to AKI or to unmeasured confounders, especially as ICU patients often develop AKI as a consequence of an underlying illness that itself could also explain mortality. However, a strong association between AKI and mortality persists after controlling for presence of underlying disease and severity of illness. Proposed mechanisms that may explain why AKI leads to increased mortality are related to the consequences of AKI and the therapies used [24, 25]. For instance, oliguria and volume resuscitation will lead to volume overload, acidosis, and electrolyte disorders, conditions associated with increased mortality [26–28]. The inflammatory response to AKI may also lead to systemic consequences and organ cross talk, leading to, e.g., ARDS [29]. Similar to CKD, it is likely that uremic toxins in AKI may impair immunity

and increase infection rates [30–32]. RRT may be life-saving for some patients with RRT, but does not entirely reverse the hazards associated with AKI [33, 34]. Finally, dosing of various drugs in AKI patients is complicated and often leads to treatment failures and adverse drug events [35, 36].

There are several limitations of this study. First, we specifically focused on patients who were admitted to ICU. Second, this study represents a snapshot in time. Especially in centers where a limited number of patients were included, this may have led to sampling bias. Third, participation of centers was on voluntary basis. It is therefore uncertain if cohorts are representative of other centers in the same country. Also, the number of patients in certain countries, continents, and regions is too low to draw firm conclusions as to differences between them. However, the similarity seen in adjusted event rates and outcomes across countries suggests that our results are widely generalizable. Fourth, the reference serum creatinine concentration was unknown in 35.0 % of patients, and estimated by either admission creatinine or back calculated by the MDRD equation, as recommend by the ADQI and KDIGO [7, 9]. Siew et al. have shown that an MDRD-derived baseline serum creatinine leads to increased AKI occurrence, whereas we previously found that this leads to very little misclassification, especially with more severe stages [37, 38]. When these patients were excluded the rate of AKI was actually higher but the impact of AKI on mortality was unchanged. Fifth, we did not collect long-term outcome data. Sixth, the multivariate models were based on a smaller number of patients as a result of missing data, thereby limiting the power of these data. Finally, we used the CKD-EPI equation for calculation of the eGFR. This equation was established in non-ICU patients with CKD, and the values calculated may therefore be less precise in our patients [39, 40].

Conclusions

This is the first multinational cross-sectional study where the epidemiology of AKI in ICU patients was explored using the complete KDIGO criteria. We found that AKI occurred in more than half of ICU patients. Approximately one-fifth of ICU patients had a maximum AKI stage 1, one-tenth AKI stage 2, and one-third 3 AKI stage 3. RRT was used in 13.5 % of ICU patients (23.5 % of patients with AKI). AKI therefore represents an important burden for health care. We found that increasing AKI severity was associated with increased mortality, and this association remained after correction for covariates that may explain mortality. After adjusting for baseline risk there was little variation in AKI occurrence and mortality between different regions in the world.

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