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Epidemiology of surgery associated acute kidney injury (EPIS-AKI): a prospective international observational multi-center clinical study

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Abstract

Purpose: The incidence, patient features, risk factors and outcomes of surgery-associated postoperative acute kidney injury (PO-AKI) across different countries and health care systems is unclear.

Methods: We conducted an international prospective, observational, multi-center study in 30 countries in patients undergoing major surgery (> 2-h duration and postoperative intensive care unit (ICU) or high dependency unit admission). The primary endpoint was the occurrence of PO-AKI within 72 h of surgery defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Secondary endpoints included PO-AKI severity and duration, use of renal replacement therapy (RRT), mortality, and ICU and hospital length of stay.

Results: We studied 10,568 patients and 1945 (18.4%) developed PO-AKI (1236 (63.5%) KDIGO stage 1500 (25.7%) KDIGO stage 2209 (10.7%) KDIGO stage 3). In 33.8% PO-AKI was persistent, and 170/1945 (8.7%) of patients with PO-AKI received RRT in the ICU. Patients with PO-AKI had greater ICU (6.3% vs. 0.7%) and hospital (8.6% vs. 1.4%) mortality, and longer ICU (median 2 (Q1-Q3, 1–3) days vs. 3 (Q1-Q3, 1–6) days) and hospital length of stay (median 14 (Q1-Q3, 9–24) days vs. 10 (Q1-Q3, 7–17) days). Risk factors for PO-AKI included older age, comorbidities (hypertension, diabetes, chronic kidney disease), type, duration and urgency of surgery as well as intraoperative vasopressors, and aminoglycosides administration.

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Conclusion: In a comprehensive multinational study, approximately one in five patients develop PO-AKI after major surgery. Increasing severity of PO-AKI is associated with a progressive increase in adverse outcomes. Our findings indicate that PO-AKI represents a significant burden for health care worldwide.

Keywords: Acute kidney injury, Epidemiology, Postoperative, Mortality, Perioperative

Introduction

Over 300 million patients undergo major surgery each year worldwide with the potential to cause acute kidney injury (AKI) [1]. Nevertheless, the exact incidence of surgery associated, postoperative AKI (PO-AKI) remains unknown [2]. Retrospective data suggest that 1.8–39.3% of the patients develop PO-AKI after abdominal [3–7] and 3.1–39.9% after cardiac surgical procedures [8, 9]. One major drawback of these retrospective studies is that they often lack data on urine output. This criterion is important for the correct diagnosis of AKI [10, 11]. Without urine output, the incidence of PO-AKI will be underestimated. Also, the presence of both Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI definition, reduction of urine output and increase of creatinine, predicts worse outcomes compared to AKI based on the creatinine criterion alone [10]. In addition, AKI rates may further vary between different patient populations across different countries. The type, duration, and technique of surgery, as well as the AKI definition used are factors that influence PO-AKI rates. Moreover, the inclusion or non-inclusion of patients from low or middle-income countries play an important role. The lack of knowledge in terms of PO-AKI incidence is a problem as it may lead to underestimates of the risk of PO-AKI in this field, the burden it poses on a global scale and fail to identify risk factors for its development.

Therefore, the aim of this study was to prospectively investigate the incidence of PO-AKI within 72 h after major cardiac and non-cardiac surgery and to evaluate pre- and intraoperative risk factors for PO-AKI in an international study with strong representation of middle and low-income countries [12].

Take-home message

One in five patients develop postoperative acute kidney injury (PO-AKI) after major surgery and adverse outcomes progressively increase with increasing severity of PO-AKI. These findings indicate that postoperative AKI represents a significant burden for health care worldwide

Methods

Study design and ethics

The epidemiology of surgery associated acute kidney injury (EPIS-AKI) study is an international prospective, observational, multicenter, cohort study. The design of the trial has been published previously [12]. Participating centers were approached by the different national societies (partly by direct inquiry, partly by presenting the study at national congresses and/or newsletters) supporting this trial (see Acknowledgements). Center participation was voluntary. Primary approval was obtained from the Research Ethics Committee of the Chamber of Physicians Westfalen-Lippe and the Westphalian Wilhelms-University Münster (2019-424-f-S). Country-specific requirements, including local ethics approval and/or study registration were fulfilled according to the local requirements and prior to patient enrollment. The trial was registered prior to initiation of the study at clinicaltrials.gov (NCT04165369, November 18th 2019). The manuscript follows the principles of "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) and the Declaration of Helsinki (Fortaleza 2013).

Patient recruitment and consenting

All patients (age $\geq$ 18 years) undergoing major surgery ($\geq$ 2 h) with the need of subsequent intensive care unit (ICU) or high dependency unit (intermediate care or post anesthesia care unit) admission were consecutively included in this study. All surgical specialties were considered (including emergencies). Exclusion criteria were: pre-existing AKI, AKI within the last 3 months, end-stage renal disease with dialysis dependency, kidney transplant. No patient was excluded from the study based on sex, ethnicity or religion. Written informed consent was obtained from patients whenever requested by local authorities before inclusion following local regulations.

Data collection

Data were collected in a protected web platform (Research Electronic Data Capture, V.10.6.22, Vanderbilt University) and confidentially stored in a

deidentified form on secured servers at the University of Münster.

Diagnosis and severity of PO-AKI were assessed by serum-creatinine and/or urine output according to the KDIGO criteria [13]. The latest serum creatinine before surgery was defined as baseline value. Serum creatinine was measured at least once a day for the first 3 days. Patients with serum creatinine increases of ≥ 0.3 mg/dl within 48 h or 1.5–1.9 times increases within 72 h after surgery were diagnosed KDIGO stage 1, patients with serum creatinine increases of 2–2.9 times within 72 h were diagnosed KDIGO stage 2, and patients with serum creatinine increases of ≥ 3 times or ≥ 4 mg/dl or with the need of renal replacement therapy (RRT) were diagnosed KDIGO stage 3. Further, patients with a urine output < 0.5 ml/kg/h for ≥ 6 h were diagnosed KDIGO stage 1, urine output < 0.5 ml/kg/h for ≥ 12 h KDIGO stage 2, and < 0.3 ml/kg/h for ≥ 24 h or anuria for ≥ 12 h KDIGO stage 3. Once the urine catheter was removed, the urine output criterion could no longer be considered. Data collection included PO-AKI diagnosis and severity.

After 90 days, a follow-up was performed by telephone by contacting either the patient or the general practitioner in order to ask for survival, need for RRT and latest creatinine value.

For country comparisons, we used different world zone classifications according to their latest publication: the United Nations (UN) geoscheme [14], and country's health expenditure as percentage of gross domestic product 2019 as reported by the World Health Organization [15].

Outcomes

The primary outcome was PO-AKI within the first 72 h after surgery. Secondary outcomes were severity of PO-AKI, duration of PO-AKI (transient < 48 h vs. persistent ≥ 48 h) [16], use of RRT including the type of RRT (continuous RRT (CRRT), prolonged intermittent RRT (PIRRT) intermittent hemodialysis (IHD)), ICU and hospital mortality, length of ICU and hospital stay as well as the occurrence of major adverse kidney events at day 90 ($MAKE_{90}$) which is a combined endpoint consisting of mortality, need for RRT and persistent renal dysfunction (defined as serum-creatinine ≥ 1.5 times as compared to baseline serum-creatinine). Furthermore, analyses were performed for the effect of pre-/perioperative risk factors on the incidence of PO-AKI.

Sample size calculation

The primary aim of the study was to estimate the rates of PO-AKI and to derive the corresponding exact two-sided 95% confidence interval (CI) according to Clopper-Pearson. Depending on the type of surgery, PO-AKI rates between 1.8 and 39.3% were reported in the literature [3–6]. Therefore, a rate of 40% was assumed for the sample size calculation as a conservative approach. Using this assumption, 10,000 patients are needed to limit the width of the 95% CI to 1.9%. Thus, with n = 10,000 patients, the incidence of PO-AKI can be estimated with at least this precision.

Statistical analysis

Statistical analyses were planned prior to reviewing the data. Frequencies, percentages, medians, quartiles and *p*-values were calculated for the baseline variables and secondary endpoints as applicable.

Fisher's exact test and Pearson's Chi-squared test were used to compare categorical variables between groups. Continuous variables were compared using Welch's t-test or Wilcoxon signed-rank test depending on whether the target variable was normally distributed in both groups or not. All secondary endpoints were censored at day 90.

CIs for binomial proportion estimates, e.g., the development of the primary endpoint PO-AKI within 72 h after surgery, were calculated using the Clopper-Pearson exact method with a 95% confidence level. For multinomial proportion estimates, e.g. KDIGO stages (1/2/3) in PO-AKI patients, simultaneous 95% CIs were calculated using Goodman's methods [17].

To identify and assess the association of further risk factors for PO-AKI, multivariable logistic regression analyses were performed. In a first step, we selected variables that, according to previous clinical knowledge, could be associated with PO-AKI. The following variables were selected in this way: sex, age, body mass index (BMI), UN-geoscheme, health expenditure, hypertension, atrial fibrillation, myocardial infarction, congestive heart failure, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), peripheral vascular disease, stroke, American Society of Anesthesiologists (ASA) score, urgency of procedure, surgery duration, type of surgery, use of cell saver, transfusion, fluid balance, blood loss, hypotensive episodes, intraoperative complications, use of nephrotoxic agents, use of vasopressors. We included all these variables in a logistic regression model and then performed a fast backward variable selection based on Akaike's Information Criterion (AIC) to identify a reasonable set of potential risk factors for PO-AKI. In each iteration, the influencing variable whose exclusion caused the greatest

reduction of the AIC compared to the current model was excluded from the current model until no omission of a single variable resulted in a further reduction of the AIC.

To further investigate the risk of different intraoperative vasopressors for PO-AKI, we restricted the data to patients who received vasopressors and formed two groups: vasopressors (received norepinephrine and/or vasopressin and/or other vasopressors) and inotropes (received epinephrine and/or dobutamine). On this data subset, we fitted a new logistic regression model including combinations of vasopressors as well as all other risk factors identified by variable selection performed in the main PO-AKI analysis.

In a final step, we repeated the variable selection and model fitting procedure on the PO-AKI subgroup to identify potential risk factors for the duration of PO-AKI (persistent vs. transient).

All *p*-values and confidence limits were two-sided. Only the confidence interval of the primary endpoint is to be interpreted confirmatory. The secondary endpoints were not adjusted for multiple testing, *p*-values of secondary statistical analyses are therefore regarded statistically noticeable (significant) in case $p \leq 0.05$. An overall significance level across all secondary statistical analyses was not determined and cannot be calculated. In all analyses, only the complete cases were considered, i.e., missing values were not imputed. Statistical analyses were conducted using *R* (Version R-4.1.2).

Results

Participants

From June 2020 to December 2021, we included 10,568 patients from 30 countries and 148 centers (Fig. 1, Supplementary eFigure 1). The median age was 62 (Q1, Q3, 52, 71) years. 6456 (59.7%) were male and 7643 Caucasian (72.3%), most surgeries were elective procedures (96.1%). Baseline characteristics are demonstrated in Table 1, surgical details in Supplementary eTable 1. There were large regional differences in included types of surgeries (Supplementary eTable 2 and eTable 3).

Postoperative acute kidney injury

Overall, 1945 of 10,568 (18.4% [95% CI 17.7–19.2%]) patients developed PO-AKI within 72 h after surgery (primary endpoint; KDIGO stage 1: 1236 (63.5% [95% CI 60.8–66.2%]), KDIGO stage 2: 500 (25.7% [95% CI 23.4–28.2%]), KDIGO stage 3: 209 (10.7% [95% CI 9.1–12.6%]) (Fig. 2).

In 33.8% [95% CI 31.7–35.9%] PO-AKI was persistent and in 1482 (76.2%) PO-AKI occurred within the first 24 h after surgery (15.8% at day 2 and 7.9% at day 3). Of PO-AKI cases, 856 (44% [95% CI 41.3–46.8%]) were diagnosed by serum-creatinine, 614 (31.6% [95% CI 29–34.2%]) by urine output and 475 (24.4% [95% CI 22.1–26.9%]) by both criteria (Fig. 2). PO-AKI was most frequent in patients undergoing urologic (162/586 (27.6%)), cardiac (802/3101 (25.9%)), vascular (132/532 (24.8%)) and general surgery 571/3170 (18%)) (Table 1).

Intra- and postoperatively, patients with PO-AKI received significantly more fluids, had significantly higher blood loss, and received significantly more vasopressors

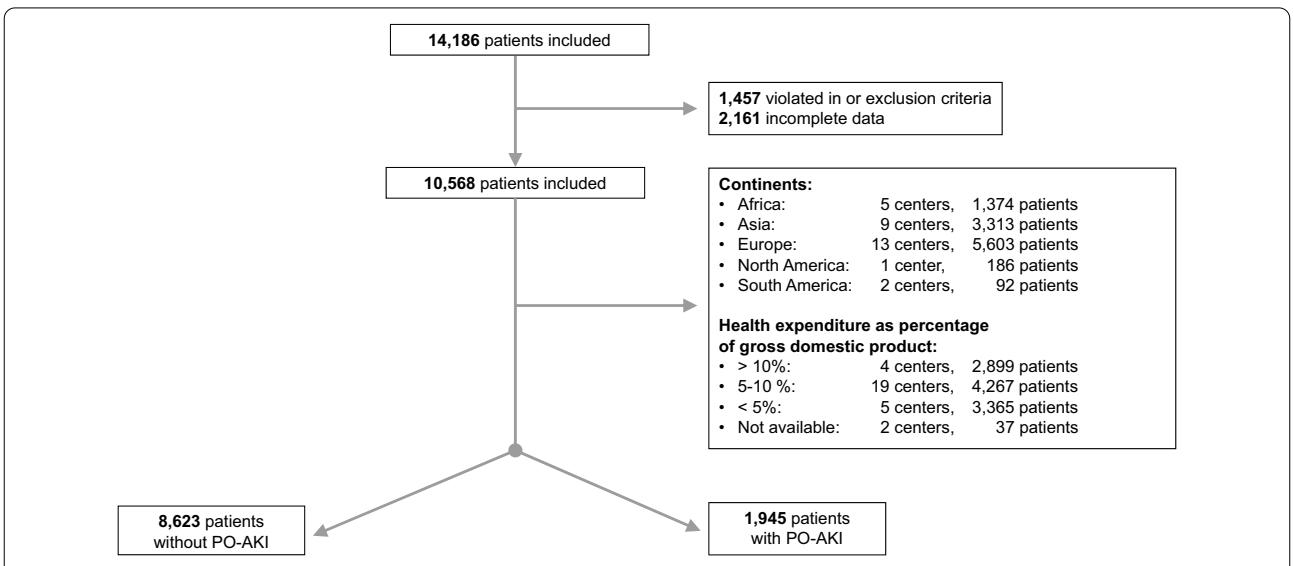

Fig. 1 Flow chart. *ICU* intensive care unit; *PO-AKI* postoperative acute kidney injury

Table 1 Patient demographics and baseline characteristics

	All patients n = 10,568	No PO-AKI n = 8623	PO-AKI n = 1945	*p* value
Baseline characteristics				
Demographics				
Age, median (Q1, Q3), years	62 (52, 71)	61 (50, 70)	67 (58, 74)	< 0.001
Male, No. (%)	6456/10568 (61.1)	5145/8623 (59.7)	1311/1945 (67.4)	< 0.001
Height, median (Q1, Q3), cm[a]	169 (162, 175)	168 (162, 175)	170 (163, 176)	< 0.001
Weight, median (Q1, Q3), kg[b]	76 (66, 86)	75 (66, 85)	79 (69, 90)	< 0.001
Body mass index, median (Q1, Q3)[c]	27 (24, 30)	26 (24, 30)	27 (24, 31)	< 0.001
Serum-creatinine, median (Q1, Q3), mg/dL[d]	0.8 (0.7, 1)	0.8 (0.7, 1)	0.9 (0.7, 1.1)	< 0.001
Race, ethnicity, no./no. total (%)				
Caucasian	7643/10568 (72.3)	6089/8623 (70.6)	1554/1945 (79.9)	< 0.001
Black	366/10568 (3.5)	313/8623 (3.6)	53/1945 (2.7)	< 0.001
Asian	1230/10568 (11.6)	1049/8623 (12.2)	181/1945 (9.3)	< 0.001
Hispanic	202/10568 (1.9)	176/8623 (2)	26/1945 (1.3)	< 0.001
Other	1127/10568 (10.7)	996/8623 (11.6)	131/1945 (6.7)	< 0.001
Comorbidities, no./no. total (%)				
Hypertension	5516/10568 (52.2)	4194/8623 (48.6)	1322/1945 (68)	< 0.001
Diabetes				
Total	2481/10568 (23.5)	1879/8623 (21.8)	602/1945 (31)	< 0.001
IDDM	576/2481 (23.2)	422/1879 (22.5)	154/602 (25.6)	
NIDDM	1905/2481 (76.8)	1457/1879 (76.5)	448/602 (74.4)	
Congestive heart failure	1862/10568 (17.6)	1335/8623 (15.5)	527/1945 (27.1)	< 0.001
NYHA stage[e]				
I	518/1862 (27.8)	436/1335 (32.7)	82/527 (15.6)	
II	703/1862 (37.8)	518/1335 (38.8)	185/527 (35.1)	
III	591/1862 (31.7)	353/1335 (26.4)	238/527 (45.2)	
IV	50/1862 (2.7)	28/1335 (2.1)	22/527 (4.2)	
Previous myocardial infarction	1423/10568 (13.5)	1073/8623 (12.4)	350/1945 (18)	< 0.001
Peripheral vascular disease	1014/10568 (9.6)	743/8623 (8.6)	271/1945 (13.9)	< 0.001
Atrial flutter/fibrillation	933/10568 (8.8)	617/8623 (7.2)	316/1945 (16.3)	< 0.001
COPD	927/10568 (8.8)	676/8623 (7.8)	251/1945 (12.9)	< 0.001
CKD GFR < 60 mL/min	725/10568 (6.9)	430/8623 (5)	295/1945 (15.2)	< 0.001
CKD Stage				
3	654/725 (90.2)	392/430 (91.2)	262/295 (88.8)	
4	63/725 (8.7)	34/430 (7.9)	29/295 (9.8)	
5	8/725 (1.1)	4/430 (0.9)	4/295 (1.4)	
Previous stroke	542/10568 (5.1)	391/8623 (4.5)	151/1945 (7.8)	< 0.001
ASA score[f]				
1	1260/10568 (11.9)	1173/8623 (13.6)	87/1945 (4.5)	< 0.001
2	4424/10568 (41.9)	3847/8623 (44.6)	577/1945 (29.7)	< 0.001
3	4087/10568 (38.7)	3097/8623 (35.9)	990/1945 (50.9)	< 0.001
4	797/10568 (7.5)	506/8623 (5.9)	291/1945 (15)	< 0.001
Medication, no./no. total (%)				
ACEi or ARB	3999/10568 (37.8)	3046/8623 (35.3)	953/1945 (49)	< 0.001
Beta-Blockers	3413/10568 (32.3)	2568/8623 (29.8)	845/1945 (43.4)	< 0.001
Aspirin	3216/10568 (30.4)	2451/8623 (28.4)	765/1945 (39.3)	< 0.001
Statins	3174/10568 (30)	2386/8623 (27.7)	788/1945 (40.5)	< 0.001
Diuretics	2029/10568 (19.2)	1401/8623 (16.3)	628/1945 (32.3)	< 0.001
Use of contrast media one week prior surgery	1943/10568 (18.4)	1530/8623 (17.7)	413/1945 (21.2)	< 0.001
NSAIDs (except Aspirin)	469/10568 (4.4)	394/8623 (4.6)	75/1945 (3.9)	0.168

Table 1 (continued)

	All patients n = 10,568	No PO-AKI n = 8623	PO-AKI n = 1945	*p* value
Vasopressors	95/10568 (0.9)	67/8623 (0.8)	28/1945 (1.4)	0.005
Perioperative characteristics				
Surgical speciality, no./no. total (%)[g]				
Abdominal/General	3170/10566 (30)	2599/8621 (30)	571/1945 (29.4)	0.492
Cardiac	3101/10566 (29.3)	2299/8621 (26.7)	802/1945 (41.2)	< 0.001
Neurosurgical	1157/10566 (11)	1089/8621 (12.6)	68/1945 (3.5)	< 0.001
Urologic	586/10566 (5.5)	424/8621 (4.9)	162/1945 (8.3)	< 0.001
Orthopaedic	575/10566 (5.4)	526/8621 (6.1)	49/1945 (2.5)	< 0.001
Vascular	532/10566 (5)	400/8621 (4.6)	132/1945 (6.8)	< 0.001
Other	483/10566 (4.6)	453/8621 (5.3)	30/1945 (1.5)	< 0.001
Gynaecologic/Obstetric	434/10566 (4.1)	380/8621 (4.4)	54/1945 (2.8)	0.001
Thoracic	416/10566 (3.9)	355/8621 (4.1)	61/1945 (3.1)	0.044
Trauma	112/10566 (1.1)	96/8621 (1.1)	16/1945 (0.8)	0.258
Urgency category, no./no. total (%)				
Elective	10,120/10568 (96.1)	8296/8623 (96.6)	1824/1945 (94.1)	< 0.001
Emergency	407/10568 (3.9)	292/8623 (3.4)	115/1945 (5.9)	< 0.001
Type of surgery, no./no. total (%)				
Open surgery	8954/10568 (84.7)	7258/8623 (84.2)	1696/1945 (87.2)	< 0.001
Laparoscopic and open surgery	1007/10568 (9.5)	888/8623 (10.3)	119/1945 (6.1)	< 0.001
Robotic and open surgery (planned)	279/10568 (2.6)	236/8623 (2.7)	43/1945 (2.2)	< 0.001
Robotic surgery	242/10568 (2.3)	190/8623 (2.2)	52/1945 (2.7)	< 0.001
Robotic and open surgery (unplanned)	86/10568 (0.8)	51/8623 (0.6)	35/1945 (1.8)	< 0.001
Details, no./no. total (%)				
CPB	3061/10568 (29)	2266/8623 (26.3)	795/1945 (40.9)	< 0.001
Cross-clamp	3055/10568 (28.9)	2261/8623 (26.2)	794/1945 (40.8)	< 0.001
Surgery times, median (Q1, Q3), min				
Duration of surgery[h]	235 (174, 315)	228 (170, 306)	258 (188, 345)	< 0.001
CPB time[i]	100 (75, 134)	99 (75, 128)	109 (77, 151)	< 0.001
Cross-clamp time[j]	69 (51, 94)	68 (51, 92)	72 (52, 104)	< 0.001

ACEi angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *ASA*, American Society of Anesthesiologists; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CPB*, cardiopulmonary bypass; *GFR*, glomerular filtration rate; *IDDM*, insulin-dependent diabetes mellitus; *NIDDM*, non-insulin-dependent diabetes mellitus; *NSAID*, Nonsteroidal anti-inflammatory drug; *NYHA*; New York Heart Association; *PO-AKI*, postoperative acute kidney injury

[a] Height: 41 missing values (38 in No PO-AKI, 3 in PO-AKI)

[b] Weight: 36 missing values (33 in No PO-AKI, 3 in PO-AKI)

[c] Body mass index: 41 missing values (38 in No PO-AKI, 3 in PO-AKI)

[d] Serum-creatinine: 54 missing values (47 in No PO-AKI, 7 in PO-AKI)

[e] NYHA classification is defined as follows: I, No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.; II, Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity; III, Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.; IV, Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients

[f] American Society of Anesthesiology classification are defined as follows grade 1, normal healthy patient; 2, patient with mild systemic disease; 3, a patient with severe systemic disease that limits physical activity; 4, a patient with severe systemic disease that is a constant threat to life; 5, moribund patient who is not expected to survive without the operation; and 6, declared brain-dead patient whose organs are being removed for donor purposes

[g] Surgical specialty: 2 missing values (2 in No PO-AKI, 0 in PO-AKI)

[h] Duration of surgery: 44 missing values (38 in No PO-AKI, 6 in PO-AKI)

[i] Only patients with CPB considered

[j] Only patients with Cross-clamp considered

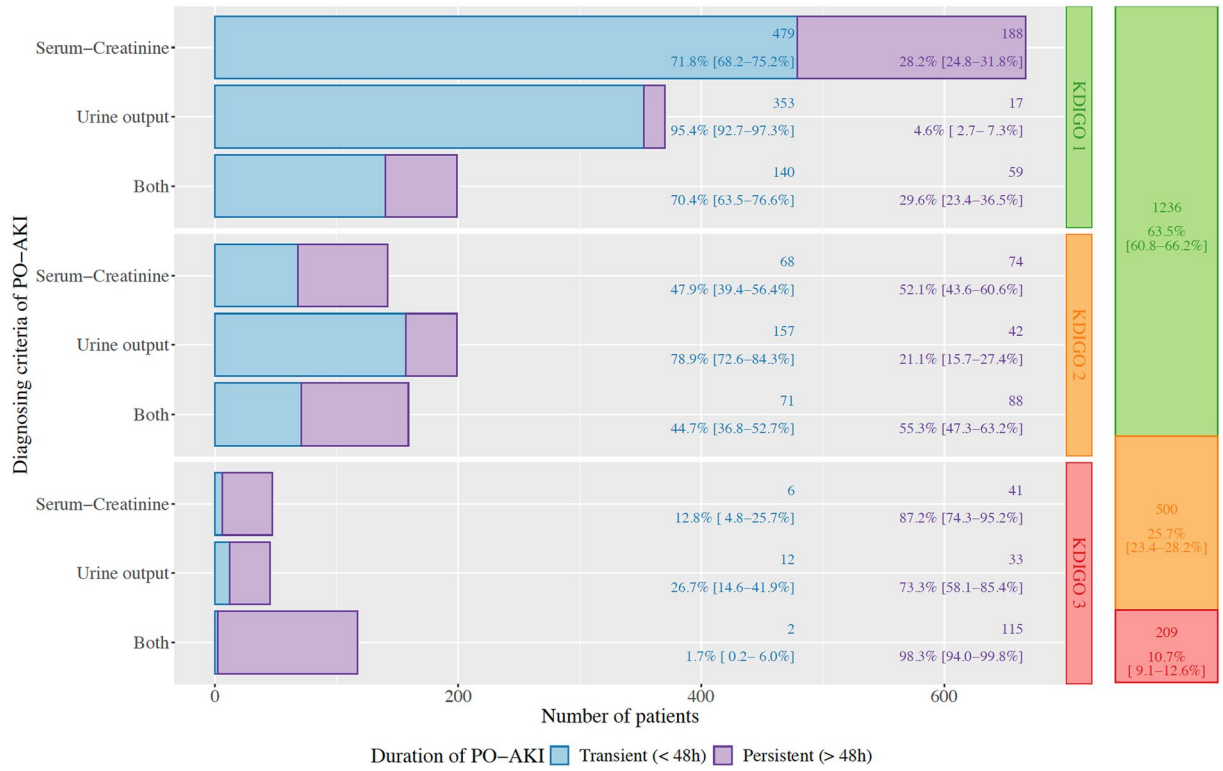

Fig. 2 Occurrence of transient/persistent PO-AKI with 95% confidence intervals according to KDIGO stage and diagnosing criteria. For example, among all patients with PO-AKI in KDIGO stage 1 diagnosed by serum creatinine alone, 71.8% turn out to be transient AKIs and 28.2% persistent AKIs

(Supplementary eTable 1). Additionally, the proportion of patients who were administered nephrotoxic agents in the postoperative phase was significantly higher compared to patients without PO-AKI (Supplementary eTable 1).

Regional differences

There were significant differences in the rates of PO-AKI according to region. North America had the highest PO-AKI rate (47.3%), followed by Europe (22.7%), Asia (13.8%), South America (13%), and Africa (8.5%) (Supplementary eTable 4, Fig. 3a).

According to percentage of health expenditure, countries with > 10% showed the highest rates (31.1%), followed by less than 5% (14.3%) and 5–10% (13%) (Fig. 3b, Supplementary eTable 4). However, the rate of persistent PO-AKI was similar across regions with nearly one third of the patients developing persistent PO-AKI. Across all regions, in-hospital mortality was significantly higher in PO-AKI patients as compared to non-PO-AKI patients. However, within the subgroup of PO-AKI, mortality rates differed across regions with Africa showing the highest mortality rates (23.9%) compared to Asia (9.8%), Europe (7.2%), and North America (4.5%).

Secondary endpoints

In total, 164 (8.4% [95% CI 7.2–9.8%]) PO-AKI patients were treated with RRT during their ICU stay (73.8% CRRT, 18.9% IHD, and 7.3% PIRRT) and 184 (9.5% [95% CI 8.2–10.8%]) PO-AKI patients during hospital stay (Table 2). Patients with PO-AKI had significantly longer ICU (median 3 (Q1, Q3, 1, 6) days vs. 2 (Q1, Q3, 1, 3) days) as well as hospital length of stays (median 14 (Q1, Q3, 9, 24) days vs. 10 (Q1, Q3, 7, 17) days), higher mortality rates in the ICU (6.3% [95% CI 5.2–7.4%] vs. 0.7% [95% CI 0.5–0.9%]) and in hospital (8.5% [95% CI 7.3–9.8% vs. 1.3% [95% CI 1.1–1.6%]) compared to non-PO-AKI patients (Table 2) ($p < 0.001$). Endpoint rates increased with increasing severity of PO-AKI (Table 2) and mortality rates were highest in KDIGO3 patients meeting both criteria of the AKI definition (Fig. 4).

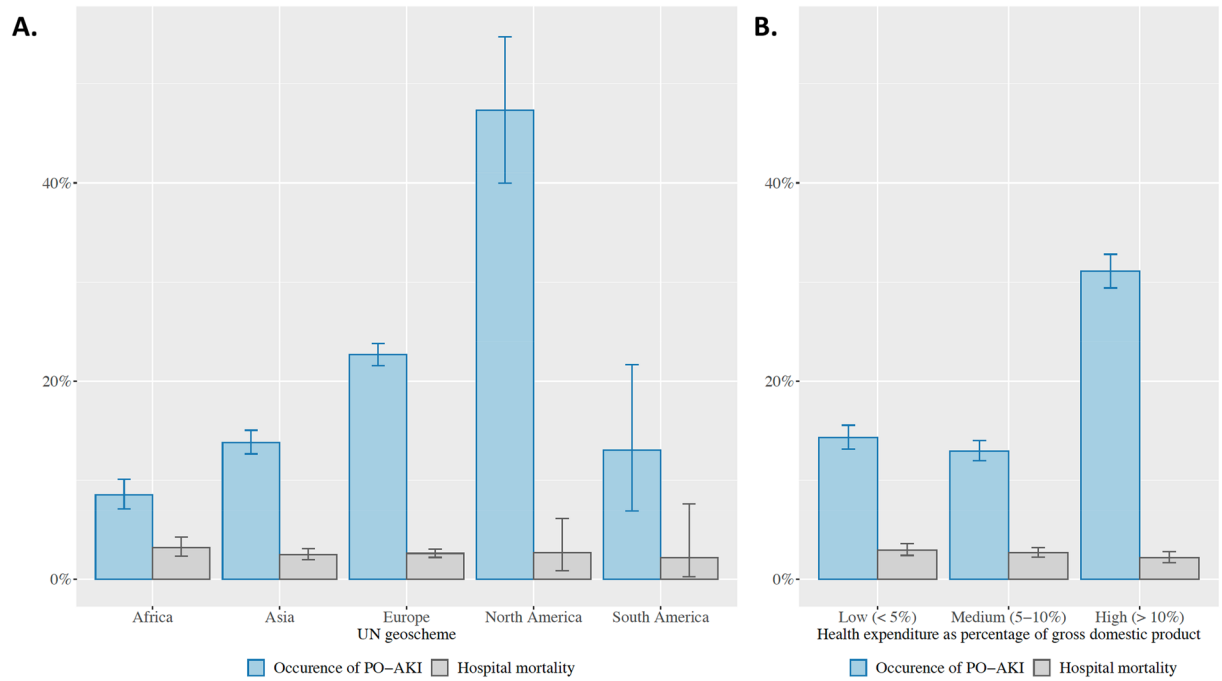

Fig. 3 Occurrence of PO-AKI and hospital mortality up to day 90 with 95% confidence intervals according to **A.** UN-geoscheme **B.** percentage of health expenditure (low < 5%, medium 5–10%, high > 10%)

Patients with PO-AKI showed significantly higher rates of $MAKE_{90}$ as compared to patients without PO-AKI (21.1% vs. 8.5%; $p < 0.001$) (Table 2). Rates increased significantly with the severity of PO-AKI (KDIGO 1, 14.9%; KDIGO 2, 23.1%; KDIGO 3, 53.1%; $p < 0.001$).

Risk factor assessment for PO-AKI

A multivariable regression analysis with backward variable selection showed that male sex, increased age, a high percentage of health expenditure, hypertension, atrial fibrillation, congestive heart failure, diabetes, COPD, CKD, high ASA score, emergency procedures, long surgery duration, certain types of surgery, cell saver, transfusion, positive fluid balance, intraoperative complications such as bleeding and pulmonary complications, aminoglycosides and intraoperative use of vasopressors were risk factors for PO-AKI; whereas the region according to UN-geoscheme was not (Table 3). When investigating the effects of different vasopressors on the risk of PO-AKI among those patients receiving vasopressors, none of the combinations showed an increased risk (Supplementary eTable 5). Pre-existing CKD was a key risk factors for persistent PO-AKI (Supplementary eTable 6).

A multivariable regression analysis for hospital mortality showed PO-AKI as a key risk factor (OR, 5.40 [95% CI 4.10, 7.13]; $p < 0.001$) (Supplementary eTable 7).

Discussion

The EPIS-AKI trial is the first prospective international observational trial that focused exclusively on PO-AKI using the full KDIGO classification across multiple geographic settings and country-based income levels. Thus, it provides important data on the occurrence rate, morbidity, and mortality of PO-AKI. EPIS-AKI shows that PO-AKI is globally common in the perioperative period affecting approximately one in five patients, with urologic, cardiac and vascular surgery patients being most commonly affected and with one third of the patients developing persistent PO-AKI. Regional comparisons showed that Africa had the lowest incidence of PO-AKI but the highest mortality rates. Moreover, EPIS-AKI found that the intraoperative use of vasopressors was a risk factor for PO-AKI as was the use of aminoglycosides. Finally, mortality and ICU and hospital length of stay were significantly higher in patients with PO-AKI.

In non-surgical ICU patients, nearly every second patient develops AKI [18] but for the surgical setting, exact PO-AKI rates are unknown. Prior studies have demonstrated large variations in rates of PO-AKI, ranging from 1.8% to 39.3% in major abdominal surgery [6, 19], and from 3.1% to 39.9% in cardiac surgery [9, 20]. These differences appear due to variations in definitions and type of surgery (e.g. some studies only

Table 2 Outcomes

	All patients n = 10,568	No PO-AKI n = 8623	PO-AKI n = 1945	*p* value
PO-AKI severity, no./no.total (%)				
KDIGO 1				
All			1236/1945 (63.5)	< 0.001
Serum creatinine			667/1236 (54)	
Urine output			370/1236 (30)	
Both			199/1236 (16.1)	
KDIGO 2				
All			500/1945 (25.7)	
Serum creatinine			142/500 (28.4)	
Urine output			199/500 (39.8)	
Both			159/500 (31.8)	
KDIGO 3				
All			209/1945 (10.7)	
Serum creatinine			47/209 (22.5)	
Urine output			45/209 (21.5)	
Both			117/209 (56)	
RRT in ICU/postoperative, no./no.total (%)[a b]				
All	170/10561 (1.6)	6/8616 (0.1)[c]	164/1945 (8.4)	
RRT modality				
CRRT		3/6 (50)[c]	121/164 (73.8)	
IHD		3/6 (50)[c]	31/164 (18.9)	
PIRRT		0 (0)[c]	12/164 (7.3)	
RRT during hospital stay, no./no.total (%)[a, d]				
All	208/10534 (2)	24/8590 (0.3)[c]	184/1944 (9.5)	< 0.001
PO-AKI severity[e]				
KDIGO 1			22/1236 (1.8)	
KDIGO 2			55/500 (11)	< 0.001
KDIGO 3			107/208 (51.4)	
> 72h[c]		24/24 (100)[c]		
Mortality, no./no. total (%)[a]				
ICU	180/10568 (1.7)	58/8623 (0.7)	122/1945 (6.3)	< 0.001
PO-AKI severity[e]				
KDIGO 1			27/1236 (2.2)	
KDIGO 2			38/500 (7.6)	< 0.001
KDIGO 3			57/209 (27.3)	
Hospital	281/10568 (2.7)	116/8623 (1.3)	165/1945 (8.5)	< 0.001
PO-AKI severity[e]				
KDIGO 1			44/1236 (3.6)	
KDIGO 2			51/500 (10.2)	< 0.001
KDIGO 3			70/209 (33.5)	
Length of stay, median (Q1, Q3), days[a]				
ICU[f]	2 (1, 3)	2 (1, 3)	3 (1, 6)	< 0.001
Hospital[g]	11 (7, 18)	10 (7, 17)	14 (9, 24)	< 0.001
$MAKE_{90}$, no./no.total (%)[a,h]				
All	1143/10517 (10.9)	733/8578 (8.5)	410/1939 (21.1)	< 0.001
PO-AKI severity[e]				
KDIGO 1			184/1233 (14.9)	
KDIGO 2			115/497 (23.1)	< 0.001
KDIGO 3			111/209 (53.1)	

Table 2 (continued)

CRRT continuous renal replacement therapy; *IHD* intermittent hemodialysis; *ICU* intensive care unit; *KDIGO* Kidney Disease: Improving Global Outcomes; *PIRRT* prolonged intermittent hemodialysis; *RRT* renal replacement therapy; *PO-AKI* postoperative acute kidney injury

[a] Censored at day 90

[b] RRT in ICU/postoperative: 7 missing values (7 in No PO-AKI, 0 in PO-AKI)

[c] Patients who developed an PO-AKI after 72 h and were therefore classified in the "No PO-AKI" group

[d] RRT during hospital stay: 34 missing values (33 in No PO-AKI, 1 in PO-AKI)

[e] Percentages in the individual KDIGO groups are calculated in relation to the total number of complete cases in the KDIGO group

[f] ICU length of stay: 49 missing values (43 in No PO-AKI, 6 in PO-AKI)

[g] Hospital length of stay: 49 missing values (44 in No PO-AKI, 5 in PO-AKI)

[h] $MAKE_{90}$: 51 missing values (45 in No PO-AKI, 6 in PO-AKI)

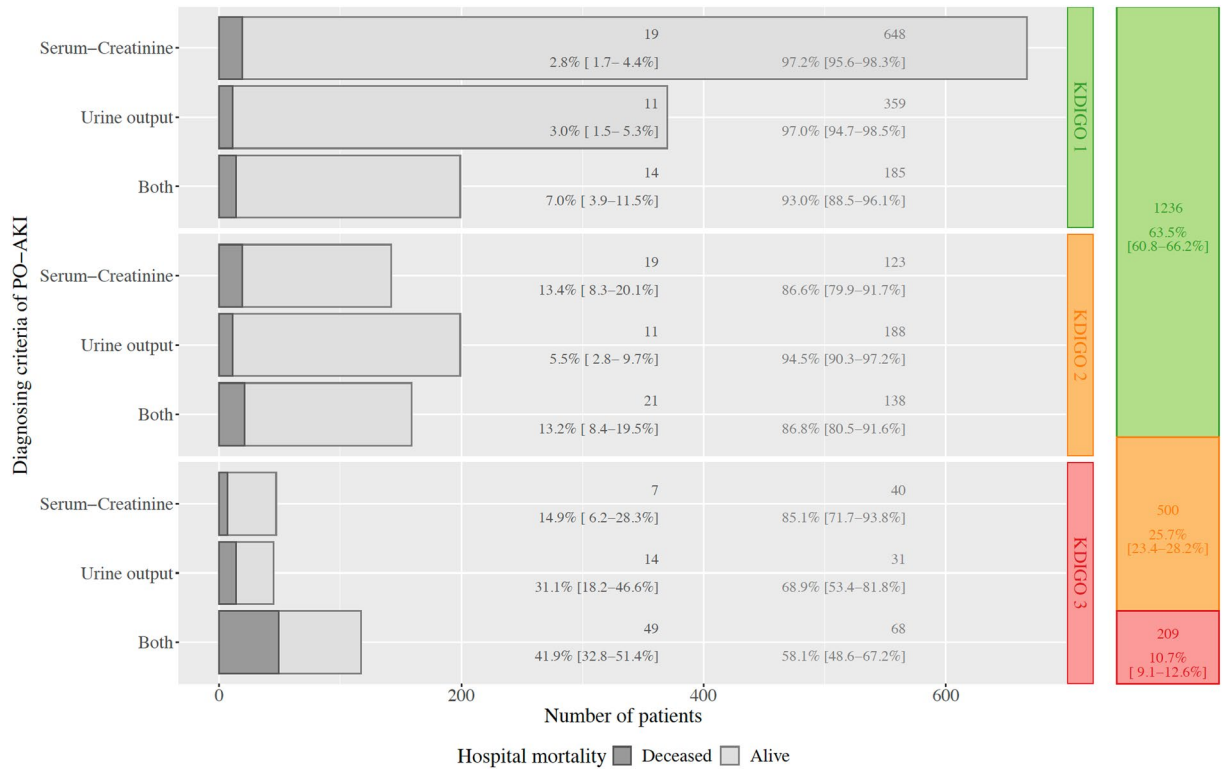

Fig. 4 Hospital mortality up to day 90 with 95% confidence intervals according to KDIGO stage and diagnosing criteria

including hepatobiliary surgery, others including all types of major abdominal surgery). The EPIS-AKI study included all types of major surgery, cardiac as well as non-cardiac surgeries, and included patients admitted to high-dependency units, not just ICU. The overall rate of PO-AKI was 18.4% when using both criteria of the KDIGO definition (serum-creatinine and urine output).

In terms of the diagnostic criteria of the KDIGO definition, the urine output criterion is difficult to assess in daily clinical routine as an exact assessment is best in patients with an indwelling urinary catheter. However, our data shows the importance of the urine output criterion, which is highly associated with adverse outcomes in patients with AKI. Thus, the urine output criterion deserves special attention and should not be underestimated.

In terms of duration of PO-AKI, no other studies exclusive to surgery patients have focused on persistent PO-AKI. However, the finding that patients meeting both criteria of the KDIGO definition show worse outcomes

Table 3 Multivariable regression analysis for PO-AKI development

Variable	OR (95% CI)	*p* value
Gender (male vs. female)	1.16 (1.02, 1.32)	0.026
Age (year)	1.01 (1.01, 1.02)	< 0.001
Percentage of health expenditure		
Medium vs. low	0.61 (0.52, 0.73)	< 0.001
High vs. low	1.59 (1.33, 1.91)	< 0.001
Hypertension (yes vs. no)	1.44 (1.25, 1.66)	< 0.001
Atrial fibrillation (yes vs. no)	1.56 (1.30, 1.88)	< 0.001
Congestive heart failure (yes vs. no)	0.84 (0.7, 0.99)	0.043
Diabetes (yes vs. no)	1.27 (1.11, 1.45)	< 0.001
COPD (yes vs. no)	1.26 (1.04, 1.52)	0.017
CKD baseline (yes vs. no)	2 (1.63, 2.45)	< 0.001
Peripheral vascular disease (yes vs. no)	1.17 (0.96, 1.43)	0.123
ASA score[a]		
2 vs. 1	1.01 (0.77, 1.35)	0.931
3 vs. 1	1.09 (0.81, 1.47)	0.564
4 vs. 1	1.57 (1.11, 2.23)	0.012
Surgery urgency (emergency vs. elective)	1.71 (1.28, 2.29)	< 0.001
Surgery duration (h)	1.11 (1.07, 1.15)	< 0.001
Type of surgery		
Cardiac vs. abdominal	0.72 (0.6,0.88)	0.001
Gynecological vs. abdominal	0.95 (0.67, 1.33)	0.786
Neurosurgical vs. abdominal	0.26 (0.19, 0.36)	< 0.001
Orthopedic vs. abdominal	0.42 (0.29, 0.59)	< 0.001
Thoracic vs. abdominal	0.78 (0.54, 1.09)	0.155
Trauma vs. abdominal	0.66 (0.34, 1.21)	0.199
Vascular vs. abdominal	0.64 (0.46, 0.88)	0.007
Urological vs. abdominal	1.67 (1.3, 2.13)	< 0.001
Other vs. abdominal	0.3 (0.19, 0.46)	< 0.001
Cell saver (yes vs. no)	2.08 (1.74, 2.5)	< 0.001
Transfusion (yes vs. no)	1.3 (1.09, 1.55)	0.003
Transfusion (l)	1.1 (0.97, 1.24)	0.124
Fluid balance	0.97 (0.94, 1)	0.036
Intraoperative complications (yes vs. no)		
Bleeding	1.75 (1.43, 2.13)	< 0.001
Pulmonary complications	2.43 (1.51, 3.83)	< 0.001
Nephrotoxic agents (yes vs. no)		
Aminoglycosides	1.6 (1.13, 2.24)	0.007
NSAIDs	0.84 (0.69, 1.02)	0.081
Radiocontrast agents	1.39 (0.92, 2.08)	0.114
Vancomycin	1.36 (0.98, 1.88)	0.066
Other nephrotoxic agents	0.73 (0.51, 1.02)	0.071
Vasopressors (yes vs. no)	1.76 (1.51, 2.05)	< 0.001

Analysis includes 9020/10568 patients. Number of events (PO-AKI): 1695

ASA American Society of Anesthesiologists; *CKD* chronic kidney disease; *COPD* chronic obstructive pulmonary disease; *NSAID* non-steroidal anti-inflammatory drugs

[a] American Society of Anesthesiology classification are defined as follows grade 1, normal healthy patient; 2, patient with mild systemic disease; 3, a patient with severe systemic disease that limits physical activity; 4, a patient with severe systemic disease that is a constant threat to life; 5, moribund patient who is not expected to survive without the operation; and 6, declared brain-dead patient whose organs are being removed for donor purposes

as compared to those meeting only the urine output criterion, is comparable to other clinical settings [10].

Regional comparisons showed that there were significant differences in the rates of PO-AKI with countries with a high expenditure on health care having the highest PO-AKI rates. This may derive from access to comprehensive resources like extensive monitoring methods (i.e., multiple laboratory testing per day, electronic patient file, etc.) but also from the fact that there were large regional differences in the type of surgeries included as well as the selection of higher risk patients. The high differences in mortality rates cannot be explained by our data but may be a result from lack of interventions and unmeasured confounders such as frailty. Additionally, there is an increasing proportion of elderly patients with multiple long-term conditions undergoing surgery in high developed countries [21], who are particularly at risk for PO-AKI. In contrast to the higher PO-AKI rate, PO-AKI-associated mortality was inversely related to the percentage of the gross domestic product spent on health expenditure. This dissociation between incidence and outcome has been observed in other studies [22, 23]. It also suggests that less severe PO-AKI may be missed in lower resourced regions with higher severity cases driving increased mortality.

At first glance, mortality appears to be high at 3% for the total cohort. However, median Acute Physiology and Chronic Health Evaluation (APACHE) score and Simplified Acute Physiology Score (SAPS) were 8 (Q1, Q3, 5–13) and 20 (Q1, Q3, 12–29), respectively, which is within the normal estimated range (APACHE 5–9) [24]. Estimated mortality rates are approximately 3% for post-OP patients with SAPS of 20 points [25].

Prevention is key in the setting of PO-AKI. However, the pathophysiology of AKI, especially in the perioperative setting, is very complex. A large number of risk factors are not modifiable such as older age or comorbidities. However, some risk factors may be modifiable. For example, in our multivariable analysis, the administration of nephrotoxic agents, especially aminoglycosides, bleeding complications and the treatment of these with transfusion as well as fluid management were identified as risk factors for AKI. Alternative drugs to nephrotoxins exist and the use of nephrotoxic drugs should be carefully considered and avoided whenever possible. In this regard, a nephrotoxic stewardship approach to oversee the use of these substances has been proposed [26]. Transfusion as well as hypervolemia are known factors associated with AKI and a critical appraisal of their use is also important [27, 28]. Surgical factors such as duration and urgency of the procedure are factors that may be modified by identifying patients who are at risk for AKI, by informing the surgical team, and by prioritizing these patients. While intraoperative hypotension was not a risk factor for

AKI, vasopressors were. This finding cannot be further explained with our data. However, it is conceivable that vasopressors represent a surrogate marker for less stable hemodynamics. On the other hand, there are also data showing that higher vasopressor use affects renal function due to decreased renal perfusion [29, 30]. Ultimately, this finding needs to be further investigated in additional studies.

The strengths of the EPIS-AKI trial are the large cohort of patients, the international setting with various participating centers and regions that have scarcely been described so far (e.g. Africa), the multiple types of surgery, the use of the full KDIGO criteria as well as detailed data on vasopressors, nephrotoxins and fluids.

However, the study has also several limitations. First, center participation was voluntary. Therefore, it remains uncertain whether the study cohorts are representative of other centers in the same country as well as non-participating countries in the same region. In addition, the number of included patients was very low in some countries and regions. Most centers originated from countries that spent $\geq 5\%$ of gross domestic product (GDP) on total health expenditure. However, EPIS-AKI is one of the few studies that included a substantial number of countries, which spent less than 5% GDP on health. Second, some specialties or procedures are underrepresented creating a degree of selection bias. Third, we cannot exclude a certain degree of measurement bias for the following reasons. In some centers or patient's creatinine may have been measured more frequently than in others. Moreover, it was not possible to consider the urine output criterion in every patient up to 3 days because of early urinary catheter removal. However, in a pragmatic study like ours, this bias cannot be controlled for as this represents daily clinical routine. Fourth, although aminoglycosides were found to be modifiable risk factors for PO-AKI, our data does not allow to perform dose-dependency analyses.

Conclusion

In a comprehensive multinational study, approximately one in five patients develop PO-AKI after major surgery. Increasing severity of PO-AKI is associated with a progressive increase in adverse outcomes. Our findings indicate that PO-AKI represents a significant burden for health care worldwide.

Supplementary Information

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Author contributions

AZ and MM conceived and designed the study; FA and MM performed statistical analysis; RW, KR, EG, AMCT, AD, VL, PR, PGM, MGA, KP, ML, WK, MOS acquired data; AZ, RW, JAK, RB, MM drafted the manuscript; RW, KR, EG, AMCT, AD, VL, PR, PGM, MGA, KP, ML, WK, MOS made critical revision of the manuscript for key intellectual component. All authors provided final approval of the final version of the manuscript.

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Declarations

Conflicts of interest

AZ received lecture fees from BioMerieux, Fresenius Medical Care and Baxter unrelated to current study and an unrestricted research grant from Baxter related to the current study. JAK is a paid consultant for BioMerieux, and a full-time employee of Spectral Medical. Patricia Galán Menéndez reports fees from

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