


ORIGINAL



# Acute kidney disease beyond day 7 after major surgery: a secondary analysis of the EPIS-AKI trial

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## Abstract

**Purpose:** Acute kidney disease (AKD) is a significant health care burden worldwide. However, little is known about this complication after major surgery.

**Methods:** We conducted an international prospective, observational, multi-center study among patients undergoing major surgery. The primary study endpoint was the incidence of AKD (defined as new onset of estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m<sup>2</sup> present on day 7 or later) among survivors. Secondary endpoints included the relationship between early postoperative acute kidney injury (AKI) (within 72 h after major surgery) and subsequent AKD, the identification of risk factors for AKD, and the rate of chronic kidney disease (CKD) progression in patients with pre-existing CKD.

**Results:** We studied 9510 patients without pre-existing CKD. Of these, 940 (9.9%) developed AKD after 7 days of whom 34.1% experiencing an episode of early postoperative-AKI. Rates of AKD after 7 days significantly increased with the severity (19.1% Kidney Disease Improving Global Outcomes [KDIGO] 1, 24.5% KDIGO2, 34.3% KDIGO3;  $P < 0.001$ ) and duration (15.5% transient vs 38.3% persistent AKI;  $P < 0.001$ ) of early postoperative-AKI. Independent risk factors for AKD included early postoperative-AKI, exposure to perioperative nephrotoxic agents, and postoperative pneumonia. Early postoperative-AKI carried an independent odds ratio for AKD of 2.64 (95% confidence interval [CI] 2.21–3.15). Of 663 patients with pre-existing CKD, 42 (6.3%) had worsening CKD at day 90. In patients with CKD and an episode of early AKI, CKD progression occurred in 11.6%.

**Conclusion:** One in ten major surgery patients developed AKD beyond 7 days after surgery, in most cases without an episode of early postoperative-AKI. However, early postoperative-AKI severity and duration were associated with an increased rate of AKD and early postoperative-AKI was strongly associated with AKD independent of all other potential risk factors.

**Keywords:** Acute kidney disease, Acute kidney injury, Chronic kidney disease, Surgery, Postoperative

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EPIS-AKI investigators are listed in the Acknowledgement section.

## Introduction

Each year, more than 310 million patients undergo major surgery worldwide and postoperative complications are associated with increased morbidity and mortality [1, 2]. Acute kidney injury (AKI) is an important and common complication after major surgery and is independently associated with morbidity and mortality in a wide range of surgical settings [3–6]. Moreover, one in five patients will develop an episode of postoperative-AKI occurring within 72 h after major surgery (early postoperative-AKI) [7]. Furthermore, the development of AKI has been associated with an increased risk for subsequent chronic kidney disease (CKD) [8, 9]. Such CKD is logically likely to be preceded by postoperative acute kidney disease (AKD). Surprisingly, the epidemiology of AKD after major surgery has not been investigated in depth and the contribution of early postoperative-AKI as well as AKI characteristics, duration, and development of AKD have not been studied in detail. Finally, additional factors occurring in the perioperative period which may be associated with AKD development remain unknown.

We aimed to test the primary hypothesis that AKD after 7 days is common after major surgery and determine whether early postoperative-AKI and its characteristics (duration, severity, and specific diagnostic criteria), patient characteristics and perioperative factors influence the development of AKD after 7 days. Additionally, we assessed the incidence of CKD progression in terms of KDIGO staging in those with pre-existing CKD and its relationship with early postoperative-AKI.

## Methods

### Study design and ethics

This is an a priori planned secondary analysis of the Epidemiology of Surgery-Associated Acute Kidney Injury (EPIS-AKI) study, an international prospective, observational, multicenter, cohort study, which has been described in detail elsewhere [10]. Briefly, 10,568 patients from 30 countries and 148 centers were enrolled from June 2020 to December 2021. All patients (age  $\geq 18$  years) undergoing major elective and emergency surgery (operative time  $\geq 2$  h) with subsequent intensive care unit (ICU) or high dependency unit admission were included regardless of surgical subspecialty. Exclusion criteria included pre-existing AKI, AKI within the last 3 months, end-stage renal disease with dialysis dependency, and kidney transplant.

The EPIS-AKI study was approved by 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

## Take-home message

One in ten patients develop acute kidney disease (AKD) beyond 7 days after major surgery, most of them without a prior episode of acute kidney injury (AKI). However, early postoperative AKI is a major risk factor for subsequent AKD. These findings have important implications for the management and prognosis of surgical patients.

were fulfilled according to the local requirements and prior to patient enrollment. The study was registered 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).

### Outcomes

The primary endpoint of this study was the development of AKD present on 7 days or later after surgery. AKD was defined as surviving to 90 days with an observed decrease in estimated glomerular filtration rate (eGFR) to  $<60$  ml/min/1.73 m<sup>2</sup>, in patients with a eGFR  $>60$  ml/min/1.73 m<sup>2</sup> prior to surgery.

Secondary endpoints were the association of early postoperative-AKI and AKI characteristics (duration, severity (as defined by Kidney Disease Improving Global Outcomes [KDIGO] stages), and specific diagnostic criteria (serum creatinine and/or urine output)) with the development of AKD after 7 days. We concentrated on early postoperative-AKI, because the majority of AKI occurs within 72 h after surgery and because this time frame reflects changes directly related to surgery and perioperative interventions [11–13]. In a subset of patients with preoperative CKD (defined by eGFR), we determined the incidence of CKD progression (progression of at least one stage of CKD) and the relationship of such progression to postoperative-AKI.

### Statistical analysis

Frequencies, percentages, medians, quartiles were calculated for the baseline variables, primary and secondary endpoints as applicable and *P*-values for primary and secondary endpoints.

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 Mann–Whitney *U* test depending on whether the target variable was normally distributed in both groups or not.

Confidence intervals (CIs) for binomial proportion estimates, e.g., the development of AKD after 7 days, 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 postoperative-AKI patients, simultaneous 95% CIs were calculated using Goodman's methods [14].

To examine the association of postoperative-AKI and AKD development beyond 7 days in detail, two univariate logistic regression models were fitted, each including a combined variable. The categories of the first variable were composed of all possible combinations of postoperative-AKI (yes/no), KDIGO stage (1/2/3), and AKI duration, defined as transient (<48 h duration) or persistent (>48 h duration) [15]. The categories of the second variable were composed of all possible combinations of postoperative-AKI (yes/no), KDIGO stage (1/2/3), and the criteria used to define postoperative-AKI (serum creatinine and/or urine output).

To identify and assess the association of potential risk factors for the development of AKD after 7 days, multivariable logistic regression analyses were performed to develop a prediction model. Firstly, we selected variables that have been proposed as being associated with the development of AKD after 7 days including gender, age, body mass index (BMI), UN-geoscheme, health expenditure, hypertension, atrial fibrillation, previous myocardial infarction, congestive cardiac failure, diabetes, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, stroke, American Society of Anesthesiologists (ASA) score, urgency of procedure, surgery duration, type of surgery, as well as intra- and postoperative transfusion, fluid balance, blood loss, complications, intra- and postoperative use of nephrotoxic agents, use of vasopressors, and early postoperative development of AKI. We included all these variables in a logistic

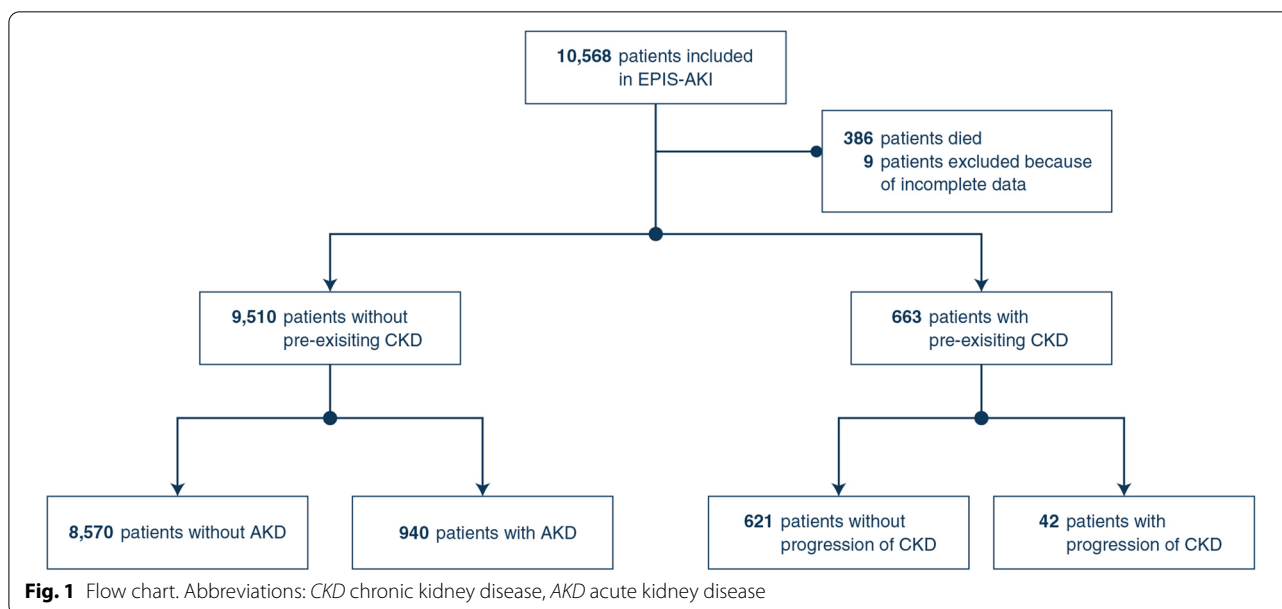
regression model and then performed a fast-backward variable selection based on Akaike's Information Criterion (AIC) to identify a reasonable set of potential risk factors for development of AKD after 7 days. In each iteration, the influencing variable whose exclusion caused the greatest reduction of 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. The variable selection and parameter estimation procedures were validated jointly using 500 bootstrap samples using the methods described by Harrell [16]. Further statistical analyses are presented in supplementary eMethods.

All *p*-values and confidence limits were two-sided. Only the confidence interval of the primary endpoint, the incidence of AKD after 7 days, is to be interpreted confirmatory. All other analyses are to be interpreted in an exploratory sense and were not adjusted for multiple testing. *P*-values are therefore considered statistically noticeable ("significant") in case  $P \leq 0.05$ . An overall significance level across all 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

### Patients

The primary analysis included 9510/10,568 (90%) evaluable patients without any pre-existing CKD who survived at least 90 days (Fig. 1). Among the survivors, pre-operative CKD was present in 663 (6.5%) patients.



**Table 1 Patient demographics and baseline characteristics according to the postoperative development of acute kidney disease after 7 days**

	No-AKD <i>n</i> = 8570	AKD <i>n</i> = 940
<b>Demographics</b>		
Age, median (Q1, Q3), years	61 (50, 68)	69 (62, 76)
Male, <i>n</i> (%)	5289 (61.7)	475 (50.5)
Height, median (Q1, Q3), cm	169 (162, 175)	167 (160, 174)
Weight, median (Q1, Q3), kg	75 (66, 86)	77 (67, 86)
Serum-creatinine, median (Q1, Q3), mg/dL	0.8 (0.7, 0.9)	1 (0.8, 1.2)
<b>Race, ethnicity, no. (%)</b>		
Caucasian	5995 (70)	743 (79)
Black	337 (3.9)	8 (0.9)
Asian	1058 (12.4)	98 (10.4)
Hispanic	174 (2)	18 (1.9)
Other	1006 (11.7)	73 (7.8)
<b>Comorbidities, no. (%)</b>		
Hypertension	4034 (47)	662 (70.4)
Diabetes	1815 (21.2)	297 (31.6)
Congestive heart failure	1249 (14.6)	233 (24.8)
Previous myocardial infarction	1023 (11.9)	165 (17.6)
Peripheral vascular disease	660 (7.7)	143 (15.2)
Atrial flutter/fibrillation	568 (6.6)	142 (15.1)
COPD	676 (7.9)	87 (9.3)
Previous stroke	361 (4.2)	73 (7.8)
<b>ASA score<sup>a</sup></b>		
1	1184 (13.8)	54 (5.7)
2	3850 (44.9)	326 (34.7)
3	3015 (35.2)	451 (48)
4	521 (6.1)	109 (11.6)
<b>Preoperative medication, no. (%)</b>		
ACEi or ARB	2934 (34.2)	481 (51.2)
Beta-Blockers	2444 (28.5)	413 (43.9)
Aspirin	2393 (27.9)	374 (40)
Statins	2274 (26.5)	370 (39.4)
Diuretics	1311 (15.3)	268 (28.5)
Use of contrast media one week prior surgery	1529 (17.8)	203 (21.6)
NSAIDs (except Aspirin)	377 (4.4)	56 (6)
Vasopressors	57 (0.7)	13 (1.4)
<b>Postoperative -AKI, No. (%)</b>		
KDIGO 1	822 (70.2)	194 (60.4)
KDIGO 2	278 (23.7)	90 (28)
KDIGO 3	71 (6.1)	37 (11.5)

Abbreviations: ACEi angiotensin converting enzyme inhibitor, AKD acute kidney disease, AKI acute kidney injury, ARB angiotensin receptor blocker, ASA American Society of Anaesthesiologists, COPD chronic obstructive pulmonary disease, KDIGO Kidney Disease Improving Global Outcomes, NSAID Nonsteroidal anti-inflammatory drug

<sup>a</sup> 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

Demographic and baseline characteristics according to the development of postoperative AKD beyond 7 days are presented in Table 1 and supplementary eFigure 1.

Surgical and postoperative details are presented in supplementary eTable 1.

The mean age in the primary analysis cohort was 59 (standard deviation [SD] 15) years, 61% were men, median serum creatinine was 0.8 (Q1, Q3, 0.7–1) mg/dl. Overall, 9129 (96.3%) patients had elective procedures and the median duration of surgery was 230 (Q1, Q3, 172, 294) minutes.

### Development of AKD after 7 days

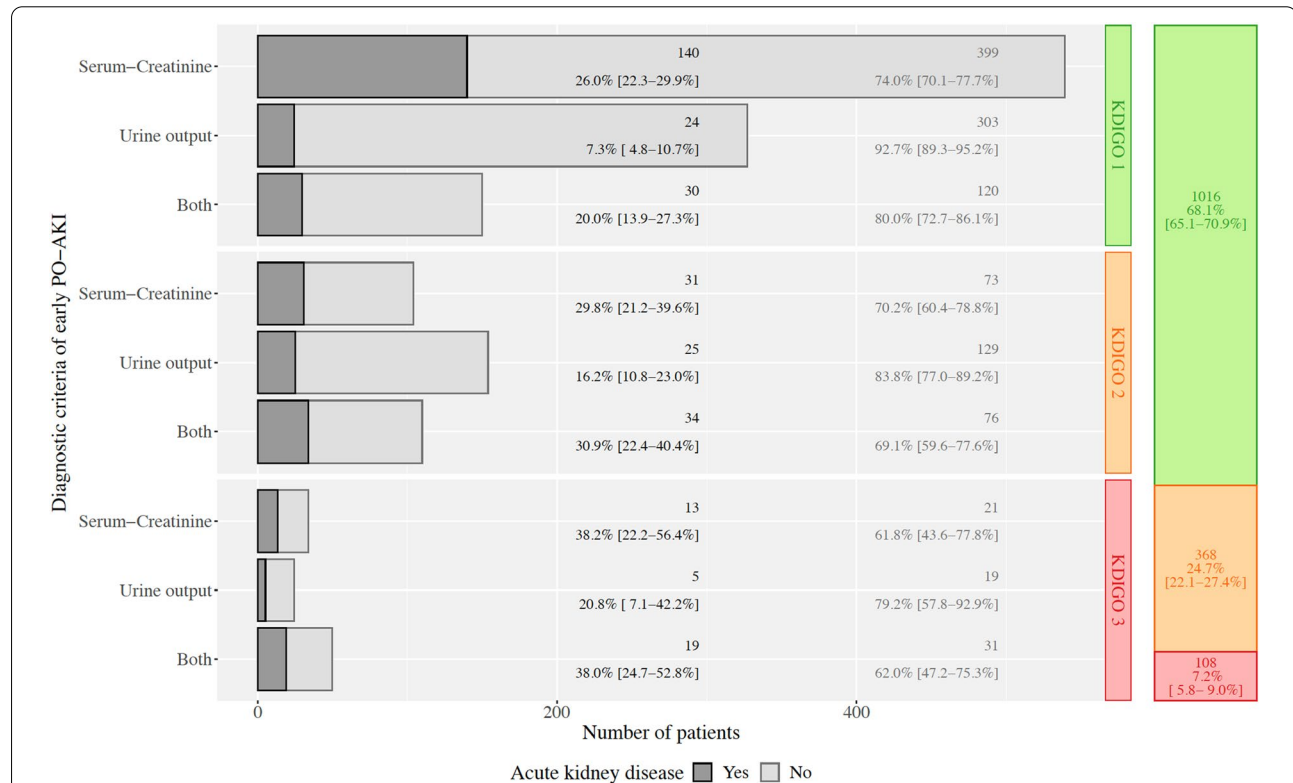
In total, 940/9,510 (9.9% [95% CI 9.3–10.5%]) patients developed AKD beyond 7 days (supplementary eTable 2). Vascular and cardiac surgery had similar rates of AKD after 7 days at 13.8% and 12.8%, respectively. In contrast, in patients undergoing orthopaedic procedures the AKD rate after 7 days was 8.4% (supplementary eTable 1). The highest rate of AKD after 7 days was seen in patients undergoing urological procedures. Patients who developed AKD after 7 days had a higher baseline serum creatinine, were older, showed higher rates of comorbidities (hypertension, diabetes, congestive heart failure, previous myocardial infarction, peripheral vascular disease, and atrial flutter/fibrillation), received more nephrotoxic

agents including contrast agents and nonsteroidal anti-inflammatory drugs (NSAIDs), and were more often treated with vasopressors (supplementary eTable 1).

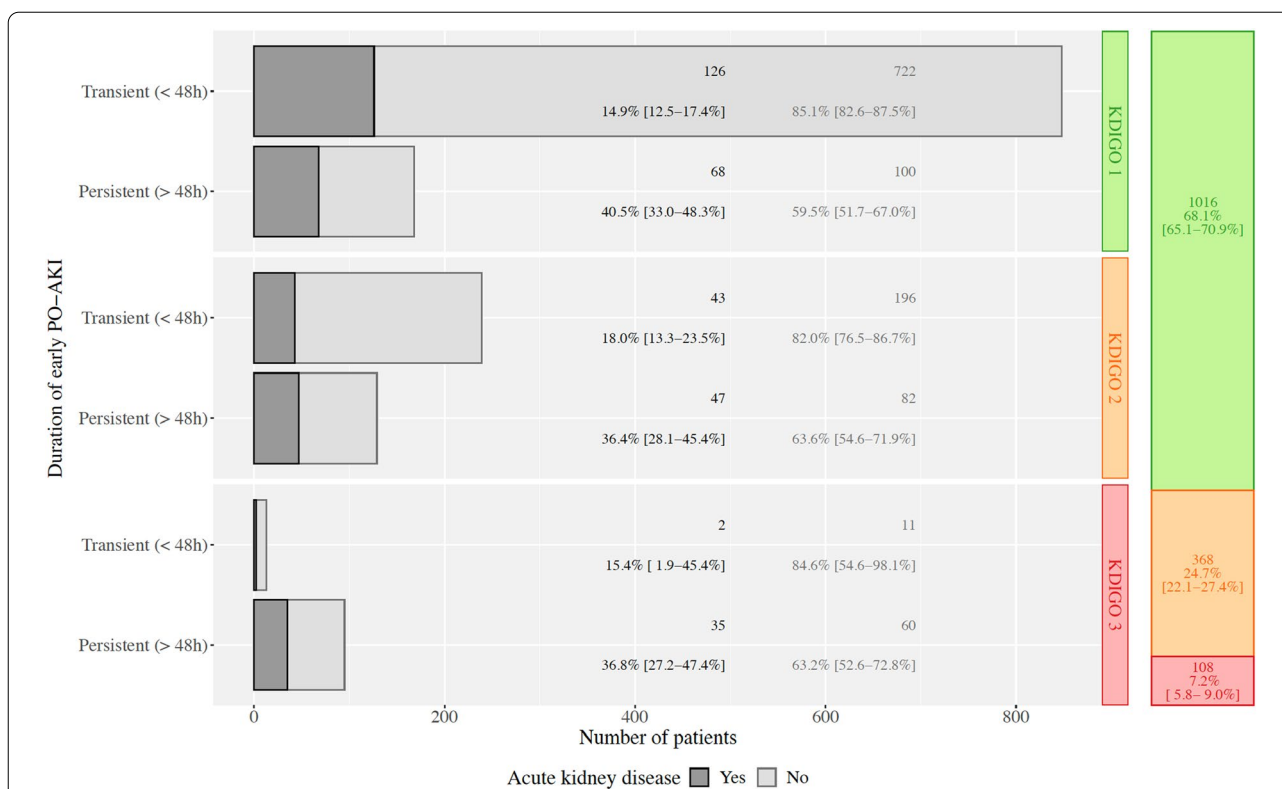
### AKI and AKD after 7 days

Overall, only 34.1% of patients who developed AKD after 7 days had a documented episode of early postoperative-AKI (Table 1 and supplementary eTable 3). However, when compared to patients who did not develop AKD after 7 days, patients with AKD after 7 days had higher rates of moderate and severe early postoperative-AKI (stage 2 and 3) (Table 1).

Rates of AKD after 7 days increased significantly with severity of early postoperative-AKI with 19.1% of patients reaching KDIGO stage 1 developing AKD after 7 days, increasing to 24.5% for KDIGO 2, and 34.3% for KDIGO stage 3 ( $P < 0.001$ ). Similarly, duration of AKI was associated with increased rates of AKD after 7 days with 15.5% of patients who had transient AKI and 38.3% in patients with persistent AKI developing AKD after 7 days ( $P < 0.001$ ) (Figs. 2 and 3) and showing increased



**Fig. 2** Development of AKD beyond 7 days with 95% confidence intervals according to KDIGO stage and diagnostic criteria in postoperative-AKI patients without CKD prior to surgery. The data in gray present patients according to the criteria used to diagnose early PO-AKI with the darker gray indicating the proportion of such patients with AKD after 7 days and the numbers indicating the actual number of patients affected. In the first thinner color panels, patients are then subdivided according to whether they had stage 1 or 2 or 3 in the first 72 h (maximum stage). In the second larger color panels, the proportion of patients in each stage as measured in the first 72 h is also presented. For example, among all patients with early postoperative-AKI in KDIGO stage 1 diagnosed by serum creatinine alone, 12.5% developed AKD after 7 days



**Fig. 3** Development of AKD after 7 days with 95% confidence intervals according to KDIGO stage and duration of postoperative-AKI in postoperative-AKI patients without CKD prior to surgery. The data in gray present patients according to transient or persistent early PO-AKI with the darker gray indicating the proportion of such patients with AKD after 7 days and the numbers indicating the actual number of patients affected. In the first thinner color panels, patients are then subdivided according to whether they had stage 1 or 2 or 3 in the first 72 h. In the second larger color panels, the proportion of patients in each stage as measured in the first 72 h is also presented. For example, among all patients with a transient postoperative-AKI in KDIGO stage 1, 14.9% developed AKD after 7 days

odds ratio (ORs) for AKD after 7 days (supplementary eTable 4a). Regarding diagnostic criteria, early postoperative-AKI patients diagnosed by serum creatinine or both serum creatinine and urine output KDIGO criteria had the highest rate of AKD after 7 days (urine output: 10.7%, serum creatinine: 27.2%, both criteria: 26.8%;  $P < 0.001$ ) and highest ORs for AKD after 7 days (supplementary eTable 4b).

#### Perioperative risk factors for AKD after 7 days

In multivariable regression analyses, early postoperative-AKI, female sex, age, comorbidities (hypertension, atrial fibrillation, myocardial infarction, peripheral vascular disease), emergency procedures, intraoperative nephrotoxic agents (vancomycin and cyclosporine or tacrolimus), postoperative nephrotoxic agents (e.g., aminoglycosides) and postoperative complications (pneumonia) were associated with subsequent AKD after 7 days (Table 2). Bootstrap validation of the model fitting process yielded a bias corrected area under the curve (AUC) of 0.768 and pseudo- $R^2$  of 0.172 for the final model

(supplementary eTable 5a and b). Of note, postoperative treatment with NSAIDs and vancomycin was associated with a lower development of AKD after 7 days. Early postoperative-AKI carried an independent OR of 2.64 (2.21, 3.15) for AKD after 7 days, the third highest OR after urological surgery and treatment with cyclosporine A or tacrolimus.

Some identified risk factors for AKD after 7 days differed between patients with and without early postoperative-AKI. However, age, gender, and the administration of nephrotoxins (cyclosporine) remained significant in both groups (supplementary eTables 6 and 7).

Combining AKD after 7 days and death at day 90 did not change the prediction model except for sepsis (supplementary eTables 8, 9 and 10).

#### Progression of CKD stage

Of 663 patients with pre-existing CKD, 42 (6.3% [95% CI 4.6–8.5%]) patients had progression of CKD; 29/251 patients with postoperative-AKI (11.6% [95% CI 7.9–16.2%]) and 13/412 patients without postoperative-AKI

**Table 2 Multivariable logistic regression analysis of possible risk factors for the postoperative development of acute kidney disease after 7 days**

Variable	OR (95% CI)	P-value
Intercept	0.006 (0.003, 0.011)	< 0.001
Sex (male vs. female)	0.45 (0.38, 0.52)	< 0.001
Age (year)	1.05 (1.04, 1.06)	< 0.001
<b>UN geoscheme</b>		
Africa vs. Europe	0.87 (0.60, 1.23)	0.436
Asia vs. Europe	0.62 (0.42, 0.91)	0.017
North America vs. Europe	1.56 (0.64, 3.98)	0.338
South America vs. Europe	0.65 (0.28, 1.37)	0.288
<b>Health expenditure</b>		
Medium vs. low	0.67 (0.46, 0.95)	0.030
High vs. low	0.43 (0.28, 0.66)	< 0.001
<b>Comorbidities (yes vs. no)</b>		
Hypertension	1.32 (1.11, 1.58)	0.002
Atrial fibrillation	1.44 (1.14, 1.79)	0.002
Previous myocardial infarction	1.25 (1.02, 1.54)	0.034
Peripheral vascular disease	1.30 (1.02, 1.65)	0.030
Surgery urgency (emergency vs. elective)	1.73 (1.19, 2.47)	0.003
<b>Surgical variables</b>		
<i>Type of surgery</i>		
Cardiac vs. abdominal	1.24 (1.00, 1.54)	0.047
Gynecological vs. abdominal	0.74 (0.45, 1.15)	0.202
Neurosurgical vs. abdominal	0.79 (0.56, 1.10)	0.178
Orthopedic vs. abdominal	0.77 (0.53, 1.11)	0.168
Thoracic vs. abdominal	1.08 (0.70, 1.61)	0.9725
Trauma vs. abdominal	0.72 (0.26, 1.64)	0.473
Vascular vs. abdominal	1.31 (0.91, 1.88)	0.144
Urological vs. abdominal	3.24 (2.45, 4.26)	< 0.001
Other vs. abdominal	0.91 (0.58, 1.39)	0.677
<i>Intraoperative variables</i>		
<b>Nephrotoxic agents (yes vs. no)</b>		
Aminoglycosides	0.53 (0.30, 0.88)	0.019
Cyclosporine/tacrolimus	6.32 (1.65, 21.72)	0.004
Vancomycin	2.06 (1.07, 3.87)	0.027
<b>Complications (yes vs. no)</b>		
Pulmonary complications <sup>1</sup>	0.54 (0.23, 1.13)	0.132
Transfusion (l)	1.12 (0.97, 1.30)	0.108
<i>Postoperative variables</i>		
<b>Blood loss (l)</b>		
Blood loss (l)	1.08 (0.98, 1.18)	0.093
<b>Nephrotoxic agents (yes vs. no)</b>		
Aminoglycosides	2.54 (1.31, 4.65)	0.004
NSAIDs	0.78 (0.64, 0.94)	0.011
Vancomycin	0.58 (0.27, 1.17)	0.147
<b>Complications (yes vs. no)</b>		
Hemodynamic instability <sup>2</sup>	0.71 (0.54, 0.93)	0.015
Reoperation	0.84 (0.55, 1.27)	0.431
Pneumonia	2.07 (1.21, 3.41)	0.006
Early postoperative-AKI (yes vs. no)	2.64 (2.21, 3.15)	< 0.001

**Table 2 (continued)**

Analysis includes 8878/9510 patients. Number of events (AKD): 891

AKI acute kidney injury, NSAID nonsteroidal anti-inflammatory drug, OR odds ratio

<sup>1</sup> Pulmonary complications (e.g., aspiration, bronchospasm)

<sup>2</sup> Hemodynamic instability was defined as new onset of vasopressor therapy or increase of norepinephrine/epinephrine  $\geq 0.02$   $\mu\text{g}/\text{kg}/\text{min}$

(3.2% [95% CI 1.7–5.3%];  $P < 0.001$ ) (supplementary eTable 11). Of these, most patients progressed by one stage of CKD (supplementary eTable 12). Progression of CKD was similar in patients with persistent and transient postoperative-AKI (14.5% vs. 9%, respectively;  $P = 0.168$ ) (supplementary eFigure 2). Postoperative-AKI patients diagnosed by serum creatinine or both KDIGO criteria showed the highest rates of CKD progression (urine output 1.6%, serum creatinine 15%, both criteria 14.7%;  $P = 0.017$ ) (supplementary eFigure 3).

## Discussion

Among patients undergoing major cardiac and non-cardiac surgery, one in ten patients developed AKD after 7 days and only one-third of patients developing AKD after 7 days had a prior episode of early postoperative-AKI. However, when early postoperative-AKI was associated with AKD after 7 days, AKD rates increased significantly with both greater severity and duration of postoperative-AKI. Patients diagnosed with early post-operative AKI by both urine output and creatinine KDIGO criteria, had the highest AKD rates. Moreover, early postoperative-AKI was strongly associated with subsequent AKD after 7 days, independent of all other potential risk factors. Other risk factors for AKD after 7 days were female sex, age, comorbidities (hypertension, atrial fibrillation, myocardial infarction, peripheral vascular disease), emergency procedures, perioperative nephrotoxic agents (intraoperative vancomycin and cyclosporine/tacrolimus, postoperative aminoglycosides), and postoperative complications (pneumonia). Finally, among patients with preoperative CKD, progression of CKD was also more frequent in patients with early postoperative-AKI.

The findings of the EPIS-AKI study align with previous findings among hospitalized patients where CKD occurred in 11% of patients (CKD stages 3–5)[17] and confirm the relationship between postoperative-AKI and AKD [18–22]. However, a small recent study of general hospitalized CKD patients, rather than patients solely undergoing surgery, showed that the association between mild and moderate AKI and worsening subsequent kidney function was small [23]. Our observations are consistent with the notion that AKI is a key driver for the development of AKD and that AKI and AKD are two

interconnected syndromes in the perioperative setting [8]. However, although early postoperative-AKI might be a significant risk factor for AKD after 7 days, our study also shows that patients undergoing major surgery are at risk for AKD after 7 days even if they did not have an episode of early postoperative-AKI.

Among early postoperative-AKI associated AKD patients, the duration and severity of early postoperative-AKI were two key risk factors. Aligned with our findings, one retrospective study among elderly patients showed that AKI duration of more than seven days increased the risk of CKD [24]. Another retrospective study found an OR of 23.7 for CKD in patients with an AKI duration of more than seven days [25]. However, the Acute Dialysis Quality Initiative (ADQI) proposed a standardized definition of persistent AKI based on the recovery of kidney function within 48 h, which is consistent with the definition used in the EPIS-AKI study [15]. Even using such a shorter 48 h cut off point, our findings align with previous studies.

Among all surgical subspecialties, urological procedures were associated with the highest risk of AKD after 7 days; however, this is partly confounded because it included urological procedures, which resulted in nephron loss (100 patients received a nephrectomy).

Nearly 8% of patients without early postoperative-AKI developed AKD after 7 days. It is conceivable that AKI might have occurred after 72 h postoperatively, as such data was not collected in the EPIS-AKI study. Subclinical (stage 1 s) AKI, which is defined by kidney damage without a functional loss (functional biomarkers serum creatinine and urine output are normal but damage biomarkers are elevated) [26], might have also occurred and affected the development of AKD as suggested by previous studies [27–30]. Nonetheless, the data suggests that this patient population has an increased susceptibility to developing kidney functional loss in the post-operative period and AKD after 7 days. Based on this increased risk, in these patients, it might be advisable to limit the use of nephrotoxic drugs whenever possible, use therapeutic drug monitoring where available, and try to optimize hemodynamic and volume status. Further trials have to address the question whether a specific drug treatment (e.g., early treatment with angiotensin converting enzyme [ACE] and/or sodium-glucose cotransporter-2 [SGLT2] inhibitors) can affect the development of AKD.

In other studies, age, female sex, and hypertension have been associated with AKD [17]. These risk factors were also found in the EPIS-AKI study, but additionally perioperative modifiable risk factors were detected. Nephrotoxic agents are known risk factors for AKI [31, 32] but, as shown here, probably also for AKD after 7 days even

in patients without early AKI. As such, intraoperative use of immunosuppressive agents was associated with a higher risk of AKD after 7 days. One could question whether this is caused by the drug itself or whether this might be related to kidney transplantation. However, kidney transplantation was an exclusion criterion for the EPIS-AKI study. Immunosuppressive agents have different indications apart from kidney transplantation (e.g., other transplantations, rheumatoid arthritis, psoriasis). Consequently, it is likely the toxicity of the drug itself was related to the increased risk of AKD after 7 days. Thus, treatment with nephrotoxic medications must be carefully considered and, if possible, avoided. The implementation of a nephrotoxic drug stewardship could help prevent AKI and maybe also prevent AKD and CKD [33]. The fact that the postoperative application of NSAIDs and vancomycin was associated with lower rates of AKI may appear counterintuitive. However, it might be explained by selection bias or that, in such cases, clinicians were alerted to the risks associated with these drugs and therefore modify their treatment.

### Strengths and limitations

The strengths of this study are the largest cohort of patients studied to date examining progression of AKD beyond 7 days postoperatively and the influence of early postoperative-AKI, the multinational setting, the multiple types of surgeries included, the detailed collection of data, the close monitoring for early post-operative AKI and the protocolized follow-up to determine the development of AKD after 7 days. As such, this is the first international multicentre study of the epidemiology of postoperative AKD and of its association with early postoperative-AKI and it provides novel insights.

We acknowledge several limitations. First, as AKI is part of the AKD definition and we wanted to distinguish between AKI and persistent renal dysfunction, we used the term “AKD beyond day 7”. The definition of AKD was based on a single assessment of kidney function beyond 7 days after surgery (mostly at day 90). In addition, we only used serum creatinine to estimate the GFR but did not consider other markers of CKD such as proteinuria. For these reasons, the term CKD could not be used [34]. It remains uncertain whether such prolonged reduced kidney function was reflective of a steady state and how it might relate to CKD. In addition, it remains unknown what factors that might have occurred between hospital discharge and day 90 may have impacted the incidence of AKD. Second, some surgical procedures were underrepresented, potentially resulting in a selection bias nor did we collect the granularity of all surgical procedures within speciality. Third, we only assessed patients for early postoperative-AKI and are unable to comment

on whether AKI, or indeed AKD, developed thereafter at any time between day 3 and day 90. Furthermore, we did not measure biomarkers other than urine output and serum creatinine which may have been elevated in the 72 h post-surgery and which could have been associated with prolonged kidney dysfunction. Finally, the findings of this study can only be generalized to survivors to 90-day but may vary between the different countries, healthcare systems, and types and complexity of surgery. Some findings, such as the lower risk of AKD after 7 days with the use of intraoperative NSAIDs, are surprising and may be related to unknown confounding factors and selection bias.

## Conclusion

In a large multicentre international study among patients undergoing major cardiac and non-cardiac surgery, one in ten patients developed AKD after 7 days. Although most patients developed AKD without a prior episode of early postoperative-AKI, early postoperative-AKI was a major risk factor for subsequent AKD after 7 days. Nephrotoxic drugs were also significant modifiable risk factors for AKD after 7 days. Moreover, among patients with preoperative CKD, progression of CKD was higher in patients with early postoperative-AKI. These findings have important implications not only for the management and prognosis of surgical patients and early postoperative-AKI but also for the design of future interventional clinical trials.

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#### Author contributions

MM and AZ conceived and designed the study; FA and MM performed statistical analysis; MM, RW, CR, HB, JFP, PR, AZ acquired data; MM, FA, RM, RB, JAK, AZ drafted the manuscript; RW, CS, HB, JFP, MR, PR, LF 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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#### Data availability

The data used in the present study are available from the corresponding author upon reasonable request.

#### Declarations

#### Conflicts of interest

MM received lecture fees from Fresenius Medical Care and Baxter unrelated to current study. JAK is a paid consultant for BioMerieux, and a fulltime employee of Spectral Medical. 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. All other authors declare no conflicts of interest.

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