Development of chronic kidney disease after major surgery

Melanie Meersch
University of Münster: Westfalische Wilhelms-Universitat Munster
Raphael Weiss
University of Münster: Westfalische Wilhelms-Universitat Munster
Christian Strauß
University of Münster: Westfalische Wilhelms-Universitat Munster
Felix Albert
University of Münster: Westfalische Wilhelms-Universitat Munster
Hendrik booke
University of Münster: Westfalische Wilhelms-Universitat Munster
Lui Forni
Royal Surrey County Hospital NHS Trust: Royal Surrey NHS Foundation Trust
Jean-Francois Pittet
University of Alabama at Birmingham
John A. Kellum
University of Pittsburgh
Mitchell Rosner
University of Virginia
Ravindra Mehta
University of California San Francisco
Rinaldo Bellomo
The University of Melbourne
Peter Rosenberger
University of Tübingen: Eberhard Karls Universitat Tubingen
Alexander Zarbock (zarbock@uni-muenster.de)
University of Münster: Westfalische Wilhelms-Universitat Munster https://orcid.org/0000-0002-2124-1714

Research Article

Keywords: chronic kidney disease, surgery, acute kidney injury, postoperative

Posted Date: September 13th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3322920/v1

Version of Record: A version of this preprint was published at Intensive Care Medicine on January 29th, 2024. See the published version at https://doi.org/10.1007/s00134-023-07314-2.

Abstract

Purpose

Chronic kidney disease (CKD) is a significant health care burden worldwide. However, little is known about its development after major surgery.

Methods

We conducted an international prospective, observational, multi-center study in 30 countries among patients undergoing major surgery. The primary study endpoint was the incidence of CKD (defined as new onset CKD with an eGFR < 60ml/min/1.73m^2 at day 90). Secondary endpoints included the relationship between early postoperative-AKI (within 72h after major surgery) and development of postoperative CKD, the identification of risk factors for CKD, and the rate and risk factors for CKD progression in patients with pre-existing CKD.

Results

We studied 9,510 patients without pre-existing CKD. Of these, 940 (9.9%) developed CKD with 34.2% experiencing an episode of early postoperative-AKI. CKD rates significantly increased with the severity of early AKI (19.1% KDIGO1, 24.5% KDIGO2, 34.3% KDIGO3; $P < 0.001$) and duration (15.5% transient vs 38.3% persistent AKI; $P < 0.001$). Independent risk factors for CKD included early postoperative-AKI, exposure to perioperative nephrotoxic agents, and postoperative pneumonia. Early postoperative-AKI carried an independent odds ratio for CKD of 2.64 (95%-CI 2.21–3.15). Of 663 patients with pre-existing CKD, 42 (6.3%) had worsening CKD at day 90 as defined. In patients with CKD and an episode of early AKI, CKD progression occurred in 11.6%.

Conclusion

One in ten major surgery patients developed postoperative CKD, most of them without an episode of early postoperative-AKI. However, early postoperative-AKI severity and duration was associated with an increased rate of CKD with early postoperative-AKI being a major independent risk factor for CKD.

Clinical trial number:

The study was registered at ClinicalTrials.gov (NCT04165369).

Take-home message

One in ten patients develop CKD after major surgery, most of them without a prior episode of AKI. However, early postoperative AKI is a major risk factor for subsequent CKD. These findings have important implications for the management and prognosis of surgical patients.

INTRODUCTION

Each year, more than 310 million patients undergo major surgery worldwide and postoperative complications are associated with both 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 develop an episode of postoperative-AKI occurring within 72 hours after major surgery (early postoperative-AKI) [7]. Furthermore, the development of AKI has been associated with an increased risk for the development of chronic kidney disease (CKD) [8,9]. Surprisingly, the epidemiology of CKD 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 CKD have not been studied in detail. Finally, additional factors occurring in the perioperative period which may be associated with CKD development remain unknown.

We aimed to test the primary hypothesis that CKD 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 CKD. 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

The Epidemiology of Surgery-Associated Acute Kidney Injury (EPIS-AKI) study is 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 ≥ 18 years) undergoing major elective and emergency surgery (operative time ≥ 2 hours) with subsequent ICU or high dependency unit admission were included regardless of surgical subspecialty. Exclusion criteria included 1. Pre-existing AKI, 2. AKI within the last 3 months, 3. End-stage renal disease with dialysis dependency, 4. 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 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 new onset CKD 90 days after surgery. This was defined as patients with an estimated glomerular filtration rate (eGFR) > 60ml/min/1.73m^2 prior to surgery, surviving 90 days with an observed decrease in eGFR to < 60ml/min/1.73m^2.

Secondary endpoints were the association of early postoperative-AKI and AKI characteristics (duration, severity (as defined by KDIGO stages), and specific diagnostic criteria (serum creatinine and/or urine output) with the development of CKD. We concentrated on early postoperative-AKI, because the majority of AKI occurs within 72 hours 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 its relationship to postoperative-AKI.

STATISTICAL ANALYSIS

Frequencies, percentages, medians, quartiles, and *P*-values were calculated for the baseline variables, primary 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 Mann-Whitney U test depending on whether the target variable was normally distributed in both groups or not.

CIs for binomial proportion estimates, e.g., the development of CKD, 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 CKD development 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 hours duration or persistent: > 48 hours 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 further risk factors for the development of CKD, multivariable logistic regression analyses were performed. Firstly we selected variables that, have been proposed as being associated with the development of CKD 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, 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 CKD development. 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.

All *p*-values and confidence limits were two-sided. Only the confidence interval of the primary endpoint, the incidence of CKD, 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 9,510/10,568 (90.0%) patients (Fig. 1). Baseline CKD was present in 663 (6.3%) patients with 9124 (96.3%) patients surviving to 90 days. Demographic and baseline data according to the development of postoperative CKD are presented in Table 1, surgical and postoperative details in Supplementary eTable 1 and Supplementary eFigure 1.

Table 1
Patient demographics and baseline characteristics according to the postoperative development of CKD

	No-CKD n = 8570	CKD n = 940	*P*
Demographics			
Age, median (Q1, Q3), years	61 (50, 68)	69 (62, 76)	< 0.001
Male, n (%)	5289 (61.7)	475 (50.5)	< 0.001
Height, median (Q1, Q3), cm	169 (162, 175)	167 (160, 174)	< 0.001
Weight, median (Q1, Q3), kg	75 (66, 86)	77 (67, 86)	0.195
Serum-creatinine, median (Q1, Q3), mg/dL	0.8 (0.7, 0.9)	1.0 (0.8, 1.2)	< 0.001
Race, ethnicity, No. (%)			< 0.001
Caucasian	5995 (70.0)	743 (79.0)	
Black	337 (3.9)	8 (0.9)	
Asian	1058 (12.4)	98 (10.4)	
Hispanic	174 (2.0)	18 (1.9)	
Other	1006 (11.7)	73 (7.8)	
Comorbidities, No. (%)			
Hypertension	4034 (47.0)	662 (70.4)	< 0.001
Diabetes	1815 (21.2)	297 (31.6)	< 0.001
Congestive heart failure	1249 (14.6)	233 (24.8)	< 0.001
Previous myocardial infarction	1023 (11.9)	165 (17.6)	< 0.001
Peripheral vascular disease	660 (7.7)	143 (15.2)	< 0.001
Atrial flutter/fibrillation	568 (6.6)	142 (15.1)	< 0.001
COPD	676 (7.9)	87 (9.3)	0.143
Previous stroke	361 (4.2)	73 (7.8)	< 0.001

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, American Society of Anaesthesiologists; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NSAID, Nonsteroidal anti-inflammatory drug, postoperative-AKI

[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.

		No-CKD n = 8570	CKD n = 940	*P*
Demographics				
ASA score[a]	1	1184 (13.8)	54 (5.7)	< 0.001
	2	3850 (44.9)	326 (34.7)	
	3	3015 (35.2)	451 (48.0)	
	4	521 (6.1)	109 (11.6)	
Medication, No. (%)				
ACEi or ARB		2934 (34.2)	481 (51.2)	< 0.001
Beta-Blockers		2444 (28.5)	413 (43.9)	< 0.001
Aspirin		2393 (27.9)	374 (40.0)	< 0.001
Statins		2274 (26.5)	370 (39.4)	< 0.001
Diuretics		1311 (15.3)	268 (28.5)	< 0.001
Use of contrast media one week prior surgery		1529 (17.8)	203 (21.6)	0.005
NSAIDs (except Aspirin)		377 (4.4)	56 (6.0)	0.030
Vasopressors		57 (0.7)	13 (1.4)	0.015
Postoperative -AKI, No. (%)		1171 (13.7)	321 (34.2)	< 0.001
KDIGO 1		822 (70.2)	194 (60.4)	
KDIGO 2		278 (23.7)	90 (28.0)	
KDIGO 3		71 (6.1)	37 (11.5)	

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, American Society of Anaesthesiologists; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NSAID, Nonsteroidal anti-inflammatory drug, postoperative-AKI

[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.

The mean age was 59 (SD 15) years, 61% were men, median serum creatinine was 0.8 (Q1, Q3, 0.7-1.0) 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 CKD

In total, 940/9,510 (9.9% [95% CI, 9.3–10.5%]) patients developed CKD. Vascular and cardiac surgery had similar rates of CKD, 16.0 and 14.7% respectively whereas in patients undergoing orthopaedic procedures a rate of 9.1% was observed (Supplementary eTables 1 and 2). The highest rate was seen in patients undergoing urological procedures. Patients who developed CKD 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 NSAIDs, and more often treated with vasopressors (Supplementary eTable 1).

AKI transition to CKD

Overall, only 34.2% of patients who developed CKD had a documented episode of early postoperative-AKI (Table 1 and Supplementary eTable 3). However, when compared to patients who did not develop CKD, patients with CKD at day 90 had higher rates of moderate and severe early postoperative-AKI (stage 2 and 3) (Table 1). It seems likely that 65.8% of patients who developed CKD transitioned through AKD to CKD without early AKI, however, data from this period was not collected.

CKD rates increased significantly with the maximum severity of early postoperative-AKI with 19.1% of patients reaching KDIGO stage 1 developing CKD, 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 CKD with 15.5% of patients who had transient AKI and 38.3% in patients with persistent AKI developing CKD ($P < 0.001$) (Fig. 2 and Fig. 3). Regarding diagnostic criteria, early postoperative-AKI patients diagnosed by serum creatinine or both urine output and creatinine KDIGO criteria had the highest CKD rates (urine output 10.7%, serum creatinine 27.2%, both criteria 26.8%; $P < 0.001$).

Patients with persistent AKI had a higher risk for CKD compared to patients with transient AKI (Supplementary eTable 4). Early postoperative-AKI patients diagnosed by serum creatinine or both urine output and creatinine KDIGO criteria had a higher risk of developing CKD compared to patients diagnosed by urine output alone (Supplementary eTable 4).

Perioperative risk factors for CKD

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 independent risk factors for subsequent CKD (Table 2). Of note, postoperative treatment with NSAIDs and vancomycin was associated with a lower development of CKD. Early postoperative-AKI carried an independent odds ratio for CKD of 2.64 (2.21, 3.15), the third highest after urological surgery and treatment with cyclosporine A or tacrolimus.

Table 2
Multivariable logistic regression analysis of possible risk factors for the postoperative development of CKD

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
UN geoscheme		
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
Health expenditure		
Medium vs. low	0.67 (0.46, 0.95)	0.030
High vs. low	0.43 (0.28, 0.66)	< 0.001
Comorbidities (yes vs. no)		
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
SURGICAL VARIABLES		
Type of surgery		
Cardiac vs. abdominal	1.24 (1.00, 1.54)	0.047
Gynecological vs. abdominal	0.74 (0.45, 1.15)	0.202

Analysis includes 8878/9519 patients. Number of events (CKD): 891.

Abbreviations: NSAID, Nonsteroidal anti-inflammatory drug.

[1] Pulmonary complications (e.g., aspiration, bronchospasm)

[2] Hemodynamic instability was defined as new onset of vasopressor therapy or increase of norepinephrine/epinephrine ≥ 0.02µg/kg/min

Variable	OR (95% CI)	*P*-value
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
INTRAOPERATIVE VARIABLES		
Nephrotoxic agents (yes vs. no)		
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
Complications (yes vs. no)		
Pulmonary complications[1]	0.54 (0.23, 1.13)	0.132
Transfusion (l)	1.12 (0.97, 1.30)	0.108
POSTOPERATIVE VARIABLES		
Blood loss (l)	1.08 (0.98, 1.18)	0.093
Nephrotoxic agents (yes vs. no)		
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
Complications (yes vs. no)		
Hemodynamic instability[2]	0.71 (0.54, 0.93)	0.015

Analysis includes 8878/9519 patients. Number of events (CKD): 891.

Abbreviations: NSAID, Nonsteroidal anti-inflammatory drug.

[1] Pulmonary complications (e.g., aspiration, bronchospasm)

[2] Hemodynamic instability was defined as new onset of vasopressor therapy or increase of norepinephrine/epinephrine ≥ 0.02µg/kg/min

Variable	OR (95% CI)	*P*-value
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
Analysis includes 8878/9519 patients. Number of events (CKD): 891.		
Abbreviations: NSAID, Nonsteroidal anti-inflammatory drug.		
[1] Pulmonary complications (e.g., aspiration, bronchospasm)		
[2] Hemodynamic instability was defined as new onset of vasopressor therapy or increase of norepinephrine/epinephrine ≥ 0.02µg/kg/min		

Some risk factors for CKD 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 5 and 6).

Progression of CKD stage

Of 663 patients with preexisting 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 (3.2% [95% CI, 1.7–5.3%]; $P < 0.001$) (Supplementary eTable 7). Of these, most patients progressed by one stage of CKD (Supplementary eTable 8). Progression of CKD was similar in patients with persistent and transient postoperative-AKI (14.5% vs. 9.0%, respectively; $P = 0.168$) (Supplementary eFigure 2). Postoperative-AKI patients diagnosed by serum creatinine or both KDIGO criteria showed highest rates of CKD progression (serum creatinine 15.0%, urine output 1.6%, 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 CKD and only one third of patients developing CKD had a prior episode of early postoperative-AKI. However, where early postoperative-AKI was associated with CKD, rates increased significantly with both greater severity and duration of postoperative-AKI. Patients diagnosed by serum creatinine or both, urine output and creatinine KDIGO criteria, had the highest CKD rates. Moreover, early postoperative-AKI was a strong independent risk factor for subsequent CKD. Other risk factors for CKD 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 the patients (CKD stages 3 to 5) [16] and confirm the relationship between postoperative-AKI and CKD [17–21]. 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 [22]. Our observations are consistent with the notion that AKI is a key driver for the development of CKD and that AKI and CKD are two interconnected syndromes in the perioperative setting [8]. However, although early postoperative-AKI is a significant independent risk factor for CKD, our study also shows that patients undergoing major surgery are at risk for CKD even if they did not have an episode of early postoperative-AKI.

Among early postoperative-AKI associated CKD 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 [23]. Another retrospective study found an odds ratio of 23.7 for CKD in patients with an AKI duration of more than seven days [24]. However, the Acute Dialysis Quality Initiative (ADQI) proposed a standardized definition of persistent AKI based on the recovery of kidney function within 48h, which is consistent with the definition used in the EPIS-AKI study [15]. Even using such a shorter 48-hour cut off point, however, our findings align with previous studies.

Nearly 8% of patients without early postoperative-AKI developed CKD. It is conceivable that AKI might have occurred after 72 hours postoperatively, as such data was not collected in the EPIS-AKI study. Subclinical (stage 1s) AKI, which is defined by a kidney damage without a functional loss (functional biomarkers serum creatinine and urine output are normal and damage biomarkers are elevated),[25] might have also occurred and affected the development of CKD as suggested by previous studies [26–29].

In other studies, age, female sex, and hypertension have been associated with CKD [16]. These risk factors were also found in EPIS-AKI study, but additionally perioperative modifiable risk factors were detected. Nephrotoxic agents are known risk factors for AKI [30,31] but, as shown here, also for CKD even in patients without previous AKI. Treatment with nephrotoxic medications should thus be carefully considered and, if possible, avoided. The implementation of a nephrotoxic drug stewardship could help prevent CKD as well as AKI [32]. The fact that the postoperative application of NSAIDs and vancomycin was associated with lower rates of AKI is counterintuitive and might be explained by selection bias or that in such cases clinicians are 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 CKD 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 CKD. As such, this is the first

international multicenter study of the epidemiology of postoperative CKD and of its association with early postoperative-AKI and its data provide novel insights.

We acknowledge several limitations. First, the definition of CKD was based on a single assessment of kidney function after 90 days. [33] Thus, it remains uncertain whether such reduced kidney function was reflective of a steady state. In addition, it remains unknown what factors that might have occurred between hospital discharge and day 90 may have impacted the incidence of CKD. 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 other biomarkers other than urine output and serum creatinine which may have been elevated in the 72 hours post-surgery, stage 1S, which could have been associated with CKD development as this has been associated with a decline in functional renal reserve. Fourth, we only used the serum creatinine levels to estimate the GFR and the presence of CKD but did not consider other markers of CKD such as proteinuria as a criterion of CKD definition. Finally, the findings of this study may not be generalizable as the risk of developing CKD may vary between the different countries, healthcare systems, and types and complexity of surgery.

CONCLUSION

In a large multicenter international study among patients undergoing major cardiac and non-cardiac surgery, one in ten patients developed CKD. Although most patients developed CKD without a prior episode of early postoperative-AKI, early postoperative-AKI was a major risk factor for subsequent CKD. Nephrotoxic drugs were also significant modifiable risk factors for CKD. Moreover, among patients with preoperative CKD, progression of CKD was less frequent but 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.

Declarations

Competing interests

MM received lecture fees from Biomerieux, 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.

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.

ACKNOWLEDGEMENTS

Funding

The study was supported by the German Research Foundation (KFO342-1, ZA428/18-1, and ZA428/21-1 to AZ and ME5413/1-1 and ME5413/1-2 to MM) and by an unrestricted research grant from Baxter (to AZ).

Support

The European Society of Anesthesiology and Intensive Care (ESAIC), among the following medical societies endorsed this study but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

However, we would like to thank these societies for their support on the promotion of EPIS-AKI:

Colegio Mexicano de Medicina Crítica (COMMEC), Colombian Association of Surgery (CAS), Czech Society of Anesthesiology and Intensive Care (CSARIM), Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI), European Society of Anaesthesiology and Intensive Care (ESAIC), Korean Society of Anesthesiologists (KSA), Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI), Société Française d'Anesthésie et de Réanimation (SFAR), South African Society of Anaesthesiologists (SASA), Spanish Perioperative Audit and Research Network (REDGERM), Turkish Anaesthesiology and Reanimation Society (TARD).

References

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet*. Apr 27 2015;385 Suppl 2:S11. doi:10.1016/S0140-6736(15)60806-6
2. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet*. Sep 22 2012;380(9847):1059-65. doi:10.1016/S0140-6736(12)61148-9
3. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. Nov 2005;16(11):3365-70. doi:10.1681/ASN.2004090740

4. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. Aug 17 2005;294(7):813-8. doi:10.1001/jama.294.7.813
5. Barrantes F, Tian J, Vazquez R, Amoateng-Adjepong Y, Manthous CA. Acute kidney injury criteria predict outcomes of critically ill patients. *Crit Care Med*. May 2008;36(5):1397-403. doi:10.1097/CCM.0b013e318168fbe0
6. Longo WE, Virgo KS, Johnson FE, et al. Risk factors for morbidity and mortality after colectomy for colon cancer. *Dis Colon Rectum*. Jan 2000;43(1):83-91. doi:10.1007/BF02237249
7. Zarbock A, Weiss R, Albert F, et al. Epidemiology of surgery associated acute kidney injury (EPIS-AKI): a prospective international observational multi-center clinical study. *Intensive Care Med*. Jul 28 2023;doi:10.1007/s00134-023-07169-7
8. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *The New England journal of medicine*. Jul 3 2014;371(1):58-66. doi:10.1056/NEJMra1214243
9. Bihorac A, Yavas S, Subbiah S, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Annals of surgery*. May 2009;249(5):851-8. doi:10.1097/SLA.0b013e3181a40a0b
10. Weiss R, Saadat-Gilani K, Kerschke L, et al. EPIdemiology of Surgery-Associated Acute Kidney Injury (EPIS-AKI): study protocol for a multicentre, observational trial. *BMJ Open*. Dec 30 2021;11(12):e055705. doi:10.1136/bmjopen-2021-055705
11. Lombardi R, Nin N, Penuelas O, et al. Acute Kidney Injury in Mechanically Ventilated Patients: The Risk Factor Profile Depends on the Timing of Aki Onset. *Shock*. Oct 2017;48(4):411-417. doi:10.1097/SHK.0000000000000871
12. Priyanka P, Zarbock A, Izawa J, Gleason TG, Renfurm RW, Kellum JA. The impact of acute kidney injury by serum creatinine or urine output criteria on major adverse kidney events in cardiac surgery patients. *J Thorac Cardiovasc Surg*. Jul 2021;162(1):143-151 e7. doi:10.1016/j.jtcvs.2019.11.137
13. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. *The New England journal of medicine*. Jun 14 2018;378(24):2263-2274. doi:10.1056/NEJMoa1801601
14. Goodman LA. On simultaneous confidence intervals for multinomial proportions. *Technometrics*. 1965;7:247-254.
15. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. Apr 2017;13(4):241-257. doi:10.1038/nrneph.2017.2
16. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS One*. 2016;11(7):e0158765. doi:10.1371/journal.pone.0158765
17. See EJ, Jayasinghe K, Glassford N, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. *Kidney Int*. Jan 2019;95(1):160-172. doi:10.1016/j.kint.2018.08.036

18. Gameiro J, Marques F, Lopes JA. Long-term consequences of acute kidney injury: a narrative review. *Clin Kidney J*. Mar 2021;14(3):789-804. doi:10.1093/ckj/sfaa177
19. Forni LG, Darmon M, Ostermann M, et al. Renal recovery after acute kidney injury. *Intensive Care Med*. Jun 2017;43(6):855-866. doi:10.1007/s00134-017-4809-x
20. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. Cost and Mortality Associated With Postoperative Acute Kidney Injury. *Annals of surgery*. Jun 2015;261(6):1207-14. doi:10.1097/SLA.0000000000000732
21. Petaja L, Vaara S, Liuhanen S, et al. Acute Kidney Injury After Cardiac Surgery by Complete KDIGO Criteria Predicts Increased Mortality. *J Cardiothorac Vasc Anesth*. Jun 2017;31(3):827-836. doi:10.1053/j.jvca.2016.08.026
22. Muiru AN, Hsu JY, Zhang X, et al. Risk for Chronic Kidney Disease Progression After Acute Kidney Injury: Findings From the Chronic Renal Insufficiency Cohort Study. *Ann Intern Med*. Jul 2023;176(7):961-968. doi:10.7326/M22-3617
23. Li Q, Li Y, Zhou F. Duration of acute kidney injury predicts 90-day mortality and chronic kidney disease progression in elderly patients. *J Intensive Med*. Apr 2022;2(2):110-117. doi:10.1016/j.jointm.2021.11.008
24. Gameiro J, Duarte I, Marques F, et al. Transient and Persistent AKI and Outcomes in Patients Undergoing Major Abdominal Surgery. *Nephron*. 2020;144(5):236-244. doi:10.1159/000506397
25. Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference: A Consensus Statement. *JAMA Netw Open*. Oct 1 2020;3(10):e2019209. doi:10.1001/jamanetworkopen.2020.19209
26. Menez S, Moledina DG, Garg AX, et al. Results from the TRIBE-AKI Study found associations between post-operative blood biomarkers and risk of chronic kidney disease after cardiac surgery. *Kidney Int*. Mar 2021;99(3):716-724. doi:10.1016/j.kint.2020.06.037
27. Ronco C, Kellum JA, Haase M. Subclinical AKI is still AKI. *Crit Care*. 2012;16(3):313. doi:10.1186/cc11240
28. Joannidis M, Forni LG, Haase M, et al. Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury. *Crit Care Med*. Oct 2019;47(10):e820-e826. doi:10.1097/CCM.0000000000003907
29. Haase M, Kellum JA, Ronco C. Subclinical AKI--an emerging syndrome with important consequences. *Nat Rev Nephrol*. Dec 2012;8(12):735-9. doi:10.1038/nrneph.2012.197
30. Perazella MA. Drug use and nephrotoxicity in the intensive care unit. *Kidney Int*. Jun 2012;81(12):1172-8. doi:10.1038/ki.2010.475
31. Goldstein SL. Medication-induced acute kidney injury. *Curr Opin Crit Care*. Dec 2016;22(6):542-545. doi:10.1097/MCC.0000000000000355
32. Gray MP, Barreto EF, Schreier DJ, et al. Consensus Obtained for the Nephrotoxic Potential of 167 Drugs in Adult Critically Ill Patients Using a Modified Delphi Method. *Drug Saf*. Apr 2022;45(4):389-398. doi:10.1007/s40264-022-01173-4

33. Summary of Recommendation Statements. *Kidney Int Suppl (2011)*. Jan 2013;3(1):5-14. doi:10.1038/kisup.2012.77

Figures

Figure 1

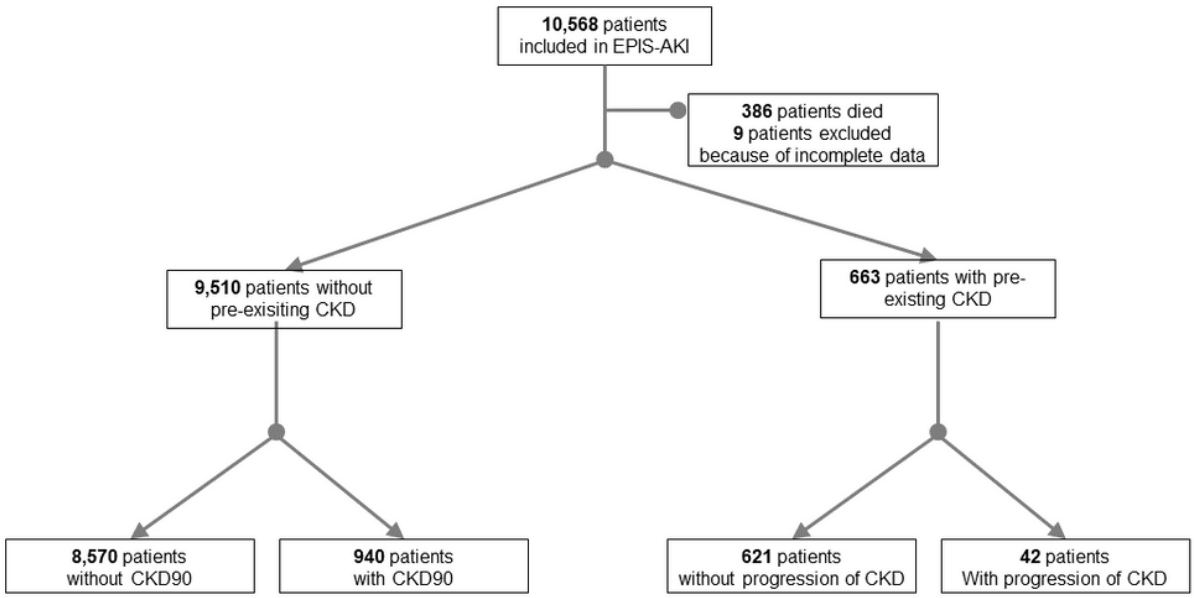

Figure 1

Flow chart. Abbreviations: CKD, chronic kidney disease.

Figure 2

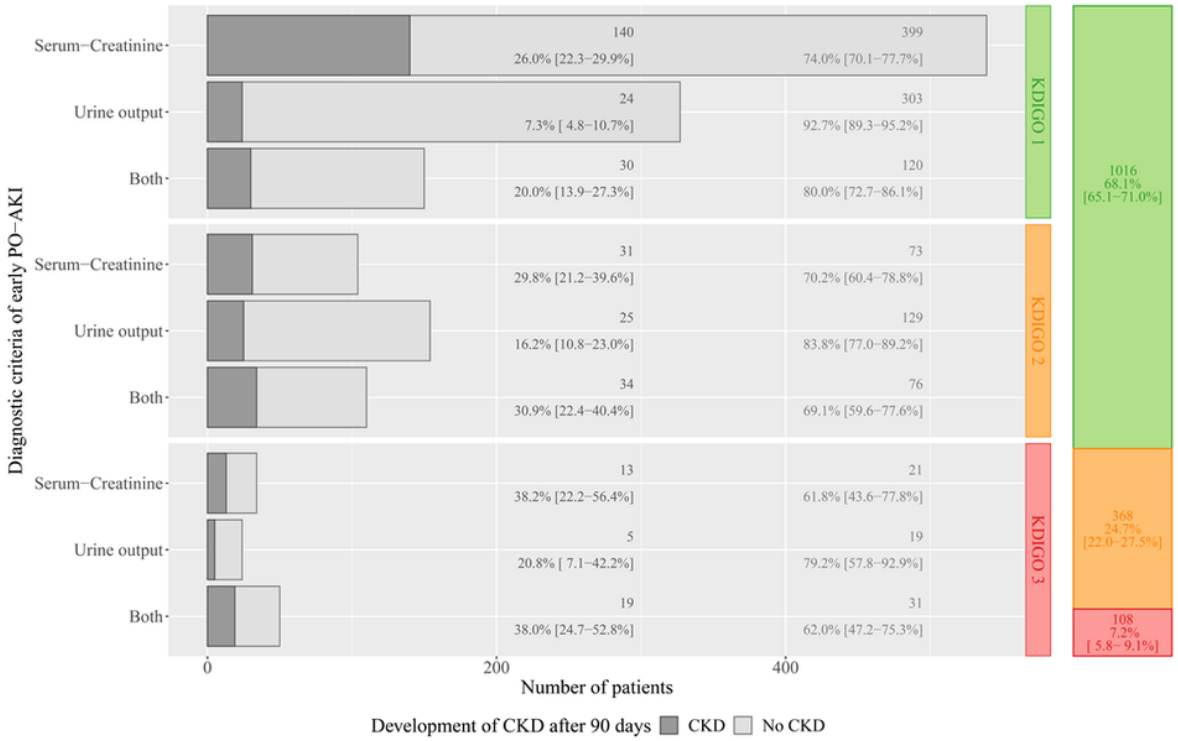

Figure 2

Development of CKD after 90 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 who progressed to CKD at 90 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 hours (maximum stage). In the second larger color panels, the proportion of patients in each stage as measured in the first 72 hours is also presented. For example, among all patients with early postoperative-AKI in KDIGO stage 1 diagnosed by serum creatinine alone, 12.5% developed a CKD after 90 days.

Figure 3

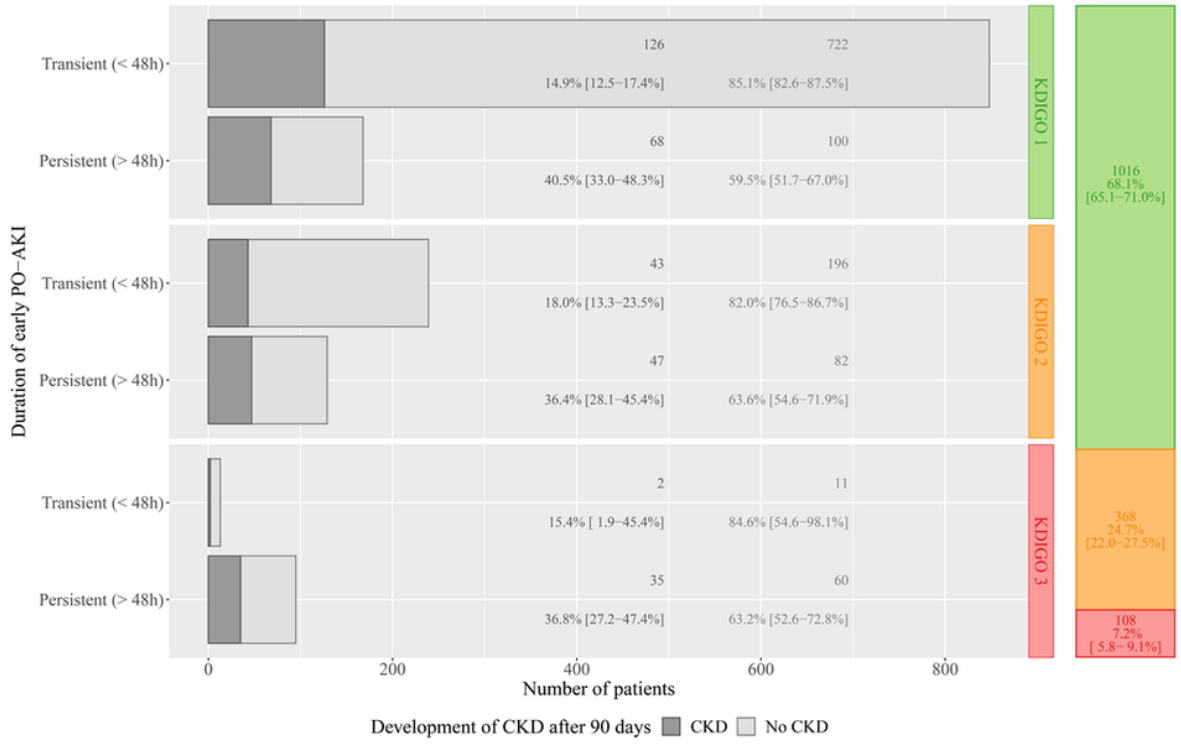

Figure 3

Development of CKD after 90 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 who progressed to CKD at 90 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 hours. In the second larger color panels, the proportion of patients in each stage as measured in the first 72 hours is also presented. For example, among all patients with a transient postoperative-AKI in KDIGO stage 1, 14.9% developed a CKD after 90 days.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBE.docx
- Supplement1EPISAKIFollowupCKD.docx