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Original Article

ORIGINAL ARTICLE

Risk of chronic kidney disease in patients with acute kidney injury following a major surgery: a US claims database analysis

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ABSTRACT

Background. Acute kidney injury (AKI) is a common complication after major surgery. This study assessed the risk of developing or worsening of chronic kidney disease (CKD) and other clinical outcomes in patients experiencing AKI after major surgery.

Methods. This retrospective observational study used Optum's de-identified Clinformatics Data Mart Database to investigate cardiorenal outcomes in adult patients at the first AKI event following major surgery. The primary outcome was CKD stage ≥3; secondary outcomes included myocardial infarction (MI), stroke, heart failure, all-cause hospitalization, end-stage kidney disease, need for dialysis or kidney transplant and composite measures. Follow-up was up to 3 years. Additionally, the effect of intercurrent events on the risk of clinical outcomes was assessed.

Results. Of the included patients ($N = 31\,252$), most were male (61.9%) and White (68.9%), with a median age of 72 years (interquartile range 64–79). The event rates were 25.5 events/100 patient-years (PY) for CKD stage ≥3, 3.1 events/100 PY for end-stage kidney disease, 3.0 events/100 PY for dialysis and 0.1 events/100 PY for kidney transplants. Additionally, there were 6.9 events/100 PY for MI, 8.7 events/100 PY for stroke and 49.8 events/100 PY for all-cause hospitalization during follow-up. Patients with AKI relapses as intercurrent events were more likely to develop CKD stage ≥3 than those with just one AKI event after major surgery.

Conclusion. This analysis demonstrated that patients experiencing AKI following major surgery are at high risk of developing severe CKD or worsening of pre-existing CKD and other cardiorenal clinical outcomes such as MI and stroke.

LAY SUMMARY

Acute kidney injury (AKI) is a disease that is common in patients who have had a serious surgery. We studied whether having AKI after a serious surgery affects the risk of developing chronic kidney disease (CKD) stage ≥3 (which is known as 'moderate–severe CKD') or the risk that pre-existing CKD progresses to moderate–severe CKD. The study also looked into how AKI affects the risks of other events, such as having a heart attack, having a stroke, experiencing heart failure, being hospitalized and experiencing other side effects. We used information from real

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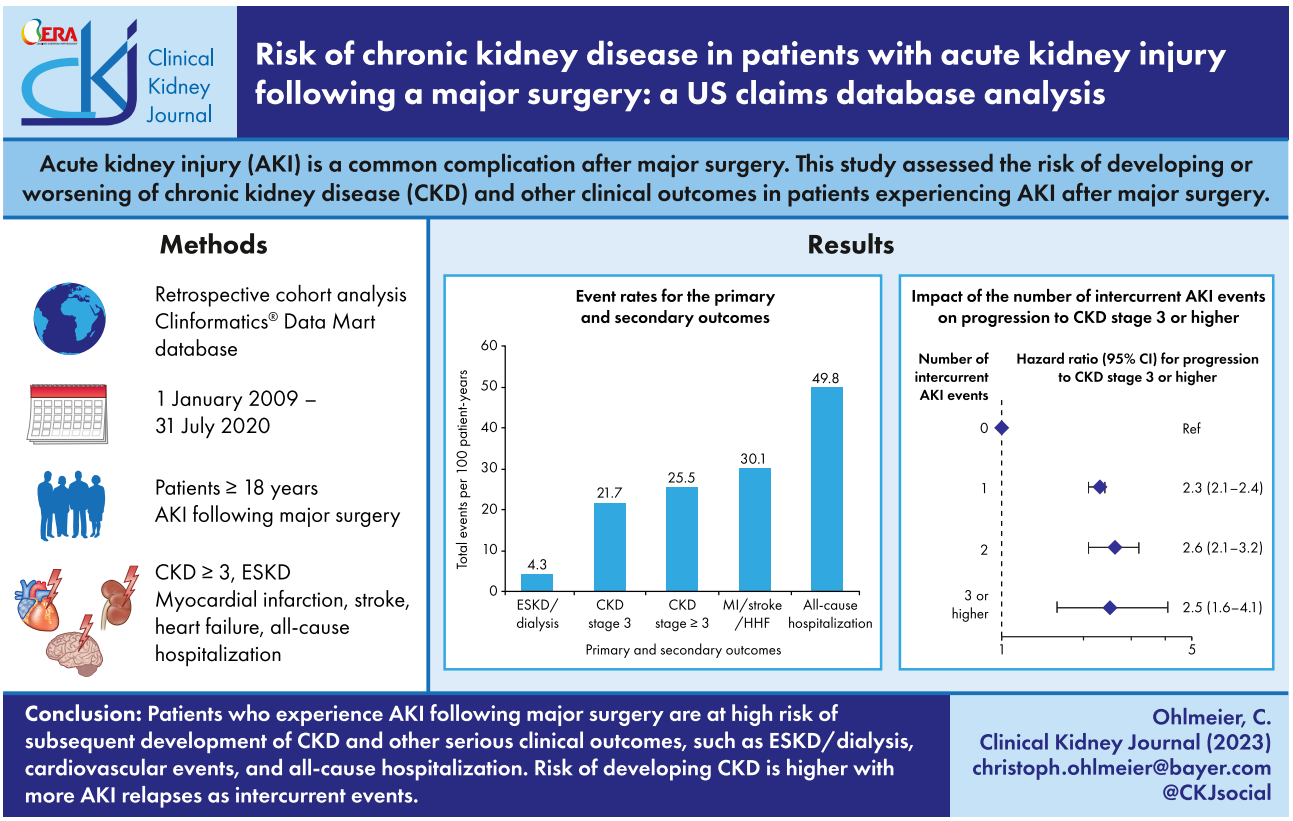
patients to study these health outcomes using insurance claims. Our research showed that patients who experienced AKI after a serious surgery are at high risk of getting moderate–severe CKD or worsening of their pre-existing CKD. Furthermore, the risk of other side effects, such as having a heart attack or stroke, was also high in these patients.

GRAPHICAL ABSTRACT



Keywords: acute kidney injury, chronic kidney disease, end-stage kidney disease, heart failure, major surgery

INTRODUCTION

Acute kidney injury (AKI) is characterized by an abrupt decrease in kidney function resulting in increased serum creatine (SCr) and decreased urine output [1]. While a variety of factors increase the risk for AKI [2], AKI is a common complication among patients undergoing major surgery, with ≈30–40% of AKI cases during hospitalization occurring in operative settings [3]. AKI is associated with substantial short- and long-term morbidity and mortality, with consequences including longer hospital stays, higher readmission rates, higher inpatient mortality and higher 1-year mortality than patients without AKI after major surgery [4].

Almost one-third of patients suffering AKI during hospitalization develop chronic kidney disease (CKD) within 1 year, even with the mildest forms of AKI and after full recovery [5]. The AKI recovery outcome (i.e. no recovery, partial recovery, relapse or recurrence) is a predictor for developing CKD and other long-term outcomes (e.g. hospital readmission, cardiovascular events, death) [6]. Patients with AKI have been reported to have a higher risk for developing CKD, end-stage kidney disease (ESKD) and premature mortality regardless of the cause of AKI [5, 7, 8]. In patients with existing CKD, AKI has been found to accelerate the progression of kidney damage to ESKD [7, 8].

AKI and CKD are risk factors for cardiovascular events, manifesting as heart failure (HF), stroke and myocardial infarction (MI) [7, 9, 10]. Because AKI prevalence is high in patients after major surgery and AKI increases the risk for CKD development or progression, further understanding of CKD and cardiovascular disease burden in patients with AKI is important to implement strategies preventing the onset, or worsening, of CKD after AKI [4]. To generate evidence on interdependencies between AKI, its relapses and subsequent clinical events in patients after major surgery as treated in routine clinical practice, a real-world evidence study using one of the largest administrative claims databases in the USA was conducted. The primary objective of this study was to investigate the risk of developing or progressing to CKD stage ≥3 in patients experiencing AKI following a major surgery. Other objectives were to describe patient characteristics to evaluate the influence of AKI relapse on the risk of clinical events such as CKD stage ≥3 and to evaluate the impact

of intercurrent CKD on hospitalization for HF (HHF) to further investigate the cardiorenal continuum in patients with cardiovascular or kidney diseases.

MATERIALS AND METHODS

Data source

This study used Optum's de-identified Clinformatics Data Mart (CDM) database, a database of administrative US claims. Optum's CDM is one of the largest population-based commercial health plans and Medicare Advantage claims databases in the USA and includes patient demographics, enrolment, laboratory results, physician facility and pharmacy claims, as well as inpatient data. It comprises a representative diverse population in terms of US regions as well as age and gender, with service dates from January 2007 to present.

Study design

This retrospective, observational, real-world evidence study was based on longitudinal patient-level data from Optum's CDM from 1 January 2009 to 30 June 2020 (Supplementary Fig. S1). All patients in the database who met selection criteria were included (Fig. 1). The population comprised patients ≥18 years of age at the first inpatient AKI event (i.e. index event) following a major surgery (maximum 30 days back from index) between 1 July 2009 and 30 June 2020. AKI events were identified based on the presence of the International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM) code 584/N17 for 'acute kidney failure'. Patients were required to have ≥180 days of continuous insurance coverage prior to the AKI index event (i.e. baseline period). Major surgeries included coronary artery bypass graft, valve replacement and laparotomy with small or large bowel restriction defined using the ICD-9-CM/10-CM Procedure Coding System (PCS) and Current Procedural Terminology-4 (CPT-4)/Healthcare Common PCS (HCPCS) procedure codes. At least one of the surgical codes had to be found on the inpatient claims in the primary or secondary positions during a 30-day period before the index AKI event.

Patients with CKD stage ≥3 or who required dialysis in the baseline period before the major surgery were excluded from the analysis, as were patients who had ESKD, experienced kidney failure or received a kidney transplant before the index AKI event (Fig. 1). Patient baseline characteristics (e.g. age, gender, comorbidities, concomitant medications, laboratory values) were assessed from the claims data closest to the index date within the 180-day baseline period. The Charlson–Deyo Comorbidity Index [11, 12], a measure of patient mortality risk based on 17 clinical conditions, ranging from 0 (no comorbidities) to 29 (maximal disease burden), was calculated. All the respective variables were defined using the ICD-9-CM/ICD-10-CM diagnosis and procedure codes, CPT-4/HCPCS procedure codes, National Drug Code numbers for medications and Logical Observation Identifiers Names and Codes for lab data.

Outcome measures

The primary outcome was CKD stage ≥3 (including ESKD), defined as either new onset or as a worsening of pre-existing CKD. The occurrence of a CKD-qualifying event, denoted by either an estimated glomerular filtration rate (eGFR) of category G3a (<60 ml/min/1.73 m^2) to G5 (<15 ml/min/1.73 m^2), ICD-9-CM/10-CM code for CKD stages 3–5 or ESKD, was used to identify CKD stage ≥3. A second CKD-qualifying event was required between 90 and 365 days of the initial CKD-qualifying event for confirmation. Secondary outcomes included HHF, MI, haemorrhagic or ischaemic stroke, all-cause hospitalization, ESKD, need for dialysis or kidney transplant and composites of MI/stroke/HHF and ESKD/need for dialysis. Regarding HHF, two cohorts were created: patients with (prevalent) and without (incident) an HF diagnosis prior to the index AKI event.

The current analysis was focused on mid- to long-term outcomes (up to 3 years) following AKI after major surgery. Furthermore, to avoid misclassification between AKI following major surgery and CKD onset, a 90-day washout period after the AKI event was introduced to allow for renal recovery, which is consistent with similar published studies [13, 14]. Events that occurred within these 90 days may have provided a key burden of events post-surgery but were beyond the focus of the study. Clinical outcomes were assessed during the follow-up period starting from 91 days after the index AKI event until the maximum period of 3 years, a clinical outcome of interest, the end of data availability, disenrollment, death or the study end, whichever occurred first. An intercurrent event was defined as an event that occurs after a given index event, i.e. after the first AKI, and either precluded a clinical outcome of interest or affected its interpretation. Two intercurrent event analyses were performed. The primary intercurrent event analysis investigated the impact of AKI relapses as intercurrent events on the clinical outcome of CKD stage ≥3. The secondary intercurrent event analysis investigated the impact of intercurrent events of CKD stage ≥3 on the risk for HHF.

Statistical analyses

Statistical analyses were descriptive in nature and performed for generation of hypotheses only. Baseline patient characteristics were described by presenting frequency distributions and basic summary statistics for the study cohort. The incidence rate was defined as the total number of events per 100 patient-years (PY) of follow-up. Primary and secondary outcomes were analysed by time-to-first-event methods (Kaplan–Meier). The analysis of a potential effect of the intercurrent event on clinical outcomes was performed using the Cox proportional hazards regression model.

RESULTS

Study population

A total of 92 629 patients were identified as having an AKI event following major surgery. Of these, 41 134 patients met the selection criteria and were included in the final cohort. Outcomes were analysed for 31 252 patients (76.2% of the final cohort), with 9882 patients lost due to death or end of enrolment during the washout period (Fig. 1). The mean follow-up time for the study cohort was 1.4 years [interquartile range (IQR) 0.3–2.8 years].

Baseline characteristics

Demographic and clinical characteristics, including comorbidities, medications and major surgery type are presented in Table 1. In this analysis cohort (N = 31 252), 11 895 (38.1%) patients were female and the median age was 72.0 years (IQR 64.0–79.0). The median eGFR and urine albumin:creatinine ratio (UACR) were 65.0 ml/min/1.73 m^2 and 25.5 mg/g, respectively. At baseline, hypertension (78.9%), hyperlipidaemia (60.0%) and

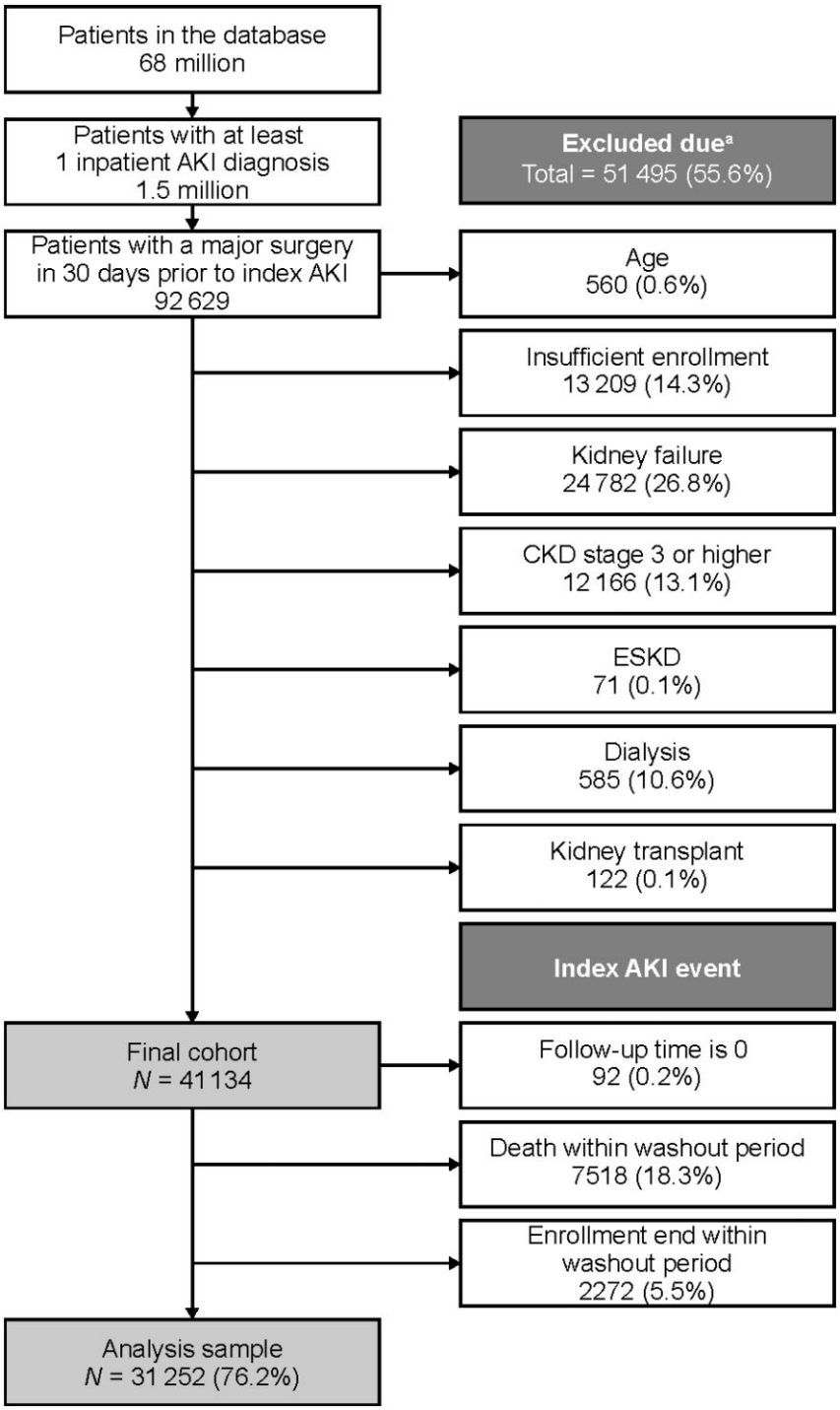


Figure 1: Patient flowchart: identification and attrition of the study patient cohort sample. [a]Enrolment end within washout period indicates that patients were no longer in the database due to a change of insurance company.

coronary artery disease (47.3%) were the most frequently observed comorbidities (full comorbidity data are available in Supplementary Table S1). The median Charlson–Deyo Comorbidity Index score was 2.0 (IQR 1.0–4.0). Coronary artery bypass graft (22.6%) and extracorporeal circulation auxiliary to open heart surgery (22.0%) were the most frequent major surgeries prior to AKI (Supplementary Table S2). Most common baseline medications were statins (43.6%) and beta-blockers (40.5%) (full medication data are available in Supplementary Table S3). An analysis of eGFR values showed that eGFR decreased sharply immediately after the AKI event and settled thereafter at a slightly lower level than in the baseline period (Fig. 2).

Table 1: Demographic: and clinical characteristics of the patient cohort at baseline

Characteristics	Study cohort ($N = 31\,252$)	
	Mean (SD)	Median (IQR)
Age, years	70.7 (11.4)	72.0 (64.0–79.0)
Sex, *n* (%)		
Female		11 895 (38.1)
Unknown		7 (0.02)
Race, *n* (%)		
White		21 519 (68.9)
Black		3824 (12.2)
Hispanic		2322 (7.4)
Asian		586 (1.9)
Unknown		3001 (9.6)
Baseline eGFR (ml/min/1.73 m^2)	66.7 (20.9) ($n = 6029$)	65.0 (52.0–81.0) ($n = 6029$)
Baseline UACR (mg/g)	273.0 (825.7) ($n = 1106$)	25.5 (7.8–116.1) ($n = 1106$)
<30	10.0 (8.3) ($n = 587$)	8.6 (3.1–15.4) ($n = 587$)
30–<300	99.3 (69.3) ($n = 354$)	74.2 (44.0–129.6) ($n = 354$)
≥300	1581 (1596.2) ($n = 165$)	934.3 (504.6–1931.1) ($n = 165$)
Baseline serum creatinine (mg/dl)	1.1 (0.4) ($n = 8439$)	1.1 (0.9–1.3) ($n = 8439$)
HbA1c (%)	7.0 (1.6) ($n = 4517$)	6.5 (5.8–7.7) ($n = 4517$)
Serum potassium (mmol/l)	4.5 (0.5) ($n = 7912$)	4.4 (4.1–4.7) ($n = 7912$)
Presence of comorbidities at baseline,[a] *n* (%)		
Charlson–Deyo Comorbidity Index	2.6 (2.2)	2.0 (1.0–4.0)
Hypertension		24 644 (78.9)
Hyperlipidaemia		18 765 (60.0)
CAD		14 778 (47.3)
Diabetes		12 370 (39.6)
Heart failure		8359 (26.7)
Pulmonary disease		7489 (24.0)
Anaemia		6859 (21.9)
Peripheral arterial disease		6721 (21.5)
Vascular disease		6379 (20.4)
Atrial fibrillation		6376 (20.4)
Concomitant medications at baseline,[a] *n* (%)		
Statins		13 636 (43.6)
Beta-blockers		12 657 (40.5)
ACE inhibitors		9210 (29.5)
Antidepressants		6522 (20.9)
Thiazide diuretics		6518 (20.9)
Calcium channel blockers		5701 (18.2)
ARB therapy		5607 (17.9)
Loop diuretics		5438 (17.4)
Biguanides		4811 (15.4)
Antiplatelet therapies		4285 (13.7)
Type of major surgery,[a] *n* (%)		
Coronary artery bypass graft		9908 (31.7)
Extracorporeal circulation auxiliary to open heart surgery		9673 (31.0)
Hip replacement		6390 (20.4)
Heart valve procedures		6113 (19.6)
Small bowel resection		2965 (9.5)
Endarterectomy lower limbs		1816 (5.8)
Peripheral vascular bypass		1758 (5.6)
Aortic resection		1186 (3.8)
Endarterectomy head and neck		1173 (3.8)
Gastrectomy		1042 (3.3)

[a]Most frequent is defined by the top 10 frequencies.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; HbA1c, glycated haemoglobin; SD, standard deviation.

Outcomes

Primary outcome

Of 31 252 patients available for outcomes analyses, the primary clinical outcome of CKD stage ≥3 was observed in 9319, with an incidence rate of 25.5/100 PY (Table 2). The 3-year cumulative risk of CKD stage ≥3 was 41.2%, with a risk of 15.5% during the first 6 months of the outcome assessment period (Fig. 3). Of those meeting the criteria for the primary outcome, 1084 patients were diagnosed with CKD stage ≥4 at the first instance post-AKI

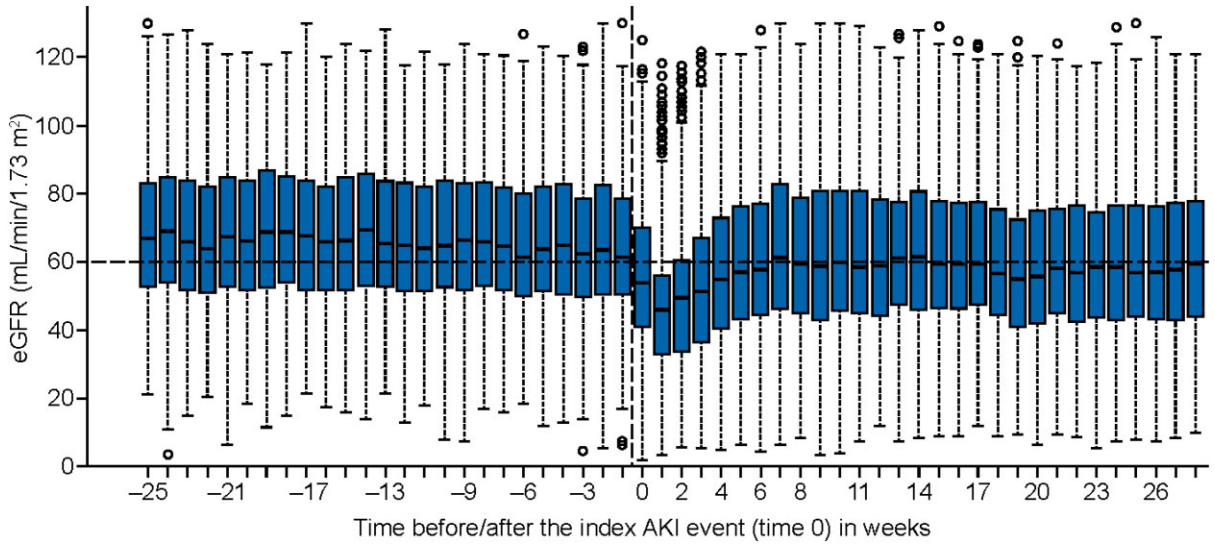


Figure 2: Time course of eGFR within the index AKI event.

Table 2: Summary of the incidence rate and cumulative risk values for the primary and secondary outcomes

Outcomes	*n*/*N* (%)	Incidence (risk per 100 PY)	Cumulative risk at 180 days (%)	Cumulative risk at 1 year (%)	Cumulative risk at 2 years (%)	Cumulative risk at 3 years (%)
Primary						
CKD stage ≥3	9319/31 252 (29.8)	25.5	15.5	23.6	33.7	41.2
Cardiovascular						
MI	3160/31 252 (10.1)	6.9	4.8	7.5	11.2	14.4
Stroke	3895/31 252 (12.5)	8.7	5.6	9.2	14.0	17.7
Kidney						
ESKD	1469/31 252 (4.7)	3.1	2.5	3.5	5.0	6.6
Need for dialysis	1412/31 252 (4.5)	3.0	2.4	3.6	4.9	6.2
Kidney transplant	29/31 252 (0.1)	0.1	0.03	0.05	0.11	0.15
CKD stage 3 alone	8235/31 252 (26.4)	21.7	12.5	20.3	30.1	37.5
Hospitalization						
All-cause hospitalization	15 556/31 252 (49.8)	49.8	23.9	38.3	53.9	64.2
Incident HHF[a]	1698/15 807 (10.7)	7.0	2.4	5.8	11.2	17.0
Prevalent HHF[b]	5979/15 445 (38.7)	35.1	18.8	30.2	43.0	51.7
Composite						
MI/stroke/HHF	11 069/31 252 (35.4)	30.1	17.5	27.3	38.6	46.9
ESKD/need for dialysis	2043/31 252 (6.5)	4.3	3.4	4.9	7.1	9.1

[a]HF in patients without HF diagnoses in the pre-index period.
[b]HF in patients with HF diagnoses in the pre-index period.

following major surgery, accounting for 11.6% of primary outcomes. The risk for the primary outcome was highest in patients with a major vascular surgery prior to the AKI event (Supplementary Fig. S2a).

Secondary kidney outcomes

The number of patients developing ESKD and needing dialysis during follow-up was 1469 (incidence rate 3.1 events/100 PY) and 1412 (3.0 events/100 PY), respectively. Twenty-nine patients received a kidney transplant, with an incidence rate of 0.1 events/100 PY. The 3-year cumulative risks of ESKD, need for dialysis and kidney transplant were 6.6%, 6.2% and 0.15%, respectively (Fig. 4; Supplementary Table S3). The risk for the secondary kidney outcomes was highest in patients with a major vascular surgery prior to the AKI event (Supplementary Fig. S2g–i).

Secondary cardiovascular outcomes

A total of 3160 patients experienced MI, with an incidence rate of 6.9 events/100 PY. Additionally, 3895 patients experienced a stroke (incidence rate 8.7 events/100 PY). The 3-year cumulative risks of MI and stroke were 14.4% and 17.7%, respectively, with the highest risk observed in the first 6 months of the follow-up period (4.8% and 5.6%, respectively) (Fig. 4; Table 2). The risk of MI or stroke was highest in patients with a major vascular

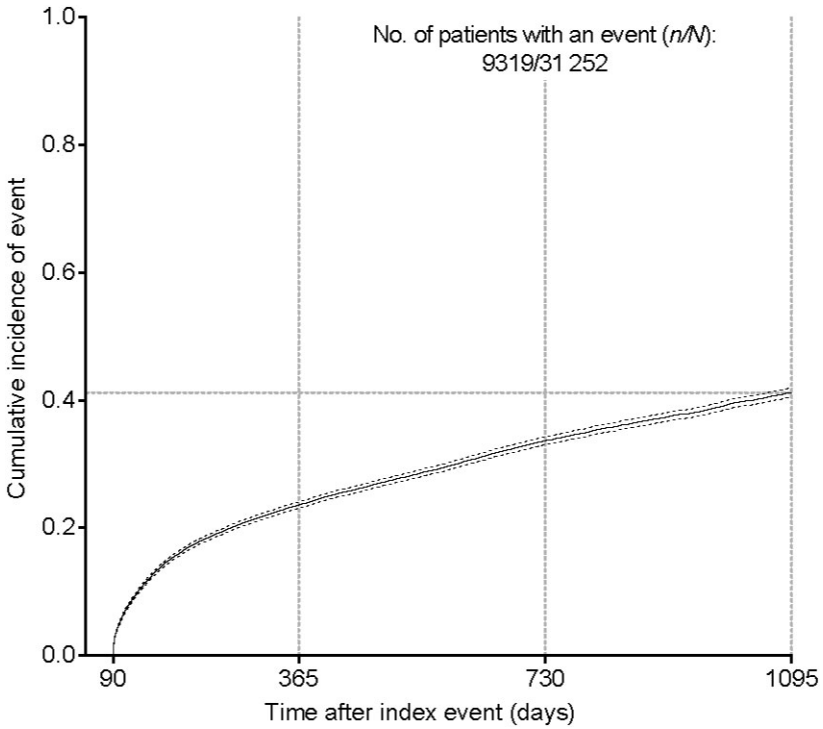


Figure 3: Cumulative incidence for the primary outcome: CKD stage ≥3.

or major cardiac surgery prior to the AKI event (Supplementary Fig. S2d, e).

Secondary hospitalization outcomes

In total, 15 566 patients were hospitalized during the follow-up period (incidence rate 49.8 events/100 PY). The 3-year cumulative risk of all-cause hospitalization was 64.2%, with a risk of 23.9% during the during the first 6 months of the outcome assessment period. Furthermore, 7677 patients experienced HHF (described independently of patients' HF diagnosis at baseline). A total of 1698 patients experienced incident HHF (without prior HF diagnosis), with a 3-year cumulative risk of 17.0%. A total of 5979 patients experienced prevalent HHF (with prior HF diagnosis). The 3-year cumulative risk was 51.7%, with an increased risk particularly in the first 6 months after index (18.8%) (Fig. 4; Table 2). The risk of secondary hospitalization outcomes was highest in patients with a major vascular surgery prior to the AKI event (Supplementary Fig. S2b, c, f).

Intercurrent event analyses

Intercurrent events were assessed to understand their impact on primary and secondary outcomes. Patients with one {hazard ratio [HR] 2.3 [95% confidence interval (CI) 2.1–2.4]}, two [HR 2.6 (95% CI 2.1–3.2)] or three or more [HR 2.5 (95% CI 1.6–4.1)] AKI relapses were more likely to develop CKD stage ≥3 compared with patients having no AKI relapse. Patients who developed CKD stage ≥3 post-index had a 2-fold increased risk of HHF [HR 2.0 (95% CI 1.9–2.1)] compared with patients without an intercurrent CKD stage ≥3 event.

DISCUSSION

This study indicated that patients experiencing AKI following major surgery are at high risk of developing CKD stage ≥3. Of these, the vast majority were classified as CKD stage 3, which occurred in the first 6 months of the outcome assessment period (≥3 months after AKI). The burden of hospitalizations was high during the post-surgical follow-up period, with a 3-year cumulative risk of 64.2%. The cumulative risks for developing ESKD, need for dialysis and kidney transplant were 6.6%, 6.2%, and 0.15%, respectively. The risk of cardiovascular and renal outcomes was highest in AKI patients with a prior cardiac or vascular surgery. AKI relapses increased the risk of developing CKD stage ≥3 and the intercurrent event of developing CKD stage ≥3 doubled the risk of HHF.

Our findings show a high cardiorenal disease burden following AKI after major surgery, which is in line with previous studies [15–17]. An observational study of an ambulatory CKD cohort revealed the median eGFR decrease over a 5-year period was significantly higher among patients with AKI compared with those without AKI (22 versus 6 ml/min/1.73 m^2) [15]. Furthermore, multiple studies have shown that AKI is associated with increases in both short-term and long-term re-hospitalization [18, 19] and that cumulative AKI events are associated with an increased risk of progressive disease [18, 20]. An analysis of patient data from the Salford Kidney Study revealed that a second AKI was two times more likely to be stage 2 or 3 compared with stage 1 among patients with AKI, representing 28.1% of patients over a median follow-up of 2.6 years [16].

Risk for ESKD and need for dialysis and kidney transplant were lower in this study than in others [7, 21]. A systematic review and meta-analysis reported a pooled incidence of

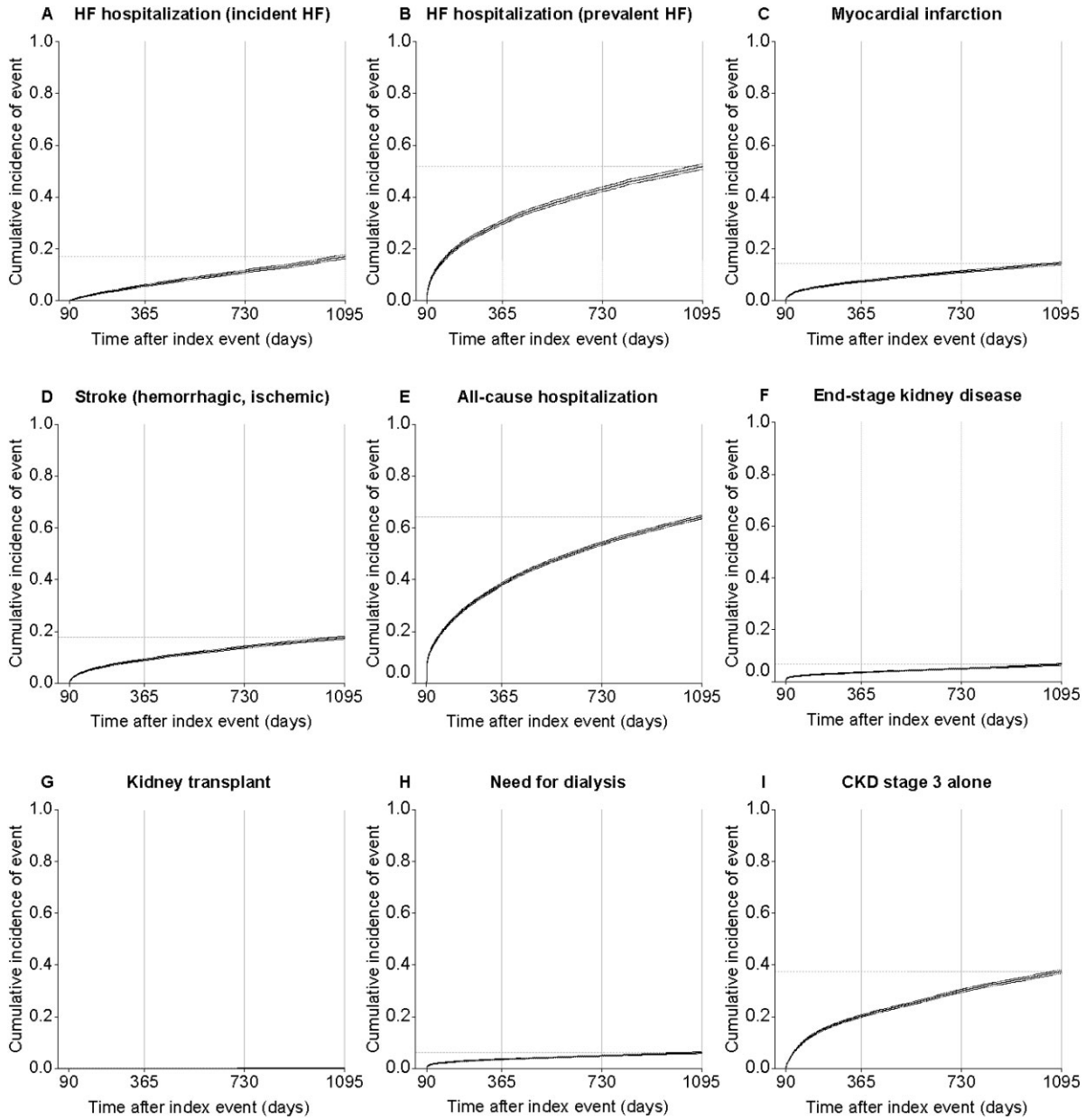


Figure 4: Cumulative incidence for the secondary outcomes.

8.6/100 PY for development of ESKD following AKI [7]. Given that CKD is a more gradual decline of kidney function and the speed of progression can be impacted by multiple factors [17, 22], the lower risk observed in this analysis may be explained by differences in demographics and disease characteristics (patients with CKD stage ≥3 at baseline were excluded) or by a comparatively shorter follow-up time (mean of 1.4 years versus 2 years), with analysis potentially ending before these outcomes occurred. In a large population of adults having an eGFR of 30–59 ml/min/1.73 m^2, accelerated progression of kidney dysfunction within 2 years affected one in four patients with diabetes and one in seven without diabetes [22]. In this study, 39.6% of patients had diabetes; however, results were not stratified by diabetic status.

Prior studies have shown that the risk for CKD following AKI is increased by pre-existing proteinuria and increased UACR, as well as by decreased baseline eGFR [23–25]. This is relevant to the current study, because some patients in the sample had an eGFR <60 ml/min/1.73 m^2 prior and very close to the date of major surgery and the subsequent AKI event without being diagnosed as CKD stage ≥3. This timing could be explained by undiagnosed CKD, temporal eGFR decline or the first signs of an AKI. Although eGFR appeared to recover during the post-AKI period, it did not reach the level of the pre-AKI period in the overall study cohort, indicating potential development of CKD shortly after AKI in some patients. Regarding UACR, the number of measurements in the baseline period was low and no analyses in the follow-up period were conducted. Low availability of UACR data indicates that this lab test is rarely performed in routine clinical practice, even in patients undergoing serious surgical procedures. This finding confirms the previously identified lack of UACR measurements in routine clinical care [26], despite UACR

assessment being recommended in high-risk CKD patients [27]. However, the commonly observed comorbidities in the patient sample, such as hypertension, coronary artery disease and diabetes, may serve as indicators of increased albuminuria among those patients not having measurements at baseline. In a previous study, patients with severely increased albuminuria had the highest burden of disease, with comorbidities such as diabetes and cardiovascular diseases being more prevalent with increasing albuminuria severity [28].

Evidence from our study also points toward a frequently occurring need for hospitalizations, with a 24% risk of all-cause hospitalization and 19% risk of HHF within the first 6 months after an AKI event. These findings are consistent with an increased risk of hospitalization among patients with CKD in the general population, with most of these hospitalizations due to cardiovascular causes [29]. Because AKI occurrence has been associated with increased hospital costs and a substantial economic burden [30–32], our findings add to an evidence base that highlights the need for novel therapies to prevent and manage AKI where no standard of care exists, as well as its consequences, and thereby reduce the long-term cardiorenal disease burden in patients who experience AKI.

STRENGTHS AND LIMITATIONS

The main strength of this study is the use of one of the largest population-based claims databases from a commercial health plan and Medicare Advantage spanning all 50 states in the USA. Individuals enrolled in the Optum's CDM are largely representative of the insured US population in terms of age, sex and region. While Optum's CDM is only based on data from a single payer and reimbursement of drugs varies across payers, generalizability of the results of this study to the entire US population should be considered acceptable.

Certain limitations of this study are relative to the data source or the nature of the study. Optum CDM laboratory data are collected from several large lab vendors and available for only a fraction (≈30%) of database members, as is common in many claims databases. Nonetheless, there is no reason to believe that selection bias is of concern, as participation of labs in the Optum CDM database is assumed to be random. Due to the mentioned restriction of lab data availability, only 26.6% of patients had SCr recorded at baseline [1]. Furthermore, only 18.8% of patients had eGFR recorded and 3.4% of patients had UACR recorded despite eGFR and UACR assessment being recommended in high-risk patients, such as those with CKD or diabetes [27].

It is known that the identification of AKI based on ICD codes from real-world evidence leads to underestimation of the true AKI burden [33]. While these findings do not limit the interpretation of results in this study population, our results may not be fully generalizable to a broader population of AKI patients without documented ICD codes and thus potentially AKI of lower severity.

The washout period was essential to generate meaningful conclusions regarding study objectives. Otherwise, results would be dominated by clinical outcomes occurring in the first 90 days, which may be directly linked to a patient's medical condition after index AKI following major surgery rather than representing long-term cardiorenal disease burden. Nevertheless, introduction of the washout period might have led to an underestimation of the cardiorenal disease burden and overestimation of the time to clinical outcomes. Additionally, the washout period might have led to an underestimation of the impact of AKI relapses on the risk for CKD stage ≥3, because missed AKI relapses might have resulted in inaccurate classification of the number of AKI relapses, leading to a diluted effect estimate.

For patients with more than one documented continuous value at baseline, e.g. lab values, the most current value was used. Due to variation, a single value can be an outlier and could lead to misclassification of baseline characteristics. In addition, characteristics documented only before the baseline period can lead to an underestimation of the comorbidity burden.

CONCLUSION

In summary, this contemporary study demonstrates that patients experiencing AKI following major surgery are at high risk of subsequent moderate–severe CKD development or progression, MI, stroke, HHF and other clinical outcomes. Given that cardiorenal diseases represent a major global concern with a significant health and economic burden alongside the frequent occurrence of AKI in patients undergoing major surgery, the findings point toward a high unmet medical need in this patient population. Early intervention and innovative therapies with cardiorenal protective effects are needed to mediate the development or progression of CKD and other clinical outcomes following AKI after major surgery, as well as AKI relapses.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Data analyses were performed by C.B. All authors contributed to the study conception and design and preparation and review of the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing underlying the findings described in this manuscript is in accordance with Bayer AG data sharing policy described at link: https://clinicaltrials.bayer.com/transparency-policy/. The details can be obtained from the corresponding author upon reasonable request. However, restrictions apply to these data, which were received from Optum® and used under license to Bayer AG for the current study by a third party. These data are not publicly available. For any questions, please contact Optum, Inc.

CONFLICT OF INTEREST STATEMENT

C.O. is an employee of Bayer AG, Berlin, Germany. J.S. and C.B. are employees of MicroDiscovery GmbH, Berlin, Germany. S.X.K. is an employee of Bayer Pharmaceuticals, Whippany, NJ, USA. C.S. is a full-time employee of Bayer PLC, Data Science and Analytics, UK. M.B. is an employee of Bayer AG, Wuppertal, Germany. TV is an employee of Bayer AG, Berlin, Germany.

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