

## CARDIOVASCULAR

## Intraoperative hypotension is associated with persistent acute kidney disease after noncardiac surgery: a multicentre cohort study

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### Abstract

**Background:** Whilst intraoperative hypotension is associated with postoperative acute kidney injury (AKI), the link between intraoperative hypotension and acute kidney disease (AKD), defined as continuing renal dysfunction for up to 3 months after exposure, has not yet been studied.

**Methods:** We conducted a retrospective multicentre cohort study using data from noncardiac, non-obstetric surgery extracted from a US electronic health records database. Primary outcome was the association between intraoperative hypotension, at three MAP thresholds ( $\leq 75$ ,  $\leq 65$ , and  $\leq 55$  mm Hg), and the following two AKD subtypes: (i) *persistent* (initial AKI incidence within 7 days of surgery, with continuation between 8 and 90 days post-surgery) and (ii) *delayed* (renal impairment without AKI within 7 days, with AKI occurring between 8 and 90 days post-surgery). Secondary outcomes included healthcare resource utilisation for patients with either AKD subtype or no AKD.

**Results:** A total of 112 912 surgeries qualified for the study. We observed a rate of 2.2% for delayed AKD and 0.6% for persistent AKD. Intraoperative hypotension was significantly associated with persistent AKD at MAP  $\leq 55$  mm Hg (hazard ratio 1.1; 95% confidence interval: 1.38–1.22;  $P < 0.004$ ). However, IOH was not significantly associated with delayed AKD across any of the MAP thresholds. Patients with delayed or persistent AKD had higher healthcare resource utilisation across both hospital and intensive care admissions, compared with patients with no AKD.

**Conclusions:** Intraoperative hypotension is associated with persistent but not delayed acute kidney disease. Both types of acute kidney disease appear to be associated with increased healthcare utilisation. Correction of intraoperative hypotension is a potential opportunity to decrease postoperative kidney injury and associated costs.

**Keywords:** acute kidney disease; acute kidney injury; electronic health record database; healthcare resource utilisation; intraoperative hypotension; mean arterial pressure; noncardiac surgery

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**Editor's key points**

- The threshold and duration of hypotension that can be tolerated intraoperatively are unclear.
- Clinically important hypotension can be expected to increase the risk of acute kidney injury.
- This study interrogated a large national data set to identify the association between intraoperative hypotension (different thresholds) and kidney disease.
- Mean arterial pressure  $\leq 55$  mm Hg was associated with persistent kidney injury.

Perioperative acute kidney injury (AKI) is commonly observed in patients undergoing surgery. It occurs in 6.3–13.4% of patients undergoing major noncardiac surgery,<sup>1–3</sup> and it is a major cause of morbidity and mortality.<sup>4,5</sup> Complications from AKI occur in 1% of these cases, associated with an eight-fold increase in all-cause mortality.<sup>6,7</sup> In addition, AKI is associated with increases in healthcare resource utilisation (HCRU), including hospital and PACU length of stay (LOS), and associated costs.<sup>8,9</sup>

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines proposed a new term, acute kidney disease (AKD), to help integrate the more established concepts of AKI and chronic kidney disease (CKD).<sup>10,11</sup> They defined AKD as any acute condition impacting kidney function, including AKI, glomerular filtration rate (GFR)  $< 60$  ml min<sup>-1</sup> (1.73 m)<sup>-2</sup>, decrease in GFR by  $\geq 35\%$ , increase in serum creatinine (SCr) of  $> 50\%$ , or any kidney damage for  $< 3$  months.<sup>10</sup> The Acute Dialysis Quality Initiative (ADQI) Workgroup further refined the definition of AKD to include acute or subacute damage or loss of kidney function for a duration of 7–90 days after exposure to an AKI-initiating event.<sup>12</sup>

AKI and CKD are both well characterised, and the link between them is well established.<sup>13,14</sup> However, to date, AKD has not been well defined in surgical populations, despite the fact that it is increasingly recognised that AKI, AKD, and CKD represent a continuum of disease, with AKD representing the progression of ongoing renal dysfunction after AKI.<sup>10,12,15</sup> Whilst some previous studies have examined AKD and its associated HCRU in noncardiac surgical populations, these studies are either restricted to one surgical type,<sup>16–18</sup> include only AKD without AKI,<sup>19</sup> or do not use KDIGO definitions of AKI/AKD.<sup>20</sup>

Given that AKD represents a critical transition period for patients, in which they can benefit from timely follow-up care and individualised drug management,<sup>10,21–23</sup> there is a need to study its epidemiology, risk factors, and disease burden.

Intraoperative hypotension (IOH) occurs frequently during noncardiac surgery<sup>24,25</sup> and is associated with several adverse postoperative outcomes, including increased odds of AKI (odds ratio: 1.05–1.35; P-value  $< 0.001$ ).<sup>25–28</sup> Understanding the relationship of AKD with the surgical insult and underlying aetiological factors may help identify opportunities to optimise care and resources.

Therefore, we hypothesised that IOH might be associated with the development of AKD after surgery, and we designed this study to evaluate the relationship between IOH and AKD in a population of patients undergoing noncardiac, non-obstetric surgery. We further hypothesised that AKD that develops early and persists longer than 7 days after surgery might have a different course than AKD that develops later.

Specifically, we studied the following two AKD subtypes as a primary outcome: (i) persistent AKD (onset within 7 days of surgery and persistence beyond 7 days up to 90 days) and (ii) delayed AKD (onset 8–90 days after surgery). The goal of this study was to use retrospective cohort analysis to examine whether IOH is associated with the two subtypes of AKD (persistent and delayed). In addition, HCRU associated with both AKD subtypes was analysed as a secondary outcome to better understand the disease burden.

**Methods****Data source**

We used electronic health records from the Optum® database to conduct this analysis. This database provides de-identified patient information, including medications, clinical events, laboratory tests, diagnoses, and procedures, from ambulatory and inpatient settings of more than 2000 hospitals and 7000 clinics. The Western Institutional Review Board (Puyallup, WA, USA) deemed this study exempt from further review, as it did not meet the definition of human subject research as per 45 Code of Federal Regulations 46.102. This report has been prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

**Study cohort**

The original cohort comprised 368 222 patients who underwent noncardiac and non-obstetric surgeries between January 1, 2008 and December 31, 2017, with  $\geq 10$  min of MAP recordings at  $\leq 5$  min intervals between readings (allowing for no more than two 5–10 min gaps between MAP readings) and had  $\geq 1$  yr of pre- and post-surgical records available.<sup>25</sup> To arrive at the final cohort for this analysis, we excluded patients if they (i) had no SCr readings in the 7 days before surgery (baseline SCr) or had baseline SCr  $> 4.0$  mg dl<sup>-1</sup>, (ii) had no SCr readings in the 7 days after surgery, (iii) had an International Classification of Diseases (ICD) 9/10 code for AKI or dialysis in the 30 days before surgery (Supplementary Table S1), (iv) were  $< 18$  yr of age at admission, or (v) had postoperative AKI only (i.e. AKI did not continue after Day 7, where Day 0 is the day of surgery).

**Outcomes**

The ADQI criteria state that AKI after a 7 day period can be considered as AKD.<sup>12</sup> We defined the following two subtypes of AKD as primary outcomes: (i) *delayed* AKD defined as AKD with delayed onset after 7 days post-surgery and (ii) *persistent* AKD defined as AKI that extended after 7 days post-surgery. We utilised KDIGO guidelines<sup>10</sup> to outline AKI criteria: (i) SCr increase by  $\geq 0.3$  mg dl<sup>-1</sup> within 48 h, (ii) SCr increase to  $\geq 1.5$  times of baseline, (iii) SCr increase to  $\geq 4.0$  mg dl<sup>-1</sup> with baseline SCr  $< 4.0$  mg dl<sup>-1</sup>, or (iv) initiation of dialysis/continuous renal replacement therapy (CRRT) defined by ICD 9/10 and Current Procedural Terminology (CPT) codes (Supplementary Table S1). We identified patients as having delayed AKD if they satisfied any AKI criteria at least once between 8 and 90 days after surgery, and they exhibited renal impairment but not AKI in the first 7 days postoperatively, evaluated based on SCr above baseline but below AKI thresholds. We identified patients with persistent AKD if they met AKI criteria within the first 7 days, and there was evidence of continuation between 8 and 90 days after surgery (Fig. 1a).<sup>12,29</sup>

**Table 1** Patient characteristics. Because of rounding, categories will not always add to 100%. SD, standard deviation. \*Four years were combined because of small sample size in 2008 and 2009. IOH, intraoperative hypotension.

Patient characteristics	Overall (n=112 912)	IOH ≤55 mm Hg (n=7948)	IOH ≤65 mm Hg (n=20 740)	IOH ≤75 mm Hg (n=42 595)
Sex, n (%)				
Male	44 560 (39.5)	3029 (38.1)	7682 (37.0)	15 453 (36.4)
Female	68 352 (60.5)	4919 (61.9)	13 058 (63.0)	27 142 (63.9)
Race, n (%)				
White	93 902 (83.2)	6678 (84.0)	17 563 (84.7)	36 299 (85.4)
Black	9420 (8.3)	478 (6.0)	1241 (6.0)	2605 (6.1)
Asian	795 (0.7)	128 (1.6)	258 (1.2)	408 (1.0)
Other	8795 (7.8)	664 (8.4)	1678 (8.1)	3283 (7.7)
Age (yr), mean [SD]	61.8 [16.1]	62.4 [16.6]	62.7 [16.3]	62.5 [16.2]
Zip-3 level median household income in \$, n (%)				
0th–24th percentile	30 109 (26.7)	1167 (14.7)	4087 (19.7)	10 280 (24.2)
25th–49th percentile	28 152 (24.9)	1604 (20.2)	4751 (22.9)	10 267 (24.2)
50th–74th percentile	26 369 (23.4)	3527 (44.4)	7202 (34.7)	11 961 (28.1)
75th–100th percentile	25 430 (22.5)	1484 (18.7)	4231 (20.4)	9031 (21.3)
Region, n (%)				
Midwest	50 963 (45.1)	3571 (44.9)	9019 (43.5)	18 567 (43.7)
North	1675 (1.5)	310 (3.9)	726 (3.5)	1082 (2.5)
South	47 813 (42.3)	1160 (14.6)	5150 (24.8)	14 667 (34.5)
West	9759 (8.6)	2745 (34.5)	5381 (25.9)	7271 (17.1)
Other	2702 (2.4)	162 (2.0)	464 (2.2)	1008 (2.4)
Surgery types (10 most common), n (%)				
Knee prosthesis	10 926 (9.7)	898 (11.3)	2456 (11.8)	5070 (11.9)
Hip prosthesis	10 551 (9.3)	885 (11.1)	2158 (10.4)	4254 (10.0)
Open reduction of fracture	12 258 (10.9)	538 (6.8)	1994 (9.6)	4839 (11.4)
Gallbladder	9788 (8.7)	372 (4.7)	1120 (5.4)	2841 (6.7)
Colon	5376 (4.8)	299 (3.8)	775 (3.7)	1699 (4.0)
Limb amputation	4128 (3.7)	462 (5.8)	1142 (5.5)	2082 (4.9)
Thoracic surgery (noncardiac, non-vascular)	4983 (4.4)	273 (3.4)	906 (4.4)	1937 (4.6)
Spinal fusion	3568 (3.2)	322 (4.1)	697 (3.4)	1252 (2.9)
Abdominal surgery	3853 (3.4)	268 (3.4)	670 (3.2)	1328 (3.1)
Craniotomy	3541 (3.1)	252 (3.2)	634 (3.1)	1207 (2.8)
Year of surgery, n (%)				
2008–11*	5945 (5.3)	354 (4.5)	954 (4.6)	2137 (5.0)
2012–3	21 000 (18.6)	790 (9.9)	2672 (12.9)	6714 (15.8)
2014–5	41 128 (36.4)	3238 (40.7)	7923 (38.2)	15 800 (37.2)
2016–7	44 839 (39.7)	3566 (44.9)	9191 (44.3)	17 944 (42.2)

We also calculated the following HCRU parameters, stratified by presence and type of AKD, as secondary outcomes: (i) 30 day readmission, (ii) 90 day length of hospitalisation, (iii) 90 day ICU rate, (iv) 90 day ICU LOS, and (v) 7 day new onsite dialysis/CRRT. We defined 30 day readmission as all-cause hospitalisations within 30 days of index visit discharge. For 90 day length of hospitalisation, we calculated hospitalised days within the postoperative 90 day period. To determine the number of patients with an ICU stay in the 90 days after surgery, we calculated a 90 day ICU rate and ICU LOS. We used CPT/ICD 9/10 codes ([Supplementary Table S1](#)) to identify new-onset intermittent haemodialysis/CRRT in the 7 days after surgery and CKD in the year before surgery and within 180 days after discharge.

### Exposure

We calculated MAP using the following formula:  $(2 \times \text{diastolic BP}] + \text{systolic BP}) / 3$ . Using a previously published method,<sup>27</sup> we identified invalid MAP data points. We defined baseline MAP as the value closest to surgery commencement. This study analysed three absolute MAP thresholds ( $\leq 75$ ,  $\leq 65$ , and  $\leq 55$  mm Hg) after assessing relevant literature.<sup>30</sup> IOH for the relevant threshold was defined by at least one MAP measurement

below the threshold. To assess the association between IOH and AKD subtypes, we utilised (i) the time-weighted average MAP (TWA-MAP) for each threshold, calculated as the area below the MAP threshold curve divided by the total time exposure was monitored, and (ii) the absolute maximum decrease (AMD) (maximum reduction below the specified MAP threshold) during surgery.<sup>25</sup>

### Statistical analysis

Development of AKD for various IOH thresholds was evaluated using two-tailed hypothesis testing. For primary outcomes, Fine–Gray competing risk Cox models were performed by treating death as a competing risk.<sup>31</sup> Sub-distribution hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Three MAP thresholds ( $\leq 75$ ,  $\leq 65$ , and  $\leq 55$  mm Hg) stratified the study analyses, and we tested goodness of fit for IOH under different thresholds using the proportional hazard assumption. The HCRU secondary outcomes were summarised using counts and percentages for binary or categorical variables, and median and inter-quartile ranges for continuous variables.

All models were adjusted for potential confounding factors (see [Tables 1 and 2](#)), including (i) patient characteristics; (ii)

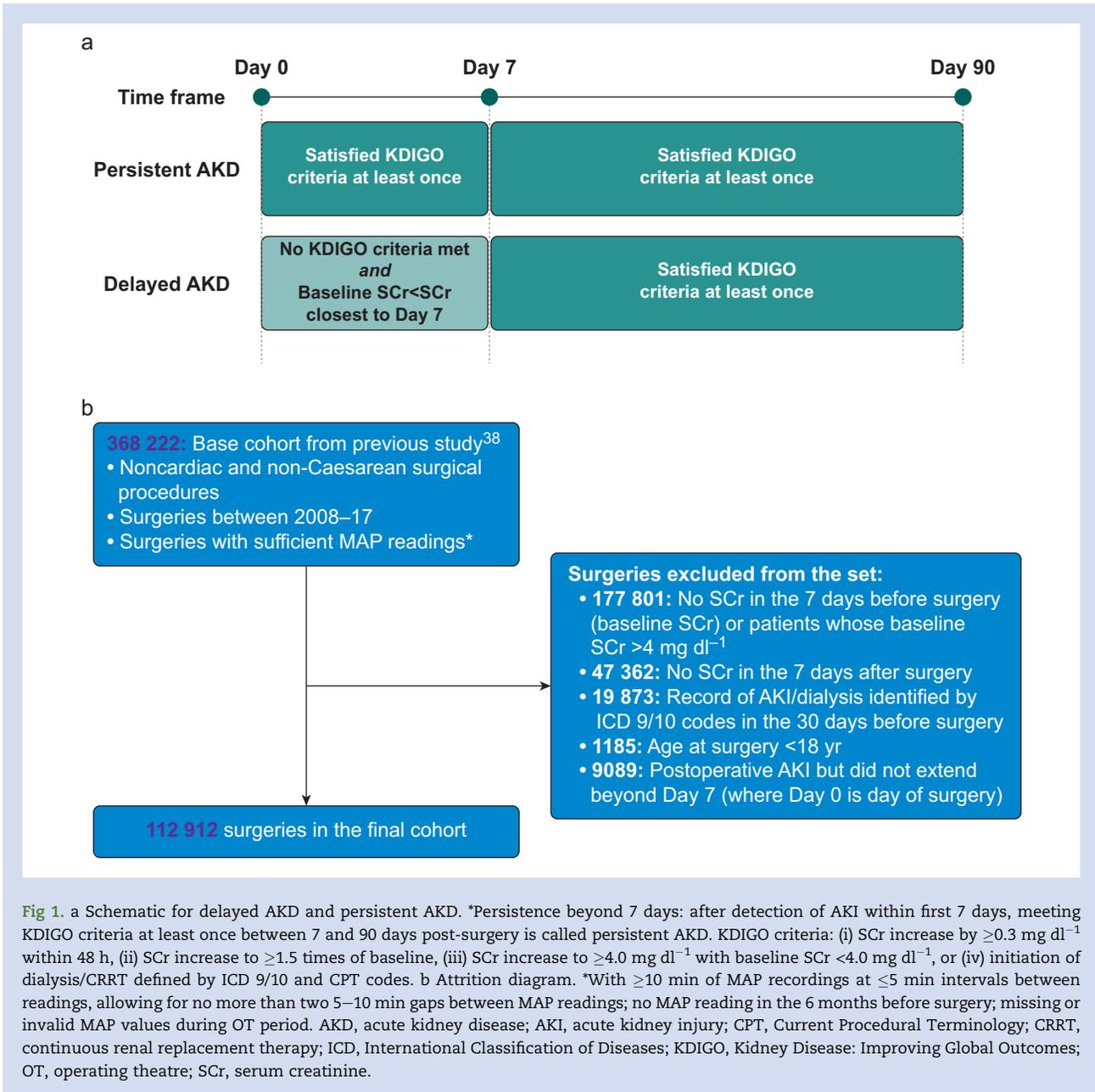
**Table 2** Patient comorbidities and additional characteristics. COPD, chronic obstructive pulmonary disease; IOH, intraoperative hypotension. Because of rounding, categories will not always add to 100%.

Patient characteristics	Overall (n=112 912)	IOH ≤ 55 mm Hg (n=7948)	IOH ≤ 65 mm Hg (n=20 740)	IOH ≤ 75 mm Hg (n=42 595)
Comorbidities, n (%)				
Myocardial infarction	8920 (7.9)	721 (9.1)	1850 (8.9)	3682 (8.6)
Cerebrovascular accident	12 284 (10.9)	962 (12.1)	2512 (12.1)	4903 (11.5)
COPD	30 965 (27.4)	2378 (29.9)	6118 (29.5)	12 291 (28.9)
Heart failure	10 982 (9.7)	979 (12.3)	2456 (11.8)	4739 (11.1)
Valvular heart disease	12 277 (10.9)	1009 (12.7)	2515 (12.1)	4955 (11.6)
Pulmonary circulatory disorder	3924 (3.5)	336 (4.2)	791 (3.8)	1609 (3.8)
Peripheral vascular disease	15 170 (13.4)	1200 (15.1)	3224 (15.5)	6321 (14.8)
Hypertension	74 854 (66.3)	5201 (65.4)	13 583 (65.5)	27 616 (64.8)
Paralysis	2900 (2.6)	323 (4.1)	692 (3.3)	1214 (2.9)
Diabetes mellitus	30 595 (27.1)	2116 (26.6)	5522 (26.6)	11 394 (26.7)
Hypothyroidism	19 842 (17.6)	1529 (19.2)	3932 (19.0)	7908 (18.6)
Renal disease	16 876 (14.9)	1264 (15.9)	3264 (15.7)	6574 (15.4)
Liver disease	10 892 (9.6)	811 (10.2)	1990 (9.6)	3929 (9.2)
Solid tumour	23 611 (20.9)	1900 (23.9)	4589 (22.1)	8900 (20.9)
Rheumatoid arthritis/connective tissue disease	5541 (4.9)	399 (5.0)	1042 (5.0)	2071 (4.9)
Coagulopathy	2581 (2.3)	277 (3.5)	613 (3.0)	1106 (2.6)
Obesity	30 801 (27.3)	1998 (25.1)	5159 (24.9)	10 592 (24.9)
Anaemia	44 154 (39.1)	3595 (45.2)	8964 (43.2)	17 906 (42.0)
Alcohol abuse	5705 (5.1)	473 (6.0)	1125 (5.4)	2088 (4.9)
Drug abuse	6734 (6.0)	549 (6.9)	1370 (6.6)	2536 (6.0)
Smoking	24 595 (21.8)	1719 (21.6)	4584 (22.1)	9347 (21.9)
Depression	29 408 (26.0)	2281 (28.7)	5626 (27.1)	11 312 (26.6)
Sleep apnoea	16 304 (14.4)	1216 (15.3)	3000 (14.5)	5958 (14.0)
Dementia	3989 (3.5)	306 (3.9)	811 (3.9)	1611 (3.8)
Coronary artery bypass graft	543 (0.5)	53 (0.7)	133 (0.6)	221 (0.5)
Percutaneous coronary intervention	756 (0.7)	63 (0.8)	169 (0.8)	314 (0.7)
Antihypertensive medication in year pre-surgery	93 887 (83.2)	6229 (78.4)	16 503 (79.6)	34 332 (80.6)
Home oxygen	2983 (2.6)	272 (3.4)	689 (3.3)	1298 (3.0)
Within 30 days before surgery, n (%)				
Acute myocardial infarction	1404 (1.2)	171 (2.2)	384 (1.9)	658 (1.5)
Acute ischaemic stroke	2654 (2.4)	218 (2.7)	572 (2.8)	1084 (2.5)
Within 7 days before surgery, n (%)				
Pre-renal medications	70 360 (62.3)	4572 (57.5)	12 458 (60.1)	26 465 (62.1)
Post-renal medications	2050 (1.8)	194 (2.4)	458 (2.2)	846 (2.0)
Intrinsic medications	105 398 (93.3)	7502 (94.4)	19 475 (93.9)	39 905 (93.7)
Delirium	2745 (2.4)	236 (3.0)	585 (2.8)	1105 (2.6)
Electrolyte disorder	23 837 (21.1)	2000 (25.2)	4851 (23.4)	9382 (22.0)
Sepsis	4554 (4.0)	571 (7.2)	1261 (6.1)	2178 (5.1)
Date of surgery, n (%)				
Weekend	22 280 (19.7)	1706 (21.5)	4295 (20.7)	8540 (20.0)
Night	9819 (8.7)	648 (8.2)	1645 (7.9)	3456 (8.1)
Admitted from, n (%)				
Home	79 100 (70.1)	5746 (72.3)	14 894 (71.8)	30 534 (71.7)
Inpatient	27 972 (24.8)	1891 (23.8)	4966 (23.9)	10 037 (23.6)
Skilled nursing facility	3019 (2.7)	215 (2.7)	534 (2.6)	1111 (2.6)
Unknown	2821 (2.5)	96 (1.2)	346 (1.7)	913 (2.1)

comorbidities and procedures (coronary artery bypass graft, percutaneous coronary intervention, and receipt of home oxygen) in the year before surgery; (iii) presence of delirium, electrolyte disorders, and sepsis in the 7 days pre-surgery; (iv) acute myocardial infarction and acute ischaemic stroke within 30 days before surgery; (v) antihypertensive medications in the year before and in the 24 h before surgery; (vi) nephrotoxic drugs in the 7 days before/on surgery date ([Supplementary Table S2](#)); (vii) surgery-related variables, such as surgery type, surgical duration, weekend vs weekday, night vs day, and surgery year; and (viii) other variables, such as referral level of care and baseline SCR. All diagnoses and procedures were

identified using CPT/ICD 9/10 codes listed in [Supplementary Table S1](#).

No statistical power calculation was conducted before the study, and sample size was based on available data. Patients with a record of an outcome or a procedure within 30 days before surgery were excluded from the corresponding outcome analyses. Model covariates were defined *a priori* based on clinical and operative factors that might affect the odds of AKD. As two primary outcomes across three hypotension thresholds were evaluated, a Bonferroni correction with a P-value of  $\leq 0.05/6$  or 0.008 was applied. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary,



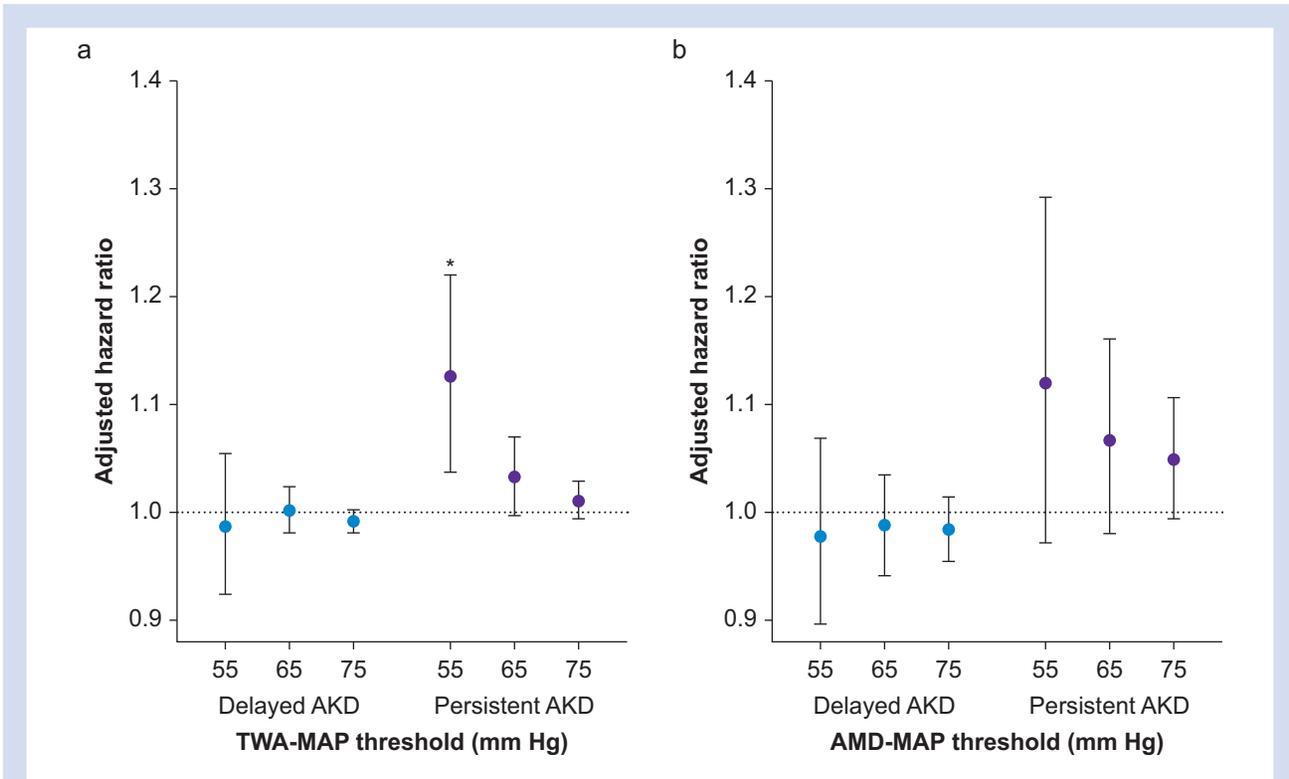
NC, USA) and R 3.5.2 (R Foundation for Statistical Foundation, Vienna, Austria). Secondary outcomes were considered exploratory and not subjected to multiple comparison correction. Subgroup analyses stratifying the cohort by characteristics, such as sex, age group, and comorbidities (such as moderate-to-severe liver disease, heart failure, and diabetes), were conducted as a *post hoc* study.

## Results

### Study cohort and patient characteristics

As shown in Figs 1b 112 912 surgeries met all inclusion/exclusion criteria. Mean [standard deviation] age of the cohort was 61.8 [16.1] yr; 60.5% were female ( $n=68\ 352$ ) and 83.2%

were Caucasian ( $n=93\ 902$ ). The overall incidence of AKD in the study population was 2.8% ( $n=3146$ ), with 2.2% ( $n=2457$ ) having delayed AKD and 0.6% ( $n=689$ ) having persistent AKD. The overall incidence of 7 day AKI in the study population was 8.7% ( $n=9778$ ), with 8.0% having 7 day AKI only ( $n=9089$ ) and 0.6% progressing to persistent AKD ( $n=689$ ). For exposure to IOH, 37.7% ( $n=42\ 595$ ) of cases experienced a MAP reading  $\leq 75$  mm Hg, 18.4% ( $n=20\ 740$ ) of patients  $\leq 65$  mm Hg, and 7.0% ( $n=7948$ )  $\leq 55$  mm Hg. Descriptive statistics are shown stratified for each IOH exposure threshold cohort (Tables 1 and 2) and for each type of renal impairment (Supplementary Table S3). Incidence of delayed AKD was highest between 7 and 30 days after surgery, decreased at 31–60 days, and further decreased at 61–90 days (Supplementary Fig. S1). We examined patients who had no baseline CKD to detect if they had new CKD after surgery.



**Fig 2.** Bonferroni-adjusted hazard ratios for the likelihood of delayed AKD and persistent AKD under intraoperative hypotension MAP threshold. The adjusted hazard ratios with 95% confidence intervals for the regression models with a TWA-MAP and b AMD-MAP during the study period are shown. AKD, acute kidney disease; AMD, absolute maximum decrease; TWA, time-weighted average. \* $P < 0.008$ .

Patients with 7 day AKI, delayed AKD, and persistent AKD had new CKD incidence of 5.9%, 11.2%, and 18.9%, respectively (Supplementary Table S4). In the persistent AKD group, a greater percentage of patients with IOH had new CKD than of patients who had no IOH (21.9% vs 18.9%).

### Association between IOH and AKD subtypes

IOH was significantly associated with persistent AKD at the lower TWA-MAP threshold of  $\leq 55$  mm Hg (HR 1.13; 95% CI: 1.04–1.22;  $P < 0.004$ ) (Fig. 2a). IOH also tended to be associated with persistent AKD at the TWA-MAP threshold of  $\leq 65$  mm Hg (HR 1.03; 95% CI: 1.00–1.07;  $P = 0.06$ ) and at AMD-MAP thresholds of  $\leq 55$  mm Hg (HR 1.12; 95% CI: 0.97–1.29;  $P = 0.12$ ) and  $\leq 65$  mm Hg (HR 1.07; 95% CI: 0.98–1.16;  $P = 0.08$ ), although the associations were not significant after Bonferroni corrections (Fig. 2b). IOH was not significantly associated with delayed AKD across any of the IOH thresholds examined (Fig. 2a and b).

### Healthcare resource utilisation amongst patients with AKD subtypes or no AKD

Table 3 contains HCRU results for patients stratified by AKD type. Patients with persistent and delayed AKD had higher HCRU across both hospital admissions (7 day new-onset intermittent haemodialysis/CRRT after surgery, 30 day readmission rate, and 90 day LOS post-surgery) and intensive care admissions (90 day ICU admission rate and ICU LOS) compared with patients with no AKD.

### Discussion

This multicentre cohort study describes the incidence of two AKD subtypes, delayed AKD and persistent AKD, in a large, noncardiac, non-obstetric surgical population. We report a rate of 2.2% for delayed AKD and 0.6% for persistent AKD, which align with previous studies that reported ranges for AKD

**Table 3** Healthcare resource utilisation across patients with delayed AKD, persistent AKD, or no AKD. AKD, acute kidney disease; CRRT, continuous renal replacement therapy; IQR, inter-quartile range.

Healthcare resource utilisation	Delayed AKD (n=2457)	Persistent AKD (n=689)	No AKD (n=109 766)
30 Day readmission, n (%)	890 (36.2)	231 (33.5)	9340 (8.5)
90 Day length of hospitalisation, median [25th, 75th]	10 [5, 18]	10 [5, 20]	3 [2, 6]
90 Day ICU rate, n (%)	179 (7.3)	57 (8.3)	4257 (3.9)
90 Day ICU length of stay, median [25th, 75th]	3 [2, 8]	5 [2, 10]	2 [1, 4]
7 Day new-onset intermittent haemodialysis/CRRT, n (%)	0 (0.0)	33 (4.8)	0 (0.0)

between 3.3% and 14.8% in patients undergoing noncardiac surgery.<sup>16,18–20</sup> Whilst most studies did not differentiate between the AKD subtypes, a large retrospective Canadian study reported an incidence rate of 3.8 per 100 patients for AKD without AKI,<sup>19</sup> which aligns with our definition for delayed AKD.

This is the first study to explore the relationship between IOH and AKD. We report a strong association between persistent AKD and IOH at lower thresholds of TWA-MAP  $\leq 55$  mm Hg. This is consistent with the well-established association between IOH and AKI and with previous studies that show that haemodynamic optimisation and avoidance of nephrotoxins are associated with a decrease in postoperative AKI.<sup>26–28,30,32,33</sup> Here, we report that delayed AKD was not significantly associated with IOH; however, given the association of postoperative haemodynamic instability with AKI,<sup>34</sup> further investigations can determine if there exists a similar association between AKD and postoperative hypotension. The differences between these two subtypes of AKD require further research and highlight the importance of the aetiology of acute deterioration in renal function. Understanding the link between different types of AKD and a modifiable factor, such as IOH, may help identify opportunities to optimise resources, care, and long-term patients' outcomes. Specifically, efforts to improve monitoring of advanced haemodynamic parameters in the operating theatre could be investigated as a potential opportunity to reduce the incidence and burden of not only short-term post-surgical complications, such as AKI, but also of longer-term disease, such as AKD. These results are important from the perspective of researchers, clinicians, payors, and caregivers given the ongoing and possibly worsening kidney dysfunction beyond the period of hospitalisation and the increasing growth globally of post-surgical complications and their long-term effects on morbidity, mortality, and quality of life.<sup>35,36</sup>

This study also provides evidence of increased HCRU, including readmissions, hospitalisation LOS, ICU rates and LOS, and dialysis/CRRT, amongst patients with AKD compared with patients without AKD. These results fill an important gap in our understanding of the HCRU burden of postoperative AKD. Whilst there are several studies highlighting HCRU and associated costs for postoperative AKI and CKD,<sup>37–39</sup> and evidence of higher requirement for postoperative CRRT in patients undergoing cardiac surgery,<sup>40</sup> there are no studies specifically focused on noncardiac postoperative AKD and HCRU. Therefore, these results close a significant gap in our understanding of the resource burden of AKD.

Although KDIGO guidelines recommend that patients be evaluated 3 months after AKI occurrence for resolution, new onset, or deterioration of pre-existing CKD,<sup>10</sup> only 50.0–69.0% of patients have their SCr measured within 3 months of an AKI episode.<sup>41,42</sup> Moreover, observational studies have reported that only 8.5–12% of AKI survivors received specialist nephrology follow-up<sup>12,43,44</sup> despite its association with improved survival.<sup>45</sup> A major hurdle in determining optimal follow-up for this high-risk population is the lack of characterisation of the disease continuum and identification of appropriate risk factors.<sup>12</sup> Our study characterises AKD subtypes based on the time course of the disease onset relative to the insult (i.e. surgery) and AKI occurrence. These results could help inform a potential layered approach to follow-up care, where the intensity and frequency of care are guided by the risk of short- and long-term morbidity and mortality and informed by a more detailed understanding of disease progression.<sup>12</sup> Whilst exploratory subgroup analyses examine the relationship between IOH and AKD in these populations

(Supplementary Table S5), prospective studies are needed to derive predictive risk factors.

We acknowledge several limitations of our study. Although we controlled for observable confounders, this study is inherently limited by its retrospective nature and is subject to residual (unobserved) confounding. Importantly, the results from this study only indicate an association between IOH and persistent AKD, and we cannot (and do not) comment on causality. There were data-set limitations as well; there is relative under-representation of the western and north-eastern US regions in the Optum data set. In addition, there is a potential impact of individual site biases, although our large sample should reduce that effect. We were also limited to using time periods that had a high frequency of MAP readings and a single pre-surgical MAP reading to represent a baseline for patients, which may not be representative for all patients. Additionally, we utilised only SCr measurements but not urine output in the AKI selection criteria, as the latter data were unavailable. However, it is worth noting that a previous meta-analysis found no difference in cohorts that used/did not use urine output in AKI definitions.<sup>46</sup> Also, other biomarkers of kidney function, such as cystatin C, neutrophil gelatinase-associated lipocalin, etc., may have produced a different result in the incidence of the two AKD subtypes, if our data set had these available, given their sensitivity/specificity. Finally, there were limitations associated with the study design and selection criteria. Whilst delayed and persistent AKD are currently not defined in guidelines, we used criteria from published guidelines and literature to define them.<sup>10,47</sup> Follow-up information, required to determine AKD status, was only limited to patients who visited a facility with the Optum database, indicating that the AKD rates seen in our study may be higher in clinical practice.

In conclusion, we observed an association between intraoperative hypotension and persistent (but not delayed) acute kidney disease in a large surgical cohort. A large proportion of patients may be exposed to intraoperative hypotension during surgery; its potentially avoidable nature, link with persistent acute kidney disease, and increased resource utilisation highlight the importance of these data, both for nephrologists and perioperative clinicians.

## Authors' contributions

Study design: ADS, WHS, AKK, NJS, AVS, IJB  
 Data collection: ADS, WHS, AKK, NJS, AVS, IJB  
 Data analysis: all authors  
 Writing of paper: all authors  
 Approval of paper: all authors

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## Declarations of interest

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## Appendix A. Supplementary data

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