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Original Article

Novel biological risk factors for 7-day postoperative kidney injury in elective major non-cardiac surgery: a retrospective observational study

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Summary

Introduction Few UK studies have explored the epidemiology of postoperative acute kidney injury after diverse types of elective major non-cardiac surgery. Fewer still have compared postoperative acute kidney injury risk factors with conditions such as peri-operative myocardial injury that might have similar pathophysiology. This study aimed to characterise postoperative acute kidney injury and its clinical consequences in elective major non-cardiac surgery, and to assess risk factors for postoperative acute kidney injury including those related to peri-operative myocardial injury.

Methods All elective major non-cardiac surgical episodes, occurring between 2015 and 2020, were identified retrospectively. Patients without measured peri-operative renal parameters were not studied. Our primary outcome was 7-day postoperative acute kidney injury rate, defined using Kidney Disease Improving Global Outcomes criteria. Multivariable logistic regression modelling was used to assess risk factors for postoperative acute kidney injury.

Results Postoperative acute kidney injury occurred in 1334/13,790 (9.7%) episodes, with 663 (49.7%) occurring on day 1. Postoperative acute kidney injury was associated with increased peri-operative complications (OR 1.8, 95%CI 1.6–2.1, $p < 0.001$), unanticipated critical care admissions (OR 2.4, 95%CI 1.6–3.5, $p < 0.001$) and in-hospital mortality (OR 8.0, 95%CI 5.1–12.5, $p < 0.001$). Independent risk factors for postoperative acute kidney injury include: raised creatinine; hypertension; anaemia; platelet: lymphocyte ratio; heart rate; male sex: renin-angiotensin-aldosterone system blockade; and intra-abdominal surgery.

Discussion Postoperative acute kidney injury is common and is associated with adverse outcomes. Prevalence peaks initially within the first 48 h, with a secondary rise seen from day 5 onwards, suggesting a different aetiology. It is determined by a combination of patient and surgical risk factors, with the former relating to physiological, rather than chronological, renal age. In common with peri-operative myocardial injury, postoperative acute kidney injury is independently associated with factors affecting autonomic tone and myeloid skewing.

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Introduction

Postoperative acute kidney injury (AKI) is defined by the Kidney Disease Improving Global Outcomes (KDIGO) consensus classifications as an AKI that meets the KDIGO criteria within 7 days of a surgical procedure [1]. It is associated with increased risks of sepsis, anaemia, coagulopathy, mechanical ventilation and mortality, as well as longer-term sequelae such as chronic kidney disease (CKD), stroke and heart failure [1–7]. Its incidence in non-cardiac surgery is reported as 1–35% [1, 3, 8, 9]. Heterogeneity in study design, inclusion criteria and renal failure endpoints have contributed to this variability and have also impacted reported risk factors and complication rates such as renal replacement therapy (RRT) utilisation and postoperative morbidity and mortality [4, 5, 9–15]. Consensus reports summarising the epidemiology of postoperative AKI were unable to grade their findings, further highlighting knowledge gaps in this area [1].

Most studies examine risk factors for postoperative AKI from the perspective of CKD, e.g. age and comorbidities. However, basic science studies show similar peri-operative risk factors and associated complications for postoperative AKI and peri-operative myocardial injury [16–18]. Despite these commonalities between peri-operative myocardial injury and postoperative AKI [19], pre- and peri-operative myocardial injury risk factors such as systemic inflammation and resting heart rate [20, 21], have not been assessed fully as contributory to postoperative AKI.

This study aimed to characterise postoperative AKI, its clinical consequences and associations in elective major non-cardiac surgery in patients who had measured peri-operative serum creatinine and/or urine output values. Additionally, we investigated pre-operative risk factors for postoperative AKI including those related to peri-operative myocardial injury.

Methods

This was a retrospective observational study that used data collected by the NHS as part of patient care at University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. Written patient consent was not required by this committee.

Patients aged ≥ 18 y who were admitted to University Hospitals Birmingham NHS Foundation Trust between 1 April 2015 and 31 March 2020, and for whom an Office of Public Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) code had been recorded, with electronic patient record data available, were included in the study. University Hospitals Birmingham NHS Foundation Trust comprises four hospitals and includes a large tertiary university hospital (Queen Elizabeth Hospital Birmingham) that is a regional specialist centre for almost all types of adult surgery.

Data were retrieved from electronic patient record systems relating to patient baseline characteristics, physiological and various haematological and biochemical parameters based on their known associations with CKD; AKI; peri-operative myocardial injury; inflammation; and ageing. Peri-operative use of drugs with the potential to modulate renal, immune or autonomic systems was also extracted, as were postoperative physiological, biochemical and clinical outcomes.

To define the subset of procedures, manual screening of OPCS4 codes was performed independently by two reviewers, with a third reviewer consulted if an agreement could not be reached. The final population was created though the following sequential exclusion: procedures were not included if they were not categorised as high-risk according to Lee's Cardiac Index or if they were not attributed a major or higher classification by BUPA Schedule of Procedures (version dated 14 April 2023) [22, 23]. Patients were also not included if they were undergoing cardiothoracic, transplant or burns surgeries; nephrectomy; partial nephrectomy; emergency procedures; returning to the operating theatre within 30 days of previous surgery; had a transplanted kidney, pre-admission stage 5 CKD or dialysis; or if there was no baseline kidney function in the previous 6 weeks or no postoperative serum creatinine or urine output measurements. Finally, to ensure a purely elective population, patients were not included if they had been admitted to the oncology or general medicine directorates during the same inpatient spell.

The primary outcome was the incidence of postoperative AKI using KDIGO-defined (creatinine and/or urine output) criteria within the first 7 days following the index surgical procedure [24]. Secondary outcomes included postoperative AKI rates stratified by surgery type; grade of postoperative AKI; postoperative admission to the ICU; requirement for RRT; postoperative hospital duration of stay; incidence of complications; and inpatient mortality. To produce a temporal profile of postoperative AKI, a postoperative window, capped at a maximum of 7 days or discharge (if earlier), was examined for each patient and the worst recorded AKI grade was plotted against time. Complications were classified as intra-operative, postoperative or unclassified.

Creatinine measurement was requested according to local protocols (at least daily in the case of patients in ICU), patient clinical state and clinician perceived risk of AKI.

University Hospitals Birmingham NHS Foundation Trust electronic patient record systems started reporting AKI grade in 2015 and clinicians were able to respond to this information in real-time [25].

Patients were catheterised intra-operatively according to standard criteria (e.g. nature and duration of surgery) or if clinical teams felt this was indicated. Postoperative urinary catheterisation occurred in response to triggers and according to local clinical protocols (e.g. urinary retention, suspected AKI or sepsis). For patients with a urinary catheter, urine output was measured with urometers and recorded hourly in the ICU, or at fixed intervals of several hours on the ward. The duration of urinary catheterisation was determined by local protocols (e.g. enhanced recovery and/or AKI protocols) and additional factors (e.g. nature of surgery and patient mobility). For patients who did not have a urinary catheter in the ICU, urine was collected and its volume measured after patient micturition. This was also the case for patients who were not on ICU and did not have a urinary catheter, according to local protocols so that patients deemed at low clinical risk of AKI had no urine output measurements.

Unscheduled admission to ICU occurred either when a high degree of observation or organ support was required in patients where this was not deemed to be futile, or if patients required nursing care that was beyond the capacity of a ward environment to deliver. Discharge from ICU occurred when the consultant intensivist deemed a patient was stable enough to be managed safely on a ward with a low risk of readmission. Decisions to initiate or cease RRT were determined by the treating consultant intensivist.

Statistical comparisons in the univariate analysis for postoperative AKI were done with X^2 tests or Fisher's exact test, otherwise, Student's t-tests or Kruskal–Wallis ANOVAs were used. Dunn's test was used to correct for multiple comparisons and two-sided tests were used in all analyses. Odds ratios (OR) and 95%CIs have been calculated where relevant. Univariate analyses were performed using Version 2022.1.2 of XL-STAT software (Data Analysis and Statistical Solution for Microsoft Excel, Addinsoft, New York, NY, USA). Significance was set at $p < 0.05$. During univariate analysis any patient's missing data were not included in the analysis of that particular parameter.

The authors approved the data collection tool and statistical method before data collection. The only additional data parameters requested after this initial planning were related to coding for peri-operative complications. To avoid bias, a statistician performed the multivariable modelling independent to the author involved with the univariate analysis. The Clinical Classifications Software Refined Code list (based on ICD-10) was used to cluster patient diagnoses. SAS™ software (SAS Institute Inc., Cary, NC, USA) was used to create multivariable logistic regression models. Any missing data in the regression analyses were imputed using fully conditional specification. Data were divided into 80% derivation and 20% validation subsets using data from 2015–2019 to 2019–2020, respectively. Variables were excluded if within the AKI data set there were < 5 counts per year. A 0.1% winsorisation was applied to continuous variables to ameliorate the effects of any extreme outliers. Logistic regression was used to create multiple models with p value retention criteria 0.05–0.15 for individual bootstrap outputs. These models then underwent re-parameterisation to avoid collinearity, before calibration and validation with the c-statistic. Within the fitting phase, continuous variables were centred and scaled by the statistical software; however, following this, model outputs were back-transformed to the original scale. Monotonic transformations were also performed on the continuous variables to look for non-linear relationships and model performance compared against those assuming linear relationships.

Results

Of 117,975 surgical episodes, 13,790 elective major non-cardiac surgical episodes were included in the final analysis. Figure 1 shows the sequential exclusion process. Patient characteristics are shown in Table 1 and baseline physiology in online Supporting Information Table S1.

Between April 2015 and March 2020, 1334/13,790 (9.7%) patients developed postoperative AKI. Of these 1134 patients, 1225 (91.8%) had postoperative urine output and postoperative creatinine measurements, of which 81 (6.6%) met the KDIGO definition of AKI with both postoperative urine output and postoperative creatinine data; 453 (37.0%) met only the postoperative urine output criteria; and 691 (56.4%) met only the postoperative creatinine criteria. When creatinine was the only metric taken into consideration, the overall postoperative AKI rate was 845/12,318 (6.9%).

In total, 663/13,288 (5.0%) patients developed postoperative AKI on the first postoperative day (not all patients had postoperative urine output or postoperative creatinine recorded on day 1), of which 492 (74.2%) were stage 1 AKI; 112 (16.9%) stage 2; and 59 (8.9%) stage 3. Overall postoperative AKI incidence peaked within the first 48 h, with decreasing numbers until postoperative day 5 (290/6889 (4.2%)). Rates began increasing again on day 6, with this trend continuing to day 7 (238/4405 (4.7%)). Although the overall prevalence of postoperative AKI tended to decrease between postoperative days 1 and 5, the proportion of patients with stage 3 AKI increased from

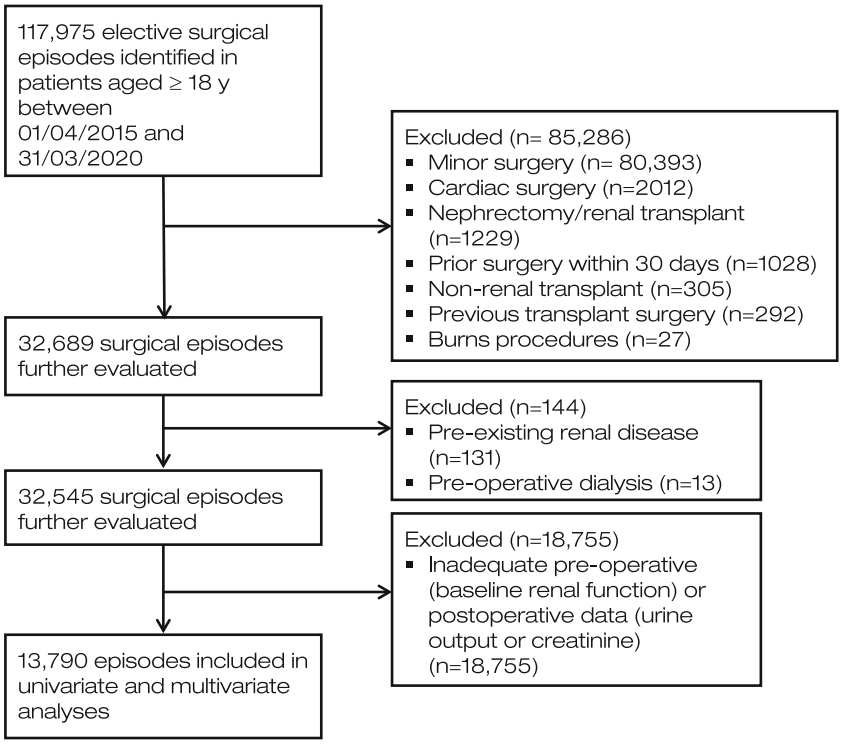

Figure 1 Sequential exclusion process.

Table 1 Characteristics of patients developing postoperative acute kidney injury (AKI) after elective major non-cardiac surgery. Values are number (proportion), mean (SD) or median (IQR [range]).

	All patients, n = 13,790	AKI-no group, n = 12,456	AKI-yes group, n = 1334	p value
Sex; male	7546 (54.7%)	6766 (54.3%)	780 (58.5%)	0.004
Age; y	59 (16.1)	58 (16.1)	63 (14.7)	< 0.001
Asian/Asian British	1091 (8.0%)	978 (7.9%)	113 (8.5%)	0.9
Black/Black British	540 (3.9%)	487 (3.9%)	53 (4.0%)	
Chinese	37 (0.3%)	33 (0.3%)	4 (0.3%)	
White	10,441 (76.0%)	9420 (75.6%)	1021 (76.5%)	
Missing	1681 (12.2%)	1538 (12.3%)	143 (10.7%)	
Comorbidity burden*	1 (1–2 [0–7])	1 (1–2 [0–7])	2 (1–3 [0–7])	< 0.001
Cardiovascular disease	5599 (40.6%)	4835 (38.8%)	764 (57.2%)	< 0.001
Respiratory disease	2384 (17.3%)	2107 (16.9%)	277 (20.8%)	< 0.001
Diabetes	1996 (14.5%)	1715 (13.8%)	281 (21.1%)	< 0.001
Neoplasms	8239 (59.7%)	7388 (59.3%)	851 (63.8%)	0.002
Peripheral vascular disease	2038 (14.8%)	1737 (14.0%)	301 (22.6%)	< 0.001
Cerebrovascular disease	396 (2.9%)	361 (2.9%)	35 (2.6%)	0.6
Renal disease	1393 (10.1%)	1203 (9.7%)	190 (14.2%)	< 0.001
Liver disease	557 (4.0%)	484 (3.9%)	73 (5.5%)	0.005
Peptic ulcer disease	258 (1.9%)	219 (1.8%)	39 (2.9%)	0.003
Rheumatological disease	2291 (16.6%)	2038 (16.3%)	253 (19.0%)	0.02
Dementia	32 (0.2%)	25 (0.2%)	7 (0.5%)	0.05

*Comorbidity burden refers to cumulative addition of comorbidities.

day 1 onwards (Fig. 2). Postoperative complications, ICU admissions, duration of ICU and overall admission stay, need for ICU readmission and mortality were all greater in the postoperative AKI group (Table 2).

Although postoperative AKI was associated with nearly double the odds of postoperative ICU admission (OR 1.8, 95%CI 1.6–2.1, $p < 0.001$) the distribution of AKI severities was similar in those patients with and without an ICU stay (online Supporting Information Table S2). The odds for a non-elective ICU admission in those patients with postoperative AKI were more than double, as was the ICU readmission rate (online Supporting Information Table S3). In general, those patients with increased age; lower BMI; higher comorbidity burden; lower baseline systolic blood pressure, heart rate, albumin, haemoglobin or glomerular filtration rate; and undergoing hepatobiliary or general surgical procedures, were more likely to require a postoperative ICU bed (online Supporting Information Table S2).

Renal replacement therapy was required by 24 (0.2%) patients within the 7-day postoperative period of interest; this occurred in 20/1334 (1.5%) patients with postoperative AKI patients. Renal replacement therapy was commenced before reaching stage 3 KDIGO AKI criteria in 11/20 (55%) patients (7/20 (35%) stage 1 AKI and 4/10 (40%) stage 2 AKI). In those patients with postoperative AKI requiring RRT, the odds for in-hospital death increased to 40.5 (95%CI 15.8–103.9, $p < 0.001$). For the postoperative AKI group as a whole, the odds of in-hospital mortality were eight-fold higher than those without postoperative AKI (OR 8.0, 95%CI 5.1–12.5, $p < 0.001$; online Supporting Information Table S3).

Univariate analyses showed significant associations between the odds of postoperative AKI and male sex; increasing age; BMI (≥ 30 $kg.m^{-2}$); and comorbidity burden (online Supporting Information Table S3). Although male patients were more likely to develop AKI, female patients were more likely to experience a worse severity of postoperative AKI (online Supporting Information Table S4). Similarly, older patients were more likely to develop postoperative AKI, but this was predominantly a milder grade with a similar proportion of those with stage 3 AKI across all age groups (online Supporting Information Table S4).

Several individual comorbidities such as cardiovascular (OR 2.1, 95%CI 1.9–2.4, $p < 0.001$) and peripheral vascular diseases (OR 1.8, 95%CI 1.6–2.1, $p < 0.001$) carried higher odds of postoperative AKI. Increased odds were also seen in patients who had been prescribed renin-angiotensin-aldosterone antagonists, diuretics and

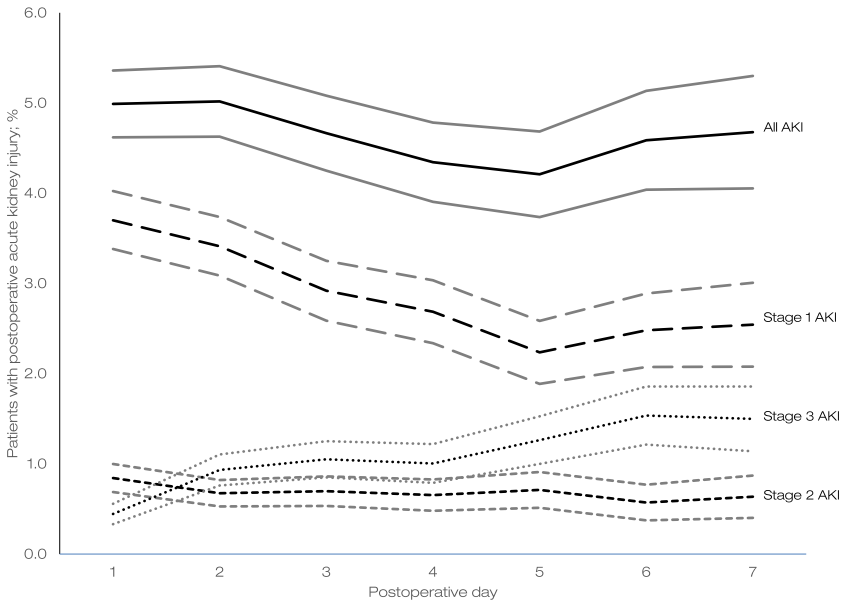

Figure 2 Temporal breakdown of development of postoperative acute kidney injury by grade (severity). Worst grade of AKI for each patient plotted from day of procedure up to postoperative day 7 or discharge (if before day 7). Within each trio of lines, the middle line (black) represents the total proportion of patients within our cohort in a particular group and the upper and lower lines (grey) reflect the 95%CIs. The solid line presents the incidence of patients with any stage of AKI. The line with the longest dashes represents patients with stage 1 AKI, the line with medium dashes those with stage 2 AKI and the line with the shortest dashes stage 3 AKI.

Table 2 Summary of patient outcomes in relation to the development of postoperative acute kidney injury (AKI) after elective major non-cardiac surgery. Values are number (proportion) or median (IQR [range]).

	All patients, n = 13,790	AKI-no group, n = 12,456	AKI-yes group, n = 1334	p value
Duration of postoperative hospital stay; d*	5 (2–14 [1–14])	4 (2–7 [1–14])	7 (4–14 [1–14])	< 0.001
All ICU admissions	4015 (29.1%)	3461 (27.8%)	554 (41.5%)	< 0.001
Elective ICU admission	3881 (96.7%)	3363 (97.2%)	518 (93.5%)	< 0.001
Non-elective ICU admission	134 (3.3%)	98 (2.8%)	36 (6.5%)	
Duration of ICU admission; d	2 (1–3 [0–72])	2 (1–3 [0–56])	3 (2–5 [0–72])	< 0.001
Duration of elective ICU admission; d	2 (1–3 [0–72])	2 (1–3 [0–56])	3 (2–5 [1–72])	< 0.001
Duration of non-elective ICU admission; d	3 (1–6 [0–18])	5 (3–8 [0–16])	2 (1–5 [0–18])	0.001
All ICU admissions requiring RRT	21 (0.5%)	4 (0.1%)	17 (3.1%)	
Elective ICU admissions: RRT	17 (0.4%)	3 (0.09%)	14 (2.7%)	0.8
Non-elective ICU admissions: RRT	4 (3.0%)	1 (1.0%)	3 (8.3%)	
ICU readmissions	68 (1.7%)	48 (1.4%)	20 (3.6%)	< 0.001
Any complication	1967 (14.3%)	1677 (13.5%)	290 (21.7%)	< 0.001
Intra-operative complications	277 (14.1%)	234 (14.0%)	43 (14.8%)	0.5
Postoperative complications	1177 (59.8%)	984 (58.7%)	193 (66.6%)	
Unclassified complications	751 (38.2%)	642 (38.3%)	109 (37.6%)	
Stage 1 AKI	818 (61.3%)			
Stage 2 AKI	207 (15.5%)			
Stage 3 AKI	309 (23.2%)			
In-hospital mortality	77 (0.6%)	42 (0.3%)	35 (2.6%)	< 0.001

*Duration of stay data collection curtailed at 14 days.
RRT, renal replacement therapy.

secondary prevention cardiovascular medications (aspirin, beta-blockers and statins) pre-operatively but not aminoglycosides, non-steroidal anti-inflammatory drugs or blood transfusions pre-operatively. Patients with an increased baseline systolic blood pressure; heart rate (> 100 beats per minute); creatinine; albumin (< 34 $g.l^{-1}$); any degree of pre-operative anaemia; and eGFR <60 $ml.min^{-1}$ had greater odds of postoperative AKI (online Supporting Information Table S3). Although there was a significantly higher neutrophil: lymphocyte ratio in those who developed postoperative AKI, unlike in peri-operative myocardial injury, a neutrophil: lymphocyte ratio cut off of 4 did not discriminate (online Supporting Information Table S1). Increasing platelet: lymphocyte ratio was also associated with increasing AKI rates, with a ratio > 600 predominantly associated with mild (stage 1) AKI 16/111 (14.4%). No patients with platelet: lymphocyte ratio < 250 developed stage 2 or 3 AKI ($p < 0.001$).

Using hepatobiliary surgery as the reference group, general surgery had the highest proportion of patients with postoperative AKI (375/2476 (15.1%); $p < 0.001$) and the greatest proportion of patients with stage 3 AKI (113/2476 (4.6%); $p < 0.001$). Neurosurgery had the lowest odds of postoperative AKI (online Supporting Information Table S3). Those specialities with higher AKI rates tended to be those including intra-abdominal procedures and older, more comorbid populations (specifically those patients with cardiovascular disease and/or diabetes), where more than 50% were male patients with lower baseline albumin and haemoglobin levels (online Supporting Information Table S5).

The characteristics of patients included in the derivation and validation groups are shown in online Supporting Information Table S6. The models containing monotonic transformations of continuous data did not perform any better or worse than those assuming linear relationships. Using a p value retention cut-off of 0.05 resulted in a final model of 29 independent variables (Table 3).

Although the odds of postoperative AKI increased by 4.3% (95%CI -1.7–10.6) per decade, age was not found to be independently associated with postoperative AKI. Similarly, BMI; pre-operative duration of stay; and cancer of the prostate, colorectal cancer and chronic obstructive pulmonary disease were not independently associated with postoperative AKI.

Female sex and increasing baseline haemoglobin were associated with a lower risk of postoperative AKI. The risk of

Table 3 Final parameters included in the multivariable logistic regression model. Baseline systolic blood pressure, creatinine, heart rate, haemoglobin and platelet: lymphocyte ratios are all continuous variables and their coefficients refer to change per unit increment.

	Reference	Coefficient	aOR (95%CI)	p value
Intercept		-2.6	0.1 (0.0–3.0)	0.1
Female sex	Male sex	-0.1	0.9 (0.8–1.0)	0.02
Angiotensin-converting enzyme inhibitor	No drug	0.3	1.4 (1.1–1.6)	0.002
Angiotensin receptor blocker	No drug	0.4	1.5 (1.1–1.9)	0.004
Ear nose and throat, maxillofacial and endocrine surgery	Hepatobiliary surgery	-0.5	0.6 (0.5–0.9)	0.03
General surgery – upper gastrointestinal surgery		0.9	2.4 (1.9–3.0)	< 0.001
General surgery – abdominopelvic		0.5	1.6 (1.3–2.0)	< 0.001
General surgery – head and neck		0.6	1.9 (1.4–2.5)	< 0.001
Neurosurgery		-0.8	0.5 (0.4–0.6)	< 0.001
Orthopaedic surgery		-0.7	0.5 (0.3–0.7)	0.001
Vascular – abdominopelvic procedures		0.7	1.9 (1.1–3.3)	0.009
Vascular other		-0.5	0.6 (0.4–0.9)	0.01
Vascular – interventional radiology		-1.0	0.4 (0.2–0.7)	0.002
Baseline systolic blood pressure; mmHg		0.01	1.0 (1.0–1.0)	< 0.001
Baseline creatinine; $\mu mol.l^{-1}$		0.01	1.0 (1.0–1.0)	< 0.001
Baseline heart rate; beats per minute		0.01	1.0 (1.0–1.0)	< 0.001
Baseline haemoglobin; $g.l^{-1}$		-0.01	1.0 (1.0–1.0)	< 0.001
Platelet: lymphocyte ratio		0.00	1.0 (1.0–1.0)	0.009
Diseases of arteries; arterioles and capillaries	No pathology	0.40	1.5 (1.0–2.2)	0.02
Diseases of the heart	No pathology	0.3	1.3 (1.1–1.5)	0.001
Bacterial infection	No pathology	0.7	2.1 (1.6–2.7)	< 0.001
Endocrine disorders: other*	No pathology	0.7	2.0 (1.4–2.7)	< 0.001
Cancer: other primary*	No pathology	-0.3	0.8 (0.6–0.9)	0.004
Cancer: male genital organs	No pathology	-0.5	0.6 (0.4–1.0)	0.03
Cancer: colorectal	No pathology	-0.3	0.8 (0.5–1.0)	0.04
Diseases of the respiratory system	No pathology	0.3	1.3 (1.1–1.5)	0.001
Diseases of the musculoskeletal system/connective tissue	No pathology	0.3	1.3 (1.1–1.6)	0.001
Mental illness	No pathology	0.2	1.3 (1.1–1.5)	0.004
Biliary tract disease	No pathology	-0.4	0.7 (0.5–0.9)	0.006
Diseases of the urinary system	No pathology	0.2	1.3 (1.0–1.6)	0.01

*Defined in online Supporting Information Appendix S1.

postoperative AKI according to surgical speciality followed a similar pattern to those in the univariate analysis with increased risk with upper gastrointestinal procedures conferring the highest risk compared with hepatobiliary surgery. Raised baseline heart rate; blood pressure; creatinine; and platelet: lymphocyte ratio were associated with increased odds of AKI. Pre-operative renin-angiotensin-aldosterone antagonists were also associated with an increased risk of postoperative AKI, with angiotensin receptor blockers having a greater impact than angiotensin-converting enzyme inhibitors. Cardiovascular disease, respiratory disease and diseases of the urinary system were associated with increased risk of AKI (Table 3).

The mean c-stat for calibration data was 73.4 (95%CI 70.1–76.5), compared with 74.3 (95%CI 70.8–77.6) in the validation data set.

Discussion

This study found that in patients with measured peri-operative renal parameters, for every 100 elective major non-cardiac surgery procedures, postoperative AKI could be expected to happen in a minimum of four and a maximum of 15 cases, with the likelihood being greatest in general surgery, hepatobiliary surgery and open abdominopelvic vascular procedures. We found that the use of urine output in addition to creatinine data increases

postoperative AKI pick up rate by 40%. Worst postoperative AKI grade was most likely reached within the first two days of surgery and was overwhelmingly dominated by mild AKI. While the numbers of overall postoperative AKI decreased after day 2, stage 3 AKI rates rose throughout the 7-day window.

Postoperative AKI was associated with peri-operative complications; a doubling of the odds of ICU admission; prolonged hospital stay; and an eight-fold increase in the odds of in-hospital mortality. Although RRT was used after fewer than two in 1000 surgeries and fewer than two in 100 postoperative AKI cases, it was associated with a 40-fold increase in mortality. This study replicated previous findings that male sex; pre-operative renin-angiotensin-aldosterone blockade; abdominal surgery; and baseline renal function are significant postoperative AKI risk factors [1, 5, 26–28]. Novel findings are associations with baseline heart rate and platelet: lymphocyte ratio but an absence of age as a risk factor in the multivariable model.

The temporal patterns suggest that early postoperative AKI is usually mild, transient and occurs due to the interaction of patient (renal reserve) and surgical factors (intra-abdominal holding the highest risk). Progression of early postoperative AKI to higher grades should be modifiable with better patient selection and clinical attention, as supported by several studies and here possibly by falling rates of higher severity postoperative AKI over the years (online Supporting Information Table S6) [18, 29, 30]. Although older patients were more likely to develop postoperative AKI, similar proportions of all age groups developed the worst grade of postoperative AKI, perhaps suggesting that when there is clinician bias leading towards postoperative AKI, more protective peri-operative measures are employed. The higher severity and later appearance of a second postoperative AKI peak might suggest a different pathophysiology of late postoperative AKI, perhaps coinciding with the development of postoperative complications and less vigilant use of AKI-prevention bundles, including the reintroduction of potentially nephrotoxic medications. As the surgical stress response can affect postoperative creatinine levels and postoperative urine output, the appearance of postoperative AKI may also be masked in the immediate postoperative period. The use of novel AKI biomarkers in prospective studies may help to elucidate changes and differentiate between aetiologies in the early timeline more clearly.

Several other groups have used multivariate modelling to propose independent risk factors and scoring tools for postoperative AKI in non-cardiac surgery [9, 10, 13, 14, 31, 32]. Unlike previous studies, our study suggests that in addition to renal reserve, dysautonomia, systemic inflammation and myeloid skewing may have important roles in postoperative AKI, and that postoperative AKI and peri-operative myocardial injury share considerable overlap in terms of propensity to injury [18, 20]. Considering that pre-operative haemoglobin and blood pressure were also associated with postoperative AKI in this study and, notwithstanding the fact that these findings need further validation in external datasets, one suggestion for the lack of association between age and postoperative AKI in this study is that the multivariable model effectively captured all parameters through which age mediates its effects on peri-operative renal risk [33–35]. It is also notable that multivariable modelling linked baseline heart rate to postoperative AKI risk but did not find pre-operative beta-adrenoceptor blocker use protective at the univariate or multivariable level; this potentially indicates a harmful effect of low vagal tone, as in peri-operative myocardial injury [36–38].

This is the largest study to come from a UK setting using KDIGO postoperative AKI criteria, utilising a recent COVID-19-free data set and including both postoperative urine output and postoperative creatinine (avoiding the possibility of under-reporting of AKI rate) and determining rates of postoperative AKI across a range of elective major non-cardiac surgeries [39]. Many meta-analyses include data that are up to 20 years old and report a postoperative AKI rate that perhaps does not reflect the advances in peri-operative care such as the introduction of AKI prevention bundles or cover the introduction of an electronic alert system for postoperative AKI mandated by NHS England in 2015 [25]. The strengths of this study are that it overcomes each of these limitations.

The single-centre, retrospective nature of this study may limit its generalisability. Daily biochemical screening did not happen in all patients and therefore some postoperative AKI will have been missed. Although we utilised postoperative urine output data to minimise this problem, urine output monitoring has its own limitations, particularly outside of the ICU setting [40]. Within our Trust, a significant number of major surgeries are undertaken as day-case procedures and do not undergo postoperative serum creatinine or rigorous urine output monitoring routinely, which led to a high exclusion rate. In addition, our ability to determine the role of intra-operative factors in postoperative AKI was limited as we could not access such data at this scale, although coding of complications in the electronic patient record was utilised as a surrogate. Issues related to coding, in

conjunction with collinearity of variables, may partly explain why some surprising associations between comorbidities and postoperative AKI were identified. Finally, in the surgical cohort, creatinine and urine output are imperfect markers of renal function, both affected by the surgical stress response, but this is a problem that plagues the entire field and is therefore not isolated to this study.

This study shows that postoperative AKI remains a common problem following non-cardiac surgery and is associated significantly with adverse patient outcomes. We report risk factors for postoperative AKI potentially representing inflammaging, including baseline heart rate and myeloid skewing, both of which are related to peri-operative myocardial injury and are novel findings for postoperative AKI. Following validation in external datasets, these parameters could lead to generalisable pre-operative postoperative AKI risk stratification tools to aid patient counselling, anaesthetic and surgical management plans and implementation of AKI preventative bundles to reduce the burden of this common complication. This is particularly important for younger patients with higher renal reserve who are currently perceived to be low-risk and who may, therefore, miss out on the use of beneficial renal protective strategies.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Full definitions of conditions listed in Table 3.

Table S1. Summary of baseline physiology and type of surgery in patients undergoing elective major non-cardiac surgery and breakdown of those developing postoperative acute kidney injury compared with those without postoperative acute kidney injury.

Table S2. Characteristics of patients undergoing elective major non-cardiac surgery grouped into those requiring any postoperative intensive care admission within 7 days of their surgery, and comparison of those with and without postoperative acute kidney injury in the elective postoperative intensive care unit admission cohort.

Table S3. Unadjusted odds ratios of risk factors for postoperative acute kidney injury in patients undergoing elective, major non-cardiac surgery.

Table S4. Breakdown of postoperative acute kidney injury risk factors by grade of acute kidney injury in patients undergoing elective, major, non-cardiac surgery.

Table S5. Comparisons of postoperative acute kidney injury risk factors and secondary outcome measures across surgical sub-specialities in patients undergoing elective, major, non-cardiac surgery.

Table S6. Cohort characteristics broken down by surgery year of patients undergoing elective major non-cardiac surgery.