

# Prognostic model to predict postoperative acute kidney injury in patients undergoing major gastrointestinal surgery based on a national prospective observational cohort study

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**Background:** Acute illness, existing co-morbidities and surgical stress response can all contribute to postoperative acute kidney injury (AKI) in patients undergoing major gastrointestinal surgery. The aim of this study was prospectively to develop a pragmatic prognostic model to stratify patients according to risk of developing AKI after major gastrointestinal surgery.

**Methods:** This prospective multicentre cohort study included consecutive adults undergoing elective or emergency gastrointestinal resection, liver resection or stoma reversal in 2-week blocks over a continuous 3-month period. The primary outcome was the rate of AKI within 7 days of surgery. Bootstrap stability was used to select clinically plausible risk factors into the model. Internal model validation was carried out by bootstrap validation.

**Results:** A total of 4544 patients were included across 173 centres in the UK and Ireland. The overall rate of AKI was 14.2 per cent (646 of 4544) and the 30-day mortality rate was 1.8 per cent (84 of 4544). Stage 1 AKI was significantly associated with 30-day mortality (unadjusted odds ratio 7.61, 95 per cent c.i. 4.49 to 12.90;  $P < 0.001$ ), with increasing odds of death with each AKI stage. Six variables were selected for inclusion in the prognostic model: age, sex, ASA grade, preoperative estimated glomerular filtration rate, planned open surgery and preoperative use of either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Internal validation demonstrated good model discrimination (c-statistic 0.65).

**Discussion:** Following major gastrointestinal surgery, AKI occurred in one in seven patients. This preoperative prognostic model identified patients at high risk of postoperative AKI. Validation in an independent data set is required to ensure generalizability.

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## Introduction

Postoperative acute kidney injury (AKI) is a common complication of major non-cardiac surgery, with a rate of approximately 13 per cent<sup>1</sup>. Postoperative AKI is associated with significantly increased risks of mortality and morbidity, and long-term progression to chronic kidney disease (CKD), even in patients whose renal function recovers to baseline following the AKI episode<sup>2–4</sup>. It is also associated

with increased lengths of hospital stay and higher health-care costs<sup>5</sup>, making AKI reduction an important target for patients, clinicians and providers.

As no definitive therapy for postoperative AKI exists, management of patients with AKI is limited to prevention and supportive treatment. In the absence of novel therapies, the key to reducing the burden of morbidity and mortality associated with AKI is the development of early interventions aimed at reducing incidence. The

National Institute for Health and Care Excellence (NICE) guidelines<sup>6</sup> recommend assessing the risk of AKI before patients undergo surgery. Sixteen prognostic models have been proposed to predict postoperative AKI (Table S1, supporting information). Most include variables of specific interest to either cardiac or liver surgery, which are not appropriate for patients undergoing gastrointestinal surgery. No previous model has been developed for patients undergoing major gastrointestinal surgery, whose risk of AKI may be determined by gastrointestinal-specific variables such as use of laparoscopy.

The aim of this study was to develop a simple, reproducible, prognostic model to stratify patients undergoing major gastrointestinal surgery by their risk of postoperative AKI.

## Methods

The externally peer-reviewed and published protocol for the multicentre prospective observational Outcomes After Kidney injury in Surgery (OAKS) study was developed by Student Audit and Research in Surgery (STARSurG), a medical student-driven collaborative network<sup>7</sup>. The research collaborative model has been described previously, successfully delivering a number of national cohort studies<sup>8,9</sup>.

Study results are reported in line with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement<sup>10</sup>. In the UK, the South-East Scotland Research Ethics Service (reference NR/1506AB4) confirmed that ethical review was not required, as this observational study collected only routine, non-patient-identifiable data. Individual participating UK centres were responsible for registering the study locally as either clinical audit or service evaluation. In Ireland, participating centres were responsible for securing research ethics approval locally, as required by institutional regulations.

## Inclusion criteria

Adult patients (aged 18 years or above) undergoing elective or emergency gastrointestinal resection, liver resection, or reversal of ileostomy or colostomy, using any operative approach, were eligible for inclusion. Consecutive patients were identified by local collaborators across multiple predefined 2-week patient inclusion periods between 23 September 2015 and 18 November 2015. Patients having repeat surgery within 30-day follow-up were considered to have had one continuous episode starting from the index operation.

## Exclusion criteria

Patients with a previous kidney transplant were excluded, as were those who had received any form of renal replacement therapy in the 90 days before their operation. Patients presenting with established AKI on admission to hospital were also excluded. Patients for whom baseline renal function (serum creatinine level) was unavailable in the 90 days preceding surgery were excluded, as were those for whom no serum creatinine measurements were available in the first 7 postoperative days.

## Primary outcome

The primary outcome of the study was the incidence of AKI within 7 days of the index surgery. Patients were identified as developing AKI if they met Kidney Disease Improving Global Outcomes (KDIGO) criteria<sup>11</sup> (26.5  $\mu\text{mol/l}$  increase in serum creatinine concentration within 48 h, or a greater than 50 per cent increase in creatinine concentration from baseline within 7 days) or underwent unplanned renal replacement therapy.

The following serum creatinine values were collected: a preadmission value measured within 90 days preceding the date of surgery; the first preoperative value measured on the index admission; the last value measured on index admission before surgery. The baseline value for identifying postoperative AKI was the closest of these values to the time of surgery that was available.

One serum creatinine value was recorded for each postoperative day. If serum creatinine was measured more than once daily, the test value taken closest to midday was recorded. In accordance with KDIGO guidelines<sup>11</sup>, if there was a decrease in serum creatinine concentration after surgery, this lower value was adopted as the baseline for identification of AKI on subsequent days.

## Secondary outcomes

Secondary clinical outcomes were measured within or at 30 days after surgery, and included: persistent AKI; requirement for temporary or permanent renal replacement therapy at any time; and occurrence of major complications. Patients were classified as having persistent AKI if the last postoperative serum creatinine level measured up to and including 30 days after surgery was at least 50 per cent greater than the preoperative baseline<sup>12</sup>. Major complications were defined as Clavien–Dindo grade III–V complications<sup>13</sup>, which include unplanned procedures under local or general anaesthesia, organ support in an intensive care setting, stroke or death.

## Data validation

Participating sites were asked to identify voluntarily an independent data validator who had not been involved in the original data collection. The validators determined case ascertainment and data accuracy rates. Case ascertainment was evaluated by independent review of theatre logbooks, operating lists and ward lists, to identify whether any eligible patients had been missed in the original data collection. Estimation of data accuracy was based on validation of 12 predefined data fields (Table S2, supporting information). The proportion of accurately submitted data fields was calculated by dividing the number of correct data fields by the total number of validated data fields.

## Selection of variables

Selection of clinically plausible candidate predictors for postoperative AKI was informed by a literature review, supplemented by discussion and input from senior nephrologists and surgeons. Variables that were feasible to collect routinely before surgery across all centres were selected (Table S3, supporting information). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the baseline estimated glomerular filtration rates (eGFR)<sup>14</sup>. Given the imprecision of measurement of eGFR above 120 ml per min per 1.73 m<sup>2</sup>, eGFR values were bounded at this level. Surgical procedures were classified as low, medium or high risk according to 30-day mortality rates reported in Hospital Episode Statistics<sup>9</sup>. Patients were split into planned open and planned laparoscopic surgery groups. Patients whose laparoscopic procedures were converted to open surgery were included in the planned laparoscopic surgery group.

## Statistical analysis

Testing between demographic and outcome groups was with the  $\chi^2$  test or, for continuous variables, Student's *t* test or the Kruskal–Wallis test. Analyses were carried out in Stata<sup>®</sup> version 14 (StataCorp, College Station, Texas, USA).

Before development of the prognostic model, three clinically relevant risk groups were prespecified: a low-risk group (risk of AKI less than 10 per cent) in which risk of AKI was all but ruled out; a medium-risk group (risk 10–20 per cent); and a high-risk group (risk more than 20 per cent) in which intervention might be appropriate.

A list of clinically plausible interactions was determined in advance of the statistical analysis. Bootstrap stability was used to select risk factors into the model. This approach estimates the proportion of times a risk factor would be

selected into the model if a different random sample of patients were taken each time. Risk factor selection was carried out in two stages. In the first stage backward variable selection, with  $P > 0.150$  as the threshold for exclusion, was carried out within each bootstrap sample. Risk factors selected using this backwards selection approach in least 70 per cent of bootstrap samples were included in a minimum model. In the second stage additional risk factors were added one at a time, and any that achieved  $P < 0.150$  in at least 70 per cent of bootstrap samples were then included in the final model. Non-parametric bootstrap resampling with 1000 bootstrap samples was again used to assess the stability of interactions selected into the model, for all interactions with  $P < 0.100$ . Interactions were added to the model one at a time, and the criterion for selection of interactions was  $P < 0.050$  in at least 80 per cent of bootstrap samples.

Calibration of the model was checked using plots of observed *versus* predicted mortality in deciles of predicted risk. The Hosmer–Lemeshow test, together with the size of differences between observed and predicted risk in deciles of risk, was used to assess calibration. The area under the receiver operating characteristic curve (*c*-statistic) was used to assess discrimination of the model within the derivation data set.

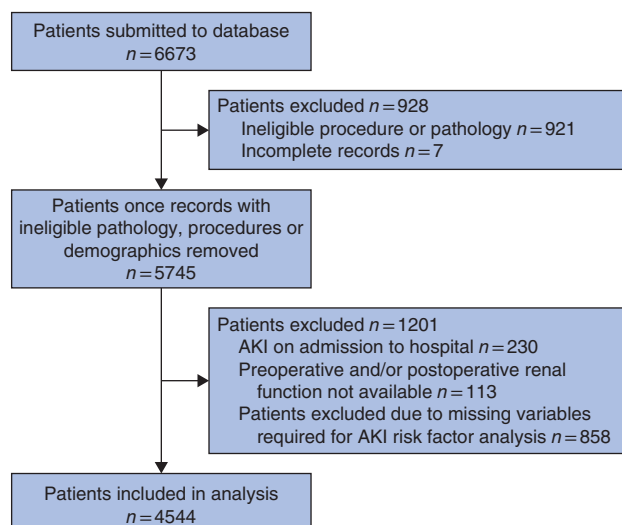
Internal model validation was carried out by bootstrap validation. The *c*-statistic was estimated in the original data, and bootstrap re-sampling was used to adjust for the overoptimism due to validating the model with the same data that were used to build the model.

## Results

A total of 169 hospitals in the UK contributed data to this study, representing about 70 per cent of all UK hospitals providing gastrointestinal surgery<sup>15</sup>. In addition, four hospitals in Ireland participated. Of 5745 otherwise eligible patients, 230 (4.0 per cent) were excluded as they were found to have AKI on admission, and 113 (2.0 per cent) were excluded as data on baseline preoperative and/or postoperative renal function were not available. Overall, a total of 4544 patients, for whom it was possible to measure AKI with complete data for all the risk factors considered for inclusion in the model, were included in the analysis (Fig. 1).

## Validation of case ascertainment and data accuracy

Independent data validation was performed at 47 of the 173 participating centres. The case ascertainment rate was 90.7 per cent. A total of 11 124 data fields were validated within



**Fig. 1** Flow chart of inclusion and exclusion of patients. AKI, acute kidney injury

927 patient records, with an overall data accuracy rate of 96.6 per cent.

### Demographics

Overall, 51.7 per cent (2350 of 4544) of patients were aged over 65 years and 55.3 per cent were men. Most patients (81.9 per cent) underwent elective surgery, with malignancy the commonest indication (60.2 per cent). Half of included patients underwent planned open surgery and half had planned laparoscopic surgery (49.9 *versus* 50.1 per cent respectively) (*Table 1*).

### Incidence of acute kidney injury

Some 14.2 per cent (646 of 4544) of patients developed AKI within 7 days of surgery, most commonly stage 1 AKI (438 of 646, 67.8 per cent). In addition, 17.5 per cent (113 of 646) and 14.7 per cent (95 of 646) experienced stage 2 and stage 3 AKI respectively (*Table 2*). The AKI rate was similar in patients who underwent surgery for malignancy or benign disease (14.9 *versus* 13.1 per cent respectively;  $P = 0.084$ ). The AKI rate was lower in patients who had stoma reversal compared with that in patients who underwent gastrointestinal resection or liver resection (9.6 *versus* 14.8 *versus* 14.2 per cent respectively;  $P = 0.008$ ). In unadjusted analyses, patients who developed AKI were older, more likely to be men, had a higher ASA grade, and were more likely to have higher-stage CKD than those who did not develop AKI (*Table 1*). Among patients excluded

**Table 1** Demographics of derivation cohort

	All included patients (n = 4544)	Patients who developed AKI (n = 646)
Age (years)		
18–55	1266 (27.9)	107 (8.5)
56–65	928 (20.4)	119 (12.8)
66–75	1297 (28.5)	212 (16.3)
76–96	1053 (23.2)	208 (19.8)
Sex (M : F)	2513 : 2031	396 : 250
M	2513 (55.3)	396 (15.8)
F	2031 (44.7)	250 (12.3)
ASA grade		
1	580 (12.8)	51 (8.8)
2	2498 (55.0)	311 (12.4)
3	1284 (28.3)	224 (17.4)
4–5	182 (4.0)	60 (33.0)
eGFR (ml per min per 1.73 m <sup>2</sup> )		
≥ 90	2022 (44.5)	209 (10.3)
60–89	1811 (39.9)	264 (14.6)
30–59	639 (14.1)	143 (22.4)
< 30	72 (1.6)	30 (42)
Ischaemic heart disease		
No	3984 (87.7)	529 (13.3)
Yes	560 (12.3)	117 (20.9)
Congestive heart failure		
No	4458 (98.1)	629 (14.1)
Yes	86 (1.9)	17 (20)
Cerebrovascular disease		
No	4326 (95.2)	605 (14.0)
Yes	218 (4.8)	41 (18.8)
Hypertension		
No	2794 (61.5)	322 (11.5)
Yes	1750 (38.5)	324 (18.5)
Diabetes mellitus		
No	3892 (85.7)	519 (13.3)
Yes	652 (14.3)	127 (19.5)
Malignancy		
No	1807 (39.8)	237 (13.1)
Yes	2737 (60.2)	409 (14.9)
Preoperative ACEi/ARB		
No	3538 (77.9)	447 (12.6)
Yes	1006 (22.1)	199 (19.8)
Preoperative transfusion		
No	4401 (96.9)	615 (14.0)
Yes	143 (3.1)	31 (21.7)
Surgical urgency		
Elective	3721 (81.9)	488 (13.1)
Emergency	823 (18.1)	158 (19.2)
Planned laparoscopic surgery		
No	2269 (49.9)	369 (16.3)
Yes	2275 (50.1)	277 (12.2)
Surgical severity		
Moderate	2864 (63.0)	387 (13.5)
High	1680 (37.0)	259 (15.4)

Values in parentheses are percentages. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

**Table 2** Association between acute kidney injury, major complications (Clavien–Dindo grade III–V) and persistent acute kidney injury

	No AKI* (n = 3898)	AKI within 7 days of surgery (n = 646)			P†
		Stage 1 (n = 438)	Stage 2 (n = 113)	Stage 3 (n = 95)	
30-day major complications					< 0.001
Yes	409 (10.5)	122 (27.9)	43 (38.1)	46 (48)	
No	3484 (89.4)	316 (72.1)	70 (61.9)	49 (52)	
Missing	5 (0.1)	0 (0)	0 (0)	0 (0)	
30-day mortality					< 0.001
Yes	32 (0.8)	26 (5.9)	11 (9.7)	15 (16)	
No	3861 (99.1)	412 (94.1)	102 (90.3)	80 (84)	
Missing	5 (0.1)	0 (0)	0 (0)	0 (0)	
30-day persistent AKI					< 0.001
Yes	29 (0.7)	20 (4.6)	6 (5.3)	12 (13)	
No	3169 (81.3)	339 (77.4)	81 (71.7)	58 (61)	
Missing	700 (18.0)	79 (18.0)	26 (23.0)	25 (26)	

Values in parentheses are percentages. \*Includes patients who developed acute kidney injury (AKI) after the seventh postoperative day. † $\chi^2$  test.

from the study owing to missing AKI risk factor data, the overall rate of AKI was 12.0 per cent (103 of 858).

### Morbidity and mortality associated with acute kidney injury

Few patients who developed AKI (51 of 646, 7.9 per cent) required renal replacement therapy. Renal function recovered in most patients who suffered AKI (482 of 520, 92.7 per cent) for whom 30-day creatinine data were available. In univariable analysis, the development of stage 1 AKI was strongly associated with both 30-day major complications (odds ratio (OR) 3.29, 95 per cent c.i. 2.61 to 4.15;  $P < 0.001$ ) and 30-day mortality (OR 7.61, 4.49 to 12.90;  $P < 0.001$ ). Major complications and mortality increased with each AKI stage (Table 2), with the odds of death being over 20 times greater in patients who developed stage 3 AKI (OR 22.62, 11.79 to 43.42;  $P < 0.001$ ).

### Selection of variables for the acute kidney injury prognostic model

Six risk factors were included in the model for prediction of AKI (Table 3). No interactions met the inclusion criteria. Age was modelled as a linear variable and eGFR as a linear plus quadratic variable. The strongest predictors of AKI were age (70 versus 30 years: OR 0.51, 95 per cent c.i. 0.38 to 0.69;  $P < 0.001$ ), ASA grade (1 versus 4–5: OR 2.81, 1.80 to 4.40;  $P < 0.001$ ) and baseline eGFR (60 versus 30 ml per min per 1.73 m<sup>2</sup>: OR 2.20, 1.74 to 2.79;  $P < 0.001$ ).

### Prognostic model calibration

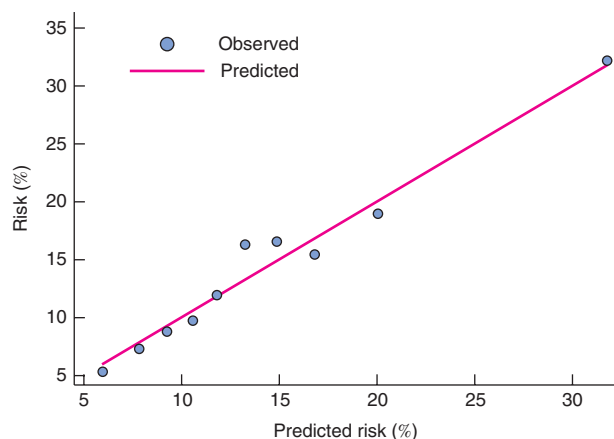
The prognostic model was reasonably well calibrated by deciles of risk (Fig. 2). The Hosmer–Lemeshow test

**Table 3** Multivariable model for prediction of acute kidney injury in the derivation cohort

	Odds ratio	P
Age (years)		< 0.001
30	0.51 (0.38, 0.69)	
50	0.72 (0.62, 0.83)	
70	1.00 (reference)	
90	1.40 (1.21, 1.62)	
Sex		0.002
M	1.00 (reference)	
F	0.76 (0.63, 0.90)	
eGFR (ml per min per 1.73 m <sup>2</sup> )		< 0.001
30	2.20 (1.74, 2.79)	
60	1.00 (reference)	
90	0.77 (0.69, 0.87)	
120	1.02 (0.76, 1.36)	
ASA grade		< 0.001
1	1.00 (reference)	
2	1.26 (0.92, 1.73)	
3	1.45 (1.03, 2.03)	
4–5	2.81 (1.80, 4.40)	
Planned surgical approach		< 0.001
Open surgery	1.00 (reference)	
Laparoscopic surgery	0.76 (0.64, 0.90)	
Preoperative ACEi/ARB		0.009
No	1.00 (reference)	
Yes	1.30 (1.07, 1.59)	

Values in parentheses are 95 per cent confidence intervals. Age and estimated glomerular filtration rate (eGFR) were modelled as continuous variables; therefore odds ratios are given for a selection of values compared with a baseline value. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

demonstrated a reasonable fit ( $P = 0.571$ ). The absolute difference between observed and predicted mortality was within 1 per cent for six of the deciles, and was never greater than 3 per cent (Fig. 2). For both age and eGFR, the continuous lines fitted the risk of AKI well (Figs S1 and S2, supporting information).



**Fig. 2** Calibration plot of observed *versus* predicted risk of acute kidney injury in deciles of predicted risk

### Classification of risk

Overall, 14.6 per cent of patients (662 of 4544) were identified as being at high risk of AKI (Tables S4 and S5, supporting information). The overall observed AKI rate in patients classified as high risk (28.5 per cent) was four times greater than that in patients classified as low risk (7.1 per cent). The sensitivity was 29.3 (95 per cent c.i. 25.8 to 32.8) per cent, and the specificity 87.9 (86.8 to 88.9) per cent.

### Discrimination and internal model validation

The c-statistic for discrimination, within the estimation data, was 0.66 (95 per cent c.i. 0.64 to 0.68), indicating good predictive performance. As expected given the large sample size, the bootstrap validation c-index was similar (0.65).

### Discussion

This study confirmed that postoperative AKI following gastrointestinal surgery is common, affecting around one in seven patients, and is associated with an increased risk of major complications and death. A prognostic model to predict a patient's risk of developing AKI was constructed from a large derivation cohort using six simple preoperative variables, and found to perform well following internal validation.

Previous studies have reported postoperative AKI rates between 2 and 39 per cent<sup>1</sup>. This wide range reflects heterogeneity among their patient populations and variability in the definitions of AKI. Most studies use either traditional AKI definitions, such as the Acute Kidney Injury Network (AKIN) definition or the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE)

criteria, both of which lack the sensitivity of the newer KDIGO AKI definition<sup>11</sup>. As even 'mild', transient episodes of AKI captured by KDIGO definitions are associated with increased mortality<sup>12</sup>, studies reliant on AKIN and RIFLE definitions probably underestimate both the incidence and burden of morbidity associated with postoperative AKI.

The overall postoperative KDIGO AKI rate was 14.2 per cent. This is in line with systematic review findings<sup>1</sup>. As in previous observational studies<sup>12,16</sup>, AKI was detected based on renal function only, because urine output data could not be collected reliably. Although determination of serum creatinine level is in routine clinical use for estimating the glomerular filtration rate, it has significant limitations, including unpredictable responses to stress, disease and nutrition. The initial stress response following surgery is associated with a decrease in serum creatinine levels<sup>12,17</sup>. This may mask the true frequency and severity of postoperative AKI and overestimate renal recovery.

In the present cohort, AKI was associated with a significantly increased risk of morbidity and mortality. Although a causative relationship between AKI and poor clinical outcomes cannot be claimed with this study design, numerous potential mechanisms for harm exist. AKI is independently associated with cytokine release, systemic inflammation and organ dysfunction<sup>18,19</sup>. AKI is an independent predictor of death<sup>20</sup>, and patients who recover from AKI remain at increased risk of cardiovascular complications, progression of CKD and end-stage renal failure<sup>21</sup>. Recent evidence<sup>12</sup> suggests that even mild transient postoperative AKI is strongly associated with an increased risk of death for up to 1 year after surgery.

National UK guidelines mandate that risk assessment of the likelihood of postoperative AKI should inform patients' clinical management<sup>6</sup>. A number of practical recommendations are made for the management of high-risk patients, aimed at reducing the incidence of AKI (Table S6, supporting information), with some evidence supporting implementation of AKI prevention bundles based on similar principles<sup>22</sup>. The prognostic model described here identified a high-risk group in which it would be feasible to implement interventions aimed at mitigating AKI.

Five of the six risk factors contributing to the score (age, sex, ASA grade, CKD stage (eGFR), ACEi/ARB use) match the variables included in the Bell score<sup>16</sup>, developed in a cohort of patients undergoing orthopaedic surgery. The identification of planned open surgery as a risk factor reflects the physiological insult and inflammatory response associated with open surgery<sup>23</sup>, which may contribute to AKI and potentiate the adverse systemic

sequelae of AKI<sup>24</sup>. The present findings suggest that, even if pneumoperitoneum during laparoscopic surgery reduces renal perfusion<sup>25</sup>, this does not necessarily translate to a greater AKI risk.

Many existing prognostic scores have focused on rare endpoints, maximizing their performance. Four previous prognostic models were developed to predict the need for renal replacement therapy (*Table S1*, supporting information). Given that only one in 100 patients required renal replacement therapy, this endpoint has limited clinical significance. The present study identified a strong association between KDIGO AKI and mortality, even in stage 1 AKI, underlining its clinical importance, although it is possible that the KDIGO definition picked up some transient episodes of very mild AKI that have limited clinical significance, thus impairing the score's discrimination.

The observational nature of this study limited the complexity of candidate variables that could be collected. For example, although simple surrogate data points such as preoperative haemoglobin level, red cell transfusion and anticipated intraoperative contamination were not found to predict AKI in this study, the collection of data on preoperative frailty, sepsis, intraoperative fluid management, blood loss and periods of prolonged hypotension may have identified additional variables that predict AKI<sup>26,27</sup>. The model's discrimination may be limited by excluding intraoperative variables, such as the use of vasopressors or goal-directed fluid therapy<sup>28</sup>, and postoperative factors, such as the development of sepsis.

To support uptake, an online calculator for patient-level AKI risk assessment has been created (<https://app.calculoid.com/#/calculator/34162>). Further external validation in an independent data set is required.

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Additional supporting information can be found online in the Supporting Information section at the end of the article.