Original article

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Cardiovascular death and progression to end-stage renal disease after major surgery in elderly patients

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Background: **Reliable estimates for risk of cardiovascular-specific mortality and progression to end-stage renal disease (ESRD) among elderly patients undergoing major surgery are not available. This study aimed to develop simple risk scores to predict these events.**

Methods: **In a single-centre cohort of elderly patients undergoing major surgery requiring hospital stay longer than 24 h, progression to ESRD and long-term cardiovascular-specific mortality were modelled using multivariable subdistribution hazard models, adjusting for co-morbidity, frailty and type of surgery.**

Results: **Before surgery, 2·9 and 11·9 per cent of 16 655 patients had ESRD and chronic kidney disease (CKD) respectively. During the hospital stay, 46·9 per cent of patients developed acute kidney injury (AKI). Patients with kidney disease had a significantly higher risk of cardiovascular-specific (CV) mortality compared with patients without kidney disease (adjusted hazard ratio (HR) for CKD without AKI 1·60, 95 per cent c.i. 1·25 to 2·01; AKI without CKD 1·70, 1·52 to 1·87; AKI with CKD 2·80, 2·50 to 3·20; ESRD 5·21, 4·32 to 6·27), as well as increased progression to ESRD (AKI without CKD 5·40, 3·44 to 8·35; CKD without AKI 8·80, 4·60 to 17·00; AKI with CKD 31·60, 19·90 to 49·90). CV Death and ESRD Risk scores were developed to predict CV mortality and progression to ESRD. Calculated CV Death and ESRD Risk scores performed well with c-statistics: 0·77 (95 per cent c.i. 0·76 to 0·78) and 0·82 (0·78 to 0·86) respectively at 1 year.**

Conclusion: **Kidney disease in elderly patients undergoing major surgery is associated with a high risk of CV mortality and progression to ESRD. Risk scores can augment the shared decision-making process of informed consent and identify patients requiring postoperative renal-protective strategies.**

Funding information
National Center for Advancing Translational Sciences of the National Institutes of Health under University of Florida Clinical and Translational Science, UL1TR000064 and UL1TR001427
National Institute of General Medical Sciences, R01 GM110240, P50 GM-111152, T32 GM-008721
National Science Foundation, Division of Information and Intelligent Systems, 1750192
Gatorade Trust, Department of Medicine, University of Florida, 127900

Presented in part to the American Society of Nephrology Kidney Week 2016, Chicago, Illinois, USA, November 2016

Paper accepted 11 September 2019
Published online 29 November 2019 in Wiley Online Library (www.bjsopen.com). **DOI:** 10.1002/bjs5.50232

Introduction

As the World's population ages, the proportion of elderly patients undergoing major surgery is increasing[1]. Both acute and chronic kidney disease are prevalent among the elderly[2,3], attributable to an age-related decreased renal mass in the elderly[4] and increased prevalence of other renal risk factors such as diabetes, hypertension and cardiac disease. Kidney disease is associated with poor short- and long-term outcomes among the general population[5]. Chronic kidney disease (CKD) is an independent risk factor for cardiovascular risk and mortality[6,7]. Acute kidney injury (AKI) also increases the risk of cardiovascular disease, either independently or through impact on CKD progression[8,9]. Both acute and chronic kidney disease increase the risk of cardiovascular mortality after major surgery[10].

Previous studies[2,11] investigating the long-term outcomes of kidney disease in elderly patients undergoing major surgery have been limited by small sample sizes. This knowledge gap is significant because elderly patients may be more susceptible to both perioperative AKI and to progression to CKD and end-stage renal disease (ESRD)[1,12], as well as having a higher prevalence of underlying cardiac disease. Characterizing associations between kidney disease and long-term outcomes, and predicting the likelihood of adverse events, can provide clinical benefit by augmenting the shared decision-making process of informed consent for surgery, identifying patients who require perioperative renal-protective strategies, providing patients with postoperative preventive plans and education, and reducing healthcare costs. Simple accurate risk scores that utilize accessible routine data to predict outcomes would improve these clinical benefits.

For the purposes of this study, it was hypothesized that elderly patients with kidney disease would be at increased risk of cardiovascular-specific (CV) mortality and progression to ESRD following major surgery, and that these events could be predicted accurately using data available before and during surgery. The aim was to analyse a large cohort of elderly patients undergoing major surgery, to characterize associations between kidney disease and long-term CV mortality and progression to ESRD, adjusting for co-morbidity, frailty and perioperative risk factors, and to develop risk scores to predict CV mortality and progression to ESRD.

Methods

A single-centre cohort analysis was performed, consisting of the elderly patients (aged 65 years or more) from a previously assembled cohort of 51 457 adults who underwent inpatient major surgery (defined as surgery requiring more than 24 h of hospital stay) over a 10-year period ending on 30 November 2010[12].

The study received approval from the Institutional Review Board and Privacy Office of the University of Florida. For all patients, CV mortality and progression to ESRD was assessed for up to 10 years after discharge, and associations with perioperative AKI and CKD were assessed by competing risk analysis.

Outcomes

Hospital records and the Social Security Death Index were used to determine date of death. The primary cause of death was obtained based on death certificates from the Florida Bureau of Vital Statistics using a matching algorithm that used full name, date of birth and date of death in the ICD-10 format. Cause of death was missing from 10·0 per cent (779 of 7768) of all death certificates, probably representing death records from other states. ICD-10 codes were used to classify deaths into CV causes (codes E10–E14, I00–I99, N00–N08, N10–N16, N17–N19, Q20–Q28), cancer-specific (codes C00–C97) and all other causes. ICD-10 codes for kidney disease and diabetes were classified in the expanded CV group to include deaths associated with CKD[6]. Sensitivity analyses were performed by: censoring all patients known to be alive or who had died after 31 October 2011; excluding records without cause of death; and using an alternative approach to classify CV deaths[13,14].

Progression to ESRD after discharge and the timing of this progression were determined by linking records of discharged patients with the US Renal Data System database[15] and calculating the time from discharge date to first ESRD service date.

Definition of kidney disease and co-variables

A reference value for creatinine was established using the minimum serum creatinine level available within 6 months before the index admission, including the value on the day of admission[16,17]. For patients with no previous creatinine value within 6 months before admission and no history of CKD, an estimated reference serum creatinine level was used. This estimated reference value was calculated based on the Modification of Diet in Renal Disease Study equation for creatinine[18], assuming a glomerular filtration rate of 75 ml per min per 1·73 m^2. All available creatinine values during the index hospital admission were then evaluated for the presence of AKI using Kidney Disease: Improving Global Outcomes (KDIGO) criteria[19], defined as an increase of at least 0·3 mg/dl in serum creatinine concentration within 48 h or a 50 per cent increase from the reference creatinine level. Renal replacement therapy was determined using daily billing charges. Complete renal recovery after AKI was defined as the serum creatinine concentration returning to within 50 per cent of the baseline creatinine value by the time of hospital discharge and the absence of renal replacement therapy. Preadmission diagnosis of CKD and ESRD was determined using a validated combination of ICD-9-CM codes. CKD was determined using a calculated reference estimated glomerular filtration rate (eGFR) based on reference serum creatinine standardized for sex, race and age, according to guidelines[16,20]. Race information was missing from 2 per cent of the cohort, which were considered as non-African American ethnicity. Patients with CKD were stratified into mild to moderate (eGFR 30 ml per min per 1·73 m^2 or above) and severe

(eGFR less than 30 ml per min per 1·73 m^2) CKD groups using reference eGFR without criteria for albuminuria according to consensus guidelines[21].

Underlying co-morbidities were identified using previously described criteria, and the combination of ICD-9-CM codes and Charlson–Deyo co-morbidity index[22,23]. Admission haemoglobin values were categorized as missing, less than 10 g/dl, 10–11·9 g/dl and at least 12 g/dl, similar to the values used previously in patients with kidney disease. These values were developed using univariable analysis of the spline function of haemoglobin values and risk of mortality[24]. Further methodological details are provided in *Appendix S1* (supporting information). Frailty is a multidimensional syndrome characterized by increased vulnerability to illness, loss of individual reserve, and decreased resistance to stressors. The intention was to capture physical and cognitive frailty, as both are critical; however, definitions of physical and cognitive frailty make it challenging to operationalize, because no clearcut diagnosis codes are available. Instead, a set of ICD-9 codes that correspond to conditions linked to physical and cognitive impairment in older adults was used to classify patients as having high, moderate or no frailty (*Table S1*, supporting information).

Statistical analysis

The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) recommendations were followed. Pairwise comparisons of kidney disease groups with respect to no known kidney disease were performed with Fisher's exact test for categorical variables and Wilcoxon's rank sum test or *t* test for continuous variables, as appropriate, using Bonferroni adjustment. Cumulative survival probabilities for all-cause mortality were calculated using Kaplan–Meier estimates. Fine–Gray proportional subdistribution hazard regression analyses were used to model CV mortality, and any other cause of death was treated as a competing risk[25]. Progression to ESRD was similarly modelled, and death from any cause before ESRD was treated as a competing risk[26]. Best estimation of the impact of model co-variables can be obtained by regression modelling directly on a cumulative incidence function[27]. In addition to occurrence of kidney disease (ESRD, CKD, AKI, and AKI with CKD), each model was adjusted for age, sex, African American ethnicity, Charlson–Deyo co-morbidity index score, surgery type, emergency surgery status, admission haemoglobin level and frailty score. Explanatory variables were selected based on their significance in a prior univariable analysis and previously reported association in the literature. Using scaled Schoenfeld residuals, it was confirmed that the proportional hazard assumption was satisfied for all variables in the model[26]. For each co-variable in the model, adjusted hazard ratios (HR) with 95 per cent c.i. were reported. Adjusted HRs, running the same models among hospital survivors as a sensitivity analysis, were also obtained. Adjusted model-based cumulative incidence functions of CV mortality and progression to ESRD were plotted by kidney disease. To produce a more representative incidence curve, directly adjusted cumulative estimates for kidney disease were obtained using the implementation of Fine and Gray's weighted estimating equation, which is part of the R 3.2.0 package cmprsk[28,29]. Statistical significance for each group compared to reference group was reported using the Wald χ^2 test based on Fine–Gray proportional subdistribution hazard regression models.

For the purpose of internal validation, and assessing the accuracy of the model, a bootstrap cross-validation method was used to train models on 1000 replicates of 16 655 observations drawn from the full data set with replacement. For each bootstrap replicate, the trained models were validated on the observations from the full data set that were not used for training. The discriminative power of competing risk models was calculated by the C-index, which is an adaptation of Harrell concordance probability estimate to the competing risk setting, using inverse probability of censoring weights to adjust for right censoring. C-index values were reported for training and validation data sets, with the 95 per cent c.i. calculated across the bootstrap samples[30]. The C-index function from the R 3.2.0 package pec (prediction error curves) was used to perform the bootstrap cross-validation and calculate the C-index value.

Two simple scores were developed to calculate the risk of progression to ESRD and CV mortality at the time of discharge, with ranges of 0–81 and 0–48 respectively, using the competing risk regression model[31]. Age was categorized into 5-year age groups (65–69, 70–74, 75–79 and 80 years or more), and other variables were kept the same in the competing risk models. For each risk factor, regression coefficients were estimated, multiplied by ten, and rounded to the nearest integer, representing the component of the score attributable to the presence of that risk factor. A score of zero was assigned for reference levels of the categorical variables, and estimated total risk scores were obtained as the sum of the scores for each risk factor[31]. Subjects were divided into five equal risk strata based on the quintiles of the estimated total risk score. Strata with similar cumulative incidence were combined and further grouped to low, moderate or high risk for simplicity. The incidence of progression to ESRD and CV mortality were then estimated for

each of the risk strata using the empirical cumulative incidence function. All significance tests were two-sided. $P < 0{\cdot}050$ was considered statistically significant. R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA) were used to perform statistical analysis. Further details are provided in *Appendix S1* (supporting information).

Results

Prevalence of kidney disease

Among 16 655 elderly patients requiring hospital admission for at least 24 h after major surgery, 8791 (52·8 per cent) had evidence of kidney disease during the hospital stay (*Table 1*; *Table S2*, supporting information). Most of this disease burden was incurred in the perioperative and postoperative settings. At the time of admission, 1984 (11·9 per cent) and 481 (2·9 per cent) patients had pre-existing diagnoses of CKD and ESRD respectively. During hospitalization, 7817 patients (46·9 per cent) developed AKI; 6326 (38·0 per cent) had *de novo* AKI with no previous history of CKD, and 1491 (9·0 per cent) had AKI superimposed on pre-existing CKD. Of these 7817 patients with AKI, 4885 (62·5 per cent) had complete renal recovery. Subjects with AKI superimposed on pre-existing CKD had lower incidence of complete renal recovery than those with *de novo* AKI (461 of 1491 (30·9 per cent) *versus* 4424 of 6326 (69·9 per cent); $P < 0{\cdot}001$). Patients with any form of kidney disease were more likely to be from older patient groups, of African American ethnicity, and to have multiple co-morbidities. Most patients with CKD (1492, 9·0 per cent) had mild to moderate kidney disease (eGFR 30 ml per min per 1·73 m^2 or above), and only 492 patients (3·0 per cent) had severe disease (eGFR less than 30 ml per min per 1·73 m^2) (*Table 1*).

Progression to end-stage renal disease

Progression to ESRD disproportionately affected patients with pre-existing CKD who developed AKI during hospital stay. Of 15 211 patients with no previous history of ESRD who were discharged alive, 278 (1·8 per cent) progressed to ESRD after discharge. When death from any cause was treated as a competing risk, the cumulative incidence of progression to ESRD within 5 years was highest in patients with CKD who developed AKI, with an adjusted cumulative incidence estimate of 8·5 per cent, compared with 0·3, 1·5 and 2·5 per cent for patients with no kidney disease, AKI with no CKD, and CKD with no AKI respectively ($P < 0{\cdot}001$) (*Fig. 1a* and *Table 2*). Patients with AKI and underlying CKD whose renal function did not return to their baseline value at the time of discharge had significantly higher progression to ESRD than those whose renal function returned to baseline (5-year cumulative incidence of ESRD 11·9 *versus* 2·3 per cent respectively; $P < 0{\cdot}001$) (*Fig. 1b*).

Based on unadjusted and adjusted models, patients who had AKI with CKD had up to a 30-fold increase in HR for progression to ESRD compared with patients with no kidney disease (adjusted HR: 5·40 (95 per cent c.i. 3·44 to 8·35) for AKI without CKD; 8·80 (4·60 to 17·00) for CKD without AKI) (*Table 3*; *Table S3*, supporting information). Adjusted HRs remained similar when models were run on the cohort excluding the 1022 patients (6·1 per cent) who died in hospital.

Charlson–Deyo co-morbidity score of three or more, and surgery type (neurological, non-cardiac general and vascular) were significantly associated with progression to ESRD. Increasing age and high frailty score had a decreased risk of progression to ESRD. Patients with higher frailty have higher mortality and lesser chance of progression to ESRD than those with no frailty. Multivariable models including the interactions between kidney disease and frailty, and between kidney disease and age, were developed as a sensitivity analysis. HRs for age and frailty in the multivariable models with and without interaction terms were similar at each level of kidney disease. Model performance was excellent in the validation data set, with C-index values of 0·86 (95 per cent c.i. 0·82 to 0·90), 0·83 (0·80 to 0·86) and 0·83 (0·80 to 0·86) at 1, 5 and 10 years respectively. No significant difference was found between the C-indices of competing risk models applied to training and validation cohorts ($P > 0{\cdot}050$).

Using a competing risk model, an ESRD Risk score was derived to calculate the risk of progression to ESRD at hospital discharge using nine clinical variables (*Table S4*, supporting information; available at https://prismap.medicine.ufl.edu/risk_calculator/esrd_risk_calculator). Patients were categorized into three risk categories: low, moderate and high. Patients in the low-risk category (ESRD Risk score below 39) had a 5-year rate of progression to ESRD of 0·4 per cent, whereas those in the high-risk category (ESRD Risk score above 47) had a 5-year rate of 6·1 per cent (*Fig. 2a*). In the validation data set, the ESRD Risk score model had C-index values of 0·82 (95 per cent c.i. 0·78 to 0·86), 0·79 (0·76 to 0·82) and 0·79 (0·75 to 0·82) at 1, 5 and 10 years respectively.

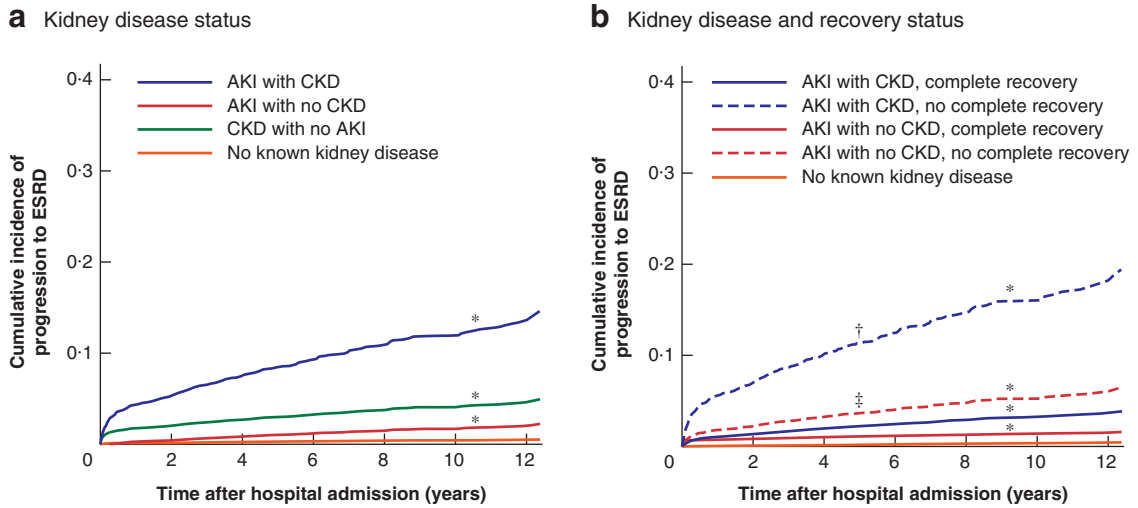
Using the ESRD Risk score, 81·4 per cent (12 938 of 15 896) of patients with no progression to ESRD after discharge had a low or moderate ESRD Risk score, whereas

Table 1 Clinical characteristics of the 16 655 patients, stratified by kidney disease

	No known kidney disease ($n = 7864$)	AKI without CKD ($n = 6326$)	AKI with CKD ($n = 1491$)	CKD without AKI ($n = 493$)	ESRD ($n = 481$)
Age (years)*	73(6)	74(6)#	75(7)#	76(7)#	72(6)#
Sex ratio (F : M)	4123 : 3741	3038 : 3288**	585 : 906**	237 : 256	183 : 298**
African American ethnicity	445 (5·7)	400 (6·3)	190 (12·7)**	44 (8·9)**	108 (22·5)**
Emergency surgery	2223 (28·3)	3001 (47·4)**	836 (56·1)**	186 (37·7)**	298 (62·0)**
Rural area residency	2342 (29·8)	1984 (31·4)**	512 (34·3)	158 (32·0)	141 (29·3)
Distance from residing neighbourhood to hospital (miles)†	30 (14–71)	32 (16–74)#	30 (14–73)	30 (14–66)	35 (13–85)
Population living in poverty in residing neighbourhood (%)*	14(8)	14(8)	15(8)#	14(8)	15(9)
Primary insurance					
Medicare	128 (1·6)	144 (2·3)**	35 (2·3)	8 (1·6)	13 (2·7)
Medicaid	7157 (91·0)	5642 (89·2)	1348 (90·4)	466 (94·5)	420 (87·3)
Private	551 (7·0)	518 (8·2)	105 (7·0)	19 (3·9)	46 (9·6)
Uninsured	28 (0·4)	22 (0·3)	3 (0·2)	0 (0)	2 (0·4)
Emergency surgery	2223 (28·3)	3001 (47·4)**	836 (56·1)**	186 (37·7)**	298 (62·0)**
Weekend admission	684 (8·7)	961 (15·2)**	259 (17·4)**	56 (11·4)	79 (16·4)**
Charlson–Deyo co-morbidity score					
0	2445 (31·1)	1123 (17·8)**	115 (7·7)**	70 (14·2)**	0 (0)**
1	1708 (21·7)	1568 (24·8)**	205 (13·7)**	66 (13·4)**	5 (1·0)**
2	1650 (21·0)	1569 (24·8)**	303 (20·3)	101 (20·5)	99 (20·6)
≥ 3	2061 (26·2)	2066 (32·7)**	868 (58·2)**	256 (51·9)**	377 (78·4)**
Co-morbidity					
Hypertension	4686 (59·6)	3753 (59·3)	905 (60·7)	358 (72·6)**	334 (69·4)**
Cancer	2245 (28·5)	1656 (26·2)**	247 (16·6)**	115 (23·3)	36 (7·5)**
Diabetes	1546 (19·7)	1273 (20·1)	431 (28·9)**	151 (30·6)**	214 (44·5)**
Chronic pulmonary disease	1432 (18·2)	1530 (24·2)**	422 (28·3)**	108 (21·9)	90 (18·7)
Peripheral vascular disease	1085 (13·8)	1461 (23·1)**	462 (31·0)**	120 (24·3)**	92 (19·1)**
Cerebrovascular disease	632 (8·0)	843 (13·3)**	176 (11·8)**	42 (8·5)	42 (8·7)
Congestive heart failure	451 (5·7)	954 (15·1)**	428 (28·7)**	81 (16·4)**	102 (21·2)**
Myocardial infarction	619 (7·9)	792 (12·5)**	242 (16·2)**	78 (15·8)**	70 (14·6)**
Liver disease	181 (2·3)	248 (3·9)**	84 (5·6)**	9 (1·8)	13 (2·7)
Surgery type					
Cardiothoracic	789 (10·0)	1476 (23·3)**	429 (28·8)**	64 (13·0)	90 (18·7)**
Neurological	1475 (18·8)	821 (13·0)**	114 (7·6)**	74 (15·0)	23 (4·8)**
Non-cardiac general surgery‡	1700 (21·6)	1578 (24·9)**	372 (24·9)	120 (24·3)	151 (31·4)**
Specialty surgery§	3368 (42·8)	1653 (26·1)**	364 (24·4)**	202 (41·0)	43 (8·9)**
Other¶	532 (6·8)	798 (12·6)**	212 (14·2)**	33 (6·7)	174 (36·2)**
Admission haemoglobin (g/dl)					
Missing	2628 (33·4)	1201 (19·0)**	274 (18·4)**	169 (34·3)	103 (21·4)**
< 10	1032 (13·1)	1221 (19·3)**	382 (25·6)**	86 (17·4)	90 (18·7)**
10–11·9	1968 (25·0)	1859 (29·4)**	456 (30·6)**	143 (29·0)	148 (30·8)
≥ 12	2236 (28·4)	2045 (32·3)**	379 (25·4)	95 (19·3)**	140 (29·1)
CKD					
Mild to moderate	n.a.	n.a.	1031 (69·1)††	461 (93·5)	n.a.
Severe	n.a.	n.a.	460 (30·9)††	32 (6·5)	n.a.
Frailty status					
None	3304 (42·0)	1637 (25·9)**	149 (10·0)**	120 (24·3)**	25 (5·2)**
Moderate	2002 (25·5)	1561 (24·7)	390 (26·2)	150 (30·4)	241 (50·1)**
High	2558 (32·5)	3128 (49·4)**	952 (63·8)**	223 (45·2)**	215 (44·7)**

Values in parentheses are percentages unless indicated otherwise: values are *mean(s.d.) and †median (i.q.r.). ‡Includes gastrointestinal, oncology and vascular operations; §includes orthopaedic, gynaecological, ear nose and throat, urological and plastic surgery; ¶includes surgery for trauma, burns and transplants. AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; n.a., not applicable. #$P < 0·050$ *versus* no known kidney disease (Wilcoxon rank sum test or *t* test as appropriate, using Bonferroni adjustment); **$P < 0·050$ *versus* no known kidney disease (Fisher's exact test, using Bonferroni adjustment); ††$P < 0·050$ *versus* CKD without AKI (Fisher's exact test).

Fig. 1 Adjusted cumulative incidence curves for progression to end-stage renal disease



a Kidney disease status and **b** kidney disease and recovery status (adjusted for age, sex, ethnicity, Charlson co-morbidity index score, emergency surgery status, frailty score, surgery type and admission-day haemoglobin level). AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease. *$P < 0{\cdot}001$ *versus* no known kidney disease; †$P < 0{\cdot}001$ *versus* AKI with CKD, complete recovery; ‡$P < 0{\cdot}001$ *versus* AKI with no CKD, complete recovery (Wald χ^2 test based on Fine–Gray proportional subdistribution hazard regression model).

Table 2 Adjusted 5-year cumulative incidence of cancer and cardiovascular-specific mortality, and progression to end-stage renal disease by kidney disease status

	No. of patients	5-year cancer-specific mortality (%)	5-year cardiovascular-specific mortality (%)	5-year progression to ESRD (%)
No known kidney disease	7864	14·8	8·1	0·3
CKD without AKI	493	8·9*	12·5*	2·5*
AKI without CKD	6326	15·6	13·2*	1·5*
AKI with CKD	1491	7·7*	20·8*	8·5*
ESRD	481	2·3*	33·8*	n.a.

ESRD, end-stage renal disease; CKD, chronic kidney disease; AKI, acute kidney injury; n.a., not applicable. *$P < 0{\cdot}001$ *versus* no known kidney disease (Wald χ^2 test based on Fine–Gray proportional subdistribution hazard regression model).

66·2 per cent (184 of 278) of those with progression to ESRD after discharge had a high ESRD Risk score. Some 18·5 per cent (34 of 184) of the patients with a high ESRD Risk score did not have CKD before surgery.

All-cause mortality and cause of death

Patients with baseline renal dysfunction who developed AKI after surgery without complete renal recovery at the time of discharge had increased long-term all-cause mortality. The median duration of follow-up for the entire cohort was 7 (maximum 13) years.

Patients with any type of kidney disease had a significantly lower long-term survival rate for all-cause mortality compared with patients with no kidney disease ($P < 0{\cdot}001$), after adjusting for all co-variables. At 5-year follow-up, the cumulative survival rate for those without kidney disease was 70·3 per cent, compared with 37·7–57·8 per cent for patients who had kidney disease (*Fig. S1a*, supporting information). Patients with AKI without complete renal recovery by the time of hospital discharge had a significant decrease in survival compared with patients who did recover, with a 5-year cumulative survival rate of 50·1 per cent for AKI superimposed on CKD with renal recovery *versus* 37·4 per cent in patients who had AKI and CKD with no recovery. In patients with AKI alone (no CKD), the cumulative survival rate was 56·5 per cent after recovery from AKI *versus* 43·7 per cent in those with no recovery from AKI ($P < 0{\cdot}001$) (*Fig. S1b*, supporting information).

Among all 7768 deaths, the top two causes were cardiovascular disease (2449 patients, 31·5 per cent) and cancer (2432, 31·3 per cent), followed by accidents, injury,

Table 3 Adjusted hazard ratios for progression to end-stage renal disease and cardiovascular-specific mortality using multivariable subdistribution hazard models

	Adjusted hazard ratio*	
	Progression to ESRD	Cardiovascular-specific mortality
Kidney disease		
No known kidney disease	1·00 (reference)	1·00 (reference)
AKI without CKD	5·40 (3·44, 8·35)†	1·70 (1·52, 1·87)†
AKI with CKD	31·60 (19·90, 49·90)†	2·80 (2·50, 3·20)†
CKD without AKI	8·80 (4·60, 17·00)†	1·60 (1·25, 2·01)†
ESRD	n.a.	5·21 (4·32, 6·27)†
Age (per 1-year increase)	0·95 (0·93, 0·97)†	1·04 (1·03, 1·04)†
Male sex (*versus* female)	0·98 (0·79, 1·23)	1·10 (1·01, 1·19)†
African American ethnicity (*versus* other)	2·08 (1·58, 2·75)†	1·12 (0·97, 1·29)
Charlson–Deyo co-morbidity score		
0	1·00 (reference)	1·00 (reference)
1	1·21 (0·88, 1·68)	1·27 (1·09, 1·47)†
2	1·55 (1·00, 2·41)	1·41 (1·22, 1·63)†
≥ 3	2·11 (1·40, 3·19)†	1·33 (1·16, 1·53)†
Emergency surgery (*versus* elective)	1·10 (0·90, 1·40)	1·38 (1·26, 1·50)†
Surgery type		
Specialty surgery	1·00 (reference)	1·00 (reference)
Cardiothoracic	1·33 (0·96, 1·86)	2·25 (1·99, 2·53)†
Neurological	0·47 (0·26, 0·85)†	1·49 (1·30, 1·71)†
Non-cardiac general surgery	1·58 (1·17, 2·14)†	1·56 (1·39, 1·75)†
Other	1·38 (0·95, 2·00)	0·72 (0·60, 0·86)†
Admission haemoglobin (g/dl)		
≥ 12	1·00 (reference)	1·00 (reference)
< 10	1·36 (0·99, 1·88)	1·06 (0·94, 1·20)
10–11·9	1·21 (0·89, 1·64)	1·12 (1·01, 1·24)†
Missing	1·21 (0·88, 1·68)	1·00 (0·89, 1·12)
Frailty status		
None	1·00 (reference)	1·00 (reference)
Moderate	0·96 (0·71, 1·29)	1·32 (1·15, 1·51)†
High	0·60 (0·44, 0·83)†	1·86 (1·64, 2·09)†
C-statistic for model at 5 years in validation data set	0·83 (0·80, 0·86)	0·83 (0·80, 0·87)

*Values in parentheses are 95 per cent confidence intervals. ESRD, end-stage renal disease; AKI, acute kidney injury; CKD, chronic kidney disease; n.a., not applicable. †$P < 0·050$.

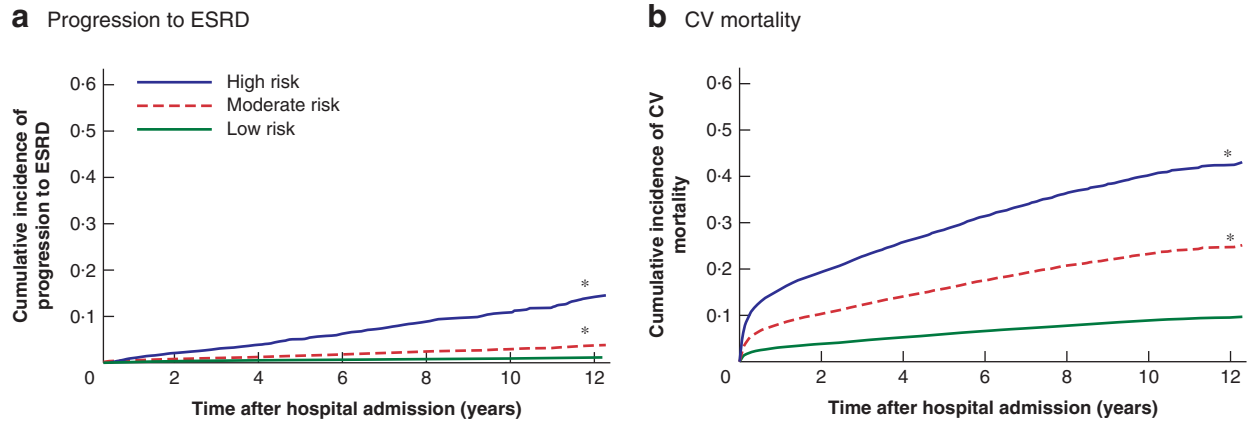
poison or homicide (322, 4·1 per cent), chronic lower respiratory disease (313, 4·0 per cent) and cerebrovascular disease (249, 3·2 per cent) (*Table S5*, supporting information). More deaths were attributed to cardiovascular disease in patients who had kidney disease of any kind compared with deaths in those without kidney disease ($P < 0·001$). In contrast, fewer deaths were attributed to cancer in patients with any type of kidney disease than in those with no kidney disease (*Fig. S2*, supporting information).

Cardiovascular-specific mortality

Patients with pre-existing CKD who developed AKI during hospital stay had increased long-term CV mortality (*Fig. 3*). At 5 years after discharge, patients who had AKI with CKD had a greater likelihood of dying from a cardiovascular cause than of progressing to ESRD or dying from cancer (*Table 2*). When stratified by age group and sex, adjusted CV mortality associated with kidney disease remained increased, with men aged 80 years or above and with the most severe kidney disease faring worse than women (5-year cumulative incidence 58·4 *versus* 32·3 per cent respectively for the ESRD group and 31·1 *versus* 23·3 per cent for the AKI with CKD group) (*Fig. S3*, supporting information).

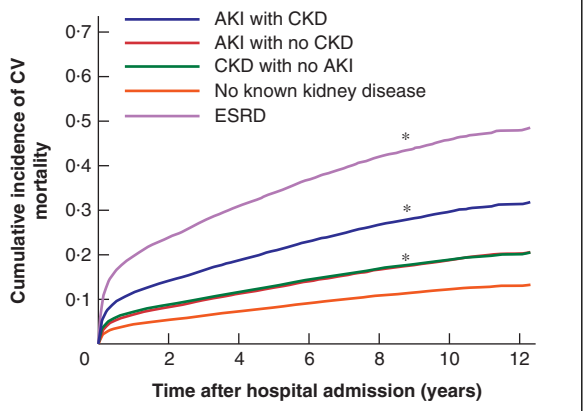
In the multivariable model, patients with kidney disease had significantly higher adjusted HRs for CV mortality, ranging from 1·60 (95 per cent c.i. 1·25 to 2·01) for patients

Fig. 2 Cumulative incidence curves of simplified score for progression to end-stage renal disease and cardiovascular-specific mortality at discharge



a Progression to end-stage renal disease (ESRD) and **b** cardiovascular-specific (CV) mortality at discharge. Low risk: ESRD Risk score less than 39, CV Death Risk score less than 20; moderate risk: ESRD Risk score 39–47, CV Death Risk score 20–24; high risk: ESRD Risk score above 47, CV Death Risk score above 24. *$P < 0{\cdot}001$ *versus* low group (Wald χ^2 test based on Fine–Gray proportional subdistribution hazard regression model).

Fig. 3 Adjusted cumulative incidence curves for cardiovascular-specific mortality by kidney disease status



Adjusted for age, sex, ethnicity, Charlson co-morbidity index score, emergency surgery status, frailty score, surgery type and admission-day haemoglobin level. CV, cardiovascular-specific; ESRD, end-stage renal disease; AKI, acute kidney injury; CKD, chronic kidney disease. *$P < 0{\cdot}050$ *versus* no known kidney disease (Wald χ^2 test based on Fine–Gray proportional subdistribution hazard regression model).

with CKD and no AKI to 5·21 (4·32 to 6·27) for those who had ESRD before admission. Adjusted HRs for AKI without CKD and AKI superimposed on CKD were 1·70 (1·52 to 1·87) and 2·80 (2·50 to 3·20) respectively (*Table 3*). Adjusted HRs for kidney disease groups were reduced slightly compared with unadjusted HRs (*Table S3*, supporting information). Age, sex, Charlson–Deyo co-morbidity score, frailty score, haemoglobin level of 10–12 g/dl on admission, emergency surgery status and surgery type were significantly associated with CV mortality. Adjusted HRs remained similar when models were run on the cohort excluding the 1022 patients who died in hospital. Model performance was excellent in the validation data set, with C-index values of 0·87 (95 per cent c.i. 0·83 to 0·91), 0·83 (0·80 to 0·87) and 0·82 (0·80 to 0·86) at 1, 5 and 10 years, respectively. There were no significant differences between the C-indices of competing risk models applied to training and validation cohorts ($P > 0{\cdot}050$).

Using a competing risk model, a CV Death Risk score was derived to calculate the risk of CV mortality at hospital discharge using nine clinical variables (*Table S6*, supporting information; available at https://prismap.medicine.ufl.edu/risk_calculator/cv_risk_calculator). Patients were categorized as having low, moderate or high risk. Patients in the low-risk category (CV Death Risk score below 20) had the lowest 5-year rate of CV death at 5·9 per cent, whereas those in the high-risk category (CV Death Risk score above 24) had a 5-year rate of 28·9 per cent (*Fig. 2b*). In the validation data set, the CV Death Risk score model had C-indices of 0·77 (95 per cent c.i. 0·76 to 0·78), 0·72 (0·71 to 0·74) and 0·70 (0·68 to 0·71) at 1, 5 and 10 years respectively.

Of 2449 patients with long-term CV mortality after surgery, 1732 (70·7 per cent) had a high CV Death Risk score. Some 53·9 per cent of these patients (934 of 1732) had no documented cardiovascular disease before surgery.

Discussion

This study of a large single-centre cohort of elderly patients undergoing surgery found that having both acute and chronic kidney disease in the perioperative period was associated with up to fivefold increased long-term CV mortality and 30-fold increased progression to ESRD. This association was independent of the underlying co-morbidity burden, frailty and type of surgery, and was particularly strong in male octogenarians compared with women. Increasing age and high frailty score had a decreased risk of progression to ESRD, which might be due to the competing risk of all causes of death occurring before progression to ESRD. Despite the fact that most patients did not have CKD before surgery, half of the cohort experienced an episode of perioperative AKI. Among patients with AKI, the absence of renal recovery was associated with an up to fourfold increased progression to ESRD and an approximately 13 per cent decreased probability of survival 5 years after discharge. Elderly patients with AKI superimposed on underlying CKD were the most vulnerable group, with a 5-year cumulative CV mortality rate of 20·8 per cent, after patients with ESRD who had a CV mortality rate of 33·8 per cent.

Progression to ESRD was significantly more common among patients with any form of kidney disease in the perioperative setting. When superimposed on pre-existing CKD, AKI may expedite progression to ESRD[9], rendering these patients more susceptible to CV death, with mortality rates comparable to those in patients with pre-existing ESRD. Non-recovery of renal function after an episode of AKI was an important contributor to ESRD progression. Patients with pre-existing CKD who developed a perioperative AKI episode without renal recovery had the highest incidence of progression to ESRD, followed by patients with *de novo* AKI and no renal recovery. Non-recovery of renal function after AKI probably places the patient at a starting point on the kidney disease spectrum closer to ESRD, with each subsequent insult decreasing renal reserve and increasing the likelihood that the next renal injury will result in ESRD. In these patients, special attention must be directed at optimization of other cardiovascular risk factors, such as management of hypertension, hyperlipidaemia, diabetes, and salt and water balance.

In this study, CV Death Risk and ESRD Risk scores were developed and validated, and performed well to predict risk of CV mortality and progression to ESRD at the time of hospital discharge. This is the first study to validate clinical scores that can easily be calculated using routinely accessible data including pre-existing kidney disease, AKI development during hospital stay and type of surgery to estimate the risk of CV mortality and progression to ESRD after discharge in elderly patients undergoing surgery. These tools can provide patients and their caregivers with accurate prognostic information and related education, augment shared decision-making processes regarding resource utilization, and identify patients who will benefit from more structured nephrology referral and secondary cardiovascular prevention after discharge. Currently there is poor adherence with appropriate specialty referral after hospital stay, with as few as 12 per cent of AKI survivors receiving nephrology follow-up[32] and less than 30 per cent of eligible patients with cardiovascular disease referred for cardiac rehabilitation[33].

Risk stratification is being used increasingly to estimate patients' risk of adverse events. The Revised Cardiac Risk Index[34] estimates postoperative cardiac events in the general population; a more recent cardiovascular risk score for elderly surgical patients had moderate accuracy[35]. Similarly, risk scores for progression to ESRD in patients with CKD[36], and specifically in the elderly[37], have performed moderately well with C-statistic values ranging from 0·82 to 0·84 on validation. Those risk scores were developed only for patients with CKD and do not consider stressor events such as surgery or AKI. The CV Death Risk and ESRD Risk scores outlined in the present study allow for determination of long-term risk in elderly patients at the time of discharge, including consideration of in-hospital events such as AKI that significantly impact the likelihood of long-term mortality.

In the general elderly population, kidney disease is a known risk factor for cardiovascular risk and mortality[6–9], as well as progression to ESRD. Surgery is associated with increased risk for both perioperative AKI development[38] and CKD progression[39]. With increasing life expectancy, more operations are being done in patients with advanced age. Simultaneously, the incidence of kidney disease in the elderly is increasing[40,41], and the association between postoperative kidney disease and death is well established[42–46]. The combination of cardiovascular and kidney disease emerges from shared pathophysiological mechanisms and may further increase the risk of mortality. Risk factors for both kidney and cardiovascular disease include hypertension, hyperlipidaemia, diabetes, alterations in mineral and water balance and in the renin–angiotensin–aldosterone axis, inflammation and endothelial dysfunction[47–51]. Elderly patients, especially those with existing CKD, are particularly vulnerable to CV mortality and progression of kidney disease after surgery. These patients require attentive perioperative management, including accurate preoperative risk stratification, AKI prevention in the preoperative and perioperative setting, and avoidance

of further kidney damage, as well as maximizing renal recovery in those with established AKI.

Limitations of this study include the retrospective design, use of ICD-9 codes to identify patients, and limited access to cause-of-death information for states other than Florida. Efforts to increase the internal validity of the competing risk models included using multivariable adjustments and evaluation of model discrimination on validation data sets. The ability to generalize the findings may be limited owing to using the characteristics of patients from a single centre; however, the study site is a large tertiary care centre receiving referrals from a large geographical area, and therefore has a diverse patient population. KDIGO consensus definitions for AKI severity categories were applied using serum creatinine changes only without urine output criteria due to low accuracy in the recording of urine output in the ward setting. The reference creatinine concentration was established using the minimum serum creatinine value available within 6 months before the index admission, including the value on the day of admission. CKD status was defined using a combination of eGFR on admission and ICD-9-CM codes. A recent systematic review[52] showed high specificity for coded CKD co-variables, with all studies reporting values of 0·90 or higher, whereas sensitivity was highly variable. Several traditional Framingham risk factors for cardiovascular disease[53], such as smoking history, systolic BP, use of antihypertensive medication, and total and high-density lipoprotein cholesterol levels, could not be included as co-variables because these risk factors were not available in the administrative database. However, information on cardiovascular co-morbidity regarding previous congestive heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease, and diabetes mellitus without and with complications was available and included.

This study has demonstrated that elderly patients with kidney disease of any type undergoing major surgery have higher risk of progression to ESRD and CV mortality. This could partly be attributable to the lack of appropriate postoperative preventive strategies and nephrology follow-up in elderly patients. The two clinical risk scores, CV Death Risk and ESRD Risk, can be calculated at hospital discharge from readily available clinical data to identify patients with kidney disease who have an increased risk of CV mortality and progression to ESRD, with good accuracy. These simplified risk scores can help clinicians to establish a more appropriate postoperative therapeutic and preventive plan to reduce these complications, and patients would benefit from accurate prognostic information and early referral to nephrology after discharge to address both progression of kidney disease as well as treatment of traditional and non-traditional cardiovascular risk factors[54].

These risk prediction models could potentially be improved by enriching the models with more granular clinical variables, such as CKD and AKI severity, potential interaction between the variables, and external model validation before being introduced as a standard clinical tool. To improve outcomes in this population, bench and bedside approaches must further elucidate pathophysiological mechanisms, emphasize appropriate perioperative management of cardiovascular and renal co-morbidities, and ensure adequate follow-up for high-risk patients.

Acknowledgements

N.L., H.H. and A.D. contributed equally to this manuscript.

This work was supported in part by a National Institutes of Health (NIH)/National Center for Advancing Translational Sciences Clinical and Translational Sciences award to the University of Florida (UL1 TR000064). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. A.B., A.D. and T.O.-B. had full access to all study data, and take responsibility for the integrity of the data and the accuracy of the data analysis.

A.B., T.O.-B. and P.R. were supported by the National Institute of General Medical Sciences (R01 GM110240). A.B., T.O.-B. and P.E. were supported by a Sepsis and Critical Illness Research Centre award (P50 GM-111152) from the National Institute of General Medical Sciences. P.R. was supported by CAREER award number 1750192 from the National Science Foundation, Division of Information and Intelligent Systems. T.O.-B. has received a grant from the National Center for Advancing Translational Sciences Clinical and Translational Sciences (UL1TR001427), and a grant from the Gatorade Trust, Department of Medicine, University of Florida (127900). T.J.L. was supported by a postgraduate training grant (T32 GM-008721) in burns, trauma and perioperative injury from the National Institute of General Medical Sciences.

Disclosure: The authors declare no conflict of interest.

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Supporting information

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