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Research Paper

Bilateral renal artery stenosis impacts postoperative complications after major vascular surgery☆

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ABSTRACT

Background: Incidental atherosclerotic renal artery stenosis (RAS) is common in patients undergoing vascular surgery and has been shown to be associated with postoperative AKI among patients undergoing major non-vascular surgeries. We hypothesized that patients with RAS undergoing major vascular procedures would have a higher incidence of AKI and postoperative complications than those without RAS.
Methods: A single-center retrospective cohort study of 200 patients who underwent elective open aortic or visceral bypass surgery (100 with postoperative AKI; 100 without AKI) were identified. RAS was then evaluated by review of pre-surgery CTAs with readers blinded to AKI status. RAS was defined as ≥50 % stenosis. Univariate and multivariable logistic regression was used to assess association of unilateral and bilateral RAS with postoperative outcomes.
Results: 17.4 % (n = 28) of patients had unilateral RAS while 6.2 % (n = 10) of patients had bilateral RAS. Patients with bilateral RAS had similar preadmission creatinine and GFR as compared to unilateral RAS or no RAS. 100 % (n = 10) of patients with bilateral RAS had postoperative AKI compared with 45 % (n = 68) of patients with unilateral or no RAS ($p < 0.05$). In adjusted logistic regression models, bilateral RAS predicted severe AKI (OR 5.82; CI 1.33, 25.53; $p = 0.02$), in-hospital mortality (OR 5.71; CI 1.03, 31.53; $p = 0.05$), 30-day mortality (OR 10.56; CI 2.03, 54.05; $p = 0.005$) and 90-day mortality (OR 6.88; CI 1.40, 33.87; $p = 0.02$).
Conclusions: Bilateral RAS is associated with increased incidence of AKI as well as in-hospital, 30-day, and 90-day mortality suggesting it is a marker of poor outcomes and should be considered in preoperative risk stratification.

Introduction

Postoperative acute kidney injury (AKI) is a frequent and serious complication of vascular surgery, reported to be as high as 59 % across a cohort of all vascular surgery patients [1]. There are significant differences in the incidence of postoperative AKI, dependent on the type of procedure performed [2] as well as patient demographics, comorbidities, and medication use [3,4]. Additionally, incidental atherosclerotic renal artery stenosis (RAS) has previously been shown to be an important factor contributing to the development of postoperative AKI [5,6]. There is a paucity of literature on renal artery stenosis and postoperative AKI in patients undergoing major vascular surgery.

In vascular surgery patients, it has been shown that AKI is associated with increased perioperative morbidity, mortality and cost [1]. Patients undergoing open aortic surgery are the highest risk vascular group for AKI with a rate of up to 76 % in patients undergoing open surgical repair for a ruptured abdominal aortic aneurysm [4]. Identification of risk factors for postoperative AKI in high risk vascular patients could aid in the creation and performance of personalized pre and perioperative risk-reduction strategies and surveillance for complications [7]. We hypothesized that preoperative renal artery stenosis would be associated with the development of AKI after elective open aortic and/or visceral bypass surgery.

Methods

Study population and design. The University of Florida Integrated Data Repository was used to assemble a single-center cohort for all patients

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admitted to the University of Florida Health and underwent elective major vascular surgery between June 1st 2014 through March 1st 2019 by integrating electronic health records (EHR) with other clinical, administrative and public databases, as previously described [1]. Patients undergoing open aortic or visceral bypass surgery, as defined using current procedural terminology (CPT) codes listed in eTable 1, were included in the study. An honest broker from the University of Florida Integrated Data Repository (IDR) selected one hundred patients from this retrospective cohort of patients with perioperative or postoperative AKI and one hundred patients without AKI with similar demographic and admission characteristics. All patients included in the study underwent computed tomography angiography (CTA) prior to surgery. The IDR team collected the imaging and removed all patient identifiers within the imaging. The images were assigned a new code number by the IDR. Three reviewers (AF, SH, and MC) who were blinded to the patients AKI status were then given temporary access to a folder created for this study within a protected shared drive. The reviewers evaluated the degree of renal artery stenosis using renal artery diameter, kidney length and cortical area as previously published [8]. The subjects were only included in the cohort if imaging was of adequate quality for analysis. The deidentified data collected by these three reviewers was then matched back to the subject ID by the honest broker and provided a data set with our IRB approved variables of interest. Only the IDR was able to identify and re-identify the subjects in this study. Of note, 39 patients were excluded from the cohort because despite having preoperative CTAs, the images had either >5 mm cuts, were without contrast or were of very poor quality and reviewers were not able to accurately obtain kidney morphological characteristics and/or renal artery diameters and the final cohort included a total of 161 patients (n = 78 with AKI, n = 83 without AKI). The University of Florida Institutional Review Board (#201600223) approved this study with waiver of informed consent.

Definitions. Renal artery stenosis determination was made by measuring the ratio between the diameter of the narrowest segment of the imaged renal artery and the diameter of a normal (reference) segment of the artery proximal to the stenosis or distal to poststenotic dilation, as previously described [8]. The grouping was done based on below definition:

RAS, if 1 - (min diameter/normal diameter) *100 ≥ 50 %.

No RAS, if 1 - (min diameter/normal diameter) *100 < 50 %.

Bilateral RAS, if ≥ 50 % stenosis in both the left and right renal arteries, or with a single perfused kidney with ≥50 % stenosis.

If there was an accessory renal artery, the largest artery was used. Renal length was referred to as the difference between the first section that showed the superior pole of the kidney, and the first section that showed the inferior pole of the kidney. Cortical thickness was assessed using six measurements: anterosuperior (AST), laterosuperior (LST), posterosuperior (PST), anteroinferior (AIT), lateroinferior (LIT), and posteroinferior (PIT). Superior cortical thicknesses were studied two centimeters below the superior pole of the kidney, and inferior cortical thicknesses two centimeters above the inferior pole of the kidney. Cortical area was defined as renal length x mean cortical thickness [9].

Outcomes. Outcomes included the following eight major common postoperative complications, as previously described [10]: wound complications, AKI (defined using the consensus Kidney Disease Improving Global Outcomes (KDIGO) criteria as at least a 50 % or 0.3 mg/dL increase in serum creatinine relative to the reference creatinine [11]) at postoperative days 3, 7 and anytime after surgery, mechanical ventilation (MV) and intensive care unit (ICU) admission for >48 h, cardiovascular (CV) complications, neurological complications, sepsis and venous thromboembolism (VTE), occurring anytime during hospitalization after the index operation. Severe AKI is defined as Stage 2 or Stage 3 AKI, as previously described [12]. The Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR) equation, which takes into consideration creatinine and patient characteristics, was used to define GFR in this cohort of patients, as previously described by Levey et al. [13]

Statistical methods. We are unaware of any analyses of patients undergoing major vascular surgery with and without postoperative AKI and incidence of renal artery stenosis; these analyses were performed in an exploratory fashion. Our group has previously published the incidence of postoperative AKI in this cohort (patients undergoing open aortic/visceral bypass surgery), which was 52 % [1]. Additionally, incidental renal artery stenosis has been described in the literature to range from 14 to 26 % [5,14–16]. Assuming class imbalance with a sampling ratio of ~15 cases without RAS per one case with RAS, power of 0.8, a type I error rate of 0.05, our analysis would be powered to detect a statistically significant difference between cohorts in the incidence of RAS. Interobserver variability between reviewers with regard to the same subject's renal artery diameter, kidney length and cortical area was assessed by determining an intraclass correlation coefficient, as previously described [17]. Univariate comparisons between patients with and without AKI were made using *t*-tests and Kruskal-Wallis test for continuous variables and using chi-square Fisher's exact tests for categorical data, as appropriate. Adjustments for multiple comparisons were made using False Discovery Rate (FDR) method. Significant associations between radiographic CTA variables and the development of postoperative AKI were further assessed using unadjusted logistic regression and then multivariable logistic regression with adjustments for GFR, BMI, age, sex, race, DM and intraoperative hypotension. All statistical analyses were performed using R and Python with two-tailed $p < 0.05$ used as the threshold for significance.

Results

Participant baseline characteristics. A total of 161 adult patients undergoing elective open aortic surgeries were included in the study. 17.4 % (n = 28) of patients had unilateral RAS while 6.2 % (n = 10) of patients had bilateral RAS. Preoperative characteristics of subjects are shown in Table 1. Median age was 70 years (IQR 61, 75) and 73 % of the population was male. Patients with bilateral RAS had similar median preadmission creatinine as compared to patients with unilateral RAS or no RAS (bilateral RAS 0.97; IQR 0.82, 1.41 vs. unilateral RAS 0.95; IQR 0.79, 1.03 vs. no RAS 0.93; IQR 0.79, 1.04), as well as similar GFRs. There were no differences in patient preoperative systolic, diastolic or mean arterial pressure.

Morphological characteristics. The morphological characteristics of patients' kidneys are illustrated in Fig. 1A–C. Patients with bilateral RAS and unilateral RAS had a smaller median renal artery diameter, as compared with no RAS; 1.2 mm (IQR 1, 1.6; $p < 0.05$) vs. 2.7 mm (IQR 2.3, 3.1; $p < 0.05$) vs. 4.6 mm (IQR 4.0, 5.4), respectively (Fig. 1A). Patients with bilateral RAS had a smaller median cortical area as compared with patients with unilateral RAS and no RAS; 606mm^2 (IQR 497, 745; $p < 0.05$) vs. 986mm^2 (IQR 832, 1166; $p < 0.05$) vs. 1130mm^2 (IQR 923, 1343). Patients with bilateral RAS also had a smaller cortical area as compared with the unilateral RAS and no RAS group (Fig. 1B). Patients with bilateral RAS had a shorter kidney length as compared with unilateral and no RAS; 90 mm (IQR 82, 95; $p < 0.05$) vs 103 (IQR 98, 109; $p < 0.05$) vs. 103 (IQR 96, 112), respectively. Patients with bilateral RAS also had a shorter kidney length as compared with the unilateral RAS and no RAS group (Fig. 1C).

Outcomes. There were no differences in preoperative characteristics or outcomes between unilateral RAS and no RAS, and the remaining analysis assessed unilateral RAS or no RAS as one variable vs. bilateral RAS. 100 % (n = 10) of patients with bilateral RAS had postoperative AKI as compared with 45 % (n = 68) of patients with unilateral or no RAS ($p < 0.05$). AKI within 3 days, 7 days and anytime after surgery was

Table 1
Preoperative characteristics of patient cohort.

	Overall (N = 161)	Bilateral RAS (N = 10, 6 %)	Unilateral RAS (N = 28, 17 %)	No RAS (N = 123, 76 %)
Demographics				
Age, median (IQR)	70 (61, 75)	73 (70, 74)	75 (66, 78)*	69 (60, 74)
Male sex, n (%)	117 (73)	6 (60)	18 (64)	93 (76)
BMI (kg/m^2), median (IQR)	25.6 (22.1, 29.8)	22.7 (21.3, 26.1)	23.5 (19.2, 28.0)	26.3 (22.6, 30.1)
African-American, n (%)	12 (7)	1 (10)	1 (4)	10 (8)
Smoking, n (%)				
Former	70 (43)	6 (60)	9 (32)	55 (45)
Current	62 (39)	2 (20)	16 (57)	44 (36)
Never	14 (9)	0 (0)	3 (11)	11 (9)
Unknown	15 (9)	2 (20)	0 (0)	13 (11)
Comorbidities, n (%)				
Peripheral vascular disease	161 (100)	10 (100)	28 (100)	123 (100)
Hyperlipidemia	50 (31)	2 (20)	11 (39)	37 (30)
Chronic kidney disease	42 (26)	6 (60)*	12 (43)*	24 (20)
Congestive heart failure	30 (19)	3 (30)	7 (25)	20 (16)
Coronary artery disease	24 (15)	2 (20)	10 (36)*	12 (10)
Diabetes mellitus	19 (12)	0 (0)	2 (7)	17 (14)
Hypertension	147 (91)	10 (100)	27 (96)	110 (89)
Preoperative blood pressure				
Systolic, median (IQR)	136 (118, 149)	133 (117, 142)	139 (125, 153)	135 (118, 148)
Diastolic, median (IQR)	75 (66, 82)	74.5 (59, 78)	71 (63, 82)	76 (67, 82)
Mean arterial pressure, median (IQR)	92 (82, 103)	87 (79, 94)	92 (86, 108)	93 (83, 103)
Preadmission Creatinine	0.94 (0.79, 1.04)	0.97 (0.82, 1.41)	0.95 (0.79, 1.03)	0.93 (0.79, 1.04)
Preadmission eGFR	76 (69, 89)	69 (49, 78)	74 (64, 89)	76 (69, 91)
Surgery type, n (%)				
AAA repair	89 (55)	5 (50)	12 (43)	72 (59)
ABF bypass	43 (27)	3 (30)	7 (25)	33 (27)
Aorta-mesenteric/renal	21 (13)	2 (2)	5 (18)	14 (11)
TAAA repair	5 (3)	0 (0)	4 (14)	1 (1)
Other	3 (1)	0 (0)	0 (0)	3 (1)

Abbreviations: RAS, Renal Artery Stenosis; BMI, Body Mass Index; PVD, Peripheral Vascular Disease; HLD, Hyperlipidemia; CKD, Chronic Kidney Disease; CHF, Chronic Heart Failure; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; HTN, Hypertension; eGFR, estimated Glomerular Filtration Rate; AAA, abdominal aortic aneurysm; ABF, aortobifemoral; TAAA, thoracoabdominal aortic aneurysm.

* p-value <0.05 when compared to No RAS, after adjustment for all pairwise comparisons.

associated with bilateral RAS (Table 2). In 20 % of patients with bilateral RAS underwent renal replacement therapy (RRT) as compared with 7 % of patients with unilateral and no RAS, although this difference was not significant (Table 2). Bilateral RAS was not independently associated with RRT when adjusted conservatively (with Bonferroni correction) for multiple comparisons (p = 0.164). As compared with unilateral and no RAS, bilateral RAS was associated with higher rate of AKI (100 % vs 45 %), neurological complications (70 % vs 32 %), in-hospital (30 % vs 7 %), 30-day (40 % vs 7 %) and 90-day mortality (40 % vs 9 %), as shown in Table 3. In a multivariable logistic regression model adjusted for GFR, BMI, age, sex, race, CAD, DM and intraoperative hypotension, bilateral RAS was associated with severe AKI (Odds Ratio [OR] 5.82; CI 1.33, 25.53; p = 0.02), in-hospital mortality (OR 5.71; CI 1.03, 31.53; p = 0.05), 30-day mortality (OR 10.56; CI 2.03, 54.05; p = 0.005) and 90-day mortality (OR 6.88; CI 1.40, 33.87; p = 0.02) (Table 4).

Discussion

In this single-center retrospective cohort of patients undergoing major vascular surgery, 6.2 % (n = 10) of patients had bilateral RAS. One hundred percent of patients with bilateral RAS had postoperative AKI as compared with 45 % of patients with unilateral or no RAS. Patients with bilateral RAS had a smaller renal diameter, smaller cortical area and decreased kidney length as compared with patients with no RAS. In a multivariable logistic regression model, bilateral RAS was associated with increased odds of severe AKI, in-hospital mortality, 30-day mortality, and 90-day mortality as compared to patients with either unilateral RAS or no RAS.

All of the patients in our study had peripheral vascular disease (PVD), which has been shown to be associated with a higher mortality as compared with patients without vascular disease [18]. Renal artery stenosis is a frequent incidental finding in patients undergoing routine angiography for PVD, with a prevalence between 5 and 40 % [16], which is consistent with our patient population. Additionally, bilateral RAS may also be associated with widespread atherosclerotic disease and co-exist with other conditions. In a study of 491 patients diagnosed with PVD, incidental RAS was an independent predictor for mortality which was true for patients with normal and mild renal functional impairment as well as in patients with moderate to severe insufficiency [19].

Renal artery stenosis and postoperative AKI has been previously demonstrated in patients undergoing non vascular surgery [5]. In a study of 212 patients undergoing aortography after cardiac surgery, Yang et al. found RAS to be associated with postoperative AKI in patients

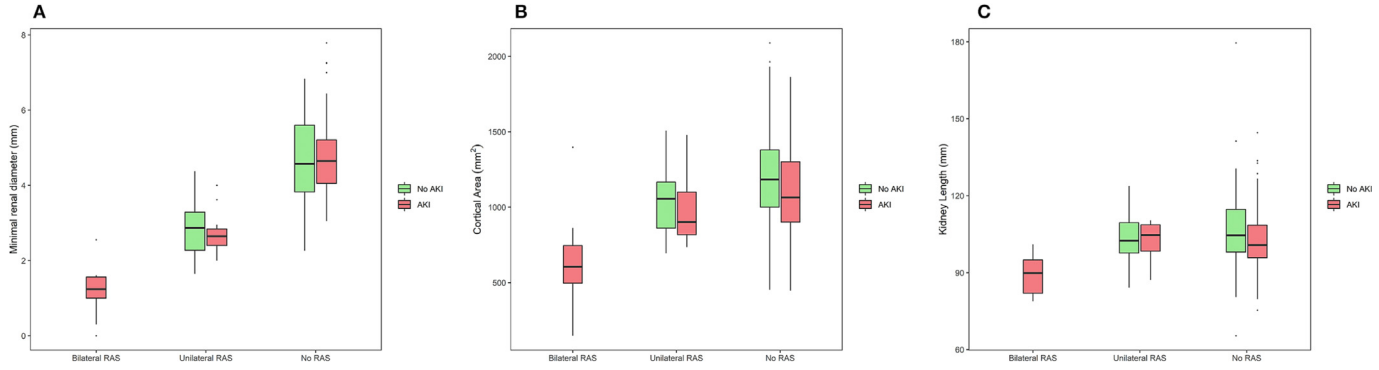

Fig. 1. Morphologic characteristics of patient kidneys. (A) Comparison of median renal artery diameter between patients with bilateral RAS, unilateral RAS and no RAS. (B) Comparison of median cortical area between patients with bilateral RAS, unilateral RAS and no RAS. (C) Comparison of median kidney length between patients with bilateral RAS, unilateral RAS and no RAS. Box represents interquartile range (IQR), thick line represents median, error bars represent minimum (Q1–1.5*IQR) and maximum (Q3 + 1.5*IQR) and dots represent outliers.

Table 2
Renal outcomes stratified by RAS status.

Outcomes	Overall (N = 161)	Bilateral RAS (N = 10, 6 %)	Unilateral + No RAS (N = 151, 94 %)
AKI			
Within 3 days of surgery	71 (44)	9 (90)*	62 (41)
Within 7 days of surgery	76 (47)	10 (100)*	66 (44)
Any time	78 (48)	10 (100)*	68 (45)
Worst stage of AKI			
Stage 1	43 (27)	4 (40)	39 (26)
Severe AKI (≥ Stage 2)	35 (22)	6 (60)	29 (19)
Stage 2	17 (11)	2 (20)	15 (10)
Stage 3	6 (4)	2 (20)	4 (3)
Stage 3 with RRT	12 (7)	2 (20)	10 (7)

Abbreviations: RAS, Renal Artery Stenosis; AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy.
Worst stage of AKI was based on AKI stage during whole hospitalization. Severe AKI is defined as Stage 2 or more AKI.
* p-value <0.05 when compared to Unilateral RAS or No RAS, after adjustment for all pairwise comparisons.

with normal or near-normal baseline renal function. In a study of 106 patients undergoing transcatheter aortic valve replacement, patients with bilateral RAS had a significantly greater odds of developing post-TAVR AKI than did subjects with unilateral or no stenosis [6]. To our knowledge, our study is the first to evaluate preoperative RAS and post-operative outcomes in patients undergoing major vascular surgery.

Cortical area and kidney length are commonly used morphological parameters of kidney function. Several studies have shown that renal artery stenosis is associated with reduced kidney size [9,20,21]. Additionally, atherosclerotic RAS results in loss of renal function or parenchyma, known as ischemic nephropathy [22]. Although there was no significant difference between serum creatinine or eGFR concentrations of patients with and without RAS, our findings of decreased cortical area and kidney length in patients with bilateral and unilateral RAS is consistent with the literature. RAS may result in excess production of angiotensin II which is a potent vasoconstrictor implicated in the activation of cell proliferation, and has been shown to be associated with endothelial dysfunction and end organ damage [23]. These effects, coupled with the intraoperative physiologic stressors such as hypoperfusion and ischemia, may partially explain the increased mortality in patients with incidental bilateral RAS in this patient population.

In this study, although the baseline renal function was not different in patients with no RAS and unilateral RAS versus bilateral RAS, the perioperative physiologic changes associated with aortic surgery led to AKI in all patients with bilateral renal artery stenosis. Based on this, consideration for perioperative risk reduction could be (1) preoperative renal artery revascularization with renal artery stenting, or (2) concomitant open renal revascularization (endarterectomy or bypass) to place patients into the lower risk unilateral or no RAS categories. Randomized trials of renal artery stenting in patients with RAS have failed to show a benefit with respect to blood pressure [24–26], kidney function [27,28], or prevention of clinical events [29]. However, patients included in these randomized trials had to have RAS and either CKD or hypertension. No randomized trials have evaluated the impact of preoperative renal artery stenting in patients with renal artery stenosis and normal blood pressure and renal function undergoing major vascular surgery. Larger prospective studies are needed to confirm the findings of this small retrospective study. If externally validated, further studies, such as a prospective pilot study to evaluate if preoperative renal artery stenting or concomitant open renal revascularization in patients with bilateral RAS undergoing elective open aortic vascular surgery would be instrumental in understanding the deleterious effects of incidental renal artery stenosis in this patient population.

Table 3
Bilateral RAS was associated with increased incidence of other complications.

Complications, n (%)	Overall (N = 161)	Bilateral RAS (N = 10, 6 %)	Unilateral + No RAS (N = 151, 94 %)
Acute kidney injury	78 (48)	10 (100)*	68 (45)
Cardiovascular complications	71 (44)	7 (70)	64 (42)
Venous thromboembolism	24 (15)	3 (30)	21 (14)
Sepsis	36 (22)	3 (30)	33 (22)
Wound complications	73 (45)	4 (40)	69 (46)
Neurological complications	56 (35)	7 (70)*	49 (32)
ICU > 48 h	148 (92)	10 (100)	138 (91)
MV > 48 h	39 (24)	4 (40)	35 (23)
In-hospital mortality	14 (9)	3 (30)*	11 (7)
30-day mortality	14 (9)	4 (40)*	10 (7)
90-day mortality	17 (11)	4 (40)*	13 (9)

Abbreviations: RAS, Renal Artery Stenosis; AKI, Acute Kidney Injury; ICU, Intensive Care Unit; MV, Mechanical Ventilation.
* p-value <0.05 when comparing Bilateral RAS to Unilateral RAS or No RAS, after adjustment for all pairwise comparisons.

Table 4
Logistic regression analysis of associations between bilateral renal artery stenosis and development of post-operative complications after vascular surgery.

	Unadjusted	Full Model*
Severe AKI	6.31 (1.67, 23.82), p = 0.007	5.82 (1.33, 25.53), p = 0.02
In-hospital mortality	5.45 (1.23, 24.09), p = 0.03	5.71 (1.03, 31.53), p = 0.05
30-day mortality	9.40 (2.28, 38.82), p = 0.002	10.56 (2.03, 54.05), p = 0.005
90-day mortality	7.08 (1.77, 28.33), p = 0.006	6.88 (1.40, 33.87), p = 0.02

Reported data shows odds ratio (95 % Confidence Interval) and p-value for bilateral renal artery stenosis.
* Model adjusted for intraoperative hypertension, sex (male), race (African American), age, eGFR, BMI, DM, CVD.

The primary limitation of this study is its observational, retrospective design. Although our study finds that bilateral RAS is associated with AKI and mortality after elective open vascular surgery, the pathophysiological mechanisms underlying this phenomenon remain unclear. There are important differences in the pathophysiology of patients undergoing surgery for aortoiliac occlusive disease as compared with aortic aneurysms which may impact outcomes but due to our limited sample size we were unable to adjust for specific surgical procedures performed. Additionally, although there were no differences between unilateral RAS and no RAS, these groups were combined due to the small sample size, which was not planned prior to the data collection. Further, technical considerations and intraoperative decision making related to the duration and placement of vascular clamps may be associated with the onset and evolution of renal ischemia [4,30,31]. Previous studies have shown duration of aortic clamp time in patients with juxtarenal AAA repair to be associated with postoperative renal dysfunction [30],as well as renal ischemia time and estimated blood loss of >1 L in patients with juxtarenal or suprarenal AAA repair [32].

Unfortunately, due to limitations in our study design we do not have specific procedural details such as clamp location and duration, intraoperative renal interventions or specific causes of death for this cohort of patients. The only information on the specifics of the procedure performed was gathered from CPT codes, which does not necessarily reflect intraoperative details. Additionally, we also lack information on preoperative medication use. However, all our patients were seen in our clinic preoperatively as these were elective cases and it is our clinical practice to ensure patients with PVD are on appropriate medical therapy. Our study was focused on perioperative AKI, and therefore we unfortunately did not collect information on permanent renal deterioration beyond hospital discharge and are unable to make conclusions for renal artery stenosis and postoperative progression to CKD.

Conclusions

Bilateral renal artery stenosis in patients undergoing open vascular surgery is independently associated with postoperative AKI, as well as in-hospital mortality, 30-day mortality, 90-day mortality. Preoperative evaluation of renal artery stenosis can help with both preoperative risk stratification as well as personalized, targeted risk-reduction strategies that mitigate preventable harm and optimize resource use. Future prospective studies should examine whether RAS is a marker or mediator of poor prognosis and whether prognosis can be improved by specific intervention such as preoperative renal artery stenting.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2023.06.001.

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Ethical approval

The University of Florida Institutional Review Board (#201600223) approved this study with waiver of informed consent.

CRediT authorship contribution statement

ACF, TOB, AB and MC contributed to study design. ACF, SHE, and MC performed data collection. ACF, SM, YR, and TOB performed the data analysis. ACF, TOB, and MC drafted the manuscript. ACF, SM, YR, TOB, SEH, MLW, CRJ, GRU AB and MC interpreted the data and provided critical revisions to the manuscript.

Declaration of competing interest

None.

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