Impact of cumulative intravascular contrast exposure on renal function in patients with occlusive and aneurysmal vascular disease

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Objective: **Patients with occlusive or aneurysmal vascular disease are repeatedly exposed to intravascular (IV) contrast for diagnostic or therapeutic purposes. We sought to determine the long-term impact of cumulative iodinated IV contrast exposure (CIVCE) on renal function; the latter was defined by means of National Kidney Foundation (NKF) criteria.**
Methods: **We performed a longitudinal study of consecutive patients without renal insufficiency at baseline (NFK stage I or II) who underwent interventions for arterial occlusive or aneurysmal disease. We collected detailed data on any IV iodinated contrast exposure (including diagnostic or therapeutic angiography, cardiac catheterization, IV pyelography, computed tomography with IV contrast, computed tomographic angiography); medication exposure throughout the observation period; comorbidities; and demographics. The primary end point was the development of renal failure (RF) (defined as NFK stage 4 or 5). Analysis was performed with the use of a shared frailty model with clustering at the patient level.**
Results: **Patients (n = 1274) had a mean follow-up of 5.8 (range, 2.2-14) years. In the multivariate model with RF as the dependent variable and after adjusting for the statistically significant covariates of baseline renal function (hazard ratio [HR], 0.95; $P < .001$), diabetes (HR, 1.8; $P = .007$), use of an angiotensin-converting enzyme inhibitor (HR, 0.63; $P = .03$), use of antiplatelets (HR, 0.5; $P = .01$), cumulative number of open vascular operations performed (HR, 1.2; $P = .001$), and congestive heart failure (HR, 3.2; $P < .001$), CIVCE remained an independent predictor for RF development (HR, 1.1; $P < .001$). In the multivariate survival analysis model and after adjusting for the statistically significant covariates of perioperative myocardial infarction (HR, 3.9; $P < .001$), age at entry in the cohort (HR, 1.05; $P = .035$), total number of open operations (HR, 1.51; $P < .001$), and serum albumin (HR, 0.47; $P < .001$), CIVCE was an independent predictor of death (HR, 1.07; $P < .001$).**
Conclusions: **Cumulative IV contrast exposure is an independent predictor of RF and death in patients with occlusive and aneurysmal vascular disease. (J Vasc Surg 2014;59:1644-50.)**

Chronic renal dysfunction can lead to progressive morbidity after advanced endovascular procedures and has been independently associated with all-cause mortality.[1] Especially after endovascular aortic aneurysm repair, 32-51% of patients will progress to chronic kidney disease (CKD) at 18 months.[2] Several risk factors that lead to worsening of renal function after endovascular procedures have been identified,[3-5] with contrast-induced nephropathy (CIN) being among the most important.

Although CIN has been mostly associated with acute kidney injury after contrast-enhanced studies through acute oxidative stress[6] and other effects that promote renal medullary hypoxia,[7] there is potential for chronic oxidative stress from a single or cumulative intravascular contrast exposure (CIVCE) as well as radiation exposure and probably other unknown factors. This risk is particularly important in vascular patients with either occlusive or aneurysmal disease undergoing repeated contrast-enhanced procedures for diagnostic, therapeutic, or surveillance purposes.

In the present study, we hypothesized that CIVCE adversely affects long-term renal function and survival after diagnostic or therapeutic procedures are performed in patients with occlusive or aneurysmal vascular disease.

METHODS

Patient population and data extraction. With the use of a retrospective cohort design, charts of consecutive patients who underwent elective operations for atherosclerotic vascular occlusive or aneurysmal disease in a single institution over a 14-year period (January 1999 to December 2012) were reviewed. We included patients who underwent carotid endarterectomy, open or endovascular intervention for aortoiliac occlusive disease, open or endovascular intervention for infrainguinal occlusive disease, and aneurysm repair (either open or endovascular). We excluded patients whom on initial presentation had CKD stage 4 or 5 as this represented the main outcome of

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interest. We also excluded patients who were observed for a period less than 2 years because we assumed that this would be a rather short time frame for the cumulative effect of contrast administration to become clinically significant.

Exposures of interest. The objective of the study was to assess the association between CIVCE and the development of renal failure (RF) defined as CKD stages 4 or 5 according to National Kidney Foundation (NKF) guidelines.[8] To calculate the CIVCE, we collected data on every exposure to iodinated contrast media that was present in the patient's chart starting from the year 1999. This included contrast used for computed tomography, digital subtraction angiography, cardiac catheterization, and intravenous pyelography. The CIVCE was calculated as the running total of individual IV contrast exposures for each particular patient.

Covariates of interest. Data were collected through review of charts located in the electronic medical record system. The Veterans Health Administration (VHA) has implemented a nationwide electronic medical record system that allows instant access to patient information even if interventions, admissions, or laboratory work are performed in different VHA facilities. Because most of the veterans tend to seek care within the VHA, capturing patient information in a comprehensive and accurate manner is feasible. Covariates of interest included demographics, comorbidities, medications on record at the time of each hospital admission, operative information, vascular and open-heart operations, baseline and postoperative laboratory values, and death. The cumulative number of open vascular reconstructions and open cardiac surgeries that were performed on the patients was also captured and included in the multiple regression models to adjust for the impact of surgical stress on the outcomes of interest.

Outcomes. The primary outcome was the development of CKD stage 4 or 5 as defined according to NKF criteria outlined below. The secondary outcome was overall patient survival.

Renal failure. For the purposes of this study, RF was defined as the development of CKD either stage 4 (estimated glomerular filtration rate [eGFR] between 15-29 $mL \cdot min^{-1}$ per 1.73 m^{-2}) or stage 5 (eGFR <15 $mL \cdot min^{-1}$ per 1.73 m^{-2}) any time during the observation period, even though in some cases this was not permanent because some patients reversed back from stage 4 or 5 to stage 3 or 2. eGFR was determined by use of the Chronic Kidney Disease Epidemiology Collaboration equation.[9] CKD stage 1-5 was classified on the basis of the NKF/Kidney Disease Outcome Quality Initiative criteria.[8]

We collected data on eGFR at various time points throughout each individual patient's follow-up period. These included baseline values on patient entry and exit of the cohort; values before a test was performed that necessitated IV contrast use; values at admission and discharge for every hospital admission; and values for every time that the patient's CKD stage changed. Given the extent of the follow-up and the multiple time points used per patient, appropriate computer logic was used to clean the data from spurious values caused by lab error. Specifically, eGFR values that were indicative of CKD status change of two stages or more were verified as being accurate when there was a confirmatory similar value obtained within 48 hours. Similar verification was performed for eGFR values that were found to deviate more than 2 standard deviations from the mean eGFR value of the three previous time periods.

Table I. Patient characteristics on entry in the study

Variables	*No.*	*%*
Stage I	461	36.2
Stage II	576	45.2
Stage III	227	18.6
HTN	1094	85.9
Hyperlipidemia	969	76.1
CAD	579	45.4
COPD	319	25.0
CHF	137	10.8
Diabetes	472	37.0
Black race	266	20.9
Plavix	185	14.5
ACE inhibitor	682	53.5
Aspirin	889	69.8
β-blockers	738	57.9
Statin	888	69.7
EVAR	356	18
Aortoiliac interventions	353	18
Infrainguinal interventions	989	51
CEA	228	12
Open AAA repair	19	1

Stage	*Age, mean (range)*	*Baseline eGFR, mean (range)*
Stage I	61 (41-86)	108 (90.1-175.3)
Stage II	62 (40-89)	73.8 (60-89.9)
Stage III	65 (48-89)	51.1 (31.3-59.9)

AAA, Abdominal aortic aneurysm; *ACE,* angiotensin-converting enzyme; *CAD,* coronary artery disease; *CEA,* carotid endarterectomy; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *eGFR,* estimated glomerular filtration rate; *EVAR,* endovascular aneurysm repair; *HTN,* hypertension; *Stage,* stage of chronic kidney disease at baseline.

Survival. Survival was captured as freedom from all-cause inpatient and outpatient deaths.

Statistical analysis. We conducted time-to-event analyses through the use of a parametric regression model with shared frailty at the patient level. Both outcomes were modeled by means of the Weibull distribution to capture the hypothesized effect of contrast on renal function, which mainly occurs at the time of contrast administration and subsequently diminishes over time. The information in the covariates of interest was structured through the use of a panel data configuration to allow capturing information for multiple admissions and contrast exposures for individual patients. Results from simple and multiple regressions are presented as hazard ratios (HRs). This is the ratio of the hazard rates that correspond to the conditions described by two levels of

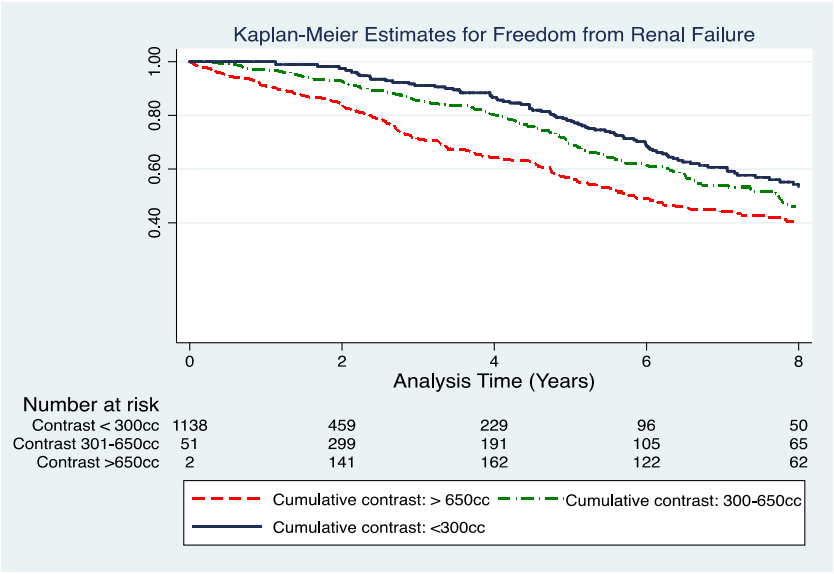

Fig 1. Kaplan-Meier estimates for freedom from stage 4 or 5 chronic kidney disease (CKD).

an explanatory variable. For instance, an HR of 1.2 for diabetes indicates that diabetic subjects have 20% greater risk of having the outcome under investigation at any given point during the study period.[10] CIVCE was analyzed as a continuous variable when computing simple and multiple regression to identify predictors of RF and survival and as a categorical variable when calculating Kaplan-Meier estimates of freedom from RF and survival. In the latter case, the cutoffs for CIVCE were set at 300 and 650 mL, values that represented the 33rd and 67th percentiles of CIVCE in our patient population. For these analyses, the HR expresses the hazard for the outcome to occur in patients receiving (1) between 300 and 650 mL of contrast and (2) more than 650 mL of contrast compared with the referent of 300 mL of contrast or less. All analyses were performed with the use of Stata version 12.1 (StataCorp, College Station, Tex).

RESULTS

Descriptive statistics. Information was available on 1274 consecutive patients who were followed up for an average of 5.8 (range, 2.2-14) years and had a median of three (range, 0-27) interventions involving the use of a median amount of 460 mL (range, 0-3581 mL) of IV contrast. The mean age was 62 (range, 40-89) years on entry in the study. Details of the patient population on entry in the study are presented in Table I. The progression to CKD stage 4 or 5 was permanent in 115 (9%) and transient in 420 (33%) patients.

Impact of CIVCE on freedom from RF. The Kaplan-Meier estimates of freedom from RF at 4 years were 87%, 80%, and 64% for patients who had received cumulative contrast <300 mL, between 300-650 mL, and >650 mL, respectively. The estimates for freedom from RF at 8 years were 53%, 46%, and 40% for patients who had received cumulative contrast <300 mL, between 300-650 mL, and >650 mL, respectively ($P < .001$; Fig 1).

Independent predictors for the development of RF. Univariate analysis showed a statistically significant association between cumulative contrast administration and the development of RF (HR, 1.12; $P < .001$; Table II). In the multiple regression model, CIVCE remained an independent predictor for the development of RF (HR, 1.1; $P < .001$) after adjusting for the statistically significant covariates of baseline renal function (HR, 0.95; $P < .001$), diabetes (HR, 1.8; $P = .007$), congestive heart failure (HR, 3.2; $P < .001$), use of an angiotensin-converting enzyme inhibitor (HR, 0.63; $P = .036$), and use of antiplatelets (HR, 0.51; $P < .01$). Patients who underwent carotid endarterectomy were less likely to progress to CKD stages 4 and 5 in the univariate analysis; however, multiple regression indicated that there was no association between the type of vascular operation and renal function deterioration (Table III).

Impact of CIVCE on survival. The Kaplan-Meier estimates of survival at 4 years were 96%, 91%, and 84% for patients who had received cumulative contrast <300 mL, between 300-650 mL, and >650 mL, respectively. The estimates of survival at 8 years was 90%, 80%, and 69% for patients who had received cumulative contrast <300 mL, between 300-650 mL, and >650 mL, respectively ($P < .001$; Fig 2).

Independent predictors of survival. Univariate analysis showed a statistically significant association between cumulative contrast administration and death (HR, 1.21; $P < .001$; Table IV). In the multiple regression model, CIVCE remained an independent predictor of death (HR, 1.07; $P = .003$) after adjusting for the statistically

Table II. Univariate analysis that outlines predictors studied for association with development of stages 4 and 5 chronic kidney disease (CKD)

Variables	*HR (95% CI)*	P *value*
CIVCE	1.12 (1.08-1.16)	<.001
eGFR	0.95 (0.94-0.96)	<.001
Age at entry	1.26 (0.89-1.79)	.184
Diabetes mellitus	2.63 (1.74-4.00)	<.001
CHF	4.81 (3.02-7.66)	<.001
Black	0.60 (0.28-1.28)	.187
Aspirin	0.90 (0.60-1.36)	.623
Plavix	0.83 (0.53-1.30)	.419
EBL	1.02 (1.01-1.03)	<.001
Hypertension	1.96 (0.83-4.62)	.123
Hyperlipidemia	0.93 (0.55-1.57)	.779
No history of smoking	0.72 (0.51-1.03)	.074
Drop in Hgb	0.67 (0.60-0.75)	<.001
β-blockers	1.13 (0.75-1.72)	.560
Statins	1.23 (0.81-1.85)	.333
ACE inhibitor	0.93 (0.66-1.32)	.688
Total open operations	1.26 (1.15-1.38)	<.001
CAD	1.52 (1.00-2.30)	.051
COPD	0.87 (0.54-1.41)	.572
Open heart	2.23 (0.78-5.4)	.311
Cardiac catheterization	1.94 (1.24-4.58)	.041
Antiplatelets	0.58 (0.35-0.96)	.034
EVAR	Reference	Reference
Aortoiliac open	1.11 (0.51-2.40)	.800
Aortoiliac endovascular	0.38 (0.13-1.07)	.067
CEA	0.37 (0.16-0.84)	.018
Infrainguinal open	1.59 (0.88-2.88)	.127
Infrainguinal endovascular	1.35 (0.77-2.35)	.293
Open AAA	5.62 (1.03-30.6)	.046
BMI	1.01 (0.97-1.05)	.627

ACE, Angiotensin-converting enzyme; *BMI,* body mass index; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *CI,* confidence interval; *CIVCE,* cumulative intravenous contrast exposure (in increments of 100 mL); *COPD,* chronic obstructive pulmonary disease; *EBL,* estimated intraoperative blood loss of open vascular operations; *eGFR,* estimated glomerular filtration rate; *HR,* hazard ratio; *Drop in Hgb,* difference between baseline serum hemoglobin and nadir postoperative serum hemoglobin; *Open heart,* open heart surgery, either coronary bypass or valve repair; *Total open operations,* total number of cardiac and vascular operations that the patients underwent during the observation time.

Table III. Multivariate regression model that summarizes the independent predictors of stages 4 and 5 chronic kidney disease (CKD)

Variables	*HR (95% CI)*	P *value*
CIVCE	1.1 (1.07-1.15)	<.001
Baseline eGFR	0.95 (0.94-0.96)	<.001
Diabetes mellitus	1.8 (1.16-2.7)	.007
Congestive heart failure	3.2 (2.05-5.19)	<.001
Use of ACE inhibitors	0.63 (0.45-0.87)	.03
Use of antiplatelets	0.51 (0.3-0.85)	.01
Total open operations	1.2 (1.07-1.31)	.001

AAA, Abdominal aortic aneurysms; *ACE,* angiotensin-converting enzyme; *CEA,* carotid endarterectomy; *CI,* confidence interval; *CIVCE,* cumulative intravenous contrast exposure (in increments of 100 mL); *EVAR,* endovascular aneurysm repair; *eGFR,* estimated glomerular filtration rate at entry in the study cohort; *HR,* hazard ratio; *Open heart,* open heart surgery, either coronary bypass or valve repair; *Total open operations,* total number of cardiac and vascular operations that the patients underwent during the observation time.

significant covariates of perioperative myocardial infarction (HR, 3.9; $P < .001$), age at entry to the cohort (HR, 1.05; $P = .035$), total number of open cardiac or vascular operations (HR, 1.51; $P < .001$), and serum albumin (HR, 0.4; $P < .001$; Table V).

DISCUSSION

In this retrospective study, we analyzed the long-term effect of repeated IV contrast exposure on renal function and survival in patients without advanced renal insufficiency at baseline who underwent interventions for vascular occlusive and aneurysmal disease. We showed that CIVCE was an independent predictor for both development of stage 4 or 5 CKD and increased mortality rates. Our study is unique in that (1) analyzed a broad patient population that shares the common feature of need for repeated contrast exposure, and (2) had a long time horizon to evaluate associations between contrast and the outcome variables.

The association between amount of contrast used for endovascular procedures and CIN is well known. Most of the published data focuses mainly on the development of acute kidney injury that occurs shortly after the administration of the contrast load.[11,12] However, recent reports[2,5,13-17] studying patients after endovascular aortic aneurysm repair have raised the possibility of a long-term adverse effect of repeated contrast use on renal function. Whereas vascular surgeons remain cognizant of issues related to changes of renal function after endovascular aortic aneurysm repair because of the need for periodic use of contrast, our data indicate that the decline in renal function appears to be a more generalized phenomenon related to IV contrast use. It is also likely that the effect of cumulative IV contrast on renal function is not limited to patients who receive vascular surgery, although this patient population represents an ideal initial patient cohort to study this problem because of the need for periodic use of contrast for diagnostic, therapeutic, or surveillance purposes.

The mechanism that underlies the harmful effect of repeated contrast exposure on kidney function is unclear. First, use of contrast may be a surrogate marker for other comorbidities that may also lead to deterioration of renal function. However, our models were adjusted for baseline renal function as well as the presence of congestive heart failure, diabetes mellitus, and hypertension. Second, there may be a direct contrast-related cytotoxic effect.[7] Third, changes in blood viscosity or patient hemodynamics may alter local renal hemodynamics and may result in regional hypoxia.[7] The latter mechanism is insidious but may be of particular importance, as evidenced by the fact that the number of open vascular operations was an independent predictor for the development of stages 4 and 5 CKD; dehydration and hemodynamic lability that accompany an

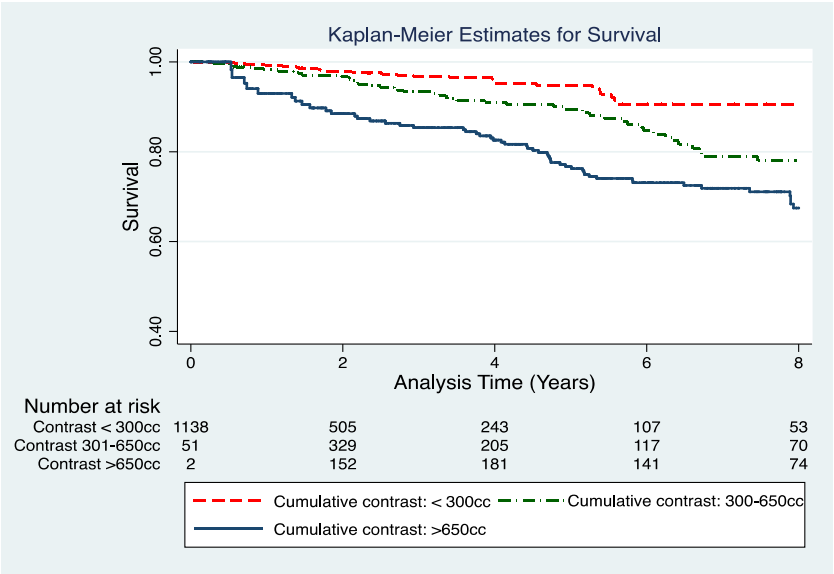

Fig 2. Kaplan-Meier estimates for survival.

operation may act in concert with IV iodinated contrast in causing progressive and irreversible damage of the renal parenchyma.

Previous studies reporting findings on the evolution of renal function in patients with vascular disease have studied mixed populations with respect to baseline renal function or have examined the impact of contrast load on patients with some degree of renal insufficiency (CKD stage 3 or higher). In our analysis and in addition to patients with CKD stage 3, we included individuals with CKD stages 1 or 2 (eGFR >60 $mL \cdot min^{-1}$ per 1.73 m^{-2}) at baseline. The rationale behind this was twofold: first, to examine the impact of cumulative IV contrast administration in a patient population that has traditionally received little attention in randomized trials of renal protection regimens; and second, to provide a more homogeneous patient cohort with respect to baseline risk factors and facilitate risk-adjusted analysis. Our findings support the notion that patients with CKD stages 1 through 3 at baseline are at risk of development of RF after repeated contrast exposure. In light of this, future trials should place some emphasis on assessing the value of renal protection measures in these patients.

Lack of standardization and various definitions of renal dysfunction have compromised the generalizability of findings and comparison of outcomes between studies looking into CIN.[13] In our view, any long-term assessment of renal function should be based on well-validated and widely accepted criteria. With this rationale, we used the CKD staging system as described by the NKF/Kidney Disease Outcomes Quality Initiative, which represents the standard in evaluation and management of CKD.

The first main finding of this study was that CIVCE is associated with the development of either transient or permanent stage 4 or 5 CKD. Admittedly, permanent RF has attracted most of the attention in the renal nephropathy literature because it has a direct impact on patient quality of life and death. Our findings indicate that the effect of cumulative contrast load on renal function is insidious as 33% of our cohort had transient development and 9% had permanent development of RF. This is a substantial number, particularly considering that 82% of the patients that we examined were at CKD stage 1 or 2 at baseline. The physiologic consequences of this phenomenon remain to be determined.

Our findings indicate that CIVCE was an independent predictor of overall survival. This was after fairly robust risk adjustment for comorbidities, including the interval development of RF that is well known to affect survival. However, caution should be used when interpreting this association. The need for higher repeated contrast exposure may simply indicate a higher baseline disease burden whose individual components were not possible to capture in a retrospective analysis. Despite this obvious limitation, this finding is intriguing enough to warrant further investigation in future prospective studies.

There are multiple limitations in this study that might result in bias and are inherent to its retrospective design. The VHA electronic medical record system is robust. However, it is possible that patients had IV contrast administered outside of the VHA system, and this was not documented in the electronic medical record. As such, it is not possible to fully account for the exact amount of contrast that any given patient

Table IV. Univariate analysis that outlines predictors studied for association with overall patient mortality

Variables	*HR (95% CI)*	P *value*
CIVCE	1.21 (1.13-1.29)	<.001
Baseline eGFR	1.00 (0.99-1.01)	.922
Age	1.06 (1.04-1.08)	<.001
Diabetes mellitus	0.66 (0.44-0.98)	.038
CHF	0.88 (0.54-1.45)	.619
Black race	0.91 (0.49-1.34)	.414
ASA	0.91 (0.63-1.31)	.617
Plavix	0.94 (0.61-1.45)	.785
EBL	1.02 (1.01-1.03)	<.001
Hypertension	0.93 (0.53-1.65)	.808
Hyperlipidemia	0.58 (0.40-0.84)	.004
Drop in Hgb	0.35 (0.021-1.91)	.285
β-blockers	0.67 (0.48-0.93)	.016
Statins	0.90 (0.62-1.31)	.596
ACE inhibitors	0.78 (0.56-1.07)	.127
Total open operations	1.97 (1.67-2.33)	<.001
Open heart operations	1.34 (0.61-5.84)	.348
Cardiac catheterization	1.73 (0.61-8.32)	.286
CAD	1.25 (0.85-1.82)	.253
COPD	1.91 (1.38-2.65)	<.001
BMI	0.94 (0.90-0.98)	.008
Antiplatelets	0.91 (0.89-0.94)	.02
EVAR	Reference	Reference
Aortoiliac open	0.37 (0.14-1.01)	.053
Aortoiliac endovascular	0.50 (0.19-1.33)	.165
CEA	0.34 (0.12-0.96)	.041
Infrainguinal open	0.70 (0.37-1.35)	.290
Infrainguinal endovascular	0.72 (0.41-1.28)	.267
Open AAA	0.98 (0.95-1.02)	.999

AAA, Abdominal aortic aneurysm; *ACE,* angiotensin-converting enzyme; *BMI,* body mass index; *CAD,* coronary artery disease; *CEA,* carotid endarterectomy; *CHF,* congestive heart failure; *CI,* confidence interval; *CIVCE,* cumulative intravenous contrast exposure (in increments of 100 mL); *COPD,* chronic obstructive pulmonary disease; *Drop in Hgb,* difference between baseline serum hemoglobin and nadir postoperative serum hemoglobin; *EBL,* estimated intraoperative blood loss of open vascular operations; *eGFR,* estimated glomerular filtration rate at entry in the study cohort; *EVAR,* endovascular aneurysm repair; *HR,* hazard ratio; *Total open operations,* total number of cardiac and vascular operations that the patients underwent during the observation time.

Table V. Multivariate regression model that summarizes the independent predictors of mortality

Variables	*HR (95% CI)*	P *value*
Cumulative amount of contrast	1.07 (1.03-1.11)	.003
Perioperative MI	3.9 (1.98-7.67)	<.001
Albumin	0.47 (0.35-0.62)	<.001
Age at entry	1.05 (1.03-1.67)	.035
Total open operations	1.51 (1.37-1.67)	<.001

CI, Confidence interval; *HR,* hazard ratio; *MI,* myocardial infarction; *Total open operations,* total number of cardiac and vascular operations that the patients underwent during the observation time.

had, which represents a major study limitation. The exact exposure length for some of the important covariates, particularly medications, was not easy to ascertain. Again, this is further confounded by the fact that some patients receive medications not reflected in the VHA electronic medical record. Last, we identified that open cardiac and vascular surgical reconstruction was an independent predictor of development of stage 4 or 5 CKD. During the observation time, some of the patients were likely to have nonvascular open surgical procedures that were not captured in our dataset. Postoperative complications linked to these operations might have contributed to the progression to higher stages of CKD, but is not captured in our analysis.

CONCLUSIONS

We have shown that in patients without renal insufficiency who undergo interventions for occlusive or aneurysmal vascular disease, the CIVCE is an independent predictor for the development of transient or permanent stage 4 or 5 CKD and death. In view of these results, a prospective study to verify these findings and expand them to patients without a history of vascular disease appears to be appropriate.

AUTHOR CONTRIBUTIONS

Conception and design: PK, GP
Analysis and interpretation: PK, NB, GP
Data collection: PK, SS, BL, AG, NB, CB, TP, GP
Writing the article: PK, SS, AG, NB, CB, TP, GP
Critical revision of the article: PK, SS, BL, AG, NB, CB, TP, GP
Final approval of the article: PK, SS, BL, AG, NB, CB, TP, GP
Statistical analysis: PK, NB
Obtained funding: PK
Overall responsibility: PK

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