



Association of chronic kidney disease with perioperative outcomes following acute lower limb revascularization^{☆,☆☆,★}



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ABSTRACT

Background: There is a paucity of data examining the impact of advancing chronic kidney disease stages on outcomes following revascularization for acute limb ischemia. The present study examined the association of chronic kidney disease with in-hospital mortality, amputation, and resource utilization following revascularization for acute limb ischemia using a nationally representative cohort.

Methods: The 2016–2018 National Inpatient Sample was queried to identify all adult hospitalizations with lower extremity acute limb ischemia requiring surgical and/or endovascular interventions. Patients were grouped according to the presence of chronic kidney disease and its severity: no chronic kidney disease, chronic kidney disease 1–3 (chronic kidney disease stages 1 through 3), chronic kidney disease 4–5 (chronic kidney disease stages 4 through 5), and end-stage renal disease. Multivariable logistic and linear models were used to evaluate association of chronic kidney disease stage with outcomes of interest.

Results: Of an estimated 82,610 patients meeting study criteria, 14.8% had chronic kidney disease (chronic kidney disease 1–3: 63.4%, chronic kidney disease 4–5: 12.1%, end-stage renal disease: 24.5%). Compared to those with chronic kidney disease, chronic kidney disease patients were on average older, were more frequently female, and had a higher median Elixhauser Comorbidity Index. Increasing severity of chronic kidney disease was associated with a stepwise increase in unadjusted mortality rates (4.7% in no chronic kidney disease to 12.6% in end-stage renal disease, $P < .001$). Following risk adjustment, only end-stage renal disease was associated with increased odds of mortality (adjusted odds ratio 3.10, 95% confidence interval 2.28–4.22) and limb amputation (adjusted odds ratio 1.99, 95% confidence interval 1.59–2.48) compared to patients with no chronic kidney disease. Similarly, advancing chronic kidney disease stage conferred increased odds of prolonged length of stay and greater hospitalization costs.

Conclusion: Advanced renal dysfunction demonstrated inferior perioperative outcomes and greater health care expenditures in the study population. These findings imply that quality improvement efforts in acute limb ischemia revascularization should target patients with chronic kidney disease 4–5 and end-stage renal disease.

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INTRODUCTION

Chronic kidney disease (CKD) affects an estimated 26.3 million adults in the United States and accounts for approximately \$114 billion in Medicare expenditures annually [1]. In addition to its renal manifestations, CKD is strongly associated with systemic atherosclerosis,

vascular calcification, and thrombosis, placing patients at increased risk for postoperative complications [2,3]. This observation has been reported in several studies investigating perioperative outcomes in CKD patients undergoing major cardiac and noncardiac surgery [4,5].

As one of the most common vascular emergencies, acute limb ischemia (ALI) occurs due to a sudden decrease in regional perfusion resulting in a spectrum of manifestations ranging from pain to tissue loss. Prior work has reported amputation rates of 15% to 50% for those with lower extremity ALI [6]. Moreover, CKD has been implicated in significantly higher rates of amputation and readmission following lower extremity revascularization [7]. However, the available literature examining outcomes of CKD and lower extremity revascularization for ALI is generally sparse, is dated, and does not account for the changing landscape of revascularization strategies over the past 2 decades [8,9].

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Moreover, the association of CKD severity with outcomes of lower limb revascularization has not been elucidated.

The present study used a nationally representative cohort of patients to examine the association between CKD stage and clinical outcomes among those presenting with lower extremity ALI. We hypothesized a stepwise increase in the risk of mortality, amputation, and resource use with increasing severity of CKD.

METHODS

This was a retrospective study using the 2016–2018 National Inpatient Sample (NIS). Maintained by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project, NIS is the largest all-payer inpatient database and accounts for approximately 97% of US hospitalizations annually. The NIS accrues data from 48 state inpatient databases and includes information regarding patient demographics, hospital characteristics, as well as diagnoses and procedures using *International Classification of Diseases, Tenth Edition (ICD-10)* codes.

All adults (≥ 18 years) undergoing open surgical, endovascular, and hybrid revascularization for lower extremity ALI were identified using a combination of *ICD-10* diagnosis and procedure codes (Supplementary Table 1). As previously reported by Kolte et al, we included both nonelective and elective hospitalizations. Although most ALI patients with limb-threatening ischemia are admitted nonelectively, a subset with more indolent symptoms may be hospitalized on an elective basis. Such inclusion criteria capture patients presenting with threatened limbs, irreversible ischemia, or viable limbs with subacute ischemia of lower extremity [10]. Records containing diagnostic angiography without intervention or with missing key data were excluded (2.2%) from further analysis (Fig 1).

Patient and hospital characteristics, including age, sex, race, primary insurance payer, hospital region, and teaching status, were defined according to the NIS data dictionary [11]. The Elixhauser Comorbidity Index was used to numerically tabulate the burden of chronic comorbidities in the cohort [12]. *ICD-10* diagnosis codes were used to stratify patients into non-CKD (NCKD), CKD stages 1 through 3 (CKD1–3), CKD stages 4 through 5 (CKD4–5), and end-stage renal disease (ESRD) groups, as previously defined [4]. Major adverse event (MAE) was defined as a composite of cardiovascular and respiratory complications as previously described elsewhere [13]. Hospitalization costs were

calculated by applying center-specific cost-to-charge ratios to total hospitalization charges and adjusted for inflation using the 2018 Personal Health Index. The primary outcome of interest was in-hospital mortality, whereas secondary end points included lower limb amputation, MAE, nonhome discharge, as well as index length of stay (LOS) and hospitalization costs.

Categorical variables are reported as proportions (%) and continuous variables as medians with interquartile range (IQR). The χ^2 and Kruskal–Wallis tests were used to compare differences between groups. Multivariable logistic and regression models were developed to assess the independent association of CKD stage with outcomes of interest. Model covariates were selected using Elastic Net regularization, which reduces collinearity and applies penalties to mitigate overfitting. Briefly, this variable selection approach allowed for the inclusion of statistically significant and clinically relevant variables while minimizing bias by reducing the dependency of prediction on a particular variable [14]. Regression outputs are reported as adjusted odds ratios (AORs) or beta coefficients (β s) with 95% confidence intervals (95% CIs). All statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX). This study was deemed exempt from full review by the Institutional Review Board at the University of California, Los Angeles.

RESULTS

Characteristics of Patients Undergoing Revascularization for ALI. Of an estimated 82,610 patients meeting inclusion criteria, 14.8% had CKD. Among these patients, the majority (63.4%) had CKD1–3, whereas 12.1% and 24.5% carried the diagnosis of CKD4–5 and ESRD, respectively. Compared to their NCKD counterparts, CKD patients were on average older (72 [62–81] vs 66 [57–74] years, $P < .001$), were more frequently female (45.5% vs 41.2%, $P < .001$), and had a higher median Elixhauser Comorbidity Index (5 [4–6] vs 3 [2–4], $P < .001$). In addition, diabetes, hypertension, and coronary artery disease were more prevalent among all CKD groups compared to NCKD. As shown in Supplementary Table 3, revascularization strategies used on ALI patients comprised surgical (52.6%), endovascular (36.7%), and hybrid (10.7%) approaches. The NCKD cohort was more likely to undergo surgical revascularization (53.5% vs 35.8%, $P < .001$), whereas ESRD patients more commonly underwent an endovascular approach (52.7% vs 37.3%, $P < .001$). Comparison of additional baseline patient and operative characteristics stratified by CKD stage is shown in Table 1.

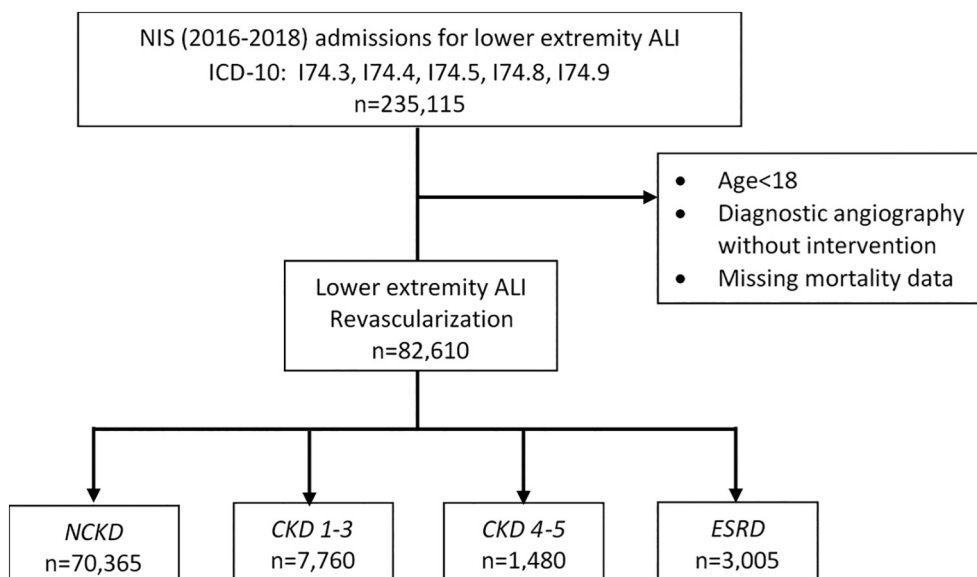


Fig 1. Consort diagram depicting inclusion and exclusion criteria.

Table 1
Characteristics of patients undergoing revascularization for acute limb ischemia stratified by CKD stage

Characteristic	NCKD (n = 70,365)	CKD1–3 (n = 7,760)	CKD4–5 (n = 1,480)	ESRD (n = 3,005)	P value
Median age, y	66 [57–74]	74 [65–82]	75 [66–84]	66 [57–73]	<.001
Female, %	41.2	45.0	43.5	47.9	<.001
Elixhauser Index	3 [2–4]	5 [4–6]	5 [4–6]	5 [4–6]	<.001
Weekend admission, %	16.1	17.5	16.5	16.3	.64
Elective admission, %	31.7	26.2	21.8	19.9	<.001
Race, %					<.001
White	77.1	75.2	71.2	47.4	
Black	12.4	13.5	16.5	27.3	
Hispanic	7.0	7.11	6.7	17.4	
Asian/Pacific Islander	1.1	1.9	4.5	3.2	
Other race	2.4	2.3	1.1	3.7	
Comorbidities, %					
Anemia	3.9	6.6	9.1	5.4	<.001
Chronic liver disease	3.9	4.4	5.4	6.1	.04
Coagulopathy	11.0	15.4	16.3	15.7	<.001
Diabetes	31.9	49.8	54.0	69.0	<.001
Hypertension	73.4	92.4	92.4	95.0	<.001
Nicotine dependence	20.6	14.6	9.8	10.5	<.001
Revascularization, %					<.001
Surgical	53.5	49.9	55.1	37.3	
Endovascular	35.8	38.5	38.2	52.7	
Hybrid	10.7	11.5	6.8	10.0	
Hospital teaching status, %					.004
Urban/nonteaching	4.1	2.6	2.2	1.8	
Urban/teaching	18.7	19.1	23.2	20.0	
Rural	77.2	78.3	74.6	78.2	
Hospital bed size, %					.89
Small	12.5	13.6	12.7	13.9	
Medium	27.5	27.7	27.5	27.5	
Large	60.1	58.8	59.8	58.6	
Insurance status, %					<.001
Medicare	57.3	77.1	76.8	79.1	
Medicaid	13.5	6.3	7.6	8.0	
Private insurance	22.6	13.8	10.5	10.7	
Other	6.7	2.8	5.1	2.2	

Categorical variables are represented as percentage. Continuous variables are represented in median and IQR. Other races include American Indian and Alaska Native. Other insurance status: self-pay, no charge, and other.

Unadjusted Outcomes Stratified by Degree of Renal Dysfunction.

Compared to NCKD, rates of in-hospital mortality were significantly greater in the CKD1–3 (6.1%), CKD4–5 (10.1%), and ESRD (12.6%) cohorts (Table 2). While the overall rate of the acute graft occlusion among patients who received surgical bypass was 17.9%, there were no differences in the rate of this complication across CKD stages. Compared to others, those with ESRD faced the highest unadjusted rates of lower limb amputation (22.5%) and MAE (46.4%). Furthermore, length of stay, index hospitalization cost, and nonhome discharge rates increased in a stepwise fashion with progressing CKD stages. Compared to NCKD, ESRD exhibited the greatest difference in LOS (10 vs 5 days, $P < .001$) and the index hospitalization costs (\$43,000 vs \$28,000, $P < .001$).

Risk-Adjusted Impact of Renal Dysfunction on Clinical Outcomes and Resource Use.

Multivariable mixed regression models were developed to account for intergroup differences and identify independent association of covariates with outcomes of interest. After risk adjustment, only ESRD remained associated with significantly increased odds of mortality (AOR 3.10, 95% CI 2.28–4.22, ref: NCKD). As shown in Table 3, several other factors associated with increased odds of mortality included advancing age, nonelective admission, female sex, and select comorbidities. Furthermore, coagulopathy, heart failure, and liver disease were among several preexisting conditions associated with increased odds of mortality (Table 2).

End-stage renal disease (AOR 1.99, 95% CI 1.59–2.48), but not CKD1–3 and CKD4–5, was associated with increased odds of lower limb

Table 2
Unadjusted outcomes following revascularization for acute limb ischemia by CKD stage

	NCKD (n = 70,365)	CKD 1–3 (n = 7760)	CKD 4–5 (n = 1480)	ESRD (n = 3005)	P value
In-hospital mortality (%)	4.7	6.1	10.1	12.6	<.001
Lower limb amputation (%)	8.8	10.0	13.9	22.5	<.001
Acute graft occlusion (%)	18.1	16.0	16.6	20.1	.109
Major adverse events (%)	26.0	37.4	50.3	46.4	<.001
Cardiovascular	10.0	18.6	27.7	22.3	<.001
Infectious	12.8	16.4	23.3	27.5	<.001
Respiratory	13.5	16.3	28.7	26.8	<.001
Nonhome discharge (%)	48.8	66.0	74.3	51.8	<.001
LOS (d)	5 [3–10]	7 [4–12]	8 [4–14]	10 [5–18]	<.001
Costs (\$1,000)	28 [17–46]	31 [20–50]	36 [22–58]	43 [26–72]	<.001

Categorical variables are represented as percentage. Continuous variables are represented in median and IQR. Other races include American Indian and Alaska Native. Other insurance status: self-pay, no charge, and other.

Table 3
Factors associated with mortality and amputation for patients undergoing revascularization for lower extremity acute limb ischemia

	Mortality		Amputation	
	AOR	95% CI	AOR	95% CI
CKD stage				
No CKD	Reference		Reference	
CKD1–3	0.90	0.70–1.17	1.03	0.85–1.25
CKD4–5	1.39	0.90–2.15	1.32	0.92–1.90
ESRD	3.10	2.28–4.22	1.99	1.59–2.48
Age	1.03	1.02–1.04	0.99	0.98–0.99
Female	1.34	1.14–1.57	0.87	0.77–0.98
Elixhauser Comorbidity Index	0.90	0.84–0.97	1.07	1.01–1.12
Weekend admission	1.27	1.06–1.53	0.98	0.83–1.14
Elective admission	0.53	0.42–0.67	0.35	0.29–0.42
Race				
White	Reference		Reference	
Black	0.74	0.56–0.97	1.40	1.20–1.64
Hispanic	1.03	0.77–1.39	1.16	0.94–1.43
Asian/Pacific Islander	1.04	0.57–1.91	1.43	0.92–2.22
Other	0.99	0.57–1.71	0.78	0.50–1.22
Arrhythmia	1.95	1.62–2.35	1.01	0.88–1.18
Cancer	1.84	1.32–2.57	1.08	0.81–1.45
Chronic liver disease	5.87	4.62–7.45	1.37	1.06–1.78
Coagulopathy	2.29	1.88–2.78	1.36	1.14–1.61
Diabetes	1.05	0.88–1.26	1.84	1.62–2.10
Heart failure	2.20	1.82–2.64	1.02	0.88–1.19
Hypertension	0.52	0.43–0.63	0.77	0.66–0.90
Hospital bed size				
Small	Reference		Reference	
Medium	1.27	0.95–1.69	1.17	0.95–1.44
Large	1.30	0.98–1.72	1.20	0.97–1.46
Hospital teaching status				
Rural	Reference		Reference	
Urban nonteaching	1.85	1.05–3.28	1.65	1.13–2.40
Urban teaching	2.01	1.16–3.50	1.40	0.97–2.01

Other races include American Indian and Alaska Native. Other insurance status: self-pay, no charge, and other.

amputation following revascularization (Fig 2). Compared to NCKD, CKD4–5 (AOR 1.55, 95% CI 1.18–2.03) and ESRD (AOR 1.64, 95% CI 1.35–2.00) were associated with greater odds of MAE (Fig 3). Progressing CKD stage was associated with a stepwise increase in LOS (Fig 4, A). The largest increment in LOS was observed among ESRD patients ($\beta + 4.6$ days, 95% CI 3.8–5.3, ref: NCKD). Relative to NCKD, CKD4–5 ($\beta + \$7,900$, 95% CI 3,200–12,600) and ESRD ($\beta + \$18,100$, 95% CI 14,700–21,500) were associated with significantly increased LOS at the patient level (Fig 4, B). Moreover, patients with CKD4–5 (AOR 1.47, 95% CI 1.08–2.01, ref: NCKD) and ESRD (AOR 2.17, 95% CI 1.73–2.72, ref: NCKD) had greater odds of discharge to a care facility

or home health (Table 4). In addition, compared to elective admission, nonelective admission was significantly associated with increased odds of mortality, limb amputation, MAE, index hospital resource utilization, and nonhome discharge (Supplementary Table 4). The endovascular approach resulted in significantly lower odds of mortality (AOR 0.28, 95% CI 0.14–0.57) and MAE (AOR 0.59, 95% CI 0.38–0.92) among ESRD patients with the surgical approach as reference (Supplementary Table 7).

DISCUSSION

Because of the substantial burden of concomitant cardiovascular comorbidities, patients with advanced renal impairment are generally at high risk for acute limb ischemia. Given the rising proportion of advanced renal dysfunction nationally, characterizing the link between CKD severity and outcomes following lower limb revascularization is particularly salient. In the present national study, we found ESRD to be associated with significantly increased odds of mortality, limb amputation, and MAE following revascularization. Patients with CKD4–5 faced an increased risk of MAE but not mortality or amputation. There was no significant difference in clinical outcomes between CKD1–3 patients and those without renal disease. Furthermore, worsening renal dysfunction was associated with a stepwise increase in LOS and hospitalization costs. Several of these findings necessitate further discussion.

Prior studies have reported an increased risk of perioperative complications and death associated with renal insufficiency in ALI patients undergoing endovascular or surgical revascularizations [15,16]. Using a more nuanced approach, we found only ESRD to confer a mortality risk, with nearly 13% such patients not surviving hospitalization. Moreover, we also noted CKD4–5 and ESRD to be associated with increased risk of major adverse events, whereas outcomes were largely similar between CKD1–3 and NCKD counterparts. The association of advanced renal dysfunction and inferior perioperative outcomes following endovascular or surgical revascularization for limb-threatening ischemia is consistent with the available literature [17–19]. Importantly, we identified a stepwise increase in LOS, hospitalization costs, and rates of nonhome discharge with advancing renal dysfunction. The financial implications of advanced kidney disease in the present study suggest mounting expenditures beyond acute hospitalization. At the systems level, programs to reduce the risk of limb ischemia may paradoxically reduce costs of care while increasing patient quality of life.

Our analysis underscores the particular vulnerability in ALI patients undergoing revascularization procedures with advanced renal dysfunction. In CKD4–5 and ESRD cohorts, inferior perioperative outcomes may be due, in part, to putative role of advancing CKD in vascular calcification, cardiac hypertrophy, and adverse cardiovascular events [20–22].

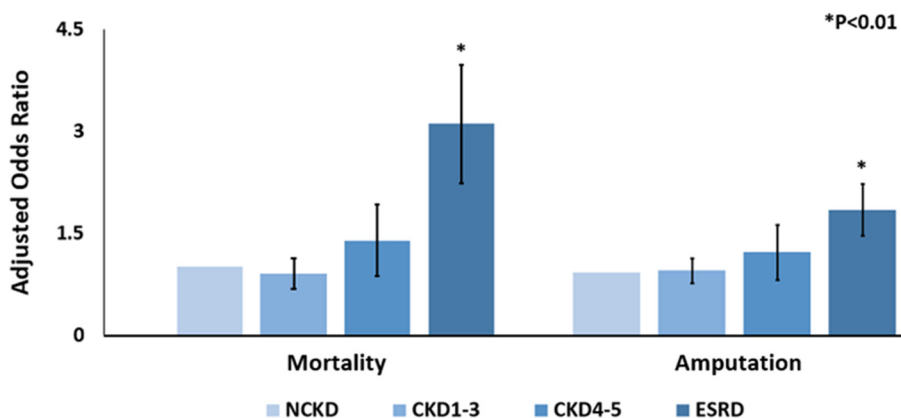


Fig 2. Adjusted odds of in-hospital mortality and lower limb amputation following revascularization for acute lower limb ischemia stratified by stages of CKD. Risk-adjusted estimates are reported as OR with 95% CI. Patients without CKD (NCKD) were used as the reference group. *P < .01.

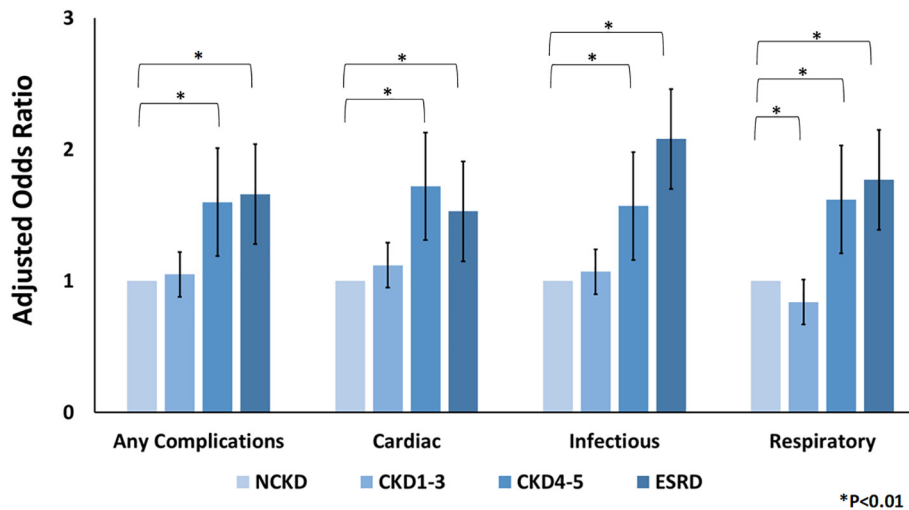


Fig 3. Adjusted odds of major adverse events and individual complication categories following revascularization for acute lower limb ischemia stratified by stages of chronic kidney disease. Risk-adjusted estimates are reported as OR with 95% CI. Patients without CKD (NCKD) were used as the reference group. **P* < .01.

Patients with advanced renal dysfunction may also face a high risk of acute respiratory failure due to associated systemic fluid overload and hypoalbuminemia [23,24]. In addition, infectious complications may be increased in such patients due to impaired immune response attributable to the reduced glomerular filtration rate and uremia-induced immunosuppression [25–28]. In the present study, dialysis-dependent patients experienced a 2-fold increase in odds of lower limb amputation following surgical or endovascular revascularization. Although ESRD independently predicts cardiovascular events and mortality, dialysis can also trigger fluid shifts and hypotension that exacerbates hypoxia in stenotic arteries and injured tissues [29,30]. Furthermore, hemodialysis is known to decrease transcutaneous oxygen level while increasing systemic inflammation, which synergistically impairs wound healing and thus threatens limb viability [31,32]. Indeed, compared to others, patients with CKD4–5 or ESRD frequently present with ALI nonelectively and thus necessitate urgent ALI intervention. Often lacking revascularization option aside from surgical bypass, the capacity to optimize these patients preoperatively is limited. Taken together with similar clinical outcomes between NCKD and CKD1–3, our findings suggest that quality

improvement efforts in ALI revascularization should target patients with CKD4–5 and ESRD.

Presently, the Trans-Atlantic Inter-Society Consensus guidelines recommend an endovascular revascularization approach for ALI patients who are at high risk for surgical complications [33,34]. Indeed, prior studies have reported primary endovascular approach treatment of ALI to have shorter LOS and better amputation-free survival compared with open surgical revascularization [35,36]. However, these recommendations do not discriminate based on the severity of CKD. Although selection bias undoubtedly plays a significant role in the observations, our present study demonstrated that endovascular revascularization for ALI results in lower odds of mortality and MAE among patients with ESRD. Interestingly, the endovascular revascularization among NCKD and CKD1–3 cohorts resulted in a higher cost despite lower LOS and lesser discharge rate to the skilled nursing facility. Although this finding necessitates a formal cost-effective analysis for ALI revascularization, the beneficial impact of the endovascular approach in patients with advanced renal dysfunction is evident [10,37,38]. Further investigation into tailored management and long-term outcomes of patients

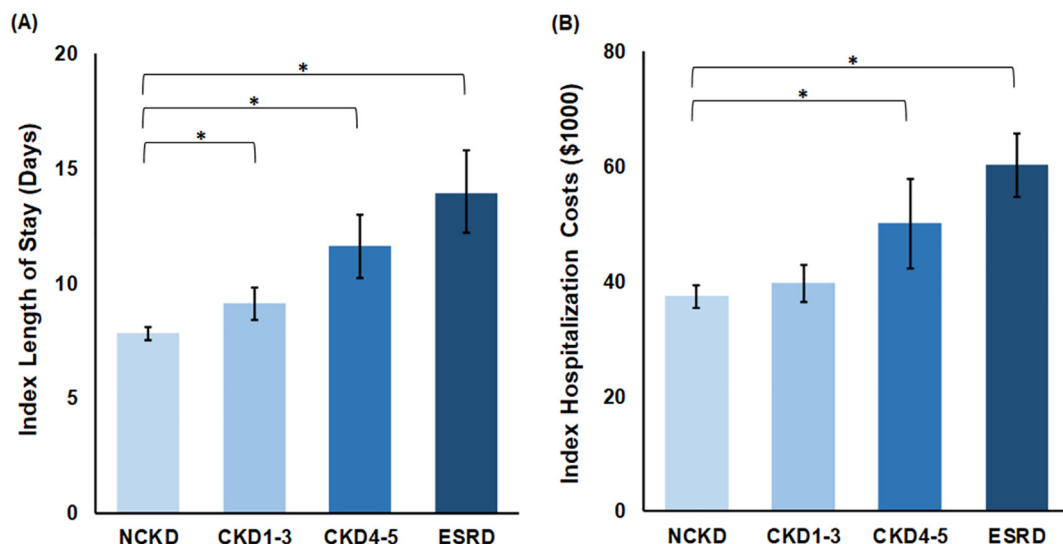


Fig 4. A and B, Risk-adjusted estimates for length of stay and index hospitalization costs stratified by CKD stage. Patients without CKD (NCKD) were used as the reference group. **P* < .01.

Table 4
Risk-adjusted patient outcomes stratified by stages of CKD

	CKD1–3		CKD4–5		ESRD	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
In-hospital mortality	0.90	0.70–1.17	1.39	0.90–2.15	3.10	2.28–4.22
Lower limb amputation	1.03	0.85–1.25	1.32	0.92–1.90	1.99	1.59–2.48
Major adverse events	1.06	0.93–1.21	1.55	1.18–2.03	1.64	1.35–2.00
Cardiovascular	1.12	0.93–1.34	1.72	1.25–2.38	1.53	1.17–1.99
Infectious	1.07	0.90–1.27	1.57	1.16–2.13	2.08	1.66–2.59
Respiratory	0.84	0.70–1.01	1.62	1.19–2.19	1.77	1.39–2.25
Nonhome discharge	1.14	0.99–1.31	1.47	1.08–2.01	2.17	1.73–2.72
Incremental LOS (d)	0.70	0.21–1.19	2.13	1.09–3.18	4.59	3.83–5.34
Incremental cost (\$1,000)	1.35	–0.87–3.57	7.91	3.20–12.62	18.1	14.7–21.5

Adjusted ratios and β coefficient by stages of CKD with NCKD as reference. LOS is reported in days; and hospitalization cost, by \$1,000 increments.

with CKD undergoing ALI revascularization is warranted to optimize the medical management in perioperative and postoperative periods.

There are several important limitations to the present study mainly due to its retrospective nature and use of an administrative data set that does not contain granular clinical information. As diagnoses and procedures were derived from ICD-10, the severity or duration of ALI symptoms could not be directly ascertained. Although CKD stages were defined using previously validated diagnosis codes, estimated glomerular filtration rate and other laboratory tests were unavailable. In addition, the NIS only reports on inpatient outcomes, and as such, data regarding the long-term impact of renal dysfunction in this cohort were not studied. Nonetheless, we used a large data set and robust statistical methods to reduce the risk of bias.

In conclusion, advanced CKD is associated with worse clinical outcomes and greater health care expenditures in patients undergoing lower limb revascularization for ALI. Although inclusion of CKD may be important for benchmarking and payment models, knowledge of this important relationship has implications for clinical care. Special pathways and programs to identify CKD patients at risk for ALI may enhance the value of care and quality of life.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sopen.2022.04.007>.

Author Contribution

Nam Yong Cho: Conceptualization, Methodology, Software, Formal Analysis, Writing. Russyan Mark Mabeza: Software, Writing. Cory Lee: Conceptualization, Writing. Arjun Verma: Writing. Joseph Madrigal: Writing. Joseph Hadaya: Writing. Christian de Virgilio: Conceptualization, Supervision. Peyman Benharash: Project Administration, Supervision, Writing, Resources, Conceptualization.

Conflict of Interest

The authors declare no conflicts of interest.

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Ethics Approval

This study was deemed exempt from full review by the Institutional Review Board at the University of California, Los Angeles.

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