Long-Term Outcome of Lower Extremity Bypass Surgery in Patients with Chronic Kidney Disease and Critical Limb Ischemia in Germany

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Background: The aim of this study is to present short- and long-term outcomes after lower extremity bypass (LEB) surgery in patients with chronic limb-threatening ischemia and chronic kidney disease (CKD), differentiated by peripheral artery disease (PAD) Fontaine stage III and IV.
Methods: Retrospective analysis of anonymized data from a nationwide German health insurance company (AOK). Data from 22,633 patients (14,523 men) who underwent LEB from 2010 to 2015 were analyzed, presenting 18,271 with CKD stage 1/2, 2,483 patients with CKD stage 3, and 1,879 with CKD stage 4/5.
Results: Perioperative mortality (60-day mortality) was 7.2% for CKD stage 1/2, 12.4% for CKD stage 3, and 19.8% for CKD stage 4/5. Patients with PAD stage IV had significantly higher perioperative mortality (10.3%) than patients with PAD stage III (4.5%). The perioperative major amputation rate depended significantly on PAD stage IV (odds ratio [OR]: 2.57 confidence interval [CI]: 2.16−3.05, $P < 0.001$), the LEB level below the knee and crural/pedal (OR: 2.49 CI: 2.14−2.90, $P < 0.001$), CKD stage 4/5 (OR: 1.28, CI: 1.06−1.54, $P = 0.009$), and the presence of diabetes mellitus type 2 (OR: 1.19, CI: 1.05−1.36, $P = 0.007$). Kaplan-Meier estimated long-term survival of up to 9 years after surgery was 31.7% for patients with CKD stage 1 and 2, 14.3% for CKD stage 3, and only 10.1% for CKD stage 4 and 5 ($P < 0.001$). PAD Fontaine stage IV versus III (hazard ratio: 1.64, CI: 1.56−1.71, $P < 0.001$), but not bypass level, had an independent adverse influence on long-term survival.
Conclusion: CKD and PAD stage were equally significant independent predictors of patient survival and major adverse cardiovascular events with higher PAD and CKD stages associated with less favorable long-term outcomes.

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INTRODUCTION

This study addresses the long-term results of lower extremity bypass (LEB) surgery in patients with chronic limb-threatening ischemia (CLTI) and renal dysfunction. The influence of chronic kidney disease (CKD) or end-stage renal disease (ESRD) (estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2) on the outcome of lower extremity revascularization has been reported on various occasions, suggesting that patients with CKD/ESRD who have undergone lower extremity peripheral artery disease (PAD) interventions have worse outcomes than those with normal renal function (meta-analyses by Anantha-Narayanan et al.[1] and Dawson et al.[2]). However, there are only a few studies on the long-term outcome depending on the respective stage of kidney disease. Ambur et al.[3] used the National Surgical Quality Improvement Program database to classify 6,978 patients with CLTI into three groups with CKD: CKD stages 3 or lower (mild to moderate CKD), CKD stages 4 or 5 (severe CKD), and patients on hemodialysis (HD). Patients with CLTI and severe CKD had an increased risk of perioperative cardiovascular events and readmission after LEB without increased mortality, but long-term data were not reported. A retrospective study examined 44,332 patients from the Vascular Quality Initiative database who underwent LEB (Naazie et al.[4]). The 30-day mortality was higher for CKD 3 and CKD 5 compared to CKD 1 and 2. Comparing CKD stages 3, 4, and 5 with CKD 1 and 2, there was a stepwise increase in the adjusted hazard of 5-year mortality. The eGFR was a useful predictor of postoperative mortality, overall survival, and/or amputation after LEB in patients with PAD. However, outcomes depending on PAD stage (rest pain or tissue loss) were not reported. PAD stage was also not considered by Owens et al.[5] In their single-center retrospective cohort study, 456 patients with vein LEB surgery (83.5% for CLTI) were included and classified in patients with CKD 1/2, 3, 4, and 5. Each increase of CKD stage in patients undergoing LEB surgery was correlated with higher rates of major amputation and death of any cause. None of the previously cited studies considered the bypass level (above the knee, below the knee, crural/pedal). The present study therefore aims to present for the first time short- and long-term outcomes after LEB in patients with CLTI and CKD, differentiated by PAD Fontaine stage III (rest pain) and IV (ulcer/gangrene) and bypass level, using a large database of a German health insurance company.

METHODS

Patient Population

This retrospective study is based on data from "AOK-Die Gesundheitskasse," a nationwide German health insurance company. The data were provided in anonymized form by WIDO (Wissenschaftliches Institut der AOK). The study involved 22,633 patients (64.2% men, 35.8% women) who underwent a LEB (OPS code: above the knee: 5-393.53, below the knee: 5-393.54 and crural/pedal: 5-393.55, 5-393.56, 5-393.61, 5-393. 62) with concomitant PAD Fontaine stage III or IV (PAD-ICD [International Classification of Diseases] codes 2010-2014: stage III: I70.22, stage IV: I70.23 and I70.24; 2015-2018: stage III: I70.23, stage IV: I70.24 and I70.25). The patients were divided into 3 groups according to their CKD stage: patients with CKD stages 1 and 2 (ICD code: N18.1 and N18.2) (n = 18,271), patients with CKD stage 3 (ICD code: N18.3) (n = 2,483), and patients with CKD stages 4 and 5 (ICD code: N18.4 and N18.5) (n = 1,879). The 3 groups were compared in terms of general patient characteristics, comorbidities, perioperative complications, and postoperative outcome as well as long-term survival. Since only the month of death was known for all deceased patients, patients who died in the month of bypass surgery and the following month were documented as perioperatively deceased. Perioperative mortality, therefore, covered a period of up to 60 days after the procedure. The follow-up ended for all patients on December 31, 2018. The average follow-up period of the patients was 55 months (standard deviation: 31.0 months).

Statistical Analysis

The data were analyzed using SPSS 28 (IBM Deutschland GmbH, Ehningen, Germany). To assess differences between the groups, the chi-square test was used for nonmetric variables and the Mann-Whitney U test for metric variables.

The Kaplan-Meier method was used to analyze overall survival and major adverse cardiovascular events (MACE, myocardial infarction, cerebral infarction, or death) during follow-up. Differences between the curves were tested using the log-rank test. To examine the influence of patient characteristics and comorbidities on survival, MACE, and major amputation rates in the perioperative period, a binary logistic regression was performed. For the follow-up, hazard ratios (HRs) were calculated using univariate Cox regression. All assessed patient characteristics and comorbidities were included in the univariate analyses. All statistically significant variables from the univariate analysis were tested for significance in a multivariate analysis. Values $P < 0.05$ were defined as statistically significant.

RESULTS

Patients

Patient characteristics and comorbidities depending on CKD stage are shown in Table I. Patients with CKD stage 4/5 were significantly ($P < 0.001$) less likely to have PAD stage III (13.9%) compared to patients with CKD stage 3 (21.3%) and CKD 1/2 (28.8%). Conversely, the proportion of patients with stage IV PAD was significantly higher in patients with CKD 4/5 than in patients with CKD 1/2 and 3.

In PAD stage IV, above-knee bypass was significantly ($P = 0.001$) more common in patients with CKD 1/2 (31.0%) than in patients with CKD 3 (27.4%) and CKD 4/5 (23.7%). In PAD IV, a crural/pedal bypass was implanted in 39.6% of patients with CKD 1/2 compared to 45.3% of patients with CKD 3 ($P < 0.001$) and 45.0% of patients with CKD 4/5 ($P < 0.001$). Both men and women were younger in stage 1/2 CKD compared to CKD 3 and 4/5.

Perioperative Outcome

The perioperative outcome is shown in Table II. Perioperative mortality was dependent on the stage of CKD in the overall patient population, with 7.2% for CKD 1/2, 12.4% for CKD 3, and 19.8% for CKD 4/5 ($P < 0.001$). Perioperative mortality was significantly higher in patients with PAD IV compared to PAD III. Both, stage of PAD and stage of CKD had a significant effect on the major amputation rate. In patients with CKD stage 1/2, major amputation was 6.0%; in CKD stage 4/5, it was 9.3% ($P < 0.001$). In PAD III, the major amputation rate was 2.9%, in PAD IV 7.6% ($P < 0.001$). The minor amputation rate was 19.3% in patients with CKD 1/2 vs. 25.2% in CKD 3 ($P < 0.001$) and 33.4% in CKD 4/5 ($P < 0.001$). Perioperative minor amputation rate was significantly higher in diabetic compared to nondiabetic patients, 26.4% vs. 16.9% in CKD stage 1/2, 30.2% vs. 18.2% in CKD stage 3, and 37.1 vs. 26.7% in CKD stage 4/5 ($P < 0.001$). MACE was significantly ($P < 0.001$) lower in patients with CKD 1/2 (9.7%) than in patients with CKD 3 (15.1%) and CKD 4/5 (23.6%) ($P < 0.001$).

In a multivariate binary logistic regression analysis, independent factors that had a significant negative impact on the perioperative mortality of patients were analyzed (Table III). These were, in order of influence, CKD stage 4/5 vs. 1/2, PAD stage IV, left heart failure, cerebral infarction before surgery, chronic obstructive pulmonary disease (COPD), LEB below the knee and crural/pedal, male gender, and age.

CKD stage 4/5, PAD stage IV, left heart failure, cerebral infarction before surgery, COPD, LEB below the knee and crural/pedal, male gender, and increasing age also significantly influenced the perioperative MACE rate (Table III).

The perioperative major amputation rate correlated significantly to PAD stage IV, bypass level below the knee and crural/pedal, CKD stage 4/5, and the presence of diabetes mellitus type 2 (Table III).

Long-Term Follow-Up

Kaplan-Meier estimated long-term survival up to 9 years depended on the stage of CKD and was 31.7% in stage 1/2, 14.3% in stage 3, and 10.1% in stage 4/5, respectively ($P < 0.001$) (Table IV). Figure 1 shows the long-term survival of patients for each stage of CKD. Long-term survival was significantly better in patients with PAD III than in patients with PAD IV, for all stages of CKD and regardless of bypass level (Table IV). The 9-year MACE rate was 75.9% in patients with CKD 1/2, 89.4% in CKD 3, and 94.4% in CKD 4/5 patients ($P < 0.001$) (Table IV).

Factors that influenced the long-term mortality of patients are shown in the multivariate Cox regression (Table V). CKD stage 4/5, PAD stage IV, COPD, left heart failure, cerebral infarction before surgery, male gender, type 2 diabetes mellitus, and age increasing by 1 year had a significant negative impact on long-term survival. Factors that negatively influenced the MACE rate were CKD stage 4/5, PAD stage IV according to Fontaine, COPD, left heart failure, a history of cerebral infarction, male gender, diabetes mellitus type 2, myocardial infarction prior to surgery, and age increasing by 1 year (Table V).

DISCUSSION

In the present study, in-hospital mortality in CLTI patients with LEB surgery depended on the stage of CKD in the overall patient population, with 7.2% in CKD 1/2, 12.4% in CKD 3, and 19.8% in CKD 4/5 ($P < 0.001$). Furthermore, hospital

Table I. Characteristics and comorbidities of CLTI patients with CKD stage 1 and 2, 3, and 4 and 5

Parameter	CKD stage 1/2 $n = 18.271$ (A)	CKD stage 3 $n = 2,483$ (B)	CKD stage 4/5 $n = 1,879$ (C)	*P* value
Male sex, *n* (%)	11.891 (65.1)	1,466 (59.0)	1,166 (62.1)	A vs. B < 0.001 A vs. C = 0.009 B vs. C = 0.044
Female sex, *n* (%)	6,380 (34.9)	1,017 (41.0)	713 (37.9)	A vs. B < 0.001 A vs. C = 0.009 B vs. C = 0.044
PAD Fontaine stage III, *n* (%)	5,270 (28.8)	528 (21.3)	262 (13.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
PAD Fontaine stage IV, *n* (%)	13.001 (71.2)	1,955 (78.7)	1,617 (86.1)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Bypass above-the-knee PAD III, *n* (%)	2,034 (38.6)	180 (34.0)	85 (32.5)	A vs. B = 0.042 A vs. C = 0.046 B vs. C = 0.664
Bypass below-the-knee PAD III, *n* (%)	1,698 (32.2)	174 (33.0)	91 (34.7)	A vs. B = 0.731 A vs. C = 0.396 B vs. C = 0.618
Bypass crural/pedal PAD III, *n* (%)	1,538 (29.2)	174 (33.0)	86 (32.8)	A vs. B = 0.070 A vs. C = 0.207 B vs. C = 0.971
Bypass above-the-knee PAD IV, *n* (%)	4,029 (31.0)	535 (27.4)	383 (23.7)	A vs. B = 0.001 A vs. C < 0.001 B vs. C = 0.012
Bypass below-the-knee PAD IV, *n* (%)	3,826 (29.4)	534 (27.3)	506 (31.3)	A vs. B = 0.055 A vs. C = 0.122 B vs. C = 0.009
Bypass crural/pedal PAD IV, *n* (%)	5,146 (39.6)	886 (45.3)	728 (45.0)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.859
Age, mean ± SD in years; median (min-max)	71.6 ± 10.6; 73 (19−101)	77.0 ± 8.8; 78 (32−101)	75.1 ± 9.7; 76 (34−99)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Age men, mean ± SD in years; median (min-max)	69.2 ± 10.0; 70 (19−99)	74.9 ± 8.5; 76 (32−97)	73.5 ± 9.4; 75 (40−97)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Age women, mean ± SD in years; median (min-max)	76.1 ± 10.2; 78 (27−101)	80.1 ± 8.2; 81 (37−101)	77.8 ± 9.5; 79 (34−99)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Arterial hypertension, *n* (%)	8,455 (46.3)	2,132 (85.9)	1,584 (84.3)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.150
Left heart failure (NYHA 2-4 and unspecified), *n* (%)	1,948 (10.7)	1,146 (46.2)	975 (51.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
History of myocardial infarction, *n* (%)	1,438 (7.9)	593 (23.9)	514 (27.4)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.009
History of stroke, *n* (%)	642 (3.5)	191 (7.7)	107 (5.7)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.010
History of intracerebral bleeding, *n* (%)	44 (0.2)	6 (0.2)	6 (0.3)	A vs. B = 0.994 A vs. C = 0.515 B vs. C = 0.628

(*Continued*)

Table I. Continued

Parameter	CKD stage 1/2 $n = 18.271$ (A)	CKD stage 3 $n = 2,483$ (B)	CKD stage 4/5 $n = 1,879$ (C)	*P* value
History of TIA, *n* (%)	255 (1.4)	80 (3.2)	74 (3.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.204
COPD, *n* (%)	1,844 (10.1)	554 (22.3)	394 (21.0)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.287
Diabetes mellitus type 2, *n* (%)	4,611 (25.2)	1,454 (58.6)	1,201 (63.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001

SD, standard deviation; NYHA, New York Heart Association; TIA, transient ischemic attack.

mortality was significantly lower in patients with PAD stage III than in patients with PAD stage IV, as was the major amputation rate. In addition, perioperative outcome was influenced by bypass level, with significantly higher hospital mortality in patients with below-the-knee bypass versus above-the-knee bypass (odds ratio [OR]: 1.18, confidence interval [CI]: 1.05−1.33, $P = 0.006$). The lowest in-hospital mortality was found in patients with CKD stage 1/2 and PAD III (3.7%), the highest in CKD 4/5 and PAD IV (20.2%).

Ambur et al.[3] reported a significantly lower postoperative mortality in patients with CLTI and LEB surgery, with only 1.6% for CKD <3, 4.0% for CKD stage 4/5, and 8.4% for HD patients, but no distinction was made with respect to PAD stage and bypass level. In addition, postoperative mortality up to 60 days after LEB surgery was recorded in the present study, compared with 30 days by Ambur et al.[3] These investigators[3] reported an amputation rate of 3.8% for CKD <3, 5.2% for CKD stage 4/5, and 6.0% for HD without considering the PAD stage. In the present study, a major amputation rate of 2.6% was observed in patients with CKD 1/2 and PAD III, but 7.4% in patients with CKD 1/2 and PAD IV ($P < 0.001$). Overall, the perioperative amputation rate was significantly more influenced by the stage of PAD (OR: 2.57, CI: 2.16−3.05, $P < 0.001$) than by the stage of CKD (OR: 1.28, CI: 1.06−1.54, $P = 0.009$).

Naazie et al.[4] observed higher hospital mortality and 30-day mortality in patients with CKD stages 3, 4, and 5 compared to CKD stages 1 and 2, regardless of bypass level and PAD stage. In their study, the 30-day mortality rates for CKD 1 and 2 were 1.1% vs. 6.4% for CKD stage 5, respectively. In their study, not only CLTI patients but also asymptomatic patients were included. Compared to patients with claudication, 30-day mortality was significantly higher for patients with ischemic rest pain (OR: 2.07, CI: 1.55−2.78, $P < 0.001$) and those with ischemic tissue loss (OR: 2.58, CI: 1.97−3.38, $P < 0.001$). Since the present study relates exclusively to CLTIs, the results are only partially comparable.

Shah et al.[6] identified in the National Inpatient Sample from 2015 to 2018 11,652 hospital admissions with CLTI alone and 2,705 with CLTI + end-stage kidney disease (ESKD). Admissions with ESKD + CLTI were less likely to undergo open arterial revascularization (13.2% vs. CLTI alone, 30.0%, $P < 0.001$) but more likely to receive endovascular intervention (43.7% vs. CLTI alone, 41.6%, $P = 0.05$). ESKD + CLTI admissions had significantly higher rates of both major (27.9% vs. CLTI alone, 17.7%, $P < 0.001$) and minor amputation (32.9% vs. CLTI alone, 24.3%, $P < 0.001$). Similarly, crude inpatient mortality was higher (4.0% vs. CLTI alone, 1.5%, $P < 0.001$).

The impact of CKD on the long-term survival of patients with LEB has also been reported earlier, but not the simultaneous impact of PAD stage and bypass level on patient outcome. In the present study, Kaplan-Meier estimated long-term survival of up to 9 years after surgery was 31.7% for patients with CKD stage 1 and 2, 14.3% for CKD stage 3, and only 10.1% for CKD stage 4 and 5 ($P < 0.001$). CKD stage 4/5 vs. 1/2, PAD Fontaine stage IV vs. III, but not LEB level (crural/pedal and below the knee vs. above the knee) had an independent negative influence on long-term patient survival (Table V). Similar trends were observed for MACE.

The fact that the PAD stage has a decisive influence on patient outcome is demonstrated by data from 2016 to 2018 of the National Inpatient Sample based on 15,896 hospitalized CLTI patients (Foley et al.[7]). The primary amputation rate for patients with pain at rest was only 4.0%, but 8.4% for patients with ulceration and 35.5% for patients with gangrene.

Table II. Perioperative outcomes of CLTI patients with CKD stage 1 and 2, 3, and 4 and 5

Parameter	CKD stage 1/2 $n = 18.271$ (A)	CKD stage 3 $n = 2{,}483$ (B)	CKD stage 4/5 $n = 1{,}879$ (C)	*P* value
Perioperative mortality all patients, *n* (%)	1,309 (7.2)	307 (12.4)	372 (19.8)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Perioperative mortality men, *n* (%)	770/11.891 (6.5)	157/1,466 (10.7)	220/1,166 (18.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Perioperative mortality women, *n* (%)	539/6,380 (8.4)	150/1,017 (14.7)	152/713 (21.3)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Perioperative mortality PAD III, *n* (%)	195/5,270 (3.7)	35/528 (6.6)	45/262 (17.2)	A vs. B $= 0.001$ A vs. C < 0.001 B vs. C < 0.001
Perioperative mortality PAD IV, *n* (%)	1,114/13.001 (8.6)	272/1,955 (13.9)	327/1,617 (20.2)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Perioperative mortality above-the-knee bypass, *n* (%)	345/6,063 (5.7)	74/715 (10.3)	76/468 (16.2)	A vs. B < 0.001 A vs. C < 0.001 B vs. C $= 0.003$
Perioperative mortality below-the-knee bypass, *n* (%)	389/5,524 (7.0)	85/708 (12.0)	135/597 (22.6)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Perioperative mortality crural/pedal bypass, *n* (%)	575/6,684 (8.6)	148/1,060 (14.0)	161/814 (19.8)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
LOS, mean ± SD in days; median (min-max)	26.0 ± 20.2; 20 (0−298)	28.6 ± 21.0; 22 (0−217)	30.3 ± 23.1; 23 (2−202)	A vs. B < 0.001 A vs. C < 0.001 B vs. C $= 0.098$
Major amputation PAD III, *n* (%)	138/5,270 (2.6)	19/528 (3.6)	19/262 (7.3)	A vs. B $= 0.186$ A vs. C < 0.001 B vs. C $= 0.024$
Major amputation PAD IV, *n* (%)	958/13.001 (7.4)	141/1,955 (7.2)	156/1,617 (9.6)	A vs. B $= 0.805$ A vs. C $= 0.001$ B vs. C $= 0.009$
Minor amputation nondiabetic patients, *n* (%)	2,308/13.660 (16.9)	187/1,029 (18.2)	181/678 (26.7)	A vs. B $= 0.293$ A vs. C < 0.001 B vs. C < 0.001
Minor amputation diabetic patients, *n* (%)	1,218/4,611 (26.4)	439/1,454 (30.2)	446/1,201 (37.1)	A vs. B $= 0.005$ A vs. C < 0.001 B vs. C < 0.001
MACE peri OP, *n* (%)	1,777 (9.7)	375 (15.1)	443 (23.6)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001

LOS, length of stay; SD, standard deviation.

Naazie et al.[4] reported unadjusted 5-year mortality rates for patients with LEB and CKD stages 1, 2, 3, 4, and 5 of 18.7%, 29.3%, 44.2%, and 56.8%, respectively. In their study, the adjusted 1-year major amputation risk did not increase progressively by CKD stage. Compared with CKD 1 and 2, the hazard of major amputation in 1 year was lower with CKD 3, similar for CKD 4, and 56% higher for CKD 5 (HR: 1.56, CI: 1.31−1.84, $P < 0.001$). PAD stage and bypass level were not considered in this analysis. Concerning amputation data, clear differentiation between ipsilateral and contralateral amputations in the follow-up was not always feasible. As a result, amputation rates of the target limb in the follow-up could not be presented here.

A retrospective analysis of all HD patients in the United States Renal Data System who underwent open LEB operation between January 2007 and

Table III. Multivariate odds ratio for perioperative mortality, MACE and major amputation rate

Parameter	Multivariate binary logistic regression for perioperative mortality			Multivariate binary logistic regression for perioperative MACE			Multivariate binary logistic regression for perioperative major amputation rate		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
CKD (stage 4/5 vs. 1/2)	2.26	1.95–2.63	<0.001	2.03	1.77–2.32	<0.001	1.28	1.06–1.54	0.009
PAD Fontaine stage IV (vs. III)	1.83	1.58–2.11	<0.001	1.68	1.49–1.90	<0.001	2.57	2.16–3.05	<0.001
Left heart failure (NYHA 2-4 and unspecified)	1.51	1.31–1.74	<0.001	1.46	1.28–1.66	<0.001	1.00	0.85–1.18	0.985
History of stroke	1.45	1.14–1.84	0.003	1.68	1.37–2.06	<0.001	-	-	-
COPD	1.42	1.22–1.65	<0.001	1.23	1.07–1.41	0.004	-	-	-
Bypass crural/pedal and below-the-knee (vs. above-the-knee)	1.18	1.05–1.33	0.006	1.22	1.10–1.35	<0.001	2.49	2.14–2.90	<0.001
Male gender (vs. female gender)	1.12	1.00–1.25	0.048	1.12	1.01–1.23	0.027	-	-	-
Age (increased by 1 year)	1.07	1.06–1.07	<0.001	1.05	1.05–1.06	<0.001	-	-	-
History of myocardial infarction	0.96	0.81–1.14	0.647	1.10	0.95–1.28	0.217	-	-	-
Diabetes mellitus type 2	0.92	0.81–1.04	0.183	0.099	0.89–1.11	0.907	1.19	1.05–1.36	0.007
Arterial hypertension	0.87	0.77–0.98	0.020	0.86	0.77–0.95	0.005	-	-	-

NYHA, New York Heart Association.

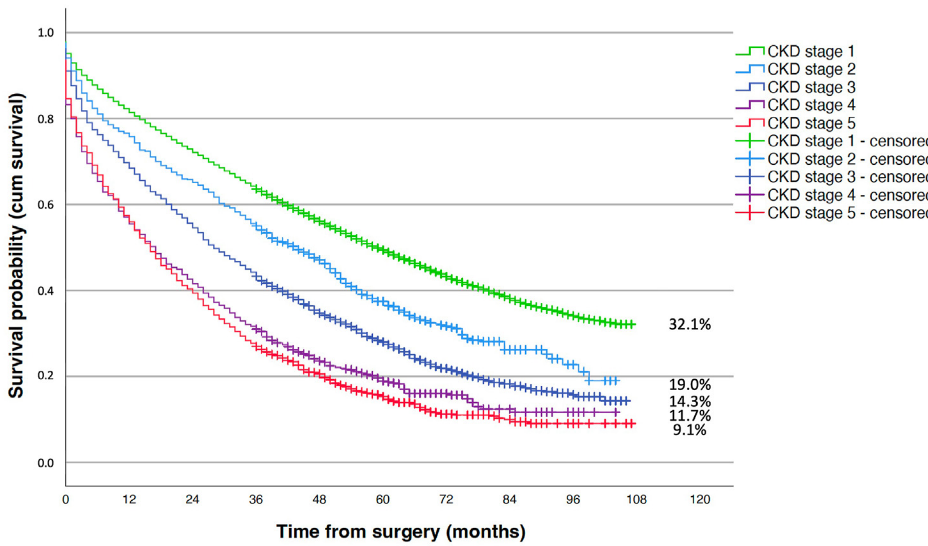
Table IV. Long-term outcomes of CLTI patients with CKD stage 1 and 2, 3, and 4 and 5 following LEB

Parameter	CKD stage 1/2 *n* = 18.271 (A)	CKD stage 3 *n* = 2,483 (B)	CKD stage 4/5 *n* = 1,879 (C)	*P* value
Survivalall patients, *n* (%)	7,801 (31.7)	632 (14.3)	294 (10.1)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival men, *n* (%)	5,221/11.891 (32.9)	388/1,466 (16.8)	178/1,166 (9.5)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival women, *n* (%)	2,580/6,380 (29.6)	244/1,017 (10.7)	116/713 (10.5)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival PAD III, *n* (%)	3,081/5,270 (46.5)	200/528 (19.2)	63/262 (17.5)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival PAD IV, *n* (%)	4,720/13.001 (25.9)	432/1,955 (12.9)	231/1,617 (8.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival above-the-knee bypass PAD III, *n* (%)	1,250/2,034 (49.2)	83/180 (21.8)	25/85 (21.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.002
Survival below-the-knee bypass PAD III, *n* (%)	992/1,698 (47.1)	58/174 (17.3)	19/91 (10.8)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival crural/pedal bypass PAD III, *n* (%)	839/1,538 (42.3)	59/174 (21.9)	19/86 (18.9)	A vs. B < 0.001 A vs. C < 0.001 B vs. C = 0.009
Survival above-the-knee bypass PAD IV, *n* (%)	1,575/4,029 (28.0)	115/535 (15.0)	55/383 (7.6)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival below-the-knee bypass PAD IV, *n* (%)	1,384/3,826 (24.4)	122/534 (11.6)	77/506 (9.7)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
Survival crural/pedal bypass PAD IV, *n* (%)	1,761/5,146 (25.2)	195/886 (13.9)	99/728 (9.1)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001
MACE after 9 years, *n* (%)	11.901 (75.9)	1,982 (89.4)	1,658 (94.4)	A vs. B < 0.001 A vs. C < 0.001 B vs. C < 0.001

Percentages are Kaplan-Meier estimates.

December 2011 was performed by Arhuidese et al.[8] There were 9,739 LEB performed in this cohort. Of these, 4,717 (48%) were femoral-popliteal, 3,321 (34%) were femoral-tibial, and 1,701 (18%) were popliteal-tibial bypasses. Acute graft failure within 30 days of open bypass surgery was 14% for bypasses constructed with autogenous conduits versus 16% for prosthetic conduits. Independent predictors of early graft failure included more distal outflow (femoral-tibial and popliteal-tibial compared to femoral-popliteal revascularization). Limb loss within 30 days of operation was 8% and depended on distal outflow, too. Thirty-day mortality was 8.3% for patients who received autogenous bypasses versus 9.6% for patients who received prosthetic bypasses. The unadjusted Kaplan-Meier estimates of patient survival were 59% vs. 55% at 1 year, and 20% vs. 18% at 5 years for patients who received autogenous bypasses versus patients who received prosthetic bypasses. These results correspond to our findings, but a distinction between autogenous and prosthetic bypasses could not been performed in our cohort.

A retrospective, single-center analysis of LEB for CLTI was performed between 2008 and 2019 by Cheng et al.[9] There were 221 LEB, and overall, 77% of patients had tissue loss. The majority (58%) of bypass procedures were to an infrapopliteal level. Kidney function was categorized as normal (eGFR >60 mL/min/1.73 m^2), CKD (eGFR



No. at risk

CKD stage 1	17,511	14,406	12,762	11,253	8707	6387	4438	2785	1386
CKD stage 2	760	582	500	422	290	184	120	51	16
CKD stage 3	2483	1731	1382	1099	733	446	238	113	42
CKD stage 4	739	422	315	234	148	90	45	17	5
CKD stage 5	1140	655	460	316	201	113	61	37	12

Fig. 1. Nine-year survival of CLTI-patients with CKD stage 1 to 5 following LEB. CLTI, critical limb threatening ischemia; CKD, chronic kidney disease; LEB, lower extremity bypass.

Table V. Multivariate hazard ratio for long-term mortality and MACE

	Multivariate Cox regression for long-term mortality			Multivariate Cox regression for MACE after 9 years		
Parameter	HR	95% CI	*P* value	HR	95% CI	*P* value
CKD (stage 4/5 vs. 1/2)	1.85	1.74−1.96	<0.001	1.76	1.66−1.87	<0.001
PAD Fontaine stage IV (vs. III)	1.64	1.56−1.71	<0.001	1.47	1.41−1.53	<0.001
COPD	1.40	1.33−1.48	<0.001	1.33	1.26−1.40	<0.001
Left heart failure (NYHA 2-4 and unspecified)	1.34	1.27−1.41	<0.001	1.27	1.21−1.34	<0.001
History of stroke	1.20	1.09−1.32	<0.001	1.26	1.15−1.38	<0.001
Male gender (vs. female gender)	1.18	1.14−1.23	<0.001	1.17	1.13−1.21	<0.001
Diabetes mellitus type 2	1.07	1.02−1.12	0.003	1.11	1.06−1.15	<0.001
Age (increased by 1 year)	1.05	1.04−1.05	<0.001	1.04	1.04−1.04	<0.001
History of myocardial infarction	1.03	0.96−1.09	0.416	1.06	1.00−1.13	0.048
Bypass crural/pedal and below-the-knee (vs. above-the-knee)	1.02	0.98−1.06	0.426	1.01	0.97−1.05	0.704
History of TIA	0.98	0.84−1.12	0.724	1.02	0.90−1.17	0.722
Arterial hypertension	0.92	0.88−0.96	<0.001	0.94	0.90−0.98	0.002

NYHA, New York Heart Association; TIA, transient ischemic attack.

15-59 mL/min/1.73 m^2), and ESRD (eGFR <15 mL/min/1.73 m^2). Kaplan-Meier 3-year analysis showed no difference between groups for primary patency or major amputation; however, ESRD, compared to CKD and normal renal function, respectively, had worse primary-assisted patency and survival. ESRD, but not CKD, was associated with higher perioperative and long-term mortality after LEB for CLTI. These results from a single-center study are not consistent with our data, as we observed a significant dependence of patient survival (Fig. 1) and MACE on CKD stages.

The present study evidently has several limitations. The comprehensiveness of the datasets relies on the coding accuracy of individual hospitals and the documentation provided by the health insurance company, leaving room for potential coding errors. The data mirror the patient demographics of a specific health insurance company, capturing its social structure, and may not necessarily reflect the situation of the entire German population. Nevertheless, it is worth noting that AOK is the largest health insurance company in Germany with a market share of 37%. The anonymity of the datasets prevented the analysis of treated hospitals and their case volumes. In addition to that, causes of death and the exact date of death remained indeterminable. Conversely, a notable strength of this study lies in its ability to document the long-term survival of all patients up to 9 years. Lastly, the study opted for the classification of PAD according to Fontaine, rather than Rutherford, due to limitations in ICD coding that hindered the distinction between Rutherford stages 5 and 6.

Nonetheless, to the best of our knowledge, this is the most extensive study, including over 22,000 patients with CLTI and LEB surgery, analyzing the long-term outcomes up to 9 years postintervention with respect to kidney function. This analysis did not solely consider the stage of CKD but also considered the stage of PAD and bypass level. Results revealed that both CKD and PAD stages had equally significant, independent influences on patient survival and MACE.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Philipp Meyer: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Johanna Surmann:** Writing – review & editing, Formal analysis, Data curation. **Jasmin Epple:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Dittmar Böckler:** Writing – review & editing, Conceptualization. **Thomas Schmitz-Rixen:** Writing – review & editing, Conceptualization. **Reinhart T. Grundmann:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Data curation.

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