Langenbeck's Archives of Surgery (2023) 408:444
https://doi.org/10.1007/s00423-023-03125-7

RESEARCH

# Long-term outcome and cancer incidence after lower extremity bypass surgery in patients with critical limb threatening ischemia

Polykarpos Michailidis[1] · Jasmin Epple[2] · Dittmar Böckler[1] · Thomas Schmitz-Rixen[3] · Reinhart T. Grundmann[4,5] on behalf of on behalf of DIGG gGmbH

Received: 24 June 2023 / Accepted: 29 September 2023


## Abstract

**Purpose** The influence of cancer development on long-term outcome after lower extremity bypass surgery in patients with critical limb threatening ischemia was investigated.

**Methods** Patient survival and cancer incidence were recorded for 21,082 patients with peripheral artery disease (PAD) stage III ($n=5631$; 26.7%) and stage IV ($n=15{,}451$; 73.3%) registered with the AOK health insurance company in Germany who underwent infrainguinal bypass surgery. All patients were preoperative and in their history cancer-free.

**Results** After a median follow-up of 44 months, 25.6% of all patients developed cancer (Kaplan–Meier estimated), with no significant differences between patients with PAD stage III and IV (cancer incidence stage III 25.7%, stage IV 25.5%; $p=0.421$). In the Cox regression analysis, male gender (HR 1.885; 95% CI 1.714–2.073, $p<0.001$) and age over 70 years (HR 1.399; 95% CI 1.285–1.522, $p<0.001$) were significant risk factors for the development of cancer. Survival was significantly lower in stage IV (23.4%) compared to stage III (44.5%) (HR 1.720; 95% CI 1.645–1.799, $p<0.001$). Cancer was a significant risk factor for overall survival in PAD stage III patients (HR: 1.326; 95% CI 1.195–1.471, $p<0.001$) but not in PAD stage IV (HR 0.976; 95% CI 0.919–1.037, $p = 0.434$).

**Conclusion** Patients with PAD stage III have significantly better survival after infrainguinal bypass surgery compared to patients with stage IV. While cancer incidence was essential for survival in stage III, it was of no importance in stage IV.

**Keywords** Infrainguinal bypass · Peripheral artery disease · Fontaine classification · Critical limb threatening ischemia · Cancer · Survival

## Introduction

The present study focuses on the long-term survival of patients with critical limb threatening ischemia (CLTI) who underwent elective bypass surgery. The aim is to examine the cancer incidence in these patients, for which there is very limited data available. While it is known that patients with peripheral artery disease (PAD) share similar risk factors with those having coronary artery disease or stroke (atherosclerosis, diabetes) and that cardiovascular death is therefore the leading cause of death among them [1], PAD patients may also have an increased risk of cancer due to smoking. However, the specific impact of cancer on the survival of bypass patients has not been investigated. Independent of interventional or surgical therapy, Sartipy et al. [2] examined long-term mortality in various stages of PAD in a Swedish cohort study involving 5080 individuals. In their study, 10-year mortality correlated with PAD stage and was significantly higher compared to the reference group (27% mortality rate there). Mortality accounted for 56% in asymptomatic PAD patients, 63% in patients with intermittent claudication (IC), and 75% in patients with severe limb ischemia. Myocardial infarction at 28% and stroke at 26% were the most common causes of death. Cancer posed a significantly lower mortality risk in PAD patients (15%) and was not increased compared to the reference group—being even lower in symptomatic patients than in asymptomatic ones, likely due to competitive risks [3]. Therefore, the aim of this cohort study was to assess the long-term cancer incidence in initially cancer-free patients with infrainguinal bypasses. The study aimed to examine whether CLTI patients differ in cancer incidence and long-term survival depending on the PAD Fontaine stages III, rest pain, and stage IV, ulcer, gangrene. While there have been smaller case series on the

Extended author information available on the last page of the article

Published online: 24 November 2023

outcomes of patients with active cancer who underwent bypass revascularization [4–6], this question has not been investigated in primarily cancer-free patients so far.

## Material and methods

In this retrospective study, anonymized data from the nationwide AOK health insurance in Germany were analyzed. The dataset comprised a total of 21,082 patients who underwent elective infrainguinal bypass surgery for CLTI due to PAD stage III ($n=5631$; 26.7%) or stage IV ($n=15{,}451$; 73.3%) between January 1, 2010, and December 31, 2015. All patients were initially cancer-free, patients with cancer diagnosed before bypass-surgery were excluded from the study. In these patients no cancer-specific ICD-codes prior to surgery were found. Patients with PAD stage III were compared to those with stage IV in terms of general patient characteristics, comorbidities, perioperative and postoperative outcomes, and malignancy incidence and survival rates. The relevant medical information for this analysis was collected based on recorded ICD-10 (International Classification of Diseases, Tenth Revision) and OPS (Surgical Procedures Coding System) codes. The ICD-Codes were I70.22 (from 2010 to 2014) and I70.23 (from 2015 to 2018) for PAD stage III and I70.23 and I70.24 (from 2010 to 2014) and I70.24 and I70.25 (from 2015 to 2018) for PAD stage IV. The OPS-Codes were 5–393.53, 5–393.54, 5–393.55, 5–393.56, 5–393.61, and 5–393.62. The codes used for cancer analysis were C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C85, C88, and C90-C97. Additionally, abdominal cancers were separately analyzed using codes C15-25, C54-56, C61-C62, C64-C67, and C74, as indicated by Markar et al. [7]. The follow-up period ended for all patients on December 31, 2018. Patients with PAD stage III were followed up for an average of $53 \pm 30$ months, while patients with PAD stage IV were followed up for an average of $40 \pm 31$ months.

### Statistical analysis

Patient information from the AOK datasets was consolidated and analyzed using SPSS software (IBM Deutschland GmbH, Ehningen, Germany). To assess differences between comparison groups, the chi-square test was used for nominal and categorical variables. The independent samples *t* test was used for metric variables. Kaplan–Meier analysis and the log-rank test were used to compare survival times and cancer incidence. Univariate Cox regressions were performed to analyze the influence of patient characteristics and comorbidities on long-term survival and on cancer incidence. Parameters showing significant influence ($p<0.05$) were subsequently included in a multivariate Cox regression analysis. The significance level was set at $p<0.05$.

## Results

### Patients

Patient characteristics and comorbidities are presented in Table 1. Of the total patients, 13,386 (63.5%) were male and 7696 (36.5%) were female. The average age of male patients at the time of surgery was 69.9 years (median 71), while that of female patients was 76.7 years (median 78) ($p<0.001$). Patients with PAD stage III ($n=5631$) had an average age of 69.9 years (median 71), whereas patients with PAD stage IV ($n=15{,}451$) had an average age of 73.3 years (median 75) ($p<0.001$). Hypertension was present in 53% of PAD stage IV patients compared to 50.8% of stage III patients ($p=0.006$). Additionally, diabetes mellitus (34.9% vs. 23.2%), stage III–V chronic kidney disease (21.0% vs. 12.4%), and left heart failure (19.3% vs. 12.2%) were significantly more common in patients with PAD stage IV.

### Cancer incidence

After a follow-up period of up to 9 years, 25.6% of all patients developed a cancer (Kaplan–Meier estimated), with no significant differences observed between patients with PAD stage III and IV (cancer incidence stage III 25.7%, stage IV 25.5%; $p=0.421$) (Table 2). This finding also applied to the incidence of abdominal cancers (stage III 11.1%, stage IV 11.6%; $p=0.531$). Postoperative cancer incidence was significantly higher in males at 30.3% compared to females at 16.4% ($p<0.001$). The most commonly cancers found in men and women are listed in Table 3. Furthermore, the cancer incidence between PAD stage III and IV patients did not significantly differ with respect to kind of cancer (Table 4).

In the Cox regression analysis, male gender (HR 1.885; 95% CI 1.714–2.073, $p<0.001$) and age over 70 years (HR 1.399; 95% CI 1.285–1.522, $p<0.001$) were significant risk factors for the development of cancer. COPD was also associated with a significantly increased risk of cancer (HR 1.397; 95% CI 1.236–1.578, $p<0.001$). However, PAD stage IV vs. III was not associated with a higher risk of overall or abdominal cancer incidence (Table 5).

### Patient survival

The patient survival, stratified by PAD stage, is shown in Fig. 1. At the end of the observation period, an estimated survival rate of 44.5% was observed in patients with PAD stage III, compared to only 23.4% in patients with stage

**Table 1** Characteristics, comorbidities, and perioperative outcomes of primary cancer-free patients with PAD stage III and IV (entire study cohort)

| Patients ($n=21{,}082$) | PAD stage III, $n$ (%) ($n=5631$) | PAD stage IV, $n$ (%) ($n=15{,}451$) | $p$-value |
|---|---|---|---|
| Patient characteristics and comorbidities | | | |
| Men, $n$ (%) | 3606 (64%) | 9780 (63.3%) | 0.324 |
| Women, $n$ (%) | 2025 (36%) | 5671 (36.7%) | 0.324 |
| Age, MW ± SD in months, median (min–max) | 69.9 ± 10.5, 71 (19–101) | 73.3 ± 10.5, 75 (22–101) | < 0.001 |
| Age men, MW ± SD in months, median (min–max) | 67.5 ± 9.9, 68 (19–96) | 70.8 ± 9.9, 72 (22–99) | < 0.001 |
| Age women, MW ± SD in months, median (min–max) | 74.1 ± 10.2, 75 (27–101) | 77.7 ± 9.8, 79 (34–101) | < 0.001 |
| CHD, $n$ (%) | 1263 (22.4%) | 3593 (23.3%) | 0.216 |
| Myocardial infarction, $n$ (%) | 581 (10.3%) | 1753 (11.3%) | 0.038 |
| Cerebral infarction, $n$ (%) | 237 (4.2%) | 636 (4.1%) | 0.757 |
| Intracerebral hemorrhage, $n$ (%) | 9 (0.2%) | 39 (0.3%) | 0.255 |
| TIA, $n$ (%) | 113 (2%) | 269 (1.7%) | 0.199 |
| Arterial hypertension, $n$ (%) | 2863 (50.8%) | 8186 (53%) | 0.006 |
| Dyslipoproteinaemia, $n$ (%) | 1800 (32%) | 4458 (28.9%) | < 0.001 |
| Diabetes mellitus, $n$ (%) | 1309 (23.2%) | 5387 (34.9%) | < 0.001 |
| COPD, $n$ (%) | 648 (11.5%) | 1805 (11.7) | 0.733 |
| Left heart failure, $n$ (%) | 688 (12.2%) | 2988 (19.3%) | < 0.001 |
| Chronic kidney disease, $n$ (%) | 697 (12.4%) | 3247 (21%) | < 0.001 |
| Perioperative outcome | | | |
| Length of hospital stay, mean ± SD in days, median (min–max) | 18.9 ± 13.7, 15 (1–217) | 29.4 ± 21.8, 23 (0–298) | < 0.001 |
| Perioperative mortality, $n$ (%) | 247 (4.4%) | 1562 (10.1%) | < 0.001 |

*Chronic kidney disease stage 3–5* glomerular filtration rate less than 60 ml/min/1.73 $m^2$

*PAD* peripheral artery disease, *TIA* transient ischemic attack, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease

**Table 2** Cancer incidence in patients with PAD stage III and IV at the end of follow-up (all patients were cancer-free at the time of surgery)

| Patients | PAD stage III, % ($n=5631$) | PAD stage IV, % ($n=15{,}451$) | $p$-value |
|---|---|---|---|
| Cancer incidence | 25.7% | 25.5% | 0.421 |
| Cancer incidence in patients < 70 years | 22.9% | 24.2% | 0.405 |
| Cancer incidence in patients > 70 years | 26.9% | 26.3% | 0.902 |
| Cancer incidence in men | 30.2% | 30.3% | 0.799 |
| Cancer incidence in women | 16.9% | 15.9% | 0.311 |
| Abdominal cancer incidence | 11.1% | 11.6% | 0.531 |
| Abdominal cancer incidence in patients < 70 years old | 9.1% | 9.6% | 0.897 |
| Abdominal cancer incidence in patients > 70 years old | 13.2% | 13% | 0.850 |
| Abdominal cancer incidence in men | 14.6% | 14.5% | 0.712 |
| Abdominal cancer incidence in women | 4.5% | 5.9% | 0.051 |

*PAD* peripheral artery disease

IV ($p < 0.001$). Additionally, the PAD stage had a negative impact on survival in the multivariate Cox regression model (stage IV (vs. III) HR 1.720; 95% CI 1.645–1.799, $p < 0.001$).

Factors influencing survival in PAD stage III and IV are shown in Table 6. The presence of cancer was a significant risk factor for survival in PAD stage III (HR: 1.326; 95% CI 1.195–1.471, $p < 0.001$) but not for PAD stage IV (HR 0.976; 95% CI 0.919–1.037, 0.434). Age had a negative influence on survival in stage III (HR 2.076; 95% CI 1.899–2.268, $p < 0.001$) and IV (HR 1.923; 95% CI 1.836–2.015, $p < 0.001$). In contrast, gender did not significantly impact survival. For more detailed information, see Table 6.

The survival of PAD III patients with and without cancer is given in Fig. 2. Up to 32 months, both groups did not differ significantly in survival (without cancer (76.7%), with cancer (77.3%); $p = 0.718$). However, thereafter, the survival of cancer-free patients was better than that of

**Table 3** Cancer incidence at the end of the observation period (December 31, 2018) by gender (percentage based on Kaplan–Meier estimates). Details for cancers with an incidence of more than 50 patients are given

| Cancer (total) | Men, *n* (%) (*n* = 13,386) | Women, *n* (%) (*n* = 7696) | *p*-value |
|---|---|---|---|
| Lung (*n* = 638) | 524 (9%) | 114 (3.9%) | < 0.001 |
| Colon (*n* = 304) | 231 (3.8%) | 73 (1.8%) | < 0.001 |
| Renal pelvis and bladder (*n* = 249) | 211 (3.5%) | 38 (0.9%) | < 0.001 |
| Skin (*n* = 239) | 180 (4.2%) | 59 (1.8%) | 0.001 |
| Prostate (*n* = 204) | 204 (3.5%) | 0 | < 0.001 |
| Lip, oral cavity, and pharynx (*n* = 193) | 172 (2.9%) | 21 (0.6%) | < 0.001 |
| Breast and gynecological cancers (*n* = 129) | 9 (0.1%) | 120 (3.6%) | < 0.001 |
| Lymphoma (*n* = 108) | 72 (1.1%) | 36 (1.2%) | 0.733 |
| Oesophagus (*n* = 93) | 83 (1.4%) | 10 (0.3%) | < 0.001 |
| Pancreas (*n* = 84) | 60 (1.1%) | 24 (0.7%) | 0.222 |
| Stomach (*n* = 83) | 59 (1.3%) | 24 (0.6%) | 0.251 |
| Leukaemia (*n* = 79) | 50 (0.7%) | 29 (1%) | 0.743 |
| Liver and gall bladder (*n* = 72) | 63 (1.1%) | 9 (0.3%) | < 0.001 |
| Sinus, middle ear, larynx, trachea (*n* = 72) | 65 (1.5%) | 7 (0.2%) | < 0.001 |
| Kidneys (*n* = 65) | 48 (0.7%) | 17 (0.5%) | 0.133 |
| Secondary (*n* = 1003) | 793 (14.3%) | 210 (6.5%) | < 0.001 |
| Others (*n* = 342) | 263 (4.7%) | 79 (2.5%) | < 0.001 |

**Table 4** Cancer incidence at the end of the observation period (December 31, 2018) by PAD-stage (percentage based on Kaplan–Meier estimates). Details for cancers with an incidence of more than 50 patients are given

| Cancer (total) | PAD stage III, *n* (%) (*n* = 5631) | PAD stage IV, *n* (%) (*n* = 15,451) | *p*-value |
|---|---|---|---|
| Lung (*n* = 638) | 224 (6.9%) | 414 (7.5%) | 0.171 |
| Colon (*n* = 304) | 87 (3.1%) | 217 (3.1%) | 0.165 |
| Renal pelvis and bladder (*n* = 249) | 81 (2.7%) | 168 (2.6%) | 0.955 |
| Skin (*n* = 239) | 66 (3.5%) | 173 (3.1%) | 0.087 |
| Prostate (*n* = 204) | 70 (2.4%) | 134 (2.2%) | 0.554 |
| Lip, oral cavity and pharynx (*n* = 193) | 57 (2.2%) | 136 (2%) | 0.408 |
| Breast and gynecological cancers (*n* = 129) | 43 (1.6%) | 86 (1.2%) | 0.788 |
| Lymphoma (*n* = 108) | 36 (1.4%) | 72 (1.0%) | 0.822 |
| Oesophagus (*n* = 93) | 30 (1%) | 63 (1%) | 0.978 |
| Pancreas (*n* = 84) | 34 (1.1%) | 50 (0.9%) | 0.122 |
| Stomach (*n* = 83) | 24 (0.7%) | 59 (1.2%) | 0.454 |
| Leukaemia (*n* = 79) | 19 (0.8%) | 60 (0.8%) | 0.128 |
| Liver and gall bladder (*n* = 72) | 23 (0.6%) | 49 (0.9%) | 0.883 |
| Sinus, middle ear, larynx, trachea (*n* = 72) | 22 (0.6%) | 50 (1.4%) | 0.739 |
| Kidneys (*n* = 65) | 17 (0.5%) | 48 (0.6%) | 0.326 |
| Secondary (*n* = 1003) | 329 (11.3%) | 674 (11.9%) | 0.970 |
| Others (*n* = 342) | 81 (3%) | 161 (3%) | 0.900 |

patients with cancer, with an estimated survival rate of 47.1% vs. 30.8% after 9 years.

In PAD stage IV, there was no difference in survival up to 63 months after the procedure between cancer and cancer-free patients (37.5% vs. 38.1%). Not before the end of follow-up at 108 months, a slightly better survival was observed in patients without cancer (24.7% vs. 15.9%) (Fig. 3).

## Discussion

In the present study, patients with PAD stage III showed a significantly better survival than patients with stage IV after infrainguinal bypass surgery, with survival rates of 44.5% vs. 23.4% after a follow-up of up to 9 years postoperatively. Comparative data on the long-term outcome

**Table 5** Hazard ratio (HR) and proportional hazard model (multivariate analysis) for cancer incidence

| Covariates | HR | 95% CI | *p*-value |
|---|---|---|---|
| Men (vs. women) | 1.885 | 1.714–2.073 | < 0.001 |
| Age > 70 (vs. < 70) years | 1.399 | 1.285–1.522 | < 0.001 |
| PAD stage IV (vs. stage III) | 1.035 | 0.951–1.127 | 0.422 |
| Diabetes mellitus | 0.861 | 0.786–0.943 | 0.001 |
| COPD | 1.397 | 1.236–1.578 | < 0.001 |

*PAD* peripheral artery disease, *HR* hazard ratio, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease

of patients undergoing lower extremity bypass are scarce, which may be due to the increasing use of endovascular procedures for CLTI. In perhaps the most extensive study, Feinglass et al. [8] reported on 28,128 patients from California who underwent infrainguinal bypass between 1996 and 1999, with a median follow-up of 62 months. In 38.5% of cases, patients had ulcers or gangrene, but the outcome with respect to PAD stages was not further investigated. Feinglass et al. reported an amputation-free survival of 34.1% after 9 years for the entire cohort. In a pooled analysis of 50 studies (28,517 patients), Rollins et al. [9] reported a mortality rate of 46.2% for CLI patients after 5 years, and after 3 years, the odds of dying were significantly higher in patients with tissue loss (OR 27.47) compared to patients with rest pain (OR 0.33). Therefore, the significantly higher risk of mortality in CLI patients with PAD stage IV compared to stage III in the present study is not surprising.

In the cohort presented here, approximately 25% of patients undergoing infrainguinal bypass developed cancer in the long term, regardless of PAD stage. Cancer incidence had a negative impact on survival only in patients with PAD stage III (HR: 1.326; 95% CI 1.195–1.471, $p < 0.001$), but not in patients with PAD stage IV (HR 0.976; 95% CI 0.919–1.037, 0.434), which can be explained by the presence of competitive cardiovascular risks in stage IV.

There are no comparable numbers available. Nicolajsen et al. [10] reported on 7840 patients with acute arterial thrombosis, among whom cancer was diagnosed in 30.4% (2384 patients). However, the majority of cancers occurred before the endovascular or surgical intervention, and only 815 (10.4%) patients were observed to develop cancer more than 24 months after hospital treatment. Since the

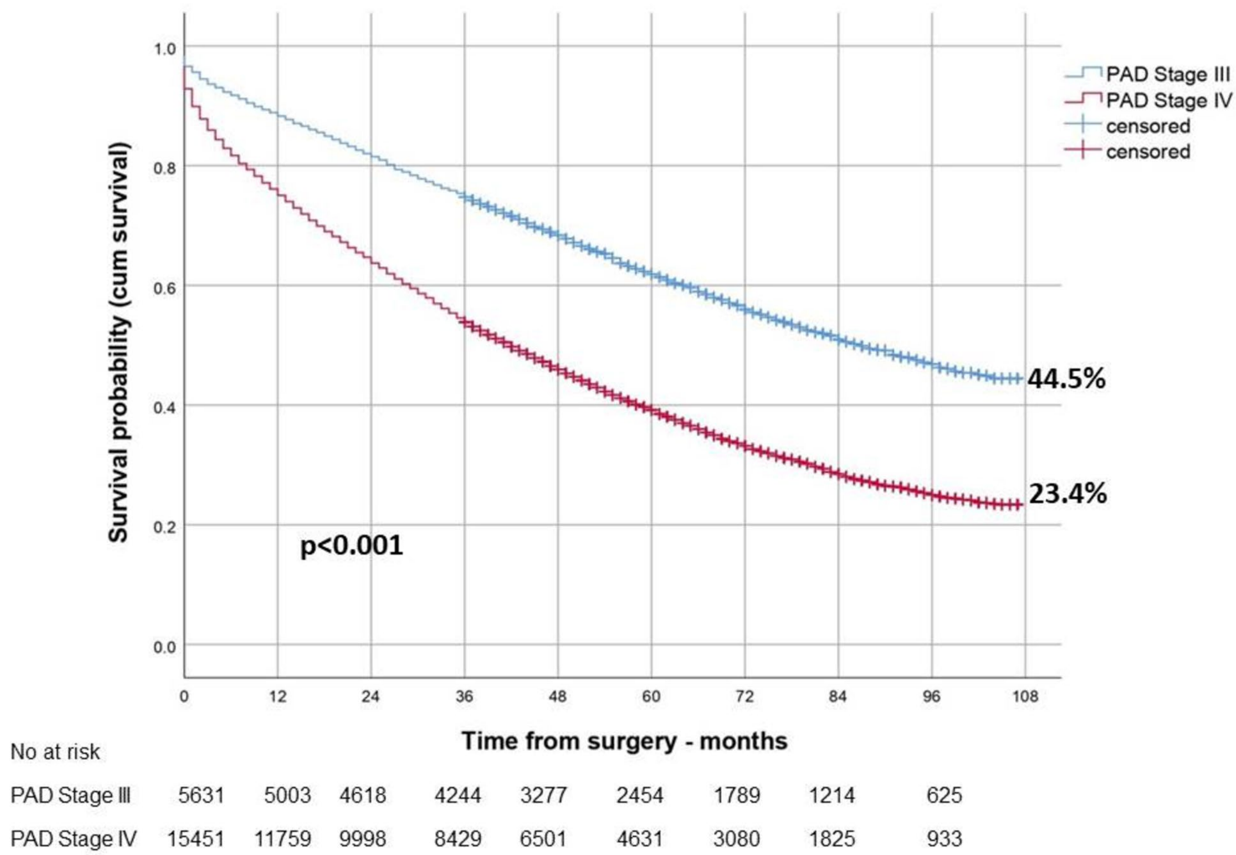


**Fig. 1** Survival of patients with critical limb-threatening ischemia after lower extremity bypass surgery, stratified by PAD stage III and IV (Kaplan–Meier estimated). Overall cohort, no distinction was made between patients with and without cancer

**Table 6** Hazard ratio (HR) and proportional hazard model (multivariate analysis) for overall survival

| Covariates | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
|---|---|---|---|---|---|---|
| | PAD stage III | | | PAD stage IV | | |
| Men (vs. women) | 1.064 | 0.977–1.159 | 0.152 | 1.000 | 0.960–1.042 | 1.000 |
| Age > 70 (vs. < 70) | 2.076 | 1.899–2.268 | < 0.001 | 1.923 | 1.836–2.015 | < 0.001 |
| Cancer | 1.326 | 1.195–1.471 | < 0.001 | 0.976 | 0.919–1.037 | 0.434 |
| Arterial hypertension | 1.055 | 0.955–1.166 | 0.289 | 0.940 | 0.896–0.986 | 0.011 |
| Left heart failure | 1.530 | 1.349–1.736 | < 0.001 | 1.400 | 1.323–1.480 | < 0.001 |
| CAD | 0.938 | 0.831–1.059 | 0.300 | 1.017 | 0.959–1.078 | 0.582 |
| Myocardial infarction | 1.092 | 0.946–1.261 | 0.228 | 1.078 | 1.006–1.156 | 0.032 |
| Cerebral infarction | 1.207 | 0.992–1.469 | 0.060 | 1.253 | 1.138–1.380 | < 0.001 |
| TIA | 1.364 | 1.050–1.771 | 0.020 | 0.959 | 0.827–1.111 | 0.574 |
| Dyslipoproteinaemia | 0.829 | 0.745–0.922 | < 0.001 | 0.858 | 0.816–0.903 | < 0.001 |
| COPD | 1.358 | 1.205–1.531 | 0.001 | 1.303 | 1.228–1.383 | < 0.001 |
| Chronic kidney disease | 1.784 | 1.591–2.001 | 0.001 | 1.522 | 1.444–1.604 | < 0.001 |
| Diabetes mellitus | 1.153 | 1.043–1.275 | 0.006 | 1.064 | 1.016–1.114 | 0.008 |

Chronic kidney disease *stage III–V* glomerular filtration rate below 60 ml/min/1.73 m$^2$

*PAD* peripheral artery disease, *HR* hazard ratio, *CI* confidence interval *COPD* chronic obstructive pulmonary disease, *TIA* transient ischemic attack, CAD coronary artery disease

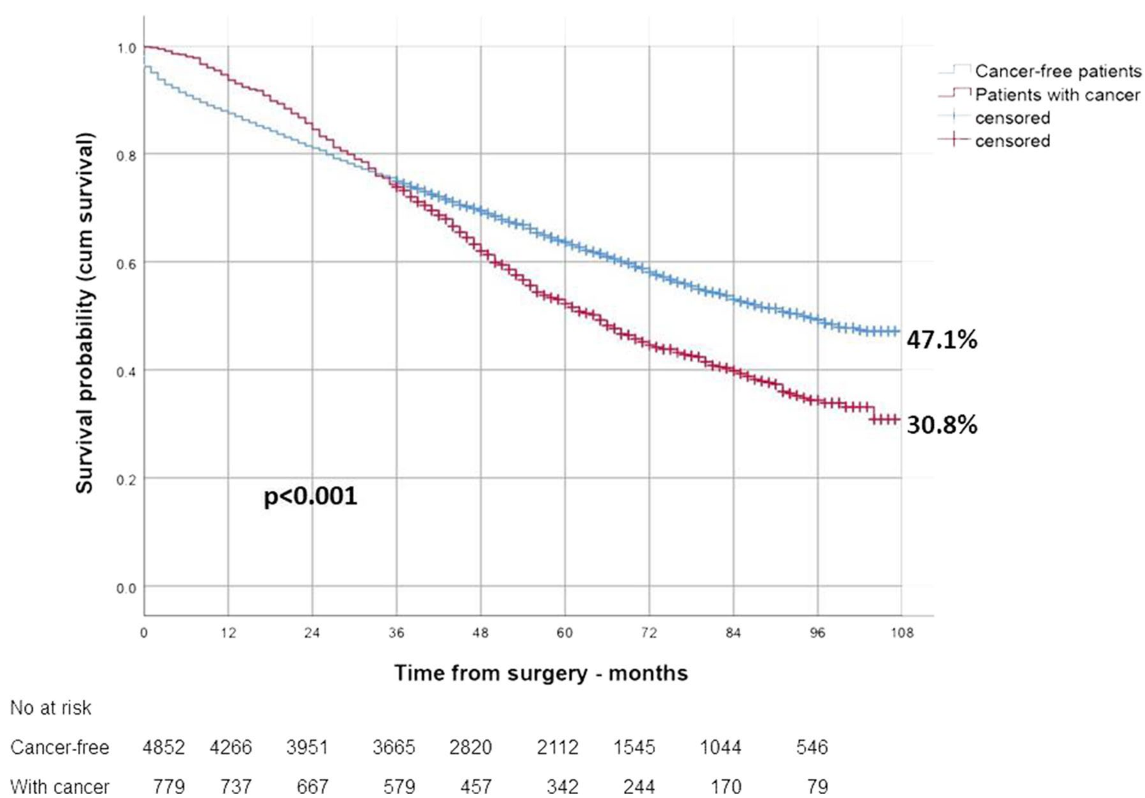


**Fig. 2** Survival of PAD stage III patients after lower extremity bypass surgery. Distinction was made between patients with and without cancer

study primarily included patients with a pre-existing history of cancer, the survival rates cannot be compared with the present study. Nicolajsen reported a median survival of 3.42 years for cancer patients vs. 4.21 years in the cancer-free control group.

The risk of cancer in patients with lower extremity arterial thrombosis was analyzed by Sundbøll et al. [11] in a Danish cohort study involving 6600 patients. They reported a risk of 2.5% for any type of cancer after 6 months, which increased to 17.9% in this cohort after

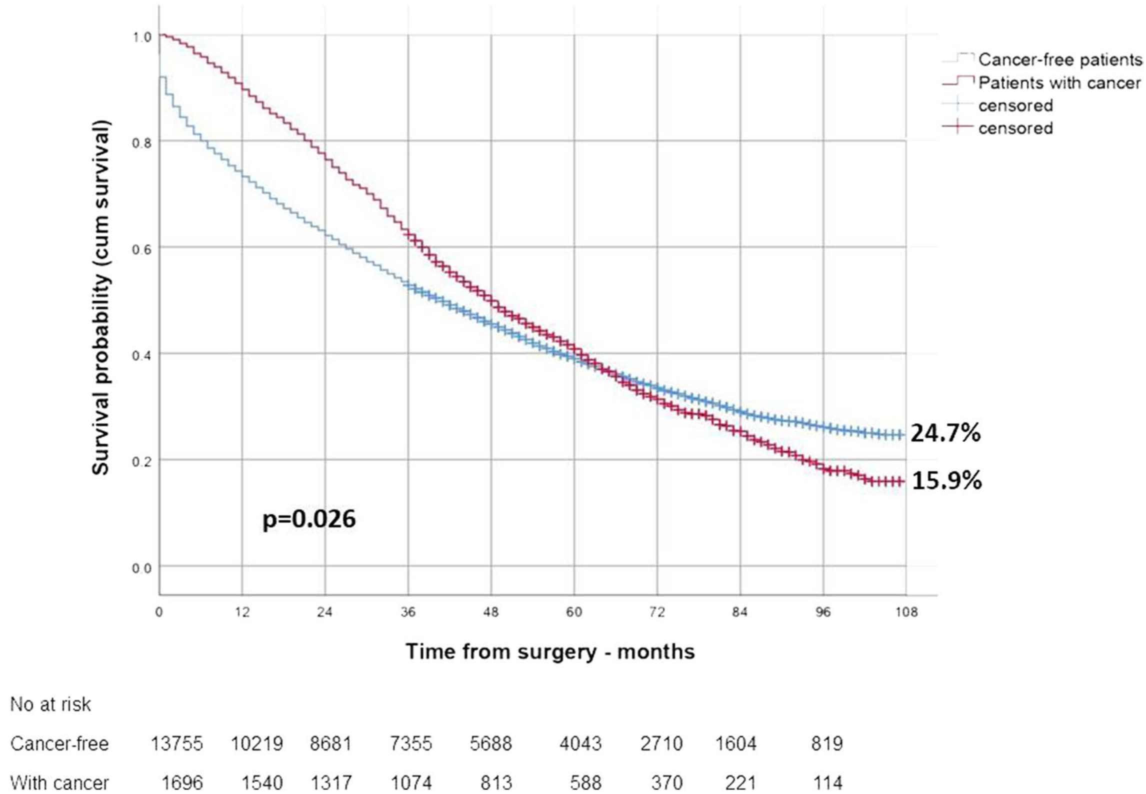


**Fig. 3** Survival of PAD stage IV patients after lower extremity bypass surgery. Distinction was made between patients with and without cancer

20 years. The most common cancers found were lung cancer ($n=888$), colon cancer ($n=323$), urinary tract and bladder cancer ($n=289$), and gender-specific prostate cancer ($n=365$) and breast cancer ($n=298$). The conclusion was that patients with arterial thrombosis have a higher risk of cancer than the general population, particularly for smoking-related cancers. The possibility of cancer screening for this population was discussed. Villemur et al. [12] also suggested cancer screening for patients with PAD due to their increased risk of cancer compared to the general population.

The long-term prognosis of patients undergoing infrainguinal bypass surgery in relation to cancer incidence, and whether this differs between patients with PAD stage III and IV, has not been investigated so far. Png et al. [13] focused on thrombosis of femoropopliteal bypasses in patients with occult cancer. An occult cancer was defined as a cancer that occurred within the first year after bypass surgery. Such cancer was detected in 5.8% of cases (621 bypasses in 517 patients). Patients with occult cancer had significantly higher bypass occlusion rates compared to the control group at 3 months (27.8% vs. 8.0%), 6 months (30.5% vs. 15.1%), and 1 year (44.4% vs. 19.8%). However, there was no significant difference in survival after 1 year between patients with and without occult cancer. The present study did not allow for an analysis of bypass occlusion rates. Occult cancer occurred in 2.8% of patients (595 cases).

In the study by Nicolajsen et al. [10], the most common cancers observed among the 815 postoperative cases were lung and mediastinal cancer (21.6%), skin and soft tissue cancer (17.6%), gastrointestinal cancer (16.8%), and urogenital cancer (13.4%). This is largely consistent with the observations made here (Table 3). The fact that lung cancer, as a typical smoking-associated cancer, ranked first was to be expected given the association between smoking and PAD. Furthermore, Bintein et al. [14] demonstrated in a meta-analysis of the literature that the incidence of lung cancer in PAD patients is approximately 3%, which is not only higher than what is found in lung cancer screening studies but also higher than the incidence observed in smokers and former smokers in general.

An important advantage of the present study was the opportunity to compare the cancer incidence after infrainguinal bypass surgery with that in patients undergoing abdominal aortic aneurysm (AAA) repair using the same observation period and data source (AOK cohort). Ettengruber et al. [15] reported a cancer incidence of 29.5% after 9 years in primarily cancer-free patients who underwent elective endovascular (EVAR) or open repair (OAR) for AAAs, which was significantly higher than the findings presented here. The patients with AAA were similar in age to the CLTI patients, but their survival was significantly better with 53.4% (OAR) and 48% (EVAR) at the end of follow up compared to 44.5% in patients with PAD stage III and only 23.4% in patients with PAD stage IV in the present study. In cancer patients, the estimated survival rate was 30.8% for PAD stage III and 15.9% for PAD stage IV ($p < 0.001$), compared to an estimated survival rate of 27.6% after EVAR and 25.7% after OAR. Both, after treatment for AAA and bypass surgery, the postoperative cancer incidence was significantly higher in men than in women.

A retrospective single-center analysis identified patients with AAA, cancer, and radiation therapy. In this study, both infield and outfield radiation exposure were associated with reduced AAA growth [16]. Markar et al. [7] speculated that specifically abdominal cancers occur more frequently after EVAR compared to OAR, and this could be explained by increased radiation exposure during EVAR (during the procedure and in follow-up). Ettengruber et al. [15] and the present study strictly followed the criteria provided by Markar et al. to analyze the tumors, in order to verify their findings. Ettengruber et al. also observed an increased risk of abdominal cancers after EVAR compared to OAR, with an abdominal cancer incidence of 17.4% after EVAR and 12.9% after OAR ($p < 0.001$). Considering that the incidence of abdominal cancers was 11.1% in patients with PAD stage III and 11.6% in PAD stage IV ($p = 0.531$), which is even lower than after OAR, this supports the assumption that patients with EVAR have an increased risk of abdominal cancer.

This study has limitations: the completeness of the datasets depends on the coding quality of individual hospitals and the documentation by the health insurance company; coding errors cannot be ruled out. The data reflect the patient clientele of one health insurance company, and its social structure and may not necessarily represent the treatment situation for the entire population in Germany. However, the AOK is the largest health insurance company with a market share of 37%. Due to the anonymity of the datasets, the treating hospitals and their case volumes could not be captured. Furthermore, causes of death and amputation rates could not be determined. Cancer stage was also not reported in the given dataset; therefore, cancer stage-related incidence and survival could not be specified. Nevertheless, this study reports for the first time on cancer incidence and long-term survival after infrainguinal bypass surgery for critical limb threatening ischemia. One strength of the study was that the survival of all patients could be assessed until the end of the follow-up period. Another strength was the ability to compare long-term outcomes and cancer incidence with an identical cohort of patients with AAA. Such a comparative study does not exist to date. Therefore, important conclusions can be drawn.

## Conclusion

- Patients with PAD stage III have a significantly better survival after lower extremity bypass surgery compared to patients with PAD stage IV. However, there were no differences in cancer incidence between the two groups.
- Men have a significantly higher cancer incidence than women, but there were no differences in long-term survival between the genders.
- Due to the poor prognosis of PAD stage IV, cancer incidence plays a minimal role in survival after surgery for this stage.
- In stage III, patients with and without cancer differ significantly in long-term survival after inguinal bypass surgery. Therefore, cancer screening is advisable for these patients in case of bypass thrombosis.
- The relatively low rate of abdominal cancer in CLTI patients suggests a need for further investigation into the significantly higher rate of abdominal cancer after endovascular AAA repair.

**Authors' contributions** All authors contributed to the study conception and design. Material preparation and data collection were performed by P. M., R. T. G., and J. E. The statistical analysis was performed by P. M. The first draft of the manuscript was written by R. T. G., J. E., and P. M., involving all authors. The final version of this paper was approved by all authors.

## Declarations

**Competing interests** The authors declare no competing interests.

## References

1. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S, Registry Investigators REACH (2007) One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 297:1197–1206. https://doi.org/10.1001/jama.297.11.1197
2. Sartipy F, Sigvant B, Lundin F, Wahlberg E (2018) Ten year mortality in different peripheral arterial disease stages: a population based observational study on outcome. Eur J Vasc Endovasc Surg 55:529–536. https://doi.org/10.1016/j.ejvs.2018.01.019
3. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD (2004) A note on competing risks in survival data analysis. Br J Cancer 91:1229–1235. https://doi.org/10.1038/sj.bjc.6602102
4. Jessen ML, Eiberg J, Sillesen H, Lawaetz M (2022) Cancer should not contravene the revascularization of chronic limb-threatening ischaemia. Vascular 22:17085381221135656. https://doi.org/10.1177/17085381221135657
5. Calderbank T, Karim A, Wall M, Syed A, Davies RSM, Saratzis A (2018) The effect of malignancy on outcomes following

revascularization for critical limb ischemia: a case-control study. Vasc Endovascular Surg 52:325–329. https://doi.org/10.1177/1538574418764055
6. El Sakka K, Gambhir RP, Halawa M, Chong P, Rashid H (2005) Association of malignant disease with critical leg ischaemia. Br J Surg 92:1498–1501. https://doi.org/10.1002/bjs.5125
7. Markar SR, Vidal-Diez A, Sounderajah V, Mackenzie H, Hanna GB, Thompson M, Holt P, Lagergren J, Karthikesalingam A (2019) A population-based cohort study examining the risk of abdominal cancer after endovascular abdominal aortic aneurysm repair. J Vasc Surg 69:1776–1785. https://doi.org/10.1016/j.jvs.2018.09.058
8. Feinglass J, Sohn MW, Rodriguez H, Martin GJ, Pearce WH (2009) Perioperative outcomes and amputation-free survival after lower extremity bypass surgery in California hospitals, 1996–1999, with follow-up through 2004. J Vasc Surg 50:776–783. https://doi.org/10.1016/j.jvs.2009.05.050
9. Rollins KE, Jackson D, Coughlin PA (2013) Meta-analysis of contemporary short- and long-term mortality rates in patients diagnosed with critical leg ischaemia. Br J Surg 100:1002–1008. https://doi.org/10.1002/bjs.9127
10. Nicolajsen CW, Dickenson MH, Budtz-Lilly J, Eldrup N (2015) Frequency of cancer in patients operated on for acute peripheral arterial thrombosis and the impact on prognosis. J Vasc Surg 62:1598–1606. https://doi.org/10.1016/j.jvs.2015.06.223
11. Sundbøll J, Veres K, Horváth-Puhó E, Adelborg K, Sørensen HT (2018) Risk and prognosis of cancer after lower limb arterial thrombosis. Circulation 138:669–677. https://doi.org/10.1161/CIRCULATIONAHA.117.032617
12. Villemur B, Roux C, Poggi JN, Elias A, Le Hello C (2022) Is it justified to search for cancer in patients with peripheral arterial disease? J Med Vasc 47:133–140. https://doi.org/10.1016/j.jdmv.2022.07.003
13. Png CYM, Wang LJ, DeCarlo CS, Latz CA, Sumpio BJ, Weinberg I, Eagleton MJ, Dua A (2021) Effect of occult malignancy on femoropopliteal bypass graft thrombosis. J Vasc Surg 74:514–520. https://doi.org/10.1016/j.jvs.2021.01.058
14. Bintein F, Yannoutsos A, Chatellier G, Fontaine M, Damotte D, Paterlini-Bréchot P, Meyer G, Duchatelle V, Marini V, Schwering KL, Labrousse C, Beaussier H, Zins M, Salmeron S, Lajonchère JP, Priollet P, Emmerich J, Trédaniel J (2021) Patients with atherosclerotic peripheral arterial disease have a high risk of lung cancer: systematic review and meta-analysis of literature. J Med Vasc 46:53–65. https://doi.org/10.1016/j.jdmv.2020.12.005
15. Ettengruber A, Epple J, Schmitz-Rixen T, Böckler D, Grundmann RT, DIGG gGmbH (2022) Long-term outcome and cancer incidence after abdominal aortic aneurysm repair. Langenbecks Arch Surg 407(8):3691–3699. https://doi.org/10.1007/s00423-022-02670-x
16. Becker von Rose A, Kobus K, Bohmann B, Lindquist-Lilljequist M, Eilenberg W, Kapalla M, Bassermann F, Reeps C, Eckstein HH, Neumayer C, Brostjan C, Roy J, von Heckel K, Hultgren R, Schwaiger BJ, Combs SE, Busch A, Schiller K (2023) Radiation therapy for cancer is potentially associated with reduced growth of concomitant abdominal aortic aneurysm. Strahlenther Onkol. https://doi.org/10.1007/s00066-023-02135-0



## Authors and Affiliations

**Polykarpos Michailidis[1] · Jasmin Epple[2] · Dittmar Böckler[1] · Thomas Schmitz-Rixen[3] · Reinhart T. Grundmann[4,5] on behalf of on behalf of DIGG gGmbH**

✉ Reinhart T. Grundmann
reinhart@prof-grundmann.de

Polykarpos Michailidis
Polykarpos.Michailidis@med.uni-heidelberg.de

Jasmin Epple
jas.epple@web.de

Dittmar Böckler
dittmar.boeckler@med.uni-heidelberg.de

Thomas Schmitz-Rixen
schmitz-rixen@dgch.de

[1] Department of Vascular and Endovascular Surgery, University Hospital Heidelberg, Heidelberg, Germany

[2] Department of Vascular and Endovascular Surgery, University Hospital Frankfurt, Frankfurt, Germany

[3] Goethe University, Frankfurt, Germany

[4] German Institute for Vascular Healthcare Research (DIGG) of the German Society for Vascular Surgery and Vascular Medicine, Berlin, Germany

[5] Department of Vascular Medicine, University Heart and Vascular Center (UHC), University Medical Center Hamburg-Eppendorf, Hamburg, Germany