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Ten Year Time Trends of Amputation Surgery in Peripheral Arterial Disease in Germany: Before and During the COVID-19 Pandemic

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Running titles:

Ten Tear Time Trends of Amputation Rates in Peripheral Arterial Disease in Germany

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WHAT THIS PAPER ADDS

Previous COVID-19 pandemic related cohort analyses have demonstrated impaired outcomes for hospitalised patient cohorts compared with standard healthcare system conditions. The present analysis aimed to put pandemic related observations into a long term context. This work demonstrates an overall favourable trend in hospitalised patients with peripheral arterial disease undergoing amputation surgery (toward lower rates of major amputation and lower in hospital mortality, and toward higher amputation related revascularisation rates) over 10 years in Germany, which was maintained in the COVID-19 pandemic despite a temporary increase in major amputations in the first lockdown period in 2020.

Objective: Peripheral arterial disease (PAD) has been associated with suboptimal treatment, high mortality, and high amputation rates. It is unclear how the COVID-19 (coronavirus disease 2019) pandemic affected this development in a long term context.

Methods: This was a register based, retrospective, nationwide cohort study including patients hospitalised with PAD as a main or secondary diagnosis and amputation surgery between 2012 – 2021 in Germany. Primary endpoints were population wide major and minor amputation rates, in hospital mortality, and in hospital mortality rates. Secondary endpoints were same admission revascularisations and in hospital mortality in case of complications, i.e., failure to rescue (FTR). Pre-pandemic and pandemic trends, focusing on lockdown periods, were analysed.

Results: A total of 365 926 patient records with PAD and amputation surgery were analysed. Median patient age was 75 years and 28.8% were female. Overall population wide amputation and in hospital mortality rates (monthly decrease –0.002/100 000, $p < .001$, and –0.001/100 000, $p < .001$, respectively) and in hospital mortality rate (8.0% for 2012 – 2014 *vs.* 6.5% for 2020 – 2021; $p < .001$) declined between 2012 and 2020. Concurrently, same admission revascularisations increased (41.0% for 2012 – 2014 *vs.* 47.0% for 2020 – 2021; $p < .001$), while FTR decreased in a subset of complications (acute ischaemia, major bleeding, compartment syndrome, and mesenterial ischaemia). In the first pandemic lockdown, there was a temporary trend change to higher major amputations rates (0.02/100 000; $p < .001$) and higher in hospital mortality rates (+0.007/100 000; $p < .001$), which changed to a decrease as of the second lockdown (–0.03/100 000, $p = .034$, and –0.010/100 000, $p < .001$, respectively) in an interrupted time series analysis. There was no statistically significant change in observed amputation rates during lockdowns, while observed in hospital mortality rates decreased by 12.0% in the first lockdown (0.22/100 000 *vs.* 0.25/100 000; $p = .005$) compared with reference periods of the two previous years.

Conclusion: Between 2012 and 2021, pre-pandemic trends toward decreasing population wide overall amputation rates, fewer major amputations, more amputation related revascularisation procedures, and lower in hospital mortality were maintained despite a temporary trend to increased major amputations and in hospital mortality during the first COVID-19-related lockdown in Germany.

Keywords: Amputation surgery, COVID-19, Epidemiology, Pandemic, Peripheral arterial disease, Revascularisation

INTRODUCTION

Peripheral arterial disease (PAD) has been under recognised and suboptimally treated for decades despite its substantial impact on global morbidity and mortality.[1–6] Patients with PAD are highly susceptible to limb events; within five years, the risk of major amputation ranges from 1% to 3%, reaching up to 50% for those with chronic limb threatening ischaemia,[7] while diabetes mellitus remains an exacerbating factor.[7–17] While major amputations have decreased in a US cohort since 2010, overlapping diabetes mellitus may be driving amputation rates.[2,18–21]

The emergence of the COVID-19 (coronavirus disease 2019) pandemic in 2020 has impacted global healthcare,[22,23] while PAD patient care suffered from low healthcare resources despite efforts to implement guidelines for PAD care during pandemic waves.[24] Internationally, hospitalisations of patients with PAD declined during the pandemic,[25] with higher case severity,[26,27] more emergency admissions,[27] and higher amputation rates.[25,27]

In Germany, under recognition of patients with PAD during the COVID-19 pandemic was also observed, including a decline in hospitalisations compared with 2019 with a reduction of revascularisation treatments, an increase of case fatality rates,[28] and a relative increase of PAD Fontaine stage IV.[29] These implications, however, have not been put into a long term context.

Prior to the pandemic, there was a relevant PAD disease burden in Germany with high hospital utilisation[30] and high amputation and mortality rates,[31] often due to low guideline adherence and unfavourable prognosis.[3,32,33] However, there has been a shift toward reduced case fatality rates and lower amputation rates until 2019 in Germany, while comorbidity of diabetes mellitus remains associated with an unfavourable prognosis regarding morbidity and mortality.[19,31]

To put pandemic related changes in hospitalised PAD patient care into a long term context, a comprehensive analysis of hospitalised patients diagnosed with PAD undergoing amputation surgery in Germany spanning 2012 – 2021 was conducted.

Population wide amputation rates and in hospital mortality including population wide in hospital mortality rates among hospitalised patients with PAD requiring amputation surgery were primary endpoints. In hospital mortality in case of complication occurrence, i.e., failure to rescue (FTR), and amputation related revascularisation procedures during the same admission were secondary endpoints. By comparing trends between 2012 and 2019 with the pandemic impacted years 2020 and 2021, the aim was to gain insights into potential shifts in the management of patients with PAD requiring amputation surgery in these time frames on the basis of defined endpoints.

MATERIALS AND METHODS

Study design and data acquisition

This was a register based, retrospective, nationwide cohort study of anonymised billing data (DRG data; data source, Diagnosis-Related Group Statistics [2012 – 2021], last remotely accessed December 2023) provided by the Statistische Bundesamt (Federal Statistical Office) in Germany. Billing records are ascertained by trained staff and the coding follows pre-defined guidelines.[34] One aspect of quality control of DRG coding is the fact that approximately 13% of patient cases are re-opened by the Medizinische Dienst der Krankenkassen, or the medical staff working for German insurance companies, of which about 50% of cases end up being altered in the process.[35] All hospital admissions are included in this report, independent of hospital status (private or public) and independent of the insurance status of the patient. Data acquisition was conducted in close contact with the Research Center of the Federal Statistical Office and in accordance with their guidelines for handling highly sensitive patient record data. No ethical approval was necessary for this large scale, nationwide cohort analysis, as established elsewhere.[36,37] This observational study was conducted and reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[38]

Definition of the study cohort

Patient identification was done using operation and procedure codes (Operationen- und Prozedurenschlüssel; OPS codes) and International Classification of Diseases codes (ICD-10, German modification, ICD-10-GM) (Supplementary Table S1). All patients with PAD as the main or secondary diagnosis were included if an amputation surgery was performed, and, in case it was not PAD, if the main diagnosis was one of the following: acute limb ischaemia, aortic aneurysm or dissection, diabetes mellitus or “other vascular disease” based on expert considerations (Supplementary Table S1). Cases admitted between 1 January 2012 and 31 December 2021 were included. No longitudinal analysis on a patient level was possible since no individual patient identifier is coded. Each patient record contained data on age, sex, an anonymised institute identifier, procedural codes, main and secondary diagnoses, length of stay, and reason for admission and discharge. If a patient is re-admitted within a certain time frame (dependent on the actual DRG reimbursement class and its “upper limit of length of stay”, e.g., 13 days for DRG F59D, i.e., PAD[39]), cases can be matched and a re-admission may be included in the original case.[40] Duplicates were identified and duplicate records were removed.

Primary and secondary endpoints, and definition of time periods

Population wide rates of amputation surgery, which were categorised into minor amputation surgery only *vs.* at least one major amputation using procedure codes (major amputation as above or including the ankle joint), and in hospital mortality, including in hospital mortality rates, were defined as primary endpoints (Supplementary Table S1). In hospital mortality in case of complication occurrence, i.e., FTR,[41] and amputation related revascularisation procedures, identified using procedure codes for revascularisation procedures, were secondary endpoints of interests.

The time of the pandemic lockdowns in Germany took place between 22 March and 4 May 2020. Since this had previously been unknown to the healthcare system, the beginning of the first lockdown was chosen to be set with a delay (1 April); since returning to standard circumstances was a transitional state, the end of the lockdown was set to end of May 2020. Furthermore, the beginning of a “lockdown light” as of 2 November 2020 (announcement mid October) was set as a second lockdown period (October 2020 – May 2021).[42] These time frames have previously been used in research of COVID-19 related lockdowns in Germany.[22]

Statistical analysis

For statistical comparison purposes, admissions were categorised into years of admission for temporal trends between 2012 and 2021 (2012 – 2014, 2015 – 2017, 2018 – 2019, and 2020 – 2021) (descriptive data, in hospital mortality, and amputation related revascularisation). Lockdown periods were defined as observation periods and were compared with reference periods of the same time frame of two previous years (April through June 2018/2019, October 2017 to May 2018, and October 2018 to May 2019) in a categorical manner (admission during lockdown *vs.* no lockdown) for descriptive data, and in a period matched manner for amputation and in hospital mortality rates.

An interrupted time series (ITS) analysis was conducted to detect overall temporal trends for 2012 – 2019 and their changes during the COVID-19 pandemic in Germany.[43] For monthly trends the segmentation was set between March/April 2020 and September/October 2020, and 2019/2020 for annual trends. Prior to the ITS analysis, visual and test based screening for autocorrelation was conducted.[44]

For risk stratification, the three category Hospital Frailty Score based on the secondary diagnoses was computed (low, intermediate, and high risk; Frailty I to III, respectively).[45,46]

Incidences were calculated in rates per 100 000 inhabitants per month to adjust for variation in the total number of inhabitants.[47]

Median values were reported with interquartile range (IQR), and range for annual amputation rates. Confidence intervals were stated for rates. Differences between reference and observation periods were compared using Student's *t* test or χ^2 test. If the assumption of normality was violated, Wilcoxon rank sum test was employed. A *p* value of ≤ .050 was considered statistically significant.

Statistical analysis was performed with Microsoft Excel version 2016 (Microsoft Corp., Redmond, WA, USA) and Stata 16.1 (StataCorp LP, College Station, TX, USA). Figures were created using GraphPad Prism 9 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

Study population

After application of inclusion and exclusion criteria, 365 926 complete patient records were included (Supplementary Table S1; Supplementary Fig. S1).

The median patient age was 75 (IQR 66, 82) years and 28.8% of patients (105 263) were female. The most common cardiovascular risk factor was diabetes mellitus (69.0%), which was the main diagnosis in 40.4% of all cases, followed by arterial hypertension (66.1%). Of 365 926 total patients, 263 155 (71.9%) received a minor amputation and 102 771 (28.1%) received a major amputation; of the 102 771 patients with a major amputation, 20 424 (19.9%; 5.6% of all) received both a minor and a major amputation. Any amputation related revascularisation during the same admission was performed in 159 953 cases (43.7% of all). Revascularisation was performed before amputation surgery in 102 893 cases (28.1% of all). In major amputation surgery, in 33.0% of patient records an amputation related revascularisation procedure was performed. The median time from admission to revascularisation and from admission to amputation surgery was four days (IQR 2, 7 days and 2, 9 days, respectively). Both time intervals were statistically significantly shorter in patients receiving minor *vs.* major amputation surgery (time to revascularisation 4, IQR 2, 7, days *vs.* 4, IQR 1, 7, days, respectively; time to amputation 4, IQR 2, 9, days *vs.* 5, IQR 2, 11, days, respectively; $p < .001$). All cause mortality (8 790, 8.0%) during the hospital admission was 3.8% after minor amputation and 15.6% after major amputation ($p < .001$) (Table 1; Supplementary Table S2).

Primary and secondary endpoints over the study period

Overall monthly amputation rates followed a periodical annual trend (Fig. 1), which were higher during late spring/summer months. The median annual population wide overall amputation rate was 46.8/100 000 (IQR 46.4, 47.8; range 45.7 – 48.5) over the years (minor, 34.6/100 000, IQR 34.5, 34.7, range 33.4 – 35.0; major, 12.3/100 000, IQR 11.8, 13.3, range 11.2 – 14.4). There was a statistically significant reduction of in hospital mortality (8.0% for 2012 – 2014 *vs.* 6.5% for 2020 – 2021; $p < .001$) over the study period (Table 2; Supplementary Table S3).

Over time, a statistically significant baseline trend toward lower population wide amputation rates overall (minor and major amputations combined: baseline monthly trend, –0.002/100 000 $p < .001$; annual trend, –0.132/100 000, $p = .012$) and population wide in hospital mortality rates for patients with PAD receiving amputation surgery (baseline monthly trend, –0.002/100 000, $p < .001$; annual trend, –0.24/100 000, $p < .001$) was noted. Stratified into minor and major amputations, the population wide amputation rate of major amputations decreased over time (baseline monthly trend, –0.003/100 000, $p < .001$; annual trend, –0.39/100 000, $p < .001$) with a simultaneous increase of minor amputations (baseline monthly trend, 0.001/100 000, $p < .001$; annual trend, 0.15/100 000, $p = .041$) (Table 3; Supplementary Table S4). Over the study period, an increase of amputation related revascularisation procedures (41.0% for 2012 – 2014, 44.7% for 2018 – 2019, and 47.0% for 2020 – 2021; $p < .001$) among all cases was observed. Simultaneously, an increased proportion of revascularisations among all cases in the analysis occurred pre-amputation (27.4% for 2012 – 2014, 28.2% for 2018 – 2019, and 28.9% for 2020 – 2021; $p < .001$) (Table 2; Fig. 2). There was a tendency to lower FTR over time (except stroke), which was statistically significant in case of acute ischaemia, major bleeding, compartment syndrome, and mesenterial ischaemia (Table 2; Supplementary Table S3).

Primary and secondary endpoints during the COVID-19 pandemic

When specifically evaluating lockdown periods *vs.* the whole time period 2020 – 2021, similar trends to pre-pandemic trends can be observed in comparison with reference periods shortly before the COVID-19 pandemic (2017 – 2019), which was done to avoid a comparative effect of long term time trends. No statistically significant trend change for combined (minor and major) amputations was observed in the ITS analysis after the first or second lockdown (0.03/100 000, $p = .20$, and –0.08/100 000, $p = .17$, respectively) until the end of the time analysis. The above stated trend to lower rates of major amputations and lower in hospital mortality rates over time was interrupted during the first lockdown with a noted increase of major amputations (+0.02/100 000; $p = .001$) and in hospital mortality rates (+0.007/100 000; $p < .001$) in this time frame, which statistically significantly changed back to a decrease as of the beginning of the second lockdown period (–0.03/100 000, $p < .034$, for major amputation rates and –0.010/100 000, $p < .001$, for in hospital mortality rates) (Table 3).

In a period matched comparison, in the first lockdown no statistically significant overall change in amputation surgery was found (–5.9%, 3.86 per 100 000 *vs.* 4.10 per 100 000; $p = .17$), while observed in hospital mortality rates decreased (0.22/100 000 per month in the first lockdown *vs.* 0.25/100 000 per month in the combined reference, –12.0%; $p = .005$). No statistically significant change was found after stratification by amputation extent (major amputations, –7.8%, $p = .070$; minor amputations, –5.2%, $p = .25$) (Table 4). During the second lockdown, no statistically significant overall change of in hospital mortality rates (change 0%) or amputation surgery (–0.5%, $p = .92$) was noted, and was statistically insignificant for all stratifications (minor amputations, +0.3%, $p = .97$; major amputations, –3.0%, $p = .61$) (Table 5). In the months following lockdown periods (July to September), no statistically significant changes of in hospital mortality rates (+9.1%, $p = .35$, in 2020; +13.6%, $p = .13$, in 2021) or in overall amputation rates (+1.8%, $p = .75$, in 2020; +6.3%, $p = .27$, in 2021) was observed (Supplementary Table S5).

In admissions during lockdown periods, no change in overall in hospital mortality (6.5% in lockdown *vs.* 6.8%; $p = .11$), higher amputation related revascularisation proportions (47.9% *vs.* 45.0%, $p < .001$; 29.6% *vs.* 28.7% before amputation surgery, *p* = .003), and lower FTR (statistically significant in case of acute ischaemia, compartment syndrome, and mesenterial ischaemia) were observed during lockdown periods compared with reference periods (Table 6; Supplementary Table S6).

DISCUSSION

In this study of hospitalised patients with PAD undergoing amputation surgery in Germany, despite the COVID-19 pandemic a trend toward lower population wide amputation rates, lower in hospital mortality, and more amputation related revascularisations, including the proportion performed pre-amputation, was maintained as an overall ten year trend between 2012 and 2021. This was interrupted by temporary trend changes toward more major amputations and higher in hospital mortality rates in the first lockdown, which was not found in observed major amputation rates and in hospital mortality rates during lockdowns compared with reference periods.

The vulnerability of patients with PAD is high: in non-revascularisable situations,[48,49] five year amputation free survival has been found to be approximately 40%;[48] while in revascularisable situations, event rates (amputation above the ankle, a major limb re-intervention, or death) in median follow ups of up to 2.7 years after revascularisation reached up to 57%.[50] The vulnerability of patients with PAD to suboptimal treatment is accentuated during healthcare system bottlenecks such as the COVID-19 pandemic, given the chronic nature and its reliance on comprehensive care.

In this analysis, PAD was defined to be coded at least as a secondary diagnosis if a pre-defined set of diagnoses was coded as the main diagnosis, most importantly diabetes mellitus. It is crucial to note that patients with PAD undergoing amputation constitute a distinctive subset of patients with PAD. Patients with PAD undergoing amputation reflect a cohort marked by advanced microvascular and or macrovascular impairment. In patients receiving revascularisation pre-amputation and ending up with amputation surgery despite revascularisation efforts, failed limb salvage has to be assumed. A long term increase in amputation related revascularisations found in this analysis can be interpreted as increasing awareness of limb salvage attempts.[49] Later presentation and advanced PAD stages, as has been described in the context of the COVID-19 pandemic,[26,28,29] is a risk factor for limb events. Since no longitudinal data are available on a patient level, however, and revascularisation procedures (in contrast to amputation surgery) are coded without coding of the side of the limb, no clear statements on individual limb salvage success can be made.

This study remains in alignment with previous findings, while focusing on patients undergoing amputation surgery, presenting a complementary perspective.[19,21,31] We cannot exclude the scenario that, based on the results of a trend to more major amputations in the first lockdown, a subset of patients suffered from more advanced PAD stages especially during the first lockdown, leading to higher rates of unsalvageable PAD. If this was the case, however, this trend changed back and re-aligned with an overall ten year trend toward lower major amputation rates as of the second lockdown. In the interpretation of the ITS analysis, comparing the annual and monthly approach, there was no second segmentation in the annual ITS, providing a less detailed picture of the lockdown periods, and the overall trend change after this first segmentation was significant to more major amputations. In this one segmented analysis, no trend to higher in hospital mortality rates was found.

This present analysis is the first to put changes during the COVID-19 pandemic in Germany into a long term context, and adds to the existing body of evidence data on the COVID-19 pandemic beyond the first lockdown period.[29] This investigation also aligns with pre-pandemic trends, reflecting a reduction in mortality and increased utilisation of amputation related revascularisation procedures for patients with PAD in Germany.[30,31] Remarkably, this trend is observed despite the persistent high mortality rates associated with this patient cohort.[3] Compared with a British and another German cohort, population wide PAD related amputation rates are comparable with the present analysis, acknowledging different inclusion criteria.[29,51]

Limitations

This study has some limitations. The lower amputation related revascularisation rates observed in this study could be attributed to the fact that PAD was not necessarily the primary diagnosis.[3] Only patients with known PAD at least as a secondary diagnosis were included. We cannot, however, conclude that PAD is the decisive pathomechanism on an individual patient or limb level. It is possible and likely that some patients were re-admitted during the study period and represent more than one patient record in this analysis. The lack of longitudinal data is therefore an important limitation of this study; long term outcomes and re-admissions remain beyond the scope of this analysis, and data on medication and laboratory results were unavailable. Due to the lack of longitudinal data, no adjustment to patient factors was conducted and no statement on limb salvage can be made. This, however, does not interfere with the primary endpoints of this analysis, which were chosen according to the study design. Since no adjustment on patient factors was appropriate, we analysed population wide rates to account for changes in the total of the overall population and conducted an ITS analysis. In addition, no data on care in the ambulatory setting are available, providing a potential bias in patient selection, for example, but not limited to, due to possible fear of hospitalisation during the COVID-19 pandemic. It is, however, to be assumed that a negligible fraction of amputations were performed in the ambulatory setting. Furthermore, its retrospective nature precludes drawing causal conclusions. Since in the process of quality control of DRG coding about 13% of patient cases are re-opened, it cannot be excluded that other miscoding is present. However, this quality authority has been advocated as a positive influence in a process towards increasing transparency and comparability of cases.[52]

Conclusion

In summary, this retrospective, nationwide, ten year analysis of lower limb amputation surgery in patients with PAD in Germany provides evidence that, even amidst the challenges posed by the COVID-19 pandemic and despite a temporary trend change to more major amputations and higher in hospital mortality rates, the ongoing trend towards lower population wide amputation rates, decreased major amputations, lower in hospital mortality, and more amputation related revascularisations among hospitalised patients with PAD receiving amputation surgery has persevered between 2012 and 2021.

CONFLICTS OF INTEREST

D.B. has received grants from Artivion, Bentley InnoMed, Cook Medical, Endologix, Getinge, and Medtronic. SS has received consulting/speakers' honorarium from Cook Medical, Boston Scientific, and iThera Medical. AS has received consulting/speakers honorarium from Abbott Vascular, BD, Boston Scientific, Cook, Reflow Medical, and Upstream Peripheral. The remaining authors have nothing to disclose.

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ETHICS STATEMENT

Data acquisition was conducted in collaboration with the Research Center of the Federal Statistical Office in Germany and in accordance with their guidelines for handling highly sensitive patient record data. No ethical vote was necessary for this large scale, nationwide cohort analysis based on national law.

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Figure 1. Change in population wide amputation rates (A) overall and by (B) minor and (C) major amputations. Individual dots represent monthly amputation rates per 100 000 inhabitants. Seasonality is approximated and depicted using sine and cosine estimates.

Figure 2. Change in total number of amputations, proportion of minor and major amputations, and amputation related revascularisations over time. Details are given in Table 2 and Supplementary Table S3. Dots represent actual total numbers, not percentages. Percentages are calculated and stated separately and refer to the total in the respective year. For clarity purposes, not all percentages are stated, and for revascularisation proportions not all years are depicted.

Table 1. Patient characteristics and in hospital mortality by level of amputation for the overall cohort (*n* = 365 926).

Characteristic	Total (*n* = 365 926)	Minor amputation (*n* = 263 155, 71.9%)	Major amputation (*n* = 102 771, 28.1%)	*p* value*
Patient characteristics				
Age – y	75 (66, 82)	75 (66, 82)	75 (66, 82)	<.001†
Age group‡ – y				<.001
≤59	40 870 (11.2)	29 840 (11.3)	11 030 (10.7)	
60–79	202 208 (55.3)	146 322 (55.6)	55 886 (54.4)	
80–89	102 745 (28.1)	73 534 (27.9)	29 211 (28.4)	
>89	20 103 (5.5)	13 459 (5.1)	6 644 (6.5)	
Hospital Frailty Score‡				<.001
Frailty I	135 930 (37.2)	113 005 (42.9)	22 925 (22.3)	
Frailty II	184 907 (50.5)	128 787 (48.9)	56 120 (54.6)	
Frailty III	45 089 (12.3)	21 363 (8.1)	23 726 (23.1)	
Female sex	105 263 (28.8)	69 325 (26.3)	35 938 (35.0)	–
Cardiovascular risk factors				
Coronary heart disease	116 185 (31.8)	83 433 (31.7)	32 752 (31.9)	.34
Ischaemic stroke in history	21 310 (5.8)	11 405 (4.3)	9 905 (9.6)	<.001
Arterial hypertension	241 917 (66.1)	177 812 (67.8)	64 105 (62.4)	<.001
Diabetes mellitus	252 647 (69.0)	193 812 (73.7)	58 835 (57.3)	<.001
Chronic kidney disease	163 294 (44.6)	119 816 (45.5)	43 478 (42.3)	<.001
Main diagnosis				
Peripheral arterial disease	208 923 (57.1)	138 110 (52.5)	70 813 (68.9)	<.001

Diabetes	147 857 (40.4)	122 757 (46.7)	25 100 (24.4)	<.001
Other[§]	9 146 (2.5)	2 288 (0.9)	6 858 (6.7)	<.001
Diagnostics				
Arteriography	155 760 (42.6)	120 878 (45.9)	34 882 (33.9)	<.001
CT arteriography	34 357 (9.4)	21 784 (8.3)	12 573 (12.2)	<.001
Treatment and outcomes				
Any amputation related revascularisation	159 953 (43.7)	126 026 (47.9)	33 927 (33.0)	<.001
Surgical revascularisation	61 862 (16.9)	44 355 (16.9)	17 507 (17.0)	.19
Revascularisation before amputation surgery	102 893 (28.1)	77 363 (29.4)	25 530 (24.8)	<.001
Minor and major amputation	20 424 (5.6)	–	20 424 (19.9)	–
Amputation on both sides	8 126 (2.2)	4 194 (1.6)	3 932 (3.8)	<.001
Length of stay – d	19 (12, 31)	17 (11, 28)	25 (14, 41)	<.001[†]
Time from admission to revascularisation – d	4 (2, 7)	4 (2, 7)	4 (1, 7)	<.001[†]
Time from admission to amputation – d	4 (2, 9)	4 (2, 9)	5 (2, 11)	<.001[†]
Overall mortality	26 219 (7.2)	10 101 (3.8)	16 118 (15.6)	<.001

Data are presented median (interquartile range) or *n* (%). Values in parentheses are percentages of total in the patient group. More data are given in Supplementary Table S2. CT = computed tomography.

[*] *p* values for comparison between amputation type.

[†] Non-parametric rank test.

[‡] Age groups and Hospital Frailty Score were all $p < .001$ for the overall χ^2 test for distribution among type of amputation; *p* values are stated once.

[§] Other main diagnoses include acute ischaemia, aortic aneurysm or dissection, and “other vascular disease” (ICD I77, I79, I99).

Table 2. Time trends for patient characteristics, amputation related revascularisations, and in hospital mortality.

	2012–2014 (*n* = 109 706)	**2015–2017 (*n* = 109 848)**	**2018–2019 (*n* = 73 592)**	**2020–2021 (*n* = 72 780)**	***p* value**
Patient characteristics					
Age group[*] – y					<.001
≤59	12 400 (11.3)	12 386 (11.3)	8 206 (11.2)	7 878 (10.8)	
60–79	62 363 (56.9)	61 196 (55.7)	39 895 (54.2)	38 754 (53.3)	
80–89	28 897 (26.3)	30 282 (27.6)	21 445 (29.1)	22 121 (30.4)	
>89	6 046 (5.5)	5 984 (5.5)	4 046 (5.5)	4 027 (5.5)	
Hospital Frailty Score[*]					<.001
Frailty I	43 953 (40.1)	39 661 (36.1)	26 442 (35.9)	25 874 (35.6)	
Frailty II	53 858 (49.1)	56 115 (51.1)	37 448 (50.9)	37 486 (51.5)	
Frailty III	11 895 (10.8)	14 072 (12.8)	9 702 (13.2)	9 420 (12.9)	
Female sex	34 549 (31.5)	31 715 (28.9)	19 811 (26.9)	19 188 (26.4)	<.001
Treatment					
Length of stay – d	21 (13, 34)	19 (12, 32)	18 (11, 30)	16 (10, 27)	<.001[†]
Any amputation related revascularisation	45 013 (41.0)	47 878 (43.6)	32 880 (44.7)	34 182 (47.0)	<.001
Surgical revascularisation	19 038 (17.4)	18 698 (17.0)	11 964 (16.3)	12 162 (16.7)	<.001
Revascularisation before amputation surgery	30 039 (27.4)	31 053 (28.3)	20 745 (28.2)	21 056 (28.9)	<.001
Minor amputation only	76 060 (69.3)	79 138 (72.0)	53 987 (73.4)	53 970 (74.2)	<.001
Major amputation only	26 926 (24.5)	24 599 (22.4)	15 634 (21.2)	15 188 (20.9)	<.001
Minor and major amputation	6 720 (6.1)	6 111 (5.6)	3 971 (5.4)	3 622 (5.0)	<.001
Amputation on both sides	2 652 (2.4)	2 426 (2.2)	1 526 (2.1)	1 522 (2.1)	<.001
Revision surgery	33 280 (30.3)	34 310 (31.2)	23 255 (31.6)	23 323 (32.1)	<.001
Complications and outcomes					
Overall mortality	8 790 (8.0)	7 868 (7.2)	4 828 (6.6)	4 733 (6.5)	<.001
Acute limb ischaemia	5 443 (5.0)	5 821 (5.3)	4 176 (5.7)	4 398 (6.0)	<.001
Mortality	753 (13.8)	781 (9.9)	514 (12.3)	504 (11.5)	.002
Major bleeding	34 000 (31.0)	31 652 (28.8)	20 569 (28.0)	20 664 (28.4)	<.001
Mortality	4 953 (14.6)	4 275 (13.5)	2 686 (13.1)	2 616 (12.7)	<.001
Compartment syndrome[‡]	1 254 (1.1)	1 555 (1.4)	1 204 (1.6)	1 253 (1.7)	<.001
Mortality	199 (15.9)	206 (13.3)	139 (11.5)	158 (12.6)	.012
Heart attack	2 058 (1.9)	1 910 (1.7)	1 110 (1.5)	1 117 (1.5)	<.001

Mortality	653 (31.7)	574 (30.1)	314 (28.3)	335 (30.0)	.24
Stroke	839 (0.8)	711 (0.7)	497 (0.7)	481 (0.7)	.005
Mortality	254 (30.3)	217 (30.5)	141 (28.4)	152 (31.6)	.74
Mesenterial ischaemia	426 (0.4)	441 (0.4)	315 (0.4)	337 (0.5)	.081
Mortality	218 (51.2)	206 (46.7)	158 (50.2)	139 (41.3)	.035
Pulmonary artery embolism	269 (0.3)	290 (0.3)	178 (0.2)	227 (0.3)	.027
Mortality	127 (47.2)	137 (47.2)	94 (52.8)	91 (40.1)	.082

Data are presented median (interquartile range) or *n* (%). Values in parentheses are percentages of total in the patient group. More data are given in Supplementary Table S3.

* Age groups and Hospital Frailty Score were all $p < .001$ for the overall χ^2 test for distribution among year groups; *p* values are stated once.

† Non-parametric rank test.

‡ Compartment syndrome stated only if surgical therapy was necessary.

Table 3. Interrupted time series analysis: impact of time of pandemic lockdowns on amputation rates and in hospital mortality rates.

Model	Parameter	Coefficient (95% CI)	*p* value
Cumulated amputations	Intercept	4.045 (3.988 – 4.102)	<.001
	Baseline trend	–0.002 (–0.003 – –0.001)	<.001
	Level change 04/2020	–0.031 (–0.202 – 0.14)	.72
	Trend change 04/2020	0.034 (–0.018 – 0.085)	.20
	Level change 10/2020	0.11 (–0.50 – 0.717)	.72
	Trend change 10/2020	–0.08 (–0.196 – 0.036)	.17
Minor amputations	Intercept	2.842 (2.801 – 2.884)	<.001
	Baseline trend	0.001 (–0.16 – 0.11)	.072
	Level change 04/2020	–0.028 (–0.164 – 0.109)	.69
	Trend change 04/2020	0.018 (–0.027 – 0.063)	.43
	Level change 10/2020	0.064 (–0.384 – 0.512)	.78
	Trend change 10/2020	–0.05 (–0.14 – 0.039)	.27
Major amputations	Intercept	1.20 (1.17 – 1.234)	<.001
	Baseline trend	–0.003 (–0.003 – –0.002)	<.001
	Level change 04/2020	–0.003 (–0.044 – 0.038)	.89
	Trend change 04/2020	0.016 (0.009 – 0.023)	<.001
	Level change 10/2020	0.046 (–0.118 – 0.209)	.58
	Trend change 10/2020	–0.03 (–0.057 – –0.002)	.034
In hospital mortality	Intercept	0.32 (0.31 – 0.33)	<.001
	Baseline trend	–0.001 (–0.001 – –0.001)	<.001
	Level change 04/2020	–0.011 (–0.02 – –0.001)	.023
	Trend change 04/2020	0.007 (0.006 – 0.008)	<.001
	Level change 10/2020	0.018 (–0.005 – 0.041)	.13
	Trend change 10/2020	–0.010 (–0.013 – –0.007)	<.001

The intercept, baseline trend, and all changes have to be interpreted as monthly population wide amputation/in hospital mortality rate per 100 000 inhabitants. The segmentation was set between March/April 2020 and September/October 2020. Annual interrupted time series analysis with a segmentation 2019/2020 is given in Supplementary Table S4. CI = confidence interval.

Table 4. Amputations and in hospital mortality by periods of interest for the first lockdown (temporal period matched trends).

	04–06 2018 (reference period)	04–06 2019 (reference period)	Change between references	Combined reference period	First lockdown, 04–06 2020	Change to combined reference period	Char 04–0 2019
Total no. of patients/month	3 448.3 (3 106.9–3 789.7)	3 360 (2 953.2–3 766.8)	–2.6%, *p* = .51	3 404.2 (3 253.5–3 554.9)	3 207.3 (2 558.5–3 856.2)	–5.8%, *p* = .18	–4.5 .44
Total no. of patients per month/100 000 people	4.15 (3.74–4.56)	4.04 (3.55–4.53)	–2.7%, *p* = .49	4.10 (3.91–4.28)	3.86 (3.08–4.64)	–5.9%, *p* = .17	–4.5 .44
Minor amputation/month	2 579 (2 357.1–2 800.9)	2 516.3 (2 144.9–2 887.7)	–2.4%, *p* = .57	2 547.7 (2 426.6–2 668.7)	2 420.7 (1 924.7–2 916.6)	–5.0%, *p* = .25	–3.8 .54
Minor amputation per month/100 000 people	3.11 (2.84–3.37)	3.03 (2.58–3.47)	–2.6%, *p* = .54	3.07 (2.92–3.21)	2.91 (2.31–3.51)	–5.2%, *p* = .25	–4.0 .54
Major amputation/month	869.3 (739.8–998.9)	843.7 (803.5–883.8)	–3.0%, *p* = .46	856.5 (817.4–895.6)	786.7 (628.4–944.9)	–8.1%, *p* = .071	–6.8 .21
Major amputation per month/100 000 people	1.05 (0.89–1.20)	1.01 (0.97–1.06)	–3.8%, *p* = .44	1.03 (0.98–1.08)	0.95 (0.76–1.14)	–7.8%, *p* = .070	–6.0 .21
In hospital mortality/month	199.7 (181–218.3)	208 (186–229.7)	+4.2%, *p* = .28	203.8 (194.8–212.8)	183 (178–188)	–10.2%, *p* = .005	–12.0 = .0
In hospital mortality per month/100 000 people	0.24 (0.22–0.26)	0.25 (0.22–0.28)	+4.2%, *p* = .30	0.25 (0.23–0.26)	0.22 (0.21–0.22)	–12.0%, *p* = .005	–12.0 = .0

"People" represents total number of people in Germany in the respective year. 95% confidence interval in brackets. *p* values are from Student's *t* test. Non-sided *p* values are stated. Interim time period (post-lockdown) is given in Supplementary Table S5.

Table 3. Amputations and in hospital mortality by periods of interest for the second lockdown (temporal period matched trends).

	10/2017–05/2018 (reference period)	10/2018–05/2019 (reference period)	Change between references	Combined reference period	Second lockdown, 10/2020–05/2021	Change to combined reference period	Change to 10/2018–05/2019
Total no. of patients/month	3 271.5 (2 960.8–3 582.2)	3 218.3 (2 877.3–3 559.3)	–1.6%, *p* = .79	3 244.9 (3 043.5 – 3 446.3)	3 236 (2 998.0–3 474.0)	–0.3%, *p* = .95	+0.5%, *p* = .92
Total no. of patients per month/100 000 people	3.94 (3.57–4.32)	3.87 (3.46–4.28)	–1.8%, *p* = .76	3.91 (3.67–4.15)	3.89 (3.60–4.17)	–0.5%, *p* = .92	+0.5%, *p* = .94
Minor amputation/month	2 433.9 (2 200.1–2 667.7)	2 400.6 (2 147.0–2 654.2)	–1.4%, *p* = .82	2 417 (2 266.8–2 567.7)	2 426.8 (2 236.0–2 617.5)	+1.1%, *p* = .94	+1.1%, *p* = .85
Minor amputation per month/100 000 people	2.93 (2.65–3.21)	2.89 (2.58–3.19)	–1.4%, *p* = .80	2.91 (2.73–3.09)	2.92 (2.69–3.14)	+0.3%, *p* = .97	+1.0%, *p* = .86
Major amputation/month	837.6 (759.6–915.7)	817.6 (725.5–909.7)	–2.4%, *p* = .70	827.6 (774.8–880.5)	809.3 (755.9–862.6)	–2.2%, *p* = .64	–1.0%, *p* = .86
Major amputation per month/100 000 people	1.01 (0.92–1.10)	0.98 (0.87–1.09)	–3.0%, *p* = .68	1.00 (0.93–1.06)	0.97 (0.91–1.04)	–3.0%, *p* = .61	–1.0%, *p* = .84
In hospital mortality/month	221.4 (189.2–253.5)	200 (175.5–224.5)	–9.7%, *p* = .23	210.7 (192.1–229.3)	207.4 (196.5–218.3)	–1.6%, *p* = .80	+3.7%, *p* = .53
In hospital mortality per month/100 000 people	0.27 (0.23–0.31)	0.24 (0.21–0.27)	–11.1%, *p* = .22	0.25 (0.23–0.28)	0.25 (0.24–0.26)	0%, *p* = .77	+4.2%, *p* = .54

“People” represents total number of people in Germany in the respective year. 95% confidence interval in brackets. *p* values are from Student’s *t* test. Non-sided *p* values are stated. Interim time period (post-lockdown) is given in Supplementary Table S5.

Table 6. Patient characteristics, amputation related revascularisations, and in hospital mortality by periods of interest (lockdown periods, categorically).

Characteristic	Total (*n* = 89 191	No lockdown (reference 2017–2019) (*n* = 55 406)	Lockdown (first and second lockdown) (*n* = 33 785)	*p* value*
Patient characteristics				
Age group – y				.11
≤59	9 707 (10.9)	6 111 (11.0)	3 596 (10.6)	
60–79	48 038 (53.9)	30 127 (54.4)	17 911 (53.0)	
80–89	26 440 (29.6)	16 071 (29.0)	10 369 (30.7)	
>89	5 006 (5.6)	3 097 (5.6)	1 909 (5.7)	
Hospital Frailty Score†				<.001
Frailty I	31 885 (35.8)	19 927 (36.0)	11 958 (35.4)	
Frailty II	45 376 (50.9)	28 158 (50.8)	17 218 (51.0)	
Frailty III	11 930 (13.4)	7 321 (13.2)	4 609 (13.6)	
Length of stay – d	17 (11, 29)	18 (11, 30)	16 (10, 27)	<.001‡
Female sex	24 263 (27.2)	15 274 (27.6)	8 989 (26.6)	.002
Main diagnosis				
Peripheral arterial disease	50 954 (57.1)	31 563 (57.0)	19 391 (57.4)	.21
Diabetes mellitus	36 080 (40.5)	22 470 (40.6)	13 610 (40.3)	.60
Other§	2 157 (2.4)	1 373 (2.5)	784 (2.3)	.15
Treatment and outcomes				
Any amputation related revascularisation	41 125 (46.1)	24 942 (45.0)	16 183 (47.9)	<.001
Surgical revascularisation	14 948 (16.8)	9 186 (16.6)	5 762 (17.1	.065

Revascularisation before amputation surgery	25 892 (29.0)	15 891 (28.7)	10 001 (29.6)	.003
Minor amputation only	65 475 (73.4)	40 524 (73.1)	24 951 (73.9)	.036
Major amputation only	18 997 (21.3)	11 888 (21.5)	7 109 (21.0)	.036
Minor and major amputation	4 719 (5.3)	2 994 (5.4)	1 725 (5.1)	.036
Amputation on both sides	1 898 (2.1)	1 132 (2.0)	766 (2.3)	.079
Revision surgery	28 231 (31.7)	17 233 (31.1)	10 998 (32.6)	<.001
Overall mortality	5 982 (6.7)	3 774 (6.8)	2 208 (6.5)	.11

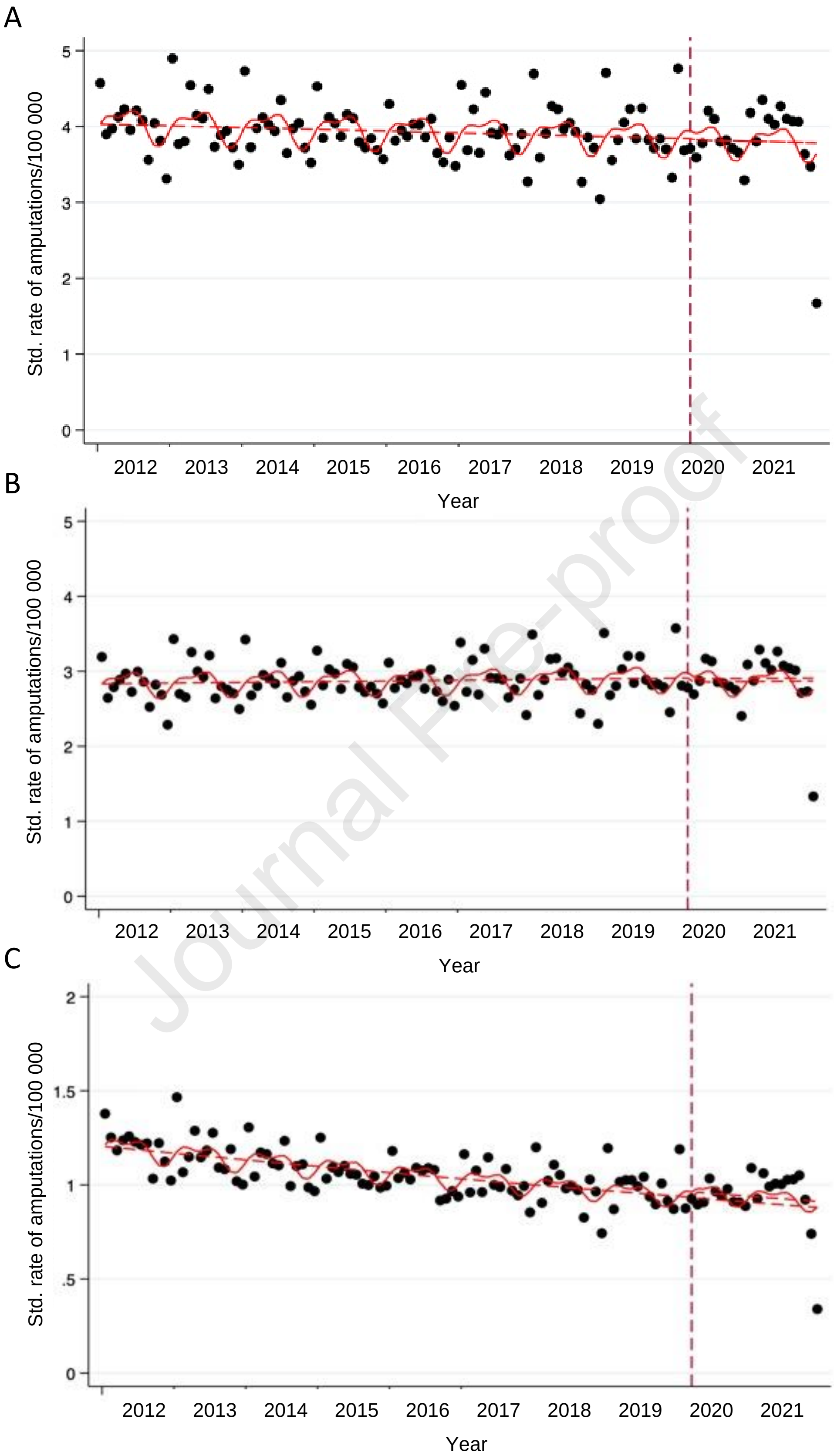
Data are presented median (interquartile range) or *n* (%). Values in parentheses are percentages of total in the patient group. More data are given in Supplementary Table S6.

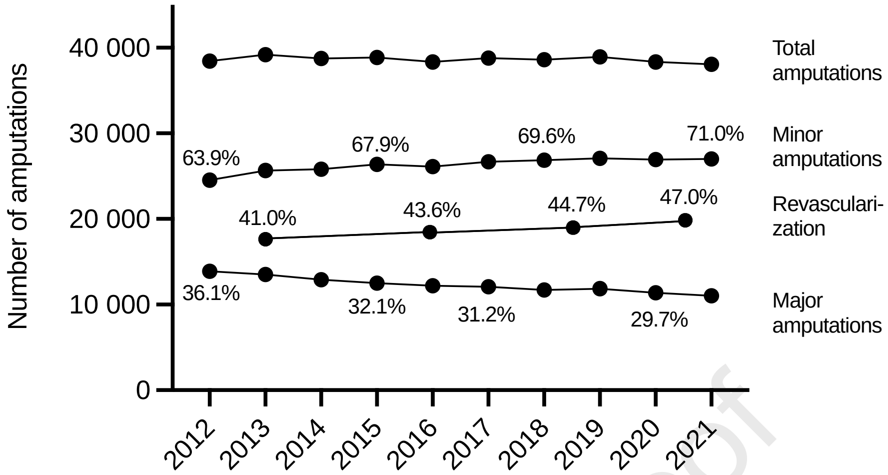
[*] *p* values compare lockdown *vs.* non-lockdown. No lockdown designates same months for comparison in two prior years. First lockdown in 2020 from April through June with respective references in 2018 and 2019, and second lockdown from October 2020 through May 2021 with respective reference periods from October 2017 – May 2018 and October 2018 – May 2019.

[†] Hospital Frailty Score was $p < .001$ for the overall χ^2 test for distribution among lockdown periods.

[‡] Non-parametric rank test.

[§] Other main diagnoses include acute ischaemia, aortic aneurysm or dissection, and "other vascular disease" (ICD I77, I79, I99).


A
Std. rate of amputations/100 000
5
4
3
2
1
0
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year
B
Std. rate of amputations/100 000
5
4
3
2
1
0
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year
C
Std. rate of amputations/100 000
2
1.5
1
.5
0
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year



Number of amputations
40 000
30 000
20 000
10 000
0
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Total amputations
Minor amputations
Revasculari-zation
Major amputations
63.9%
67.9%
69.6%
71.0%
41.0%
43.6%
44.7%
47.0%
36.1%
32.1%
31.2%
29.7%