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Sarcopenia Influences Clinical Outcome in Hospitalized Patients with Peripheral Artery Disease Aged 75 Years and Older

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Background: Sarcopenia represents a relevant comorbidity in patients with peripheral artery disease (PAD). However, only few studies exist assessing the clinical burden of sarcopenia in PAD.

Methods: All hospitalizations of patients aged ≥75 years who were admitted due to PAD within 2005–2020 in Germany were included in the study and stratified for sarcopenia. Temporal trends and the impact of sarcopenia on treatment procedures as well as adverse in-hospital events were investigated.

Results: Overall, 1,166,848 hospitalization cases of patients admitted due to PAD (median age 81.0 [78.0–85.0] years; 49.5% female sex) were included, of which 2,109 (0.2%) were coded with sarcopenia. Prevalence of sarcopenia in these patients increased during the observational period from 0.05% in 2005 to 0.34% in 2020 (β 2.61 [95%CI 2.42–2.80], $P < 0.001$). Sarcopenic PAD patients were more often female (52.1% vs. 49.5%, $P = 0.015$), obese (6.6% vs. 5.5%, $P = 0.021$), and revealed higher prevalences of comorbidities (Charlson comorbidity index, 7.00 [6.00–9.00] vs. 6.00 [5.00–7.00], $P < 0.001$). Sarcopenia was associated with reduced usage of reperfusion treatments (endovascular intervention: odds ratio (OR) 0.409 [95%CI 0.358–0.466], $P < 0.001$; surgical revascularization: OR 0.705 [95%CI 0.617–0.805], $P < 0.001$) but higher conduction of amputation (OR 1.365 [95%CI 1.231–1.514], $P < 0.001$) and higher rates of major adverse cardiovascular and cerebrovascular events (MACCE) (OR 1.313 [95%CI 1.141–1.512], $P < 0.001$) and in-hospital death (OR 1.229 [95%CI 1.052–1.436], $P = 0.009$).

Conclusions: Sarcopenia is an under-recognized condition in PAD patients of high clinical relevance causing a crucial disease burden. Awareness of the ailment needs to be increased in daily clinical practice to identify sarcopenia and improve the clinical outcome of this vulnerable patient group.

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INTRODUCTION

Sarcopenia is a progressive, generalized skeletal muscle disease caused by adverse muscle alterations. The ailment can occur acute or chronically and particularly affects people of older age but may also emerge during younger lifetime. Sarcopenia is defined by low muscle strength, low muscle quantity and quality, and low physical performance.[1] The disease represents an important risk factor in the development of functional impairment and disability. Hence, people with sarcopenia are faced by crucial life changes, including reduced quality of life and higher risk for falls, functional disability, frailty, morbidity, and mortality.[2–9] Besides the fate of affected people, sarcopenia represents a crucial financial burden for the healthcare systems. Patients with sarcopenia bare an elevated risk for hospitalization and costs for in-hospital care are significantly higher in presence of sarcopenia during hospitalization.[1,10] The prevalence of sarcopenia was in epidemiological studies similar in women and in men. Nevertheless, some differences like a higher risk of malnutrition in female sarcopenic subjects were detected.[11] Also, as an accompanying illness, sarcopenia represents a relevant risk factor for the outcome of various underlying diseases. By this, the presence of sarcopenia has a significant impact on morbidity and mortality of patients with peripheral artery disease (PAD).[12] PAD is defined as a constriction or occlusion of peripheral arteries leading to impaired blood supply predominantly of the lower limbs. Atherosclerosis represents the main cause of PAD and consequently cardiovascular risk factors, like diabetes mellitus, hypertension, smoking, obesity, and dyslipidaemia, are important risk factors for the disease. Clinically, PAD is associated with intermittent claudication, rest pain, wounds, and wound healing disturbances, including wound infection. Hence, patients with PAD bear an elevated risk for limb amputation as well as morbidity and mortality.[13,14] PAD is often accompanied by sarcopenia, and the quality of life as well as prognosis are even worsened in PAD patients with a sarcopenic condition.[9,12,15,16] In patients with critical limb ischemia, the most vulnerable group of patients with PAD, sarcopenia was associated with a higher risk for cardiovascular events, amputation, and mortality.[17,18] In general, sarcopenia is often disregarded by physicians in daily clinical routine, and consequently, the presence of sarcopenia in patients with PAD is probably frequently undiagnosed.[12] Hence, sarcopenia represents a highly underestimated threat in diseases like PAD. The aim of the present study was to investigate the impact of sarcopenia in hospitalized patients with PAD aged 75 years and older. To meet this issue, a large cohort from Germany was analyzed within an investigation period of 16 years with the goal to investigate the incidence of and clinical burden caused by sarcopenia in hospitalized patients aged 75 years and older suffering from PAD.

METHODS

Data Source

We analyzed all hospitalization cases of patients aged ≥75 years, with a main diagnosis of PAD in Germany during the timeframe of the years 2005–2020 (source: Research Data Center (RDC) of the Federal Statistical Office and the Statistical Offices of the federal states, diagnosis-related group (DRG) Statistics 2005–2020, and own calculations). For the present analysis, we included all hospitalized patient cases of patients aged ≥75 years with a main diagnosis of PAD (International Classification of Disease [ICD]-code I70.2). Patients' main diagnosis is that diagnosis, which is mainly and primarily responsible for patients' hospitalization (admission to the hospital).[19]

In Germany, the diagnoses have to be coded according to the established coding guidelines ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification) and diagnostical, surgical, and interventional procedures with Operationen-und Prozedurenschlüssel (OPS) codes (surgery, diagnostic, and procedures codes [OPS])[20,21] and the Federal Statistical Office of Germany (Statistisches Bundesamt, Wiesbaden, Germany) gathers all data from all inpatient cases in Germany coded and processed according to the DRG system. The statistical analyses of the study were computed on our behalf by the RDC of the Federal Bureau of Statistics (Wiesbaden, Germany); aggregated statistics were provided by the RDC on the basis of our generated and supplied SPSS codes (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 20.0. IBM Corp: Armonk, NY, USA).

In this study, we included all hospitalizations of patients admitted due to PAD (identified by the main ICD-code I70.2) during the observational period in Germany. Within the included hospitalization cases of PAD, patients were stratified for the presence of sarcopenia (ICD-code M62.5). We analyzed the impact of sarcopenia on cardiovascular profile, reperfusion treatments, and amputation rate

as well as adverse in-hospital events in PAD patients. Additionally, temporal trends in these patients regarding total numbers, outcomes, and mentioned treatments were investigated.

Study Outcomes and Adverse In-Hospital Events

The primary study outcome was defined as in-hospital case fatality of all causes, whereas the secondary study outcome comprised major adverse cardiovascular and cerebrovascular events (MACCE, composite of all-cause in-hospital death, acute myocardial infarction [ICD-code I21], and/or ischemic stroke [ICD-code I63]). Further, the prevalence of other adverse events during in-hospital stay, such as cardio-pulmonary resuscitation (CPR; OPS-code 8-77), pneumonia (ICD-codes J12-J18), pulmonary embolism (PE, ICD-code I26), deep venous thrombosis and/or thrombophlebitis (DVT, ICD-code I80, I81, and I82), myocardial infarction (MI, ICD-codes I21 and I22), acute kidney injury (AKI, ICD-code *N*17), stroke (ischemic and hemorrhagic stroke, ICD-codes I61-64), intracerebral bleeding events (ICD-code I61), gastro-intestinal bleeding (ICD-codes K920-K922), and bleeding events, with the necessity of transfusion of blood components (OPS code 8-800), were assessed.

Definitions

In this study, obesity was defined as a body mass index ≥30 kg/m^2 according to the recommendations of the WHO (World Health Organization).[22] Shock as well as CPR were defined according to the current European guidelines.[23–25] Major amputations comprised surgeries with amputations above the ankle (OPS-code: 5-864), whereas minor amputations were defined as surgeries comprising amputations below the ankle (OPS-code: 5-865). Amputations of the upper extremities and amputations due to reasons other than limb ischemia, such as venous ulceration, trauma, and malignancy, were consistently not included in our present analysis.[14,26,27] Surgical peripheral artery revascularization of the lower extremity comprised peripheral artery bypass operations, incision with embolectomy, or thrombectomy and/or patch plastic operations of the legs (OPS codes 5-393.35, 5-393.36, 5-393.38, 5-393.42, 5-393.43, 5-393.44, 5-393.45, 5-393.46, 5-393.5, 5-393.6, 5-393.7, 5-380.7, 5-380.8, 5-395.7, and 5-395.8), while peripheral endovascular intervention of the lower extremity comprised all interventional angioplasty treatments, including balloon dilatation and stent implantation (OPS codes 8-836.0c, 8-836.0s, 8-836.1c, 8-836.1k, 8-836.2c, 8-836.2k, 8-836.3c, 8-836.3k, 8-840.0c, 8-840.1c, 8-840.2c, 8-840.3c, 8-840.4c, 8-840.5c, 8-840.0s, 8-840.1s, 8-840.2s, 8-840.3s, 8-840.4s, and 8-840.5s).

Ethical Aspects

In accordance with the German law, an approval by an ethical committee as well as informed consent of the patients were both not required, since the present study did not involve a direct access of the study investigators to the data of individual patients, but only on summarized or aggregated data provided by the RDC.

Statistical Methods

Descriptive statistical comparisons of PAD patients aged ≥75 years with and without sarcopenia were calculated as median and interquartile range (IQR) or as absolute numbers and corresponding percentages. Continuous variables were compared by using the Mann-Whitney U test and for categorical variables using the Fisher's exact or the chi^2 test, as appropriate.

Temporal trends of hospitalizations of PAD patients and PAD patients with sarcopenia as well as case fatality and MACCE rate, performed reperfusion and amputation treatments that were calculated on an annual and age-dependent (age-decade) basis. Linear regressions were used to assess trends over time, and the results are shown as beta (β) with corresponding 95% confidence intervals (CI).

The investigation of the impact of sarcopenia on adverse in-hospital events and in-hospital case fatality in PAD patients was performed using univariable and multivariable logistic regression models given as odds ratio (OR) and 95% CI. The multivariable regression models were adjusted for age, sex, obesity, hyperlipidemia, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and/or chronic kidney failure, diabetes mellitus, and atrial fibrillation or flutter.

This epidemiological approach regarding the adjustment was used to guarantee a wide independence of the influence of sarcopenia on adverse in-hospital events during hospitalization. Statistical significance was presupposed in cases of a *P* value <0.05 (2-sided). Statistical analyses were performed with the software SPSS (version 20.0; SPSS Inc., Chicago, Illinois, USA).

RESULTS

Overall, 1,166,848 hospitalizations of patients aged ≥75 years admitted due to PAD (median age 81.0 [78.0−85.0] years; 49.5% female sex) were counted in Germany in the time frame of the years 2005−2020. The median length of in-hospital stay was 8.0 (IQR 3.0−16.0) days. Among these hospitalizations, 2109 (0.2%) were coded with sarcopenia (Table I). Total numbers of sarcopenic PAD patients increased from 25 (0.05%) in the year 2005 to 256 (0.34%) in 2020 (β 2.61 [95%CI 2.42−2.80], $P < 0.001$) and also a significant increase with age was observed (β 0.23 [95%CI 0.19−0.27], $P < 0.001$) (Fig. 1).

Patient Characteristics

PAD patients with sarcopenia were more often female (52.1% vs. 49.5%), $P = 0.015$) and obese (6.6% vs. 5.5%, $P = 0.021$) (Table I). Although female sex was associated with sarcopenia in the univariate logistic regression analysis (OR 1.11 [95%CI 1.02−1.21], $P = 0.016$), after adjustment for age and comorbidities, female sex remained not independently associated with sarcopenia (adjusted OR 1.07 [95%CI 0.98−1.17], $P = 0.161$) in PAD patients. Sarcopenic PAD patients revealed an aggravated comorbidity profile with increased prevalence of the cardiovascular comorbidities, such as heart failure (38.4% vs. 19.2%, $P < 0.001$), coronary artery disease (33.5% vs. 30.9%, $P = 0.009$), and atrial fibrillation or flutter (37.1% vs. 25.1%, $P < 0.001$), but also diabetes mellitus (39.5% vs. 35.3%, $P < 0.001$), chronic obstructive pulmonary disease (12.9% vs. 9.3%, $P < 0.001$), acute or chronic kidney failure (53.8% vs. 37.8%, $P < 0.001$), cancer (3.2% vs. 2.0%, $P < 0.001$), and chronic anemia (22.7% vs. 7.5%, $P < 0.001$). Consecutively, the median Charlson comorbidity index was higher in PAD patients with sarcopenia than without (7.00 [6.00−9.00] vs. 6.00 [5.00−7.00], $P < 0.001$ (Table I).

Interventional and Surgical Treatments

PAD with sarcopenia was less often treated with reperfusion treatments, such as peripheral endovascular intervention of the lower extremity (12.0% vs. 25.1%, $P < 0.001$) and surgical peripheral artery revascularization of the lower extremity (11.9% vs. 16.2%, $P < 0.001$) (Table I). In contrast, amputations (23.3% vs. 15.4%, $P < 0.001$) comprising minor (11.9% vs. 10.2%, $P = 0.011$) and major amputations (14.5% vs. 6.2%, $P < 0.001$) were more often detected in PAD patients with than without sarcopenia (Table I).

Logistic regression analyses confirmed that the reperfusion treatments peripheral endovascular intervention of the lower extremity (adjusted OR 0.409 [95%CI 0.358−0.466], <0.001) and surgical peripheral artery revascularization of the lower extremity (adjusted OR 0.705 [95%CI 0.617−0.805], $P < 0.001$) were both less often used in PAD patients with sarcopenia independent of age, sex, cardiovascular risk factors, and comorbidities (Table II). While reperfusion treatments were less often used in sarcopenic PAD patients, amputations (adjusted OR 1.365 [95%CI 1.231−1.514], $P < 0.001$) were more often performed in PAD patients with sarcopenia (Table II).

The temporal trends of reperfusion and amputation treatments in hospitalized PAD patients with sarcopenia showed a slight increase regarding the use of peripheral endovascular intervention of the lower extremity, while other treatments were widely constant over time (Fig. 2B). Amputation and surgical peripheral artery revascularization of the lower extremity were less often performed with increasing age (Fig. 2D).

Length Of In-Hospital Stay

The length of in-hospital stay was longer in PAD patients with sarcopenia than without (20.00 [13.00−28.00] vs. 8.00 [3.00−16.00] days, $P < 0.001$). Consecutively, a prolonged in-hospital stay >10 days (80.1% vs. 40.8%, $P < 0.001$) was also more often identified in PAD patients with sarcopenia (Table I). Sarcopenia in PAD patients was independently associated with the length of in-hospital stay >10 days (OR 4.882 [95%CI 4.378−5.445], $P < 0.001$) (Table II).

Adverse In-Hospital Events

In-hospital mortality (8.9% vs. 4.9%, $P < 0.001$) and MACCE (11.2% vs. 6.0%, $P < 0.001$) were more often detected in sarcopenic PAD patients (Table I). In addition, the adverse in-hospital events DVT (1.5% vs. 0.6%, $P < 0.001$), PE (0.4% vs. 0.2%, $P = 0.006$), acute kidney failure (9.1% vs. 3.0%, $P < 0.001$), pneumonia (7.8% vs. 2.7%, $P < 0.001$), and bleeding events with the necessity of the transfusion of blood constituents (24.0% vs. 13.6%, $P < 0.001$) occurred more often in PAD patients with sarcopenia in comparison to those without (Table I).

The logistic regression analyses also showed an independent association between sarcopenia in PAD patients with increased risk for in-hospital

Table I. Patients' characteristics, medical history, presentation, and adverse in-hospital events of the 1,166,848 hospitalizations of patients admitted due to PAD aged ≥75 years in Germany in the years 2005–2020 stratified for the presence of sarcopenia

Parameters	PAD patients with sarcopenia (n = 2109; 0.2%)	PAD patients without sarcopenia (n = 1,164,739; 99.8%)	P-value
Age	82.00 (78.00–87.00)	81.00 (78.00–85.00)	**<0.001**
Female sex	1,099 (52.1%)	576,735 (49.5%)	**0.015**
In-hospital stay (days)	20.00 (13.00–28.00)	8.00 (3.00–16.00)	**<0.001**
In-hospital stay >10 days	1,690 (80.1%)	475,066 (40.8%)	**<0.001**
Cardiovascular risk factors			
Obesity	139 (6.6%)	63,492 (5.5%)	**0.021**
Essential arterial hypertension	1255 (59.5%)	770,902 (66.2%)	**<0.001**
Diabetes mellitus	834 (39.5%)	411,397 (35.3%)	**<0.001**
Hyperlipidemia	607 (28.8%)	367,576 (31.6%)	**0.006**
Comorbidities			
Heart failure	810 (38.4%)	223,734 (19.2%)	**<0.001**
Coronary artery disease	707 (33.5%)	359,962 (30.9%)	**0.009**
Atrial fibrillation or flutter	782 (37.1%)	291,894 (25.1%)	**<0.001**
Chronic obstructive pulmonary disease	273 (12.9%)	107,837 (9.3%)	**<0.001**
Acute or chronic kidney failure	1,134 (53.8%)	440,112 (37.8%)	**<0.001**
Cancer	68 (3.2%)	23,252 (2.0%)	**<0.001**
Chronic anemia	478 (22.7%)	87,650 (7.5%)	**<0.001**
Charlson comorbidity index	7.00 (6.00–9.00)	6.00 (5.00–7.00	**<0.001**
Treatment			
Amputation	492 (23.3%)	179,166 (15.4%)	**<0.001**
Minor amputation	250 (11.9%)	118,635 (10.2%)	**0.011**
Major amputation	305 (14.5%)	72,582 (6.2%)	**<0.001**
Peripheral endovascular intervention of the lower extremity	254 (12.0%)	292,010 (25.1%)	**<0.001**
Surgical peripheral artery revascularization of the lower extremity	250 (11.9%)	188,601 (16.2%)	**<0.001**
Intensive care unit	194 (9.2%)	57,018 (4.9%)	**<0.001**
Adverse events during hospitalization			
In-hospital case fatality	188 (8.9%)	57,258 (4.9%)	**<0.001**
MACCE	237 (11.2%)	69,934 (6.0%)	**<0.001**
Cardio-pulmonary resuscitation	36 (1.7%)	9,539 (0.8%)	**<0.001**
MI	30 (1.4%)	13,270 (1.1%)	0.220
Shock	34 (1.6%)	10,911 (0.9%)	**0.001**
DVT	31 (1.5%)	7,347 (0.6%)	**<0.001**
PE	9 (0.4%)	1,762 (0.2%)	**0.006**
Acute kidney failure	191 (9.1%)	35,018 (3.0%)	**<0.001**
Pneumonia	164 (7.8%)	30,948 (2.7%)	**<0.001**
Stroke (ischemic or hemorrhagic)	36 (1.7%)	7,297 (0.6%)	**<0.001**
Intracerebral bleeding	3 (0.14%)	451 (0.04%)	0.050
Gastro-intestinal bleeding	46 (2.2%)	7,214 (0.6%)	**<0.001**
Transfusion of blood constituents	507 (24.0%)	158,922 (13.6%)	**<0.001**

Bold indicates statistical significance was presupposed in cases of a P value <0.05.

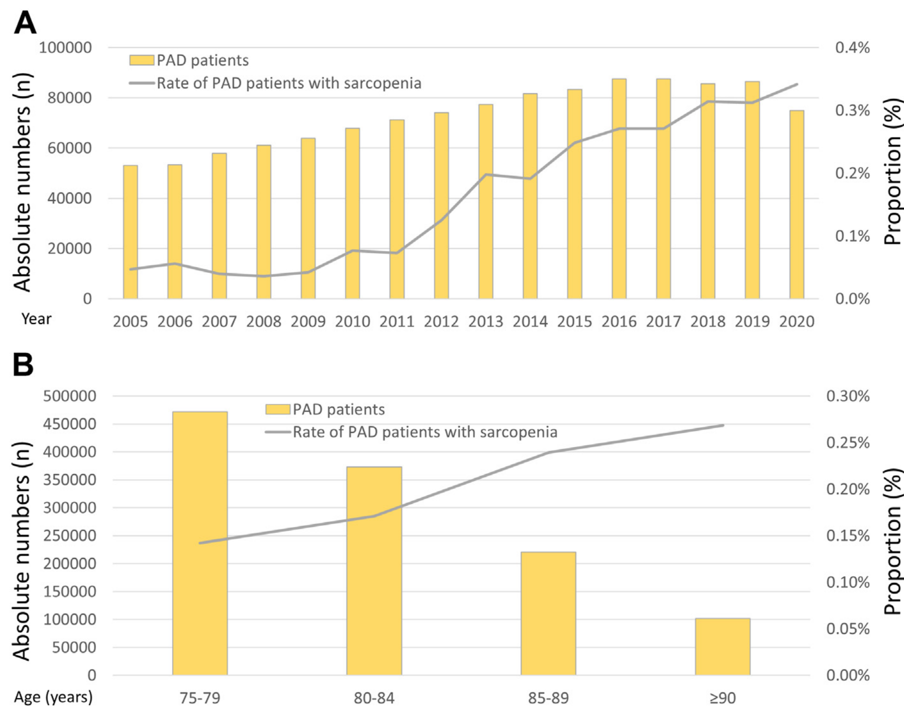

Fig. 1. Temporal trends regarding hospitalizations of patients aged ≥75 years with PAD and proportion of additional sarcopenia. Panel **A** —total numbers regarding hospitalizations of patients admitted due to PAD and proportion of PAD patients with sarcopenia stratified for treatment year (2005—2020) Panel **B**—total numbers regarding hospitalizations of patients admitted due to PAD and proportion of PAD patients with sarcopenia stratified for age.

mortality (adjusted OR 1.229 [95%CI 1.052—1.436], $P = 0.009$), MACCE (adjusted OR 1.313 [95%CI 1.141—1.512], $P < 0.001$), DVT (adjusted OR 2.007 [95%CI 1.406—2.865], $P < 0.001$), PE (adjusted OR 2.071 95% CI 1.073—3.997], $P = 0.030$), pneumonia (adjusted OR 2.066 [95% CI 1.752—2.436], $P = 0.011$), acute renal failure (adjusted OR 1.993 [95%CI 1.701—2.335], $P < 0.001$), and necessity of the transfusion of blood constituents (adjusted OR 1.587 [95%CI 1.433—1.759], $P < 0.001$) independent of age, sex, cardiovascular risk factors, and comorbidities (Table II).

In-hospital mortality and MACCE rates of PAD patients with sarcopenia were highest in the years 2007—2011 and decreased in later years (Fig. 2A). Remarkably, in-hospital mortality and MACCE rates were lowest in PAD patients with sarcopenia aged 80—84 years and increased in older patients aged ≥85 years (Fig. 2C).

DISCUSSION

In the present study, the impact of sarcopenia on hospitalized patients with PAD aged 75 years and older was investigated in the German nationwide inpatient sample within a timeframe of 16 years. The main results could be summarized, as follows: a) overall, in 0.2% of PAD patients, sarcopenia was present with a raising prevalence over time. b) Affected patients were more often of female sex, obese, and diabetics. c) In patients with PAD, the presence of sarcopenia was associated with an unbeneficial cardiovascular risk and comorbidity profile. d) Interventional and surgical reperfusion treatments were less often performed in sarcopenic PAD patients and in return amputation was more often performed. e) In PAD patients, sarcopenia was associated with an elevated length of in-hospital stay, higher rates of adverse in-hospital events, and increased in-hospital mortality.

Reporting regarding the prevalence of sarcopenia in patients with PAD is inconsistent in the literature.[28] A meta-analysis based on 17 studies, including 2,362 PAD patients with a mean patient age of 72.4 years, found a prevalence of sarcopenia in 34.6% of the patients.[12] Given the data of the literature, the prevalence of sarcopenia was remarkably low in the present analysis. Most probably, this may be reasoned in underdiagnosis, and therefore

Table II. Impact of sarcopenia on in-hospital case fatality and adverse events during in-hospital stay in patients aged ≥75 years admitted due to PAD

	Univariate regression model		Multivariate regression model[a]	
	Or (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Adverse events during in-hospital stay				
In-hospital case fatality	1.893 (1.629–2.199)	**<0.001**	1.229 (1.052–1.436)	**0.009**
MACCE	1.982 (1.731–2.269)	**<0.001**	1.313 (1.141–1.512)	**<0.001**
In-hospital stay >10 days	5.852 (5.258–6.513)	**<0.001**	4.882 (4.378–5.445)	**<0.001**
Pneumonia	3.089 (2.633–3.624)	**<0.001**	2.066 (1.752–2.436)	**<0.001**
DVT	2.351 (1.648–3.354)	**<0.001**	2.007 (1.406–2.865)	**<0.001**
PE	2.830 (1.468–5.456)	**0.002**	2.071 (1.073–3.997)	**0.030**
Acute renal failure	3.213 (2.768–3.729)	**<0.001**	1.993 (1.701–2.335)	**<0.001**
Cardio-pulmonary resuscitation	2.104 (1.513–2.927)	**<0.001**	1.442 (1.034–2.011)	**0.031**
MI	1.253 (0.873–1.797)	0.221	0.852 (0.592–1.227)	0.390
Stroke (ischemic or hemorrhagic)	2.755 (1.980–3.833)	**<0.001**	2.253 (1.618–3.138)	**<0.001**
Intracerebral bleeding	3.677 (1.181–11.454)	**0.025**	3.217 (1.032–10.035)	**0.044**
Gastro-intestinal bleeding	3.578 (2.669–4.796)	**<0.001**	2.599 (1.935–3.489)	**<0.001**
Transfusion of blood constituents	1.999 (1.809–2.209)	**<0.001**	1.587 (1.433–1.759)	**<0.001**
Treatments				
Amputation	1.674 (1.513–1.852)	**<0.001**	1.365 (1.231–1.514)	**<0.001**
Minor amputation	1.186 (1.039–1.353)	**0.011**	0.973 (0.851–1.113)	0.689
Major amputation	2.544 (2.253–2.873)	**<0.001**	2.099 (1.854–2.375)	**<0.001**
Peripheral endovascular intervention of the lower extremity	0.409 (0.359–0.467)	**<0.001**	0.409 (0.358–0.466)	**<0.001**
Surgical peripheral artery revascularization of the lower extremity	0.696 (0.610–0.794)	**<0.001**	0.705 (0.617–0.805)	**<0.001**
Intensive care unit	1.969 (1.698–2.283)	**<0.001**	1.454 (1.250–1.691)	**<0.001**

Data were analysed with univariate and multivariate logistic regression models. Bold indicates statistical significance was presupposed in cases of a *P* value <0.05.

[a]Adjustment: Adjusted for age, sex, obesity, hyperlipidemia, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and/or chronic kidney failure, diabetes mellitus, and atrial fibrillation/flutter.

undercoding, of sarcopenia in patients with PAD in Germany due to several reasons: In 2010, a definition of sarcopenia was published by the European Working Group on Sarcopenia in Older People (EWGSOP) in order to improve identification of and care for affected people.[6] However, despite this effort, sarcopenia still remained underdiagnosed, overlooked, and undertreated in daily practice.[8] In general, the awareness regarding sarcopenia in nongeriatric physicians is low.[29] The possible reasons were identified in challenging diagnostics, including the complex determination of which variables should be measured and how the measurements should be performed, which are values that should be used for diagnosis or to evaluate treatment and how therapy efficiency could be estimated.[30] To further improve awareness and care of sarcopenia, the working group met again in 2018 (EWGSOP2) and updated its definition and diagnostic strategies.[1] Hence, the low prevalence of sarcopenia in the present study mirrors the ubiquitous inadequate awareness and underdiagnosis of this disease in hospitalized PAD patients. Studies that revealed a higher prevalence were often composed to investigate this issue and therefore focused on sarcopenia, which does not reflect daily clinical routine in hospitalized patients with PAD. In line with the literature, in the present study, sarcopenia was associated with an unbeneficial cardiovascular risk factor and comorbidity profile. Since sarcopenia is associated to unbeneficial conditions like the metabolic syndrome—and therefore to various metabolic discrepancies, like arterial hypertension, diabetes mellitus, hyperlipoprotienaemia, and obesity —a consecutively increased risk for cardiovascular disease is conclusive, including in patients with PAD.[12–14,31] Interestingly, obesity is a known and often underestimated risk factor in patients with sarcopenia, whereas the definition of sarcopenic obesity still needs to be clarified.

Fig. 2. Temporal trends of hospitalizations of PAD patients aged ≥75 years with sarcopenia, adverse in-hospital events, and treatments. Panel **A** – the temporal trends regarding the total number of patients with coprevalence of PAD and sarcopenia, MACCE, and in-hospital case fatality stratified for treatment year. Panel **B**–temporal trends regarding interventional and surgical treatments stratified for treatment year. Panel **C** – temporal trends regarding the total number of patients with coprevalence of PAD and sarcopenia, MACCE, and in-hospital case fatality stratified for age. Panel **D**–temporal trends regarding interventional and surgical treatments stratified for age.

Furthermore, due to the differing clinical risk of both conditions, the subclassification of people with sarcopenic visceral and/or subcutaneous obesity is suggested.[12,32] The metabolic syndrome and its single components like diabetes mellitus lead to several alterations, which contribute to the genesis of disease-underlying conditions like atherosclerosis. Pathophysiologically, sarcopenia affects the skeletal muscle by the following mechanisms: decreased muscle strength and function, alteration of muscle histology, oxidative stress, inflammation, mitochondrial impairment, and disturbed signaling pathways. In PAD patients, several alterations of the skeletal muscle were found like reduced baseline strength and function as well as divergent muscle histology. Of interest, despite the definition of sarcopenia occuring clinically up to now, the underlying mechanisms like oxidative stress, inflammation, and mitochondriopathy were also found in PAD.[12] The metabolic syndrome is associated with increased systemic inflammation, which also represents an important condition in PAD and likely contributes to skeletal muscle impairment. In patients with PAD, several inflammatory cytokines are increased. The inflammatory pattern was associated with poor clinical conditions like reduced walking distance. After exercise training, the inflammatory markers were shown to be reduced accompanied by an increased walking distance. Inflammation is supposed to play a crucial role also regarding sarcopenia in patients with PAD, possibly by dysregulation of various inflammatory

cytokines.[12–14,33–39] In PAD patients with chronic limb-threatening ischemia, an even aggravated inflammatory state was detected. This included an increased systemic inflammation with elevated proinflammatory cytokines and inflammatory markers like C-reactive protein as well as inflamed skeletal muscle with increased levels of leukocytes. Importantly, increased inflammation and especially muscle inflammation was postulated to contribute to muscle loss emphasizing the need to break the inflammatory cycle. Ferreira et al. showed that the inflammatory environment in chronic limb-threatening ischemia can partially be reverted by dissolving the ischemic process and underscore the importance of early revascularization.[40–43] Besides inflammation, oxidative stress induces multiple alterations on cellular and subcellular levels, representing an important underlying pathomechanism for various ailments, including the genesis of atherosclerosis. Reactive oxygen species promote endothelial dysfunction, mitochondrial impairment, and DNA damage. Alike, in other cardiovascular diseases also, in PAD redox regulation and oxidative stress were shown to play a decisive role. It is supposed that reactive oxygen species are increased in PAD patients due to platelet activation and inflammation, both inducing additional formation of reactive oxygen species by the endothelium, which again leads to even more platelet activation, promoting a vicious cycle of reactive oxygen species formation. The high burden of oxidative stress leads to endothelial dysfunction and atherosclerosis. In patients with claudication, endothelial dysfunction was independently associated with the risk for mortality. On the other hand, in PAD patients, the burden of oxidative stress was reduced in consequence of exercise training. Regarding skeleton muscle, in PAD the extent of oxidative damage of the gastrocnemius muscle was related to the disease stage and myofiber damage.[12,14,38,44–46] Since oxidative stress reduces muscle condition also in sarcopenia[47,48] and sarcopenic obesity,[49] additive negative effects of patients suffering from both PAD and sarcopenia can be supposed. Furthermore, oxidative stress is a main component for mitochondrial damage by depolarization of the mitochondrial membrane potential with subsequent disturbance of permeability and mitochondrial swelling, leading to an alteration of electron transport chain activity and cell death.[50,51] In skeletal muscle tissue of PAD patients, increased mitochondrial DNA injuries, and in ischemic muscle an impaired mitochondrial respiratory activity were found.[12,52,53] However, it has to be concluded that the complex pathomechanisms, which underly PAD and sarcopenia—including inflammation, oxidative stress, and mitochondrial damage—are until today insufficiently known and understood. With the aim of identifying promising targets for therapy, further investigation is required to improve prevention and therapy options of affected patients.

In the present study, sarcopenia was associated with less performance of revascularization treatment, higher rates of amputation and adverse in-hospital events, increased length of in-hospital stay, and higher in-hospital mortality. Little data exists on clinical outcome of sarcopenic PAD patients in the literature. In daily clinical routine, muscular function is not assessed before and after revascularization procedures, so in general it remains unknown if an (ischemia-related) reduction of muscle function is improved after treatment or if the ailments persist.[12] However, one study by Landry et al. prospectively investigated 18 patients suffering from critical limb ischemia who were treated by lower extremity bypass surgery. After revascularization, an improved muscle function was present, including an increase of leg muscle strength, elevated 6-minute walk distance, improved quality of life, and reduced bodily pain.[54] Few other studies investigated clinical outcomes of sarcopenic PAD patients. In these studies, in patients treated by endovascular revascularization, due to limb-threatening ischaemia, the presence of sarcopenia was associated with increased amputation rates and mortality.[17,55] Furthermore, sarcopenia was identified as an independent risk factor for cardiovascular events after revascularization in patients with critical limb ischemia.[18,56] In this context, the study by Selçuk et al. assessed patients after surgical revascularization to treat critical limb ischemia and found sarcopenia to be associated with an increased perioperative mortality as well as more frequent 30-day major adverse cardiac events, whereas the 30-day major adverse limb events were not elevated in patients with sarcopenia.[56] These results may underline the complex and systemic alterations of sarcopenia. Sarcopenia was furthermore revealed as a risk factor for diabetic foot disease and was associated with more foot ulcers and higher rates of amputation compared to nonsarcopenic patients suffering from diabetic foot disease.[57] In contrast, in their study on risk factors affecting amputation in diabetic foot, Lee et al. found no association between amputation and sarcopenia; however, the authors supposed that this result may be due to the tools they used to assess sarcopenia[58] – mirroring the complexity and inconsistency of sarcopenia diagnostics, which was recently claimed by the

European working group on Sarcopenia.[1] Altogether, the few pre-existing as well as the present studies clearly elucidate an urgent need for action regarding the awareness of sarcopenia in patients with PAD to improve diagnostics and therapy strategies in this vulnerable patient group.

Limitations

Regarding the present study, some important limitations should be mentioned. Due to the nature of an ICD- and OPS-code-based study, the analysis for hospitalized patients, under-reporting, and under-coding may be the possible biasing factors. In addition, data on concomitant medication or laboratory markers are not available, and no follow-up evaluation is possible since data are only assessed and therefore limited to the timeframe of the in-hospital course.

CONCLUSIONS

Sarcopenia represents a widely unconsidered and highly underestimated but eminently relevant risk factor in patients with PAD. The present study identified sarcopenia as a crucial disease burden in older patients suffering from PAD, causing higher risk for amputation, increased length of in-hospital stay, and elevated risk for death. Sarcopenic patients furthermore revealed an unbeneficial clinical risk profile regarding risk factors and comorbidities. Due to the vast impact of sarcopenia on clinical outcome of patients with PAD, efforts of improvement are required starting with recognition of and sensibilisation for the ailment in order to even diagnose the disease and identify the patients at risk. The first possibly valuable step might be the extension of the existing clinical tests of PAD, like walking distance evaluation, by additional tests of muscle strength. Thereby, clinical screening of sarcopenia in PAD patients, for instance, using the algorithm suggested by the European working group on sarcopenia in older people,[1] may help to identify affected patients and improve awareness and clinical outcome of this unrecognized patient group by an optimized therapy concept.

DATA AVAILABILITY STATEMENT

All ICD and OPS codes used in this study are publicly available online. The data used in this study are aggregated results provided by the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis), which were analyzed on patient-level data at the RDC (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005−2020, and own calculations). Individual patient-level data are gathered and analyzed from and at the RDC and will not be made publicly available.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Volker H. Schmitt: Writing − review & editing, Writing − original draft, Investigation, Conceptualization. **Lukas Hobohm:** Writing − review & editing, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christoph Brochhausen:** Writing − review & editing. **Christine Espinola-Klein:** Writing − review & editing. **Philipp Lurz:** Writing − review & editing. **Thomas Münzel:** Writing − review & editing. **Omar Hahad:** Writing − review & editing. **Karsten Keller:** Writing − review & editing, Writing − original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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