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Effect of muscle depletion on survival in peripheral arterial occlusive disease: Quality over quantity

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ABSTRACT

Objective: Patients with peripheral arterial occlusive disease (PAOD) have a poor prognosis and a high prevalence of comorbidity. This study investigated whether sarcopenia and/or myosteatosis negatively affect long-term survival in patients with PAOD.

Methods: This was a single-center, retrospective cohort study of 686 consecutive patients diagnosed and treated for PAOD and who underwent computed tomography scanning. Cross-sectional muscle measurements were obtained at the level of the third lumbar vertebra. Optimal stratification was used to define sex-specific and body mass index-specific cutoff values for sarcopenia and myosteatosis, respectively. The Cox proportional hazards model was used to determine the effect of sarcopenia and myosteatosis on overall survival.

Results: Sarcopenia was associated with age, body mass index, myosteatosis, malignancy, congestive heart failure, hemodialysis, and Fontaine 4 classification. Myosteatosis was associated with age, sarcopenia, type 2 diabetes mellitus, hypertension, chronic obstructive pulmonary disease, malignancy, congestive heart failure, ischemic stroke, and Fontaine 4 classification. Sarcopenia (hazard ratio [HR], 2.82; 95% confidence interval [CI], 2.05-3.86; $P < .001$) and myosteatosis (HR, 4.13; 95% CI, 3.03-5.63; $P < .001$) were both associated with reduced survival in univariable analysis. When adjusted for other prognostic markers, myosteatosis (HR, 2.09; 95% CI, 1.46-2.99; $P < .001$) was still associated with lower overall survival in the multivariable model, but sarcopenia (HR, 1.40; 95% CI, 0.97-2.01; $P = .073$) was not.

Conclusions: Muscle depletion is independently associated with a poorer overall survival in patients with PAOD. Myosteatosis is a stronger predictor than sarcopenia, which indicates that quality is more important than quantity. Results should be interpreted with caution owing to missing data on medication usage. (J Vasc Surg 2020;72:2006-16.)

Keywords: PAOD; Sarcopenia; Myosteatosis; Intramuscular fat; Survival; Outcome

Peripheral arterial occlusive disease (PAOD) is an increasingly common disease, with an expected increase to more than 150 million affected patients in 2015 in conjunction with the aging Western population.¹ Owing to PAOD's poor prognosis in selected patients, as well as interventional financial implications, new prognostic markers are becoming increasingly important to benefit clinical decision making.

Changes in body composition, for example, muscle wasting (sarcopenia) and the accumulation of

intermuscular and intramuscular fat (myosteatosis), have been described as strong prognostic markers in a wide variety of noncardiovascular conditions,²⁻⁴ as well as in cardiovascular disease, such as aortic aneurysm patients after surgical or endovascular repair.⁵⁻⁷

Several pathophysiologic similarities between PAOD and sarcopenia exist. Inflammation plays a major role in the formation of atherosclerosis.⁸ C-reactive protein (CRP) is an independent predictor in the development of PAOD among healthy men.⁹ Inflammatory cytokines are also involved in the pathophysiology of sarcopenia.^{10,11} Oxidative stress is another factor associated with the development of sarcopenia and PAOD.^{12,13} Skeletal muscle mitochondria release reactive oxygen species during ischemia, which leads to oxidative stress. Prolonged release of reactive oxygen species damages mitochondrial DNA.¹⁴ In patients with unilateral PAOD, it has been shown that there is systemic damage of the mitochondria.^{15,16}

The underlying mechanisms of myosteatosis are less well-understood. Aging, glucocorticoid treatment, and disuse are associated with an accumulation of intermuscular and intramuscular fat.¹⁷ Lipid accumulation within myofibers has been linked to inflammation, insulin insensitivity, and oxidative phosphorylation, all of which are associated with both PAOD and sarcopenia.^{18,19}

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To date, the effect of myosteatorsis on patient survival in PAOD has not yet been investigated, and only one study looked at sarcopenia and survival in patients with critical limb ischemia, reporting that sarcopenia may be an independent prognostic marker.²⁰ This study was, however, small, including only 64 patients in an Asian population. No studies have investigated the role of sarcopenia in PAOD in the Western population. The aim of this study was to investigate whether sarcopenia and/or myosteatorsis affect long-term survival and to describe the relationship between sarcopenia and myosteatorsis with regard to different prognostic variables in patients with PAOD. These data in turn may help in clinical decision making as well as providing new insights for the development of potential prophylactic and therapeutic strategies.

METHODS

This was a single-center retrospective cohort study of patients with PAOD who were treated at The University Medical Center Groningen (UMCG) between January 1, 2005, and December 31, 2017. The UMCG serves as both a primary and secondary referral center for vascular pathology and is located in the Northern region of The Netherlands.

Patients were identified by querying the picture archiving and communications system (PACS) of the hospital. All patients referred by the vascular surgeons for computed tomography (CT) angiography of the lower extremity arteries during the study period were considered for inclusion into this study. Patients were included if diagnosed with PAOD and diagnostic CT imaging was available within 1 year before the intervention. If a patient had been scanned multiple times throughout the study, only the first CT scan was included. Patients were excluded if they were aged younger than 18 years or had a history of muscular disease.

The Institutional Review Board approved the study (METc 2018/334). Research studies involving the retrospective review, collection, and analysis of patient records do not fall under the scope of the Dutch Act on Medical Scientific Research involving Human Beings; therefore, individual patient informed consent was not required. Data were stored and analyzed anonymously.

Patient demographics. Clinical data and other possible prognostic factors were extracted from the medical records, including age, sex, body mass index (BMI), smoking, diabetes mellitus (DM), hypertension, hypercholesterolemia, hyperhomocysteinemia, chronic obstructive pulmonary disease (COPD), coronary artery disease, malignancy, congestive heart failure, need for

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cohort study
- **Key Findings:** Among 686 patients with peripheral arterial occlusive disease, muscle depletion (sarcopenia and myosteatorsis) was independently associated with a poorer survival. When adjusted for other variables, myosteatorsis (hazard ratio, 2.09; 95% confidence interval, 1.46-2.99; $P < .001$) was a stronger predictor than sarcopenia (hazard ratio, 1.40; 95% confidence interval, 0.97-2.01; $P = .073$).
- **Take Home Message:** Muscle quality is more important than muscle quantity on survival of patients with peripheral arterial occlusive disease.

hemodialysis (renal failure), transient ischemic attack, ischemic stroke, type of intervention, CRP, disease classification (Fontaine stadia or acute limb ischemia), and survival.

Muscle imaging and morphometric measurements.

CT imaging was performed on a Siemens SOMATOM Definition (AS, Edge, Flash), Force, or Sensation (Siemens Medical, Erlangen, Germany) scanner. Slice thickness varied between 1 and 5 mm. All scans were performed with intravenous contrast in the arterial phase.

Cross-sectional muscle measurements were obtained at the level of the third lumbar vertebra on the slice where both transverse processes were shown.²¹ The measurements consisted of the musculus psoas major and abdominal wall, including erector spinae, quadratus lumborum, transversus abdominalis, obliquus internus, obliquus externus, and rectus abdominis.

In-house developed software (SarcoMeas 0.34; UMCG, Groningen, The Netherlands) was used to assess the skeletal muscle mass. This software allows for manual delineation of the area of interest with semiautomatic assessment of skeletal muscle area based on tissue attenuation. The thresholds used for defining skeletal muscle were from -29 Hounsfield units (HU) to +150 HU and for adipose tissue were from -190 HU to -30 HU (Fig 1).²² The computed skeletal muscle area was normalized to patient height to form the skeletal muscle index (SMI). The SMI is used as index for sarcopenia. The mean HU of these delineated muscle areas is used to quantify myosteatorsis.

All cross-sectional muscle values were determined by a single observer (I.V.). Interobserver and intraobserver coefficients were determined on 50 randomly selected scans that were analyzed by an experienced musculoskeletal radiologist (A.V.), as well as reanalyzed by the primary observer after 8 weeks. Excellent interobserver and

Fig 1. Cross-sectional muscle measurement at the level of the third lumbar vertebra. **A**, Nonmyosteototic and nonsarcopenic (male; skeletal muscle index [SMI], 54.4; mean Hounsfield unit [HU], 44.6). **B**, Myosteototic and nonsarcopenic (female; SMI, 42.4; mean HU, 15.2). **C**, Nonmyosteototic and sarcopenic (female; SMI, 23.0; mean HU, 37.5). **D**, Myosteototic and sarcopenic (male; SMI, 27.1; mean HU, 23.7).

intraobserver intraclass correlation coefficients were found, with values similar to other comparable software packages ([Supplementary Table](#), online only).²³

Treatment and follow-up. Treatment was chosen based on patient characteristics, patient preference, target lesion location, and, in most cases, after consulting a multidisciplinary vascular and endovascular treatment board, including vascular surgeons and interventional radiologists. All patients who underwent revascularization had an initial follow-up within 6 weeks of treatment. Additional follow-up was determined by the selected treatment. The national civil registry was consulted for definitive survival data. Patients who were alive on October 1, 2018, were marked as censored.

Statistic analyses. The Student *t*-test was used to assess differences between groups for continuous variables. All continuous variables were normally distributed. The χ^2 test or Fisher exact test was used for assessing associations between categorical variables, depending on the sample size (<5 for the Fisher exact test). Overall survival was analyzed using the Kaplan-Meier method with log-rank testing. Optimal stratification was used to acquire sex-specific cutoff points for sarcopenia and BMI-specific cutoff points for myosteotosis. Optimal stratification is a

technique, based on log-rank statistics, that has been used in previous studies to determine at which cutoff values the most significant difference would occur with regard to a binary or a time-to-event outcome, such as death.^{21,24-26}

The ascertained groups and potential prognostic factors, as detailed elsewhere in this article, were analyzed using a univariable Cox proportional hazards model. Variables that had fewer than 10 events (deaths) were subsequently excluded from the univariable and multivariable Cox models.²⁷ All values were checked for interaction and confounding. Variables that were associated with death at univariable analysis were included in the multivariable model. A forward likelihood ratio (LR) method was used for model fitting. This stepwise selection method bases the entry on the significance of the score statistic and tests removal based on the probability of an LR statistic, based on the maximum partial likelihood estimates. Analyses were performed using IBM SPSS Statistics 23.0.0.3 software (IBM, Armonk, NY). A *P* value of less than .05 was considered to be statistically significant.

RESULTS

The PACS query yielded 1173 scans of patients who were treated between January 1, 2005, and December 31, 2017, of which 686 were eligible for inclusion in the current

Fig 2. Workflow and reasons for exclusion. CT, Computed tomography; PACS, picture archiving and communications system.

study (Fig 2). The patient characteristics are reported in Table I. The mean follow-up was 3.1 ± 2.4 years, in which 183 deaths occurred. Kaplan-Meier survival curves are shown in Fig 3.

For sarcopenia, the calculated sex-specific cutoff values were $41.2 \text{ cm}^2/\text{m}^2$ for men and $31.5 \text{ cm}^2/\text{m}^2$ for women. Compared with nonsarcopenic patients, sarcopenic patients were older (70.0 ± 11.5 years vs 64.2 ± 10.5 years; $P < .001$), BMI was decreased ($23.5 \pm 4.9 \text{ kg}/\text{m}^2$ vs $26.5 \pm 4.7 \text{ kg}/\text{m}^2$; $P < .001$), and mortality was increased (42.1% vs 22.7% ; $P < .001$). Sarcopenic patients were also associated with an increased incidence of myosteatosis (65.7% vs 32.1% ; $P < .001$), malignancy (24.3% vs 13.5% ; $P = .002$), congestive heart failure (15.0% vs 7.9% ; $P = .01$), and the need for hemodialysis (8.6% vs 3.1% ; $P = .004$). In addition, sarcopenic patients more often had Fontaine 4 classification (44.9% vs 23.4% ; $P < .001$), whereas nonsarcopenic patients more often had Fontaine 2b classification (38.7% vs 19.1% ; $P < .001$). Overall survival was significantly worse for sarcopenic patients compared with nonsarcopenic patients ($P < .001$). Survival at 1, 3, and 5 years was 78%, 53%, and 47% for sarcopenic patients and 91%, 82%, and 75%, respectively, for nonsarcopenic patients (Fig 3).

For myosteatosis, the calculated BMI-specific cutoff values were 33.6 mean HU for BMI lower than $25 \text{ kg}/\text{m}^2$ and 25.8 mean HU for a BMI of $25 \text{ kg}/\text{m}^2$ or higher. Compared with nonmyosteatotic patients, myosteatotic patients were older (70.5 ± 9.8 years vs 62.1 ± 10.5 years; $P < .001$) and mortality was increased (41.9% vs 14.6% ;

$P < .001$). Other variables more prevalent in myosteatotic patients were sarcopenia (34.5% vs 11.5% ; $P < .001$), type 2 DM (34.5% vs 25.8% ; $P = .015$), hypertension (70.1% vs 62.3% ; $P = .022$), COPD (31.1% vs 20.3% ; $P = .001$), malignancy (21.3% vs 12.2% ; $P = .001$), congestive heart failure (12.7% vs 7.2% ; $P = .014$), and ischemic stroke (13.1% vs 6.4% ; $P = .003$). Myosteatotic patients were more often classified as Fontaine 4 (44.9% vs 17.3% ; $P < .001$) and nonmyosteatotic patients more as Fontaine 2a (16.6% vs 7.5% ; $P = .001$) and 2b (40.8% vs 24.8% ; $P < .001$). Similar to sarcopenia, overall survival was significantly worse for myosteatotic patients compared with nonmyosteatotic patients ($P < .001$). Survival at 1, 3, and 5 years was 79%, 58%, and 47% for myosteatotic patients and 95%, 88%, and 85%, respectively, for nonmyosteatotic patients (Fig 3).

Patients with sarcopenia but without myosteatosis had better survival than patients without sarcopenia but with myosteatosis (Fig 4). The 5-year survival rates were 81% and 55%, respectively. Patients who had both sarcopenia and myosteatosis had a 5-year survival rate of 28%, which was almost halved the rate for patients who had myosteatosis alone.

In the univariable model, as reported in Table II, sarcopenia (hazard ratio [HR], 2.82; 95% confidence interval [CI], 2.05-3.86; $P < .001$) and myosteatosis (HR, 4.13; 95% CI, 3.03-5.63; $P < .001$) were both significantly associated with overall survival. Other factors univariably associated with overall survival were age, smoking, type 2 DM, COPD, coronary artery disease, malignancy, congestive heart failure, hemodialysis, ischemic stroke, CRP, and disease classification. Subsequently, all of the previous variables were included in a multivariable model. Univariable significant variables excluded by the forward LR model fit were smoking ($P = .863$), type 2 DM ($P = .087$), COPD ($P = .431$), coronary artery disease ($P = .532$), and ischemic stroke ($P = .660$). After adjusting for covariates, myosteatosis (HR, 2.09; 95% CI, 1.46-2.99; $P < .001$) was still associated with overall survival, but sarcopenia (HR, 1.40; 95% CI, 0.97-2.01; $P = .073$) was not. Other independent associated factors were age ($P < .001$), malignancy ($P = .031$), congestive heart failure ($P < .001$), hemodialysis ($P < .001$), CRP ($P = .001$), and the disease classification ($P = .006$).

A subgroup analysis was conducted to investigate survival in patients who underwent surgical or endovascular intervention ($n = 547$). Table III reports the univariable and multivariable models. Sarcopenia and myosteatosis had a higher HR of 1.48 (95% CI, 0.99-2.23; $P = .058$) and 2.48 (95% CI, 1.64-3.74; $P < .001$), respectively, compared with the overall group.

DISCUSSION

This study shows that myosteatosis is an independent prognostic marker for overall survival in patients with PAOD, with mortality rates more than two-fold

Table I. Patient characteristics (N = 686)

	Sarcopenia			Myosteatorsis		
	No (n = 546)	Yes (n = 140)	P value	No (n = 419)	Yes (n = 267)	P value
Age, years	64.2 ± 10.5	70.0 ± 11.5	<.001^c	62.1 ± 10.5	70.5 ± 9.8	<.001^b
Sex			.005^a			.002^a
Male	315 (57.7)	99 (70.7)		272 (64.9)	142 (53.2)	
Female	231 (42.3)	41 (29.3)		147 (35.1)	125 (46.8)	
BMI, kg/m ²	26.5 ± 4.7	23.5 ± 4.9	<.001^c	25.9 ± 4.9	25.8 ± 4.9	.764 ^c
Death	124 (22.7)	59 (42.1)	<.001^a	61 (14.6)	112 (41.9)	<.001^a
SMI male cm ² /m ² (n = 414)	51.5 ± 7.0	36.4 ± 3.6	<.001^c	50.6 ± 8.2	42.6 ± 8.2	<.001^c
SMI female cm ² /m ² (n = 272)	40.4 ± 6.4	27.8 ± 2.9	<.001^c	39.8 ± 7.5	37.0 ± 7.3	.003^c
Mean HU BMI <25 (n = 327)	36.3 ± 7.5	30.1 ± 9.3	<.001^c	40.7 ± 5.0	27.1 ± 5.5	<.001^c
Mean HU BMI >25 (n = 359)	30.8 ± 8.5	22.0 ± 8.4	<.001^c	34.7 ± 6.0	19.7 ± 4.9	<.001^c
Sarcopenia	—	—	—	48 (11.5)	92 (34.5)	<.001^a
Myosteatorsis	175 (32.1)	92 (65.7)	<.001^a	—	—	—
Smoking	318 (58.2)	76 (54.3)	.398 ^a	264 (63.0)	130 (48.7)	<.001^a
DM type 1	11 (2.0)	1 (0.7)	.476 ^b	11 (2.6)	1 (0.4)	.034^b
DM type 2	163 (29.9)	37 (26.4)	.426 ^a	108 (25.8)	92 (34.5)	.015^a
Hypertension	365 (66.8)	85 (60.7)	.173 ^a	261 (62.3)	189 (70.1)	.022^a
Hypercholesterolemia	452 (82.8)	106 (75.7)	.055 ^a	349 (83.3)	209 (78.3)	.100 ^a
Hyperhomocysteinemia	3 (0.5)	1 (0.7)	.819 ^b	1 (0.2)	3 (1.1)	.138 ^b
COPD	126 (22.3)	42 (30.0)	.089 ^a	85 (20.3)	83 (31.1)	.001^a
Coronary artery disease	194 (35.5)	53 (37.9)	.609 ^a	139 (33.2)	108 (40.4)	.053 ^a
Malignancy	74 (13.5)	34 (24.3)	.002^a	51 (12.2)	57 (21.3)	.001^a
Congestive heart failure	43 (7.9)	21 (15.0)	.010^a	30 (7.2)	34 (12.7)	.014^a
Hemodialysis	17 (3.1)	12 (8.6)	.004^a	14 (3.3)	15 (5.6)	.148 ^a
TIA	28 (5.1)	8 (5.7)	.781 ^a	24 (5.7)	12 (4.5)	.480 ^a
Ischemic stroke	49 (9.0)	13 (9.3)	.909 ^a	27 (6.4)	35 (13.1)	.003^a
Type of intervention	—	—	.603 ^a	—	—	.423 ^a
Surgical	146 (26.7)	30 (21.4)	.199 ^a	111 (26.5)	65 (24.3)	.530 ^a
Endovascular	238 (43.6)	68 (48.6)	.290 ^a	188 (44.9)	118 (44.2)	.863 ^a
Hybrid	51 (9.3)	13 (9.3)	.984 ^a	33 (7.9)	31 (11.6)	.101 ^a
BMT	111 (20.3)	29 (20.7)	.920 ^a	87 (20.8)	53 (19.9)	.772 ^a
CRP, mg/dL			.030^a			<.001^a
<5	194 (35.5)	38 (27.1)	.061 ^a	160 (38.2)	72 (27.0)	.002^a
5-30	128 (23.4)	30 (21.4)	.613 ^a	90 (21.5)	68 (25.5)	.226 ^a
>30	65 (11.9)	29 (20.7)	<.001^a	35 (8.4)	59 (22.1)	<.001^a
Missing	159 (29.1)	43 (30.7)	.712 ^a	134 (32.0)	68 (25.5)	.068 ^a
Classification (n = 658)			<.001^a			<.001^a
Fontaine 2a	71 (13.6)	15 (11.0)	.466 ^a	67 (16.6)	19 (7.5)	.001^a
Fontaine 2b	202 (38.7)	26 (19.1)	<.001^a	165 (40.8)	63 (24.8)	<.001^a
Fontaine 3	100 (19.2)	27 (19.6)	.792 ^a	79 (19.6)	48 (18.9)	.773 ^a
Fontaine 4	123 (23.4)	61 (44.9)	<.001^a	70 (17.3)	114 (44.9)	<.001^a
Acute limb ischemia	26 (5.0)	7 (5.2)	.907 ^a	23 (5.7)	10 (3.9)	.298 ^a

BMI, Body mass index; BMT, best medical treatment; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HU, Hounsfield unit; SMI, skeletal muscle index; TIA, transient ischemic attack.

Values are mean ± standard deviation or number (%). Boldface entries indicate statistical significance.

^aχ² test.

^bFisher exact test.

^cStudent t-test.

Fig 3. Kaplan-Meier survival curves of patients with sarcopenia and myosteatosi (both log-rank $P < .001$). SE, Standard error

compared with nonmyosteatot patients. To our knowledge, this is the first time this relationship has been described. The effects of sarcopenia and myosteatosi on survival seem to enhance each other with a similar magnitude, as reported by Kays et al⁷ in patients who underwent abdominal aortic aneurysm repair. Interestingly, in the current study, sarcopenia was only borderline significant with regard to survival. Matsubara et al²⁰ did report that sarcopenia may be an individual prognostic marker in patients with critical limb ischemia. Their population was much smaller, however, and more important, their analysis did not include myosteatosi.²⁰ Although they are two independent entities, sarcopenia and myosteatosi have pathophysiologic similarities, making some confounding between the two inevitable. A study

done by Sugai et al²⁸ looked at the association between major adverse cardiovascular and limb events and psoas muscular area and mean HU in 327 patients with PAOD. They reported similar results compared with ours, with mean HU being a significant predictor of major adverse cardiovascular and limb events, whereas muscle area is not. The current study has enough power to justifiably claim that myosteatosi has a larger effect on survival than sarcopenia.

The Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL) randomized controlled trial compared bypass surgery vs angioplasty on overall outcome and amputation-free survival.²⁹ The study showed that patients who were randomized to undergo bypass surgery had superior clinical outcomes, but only if they lived

Fig 4. Kaplan-Meier curves of patients with or without different forms of muscle depletion (log rank $P \leq .001$). SE, Standard error.

more than 2 years. The current study showed that patients without sarcopenia and myosteatorsis did have a high survival rate, but that 50% of the patients with sarcopenia and myosteatorsis had died within 2 years, making it difficult to choose the best treatment option. Future studies should look into this group of patients to determine which treatment option will suit them the most, both for gain in quality of life and for cost effectiveness.

There is a strong correlation between type 2 DM and myosteatorsis, similar to previously published literature.^{30,31} The accumulation of certain bioactive lipids in skeletal muscle leads to insulin resistance in mice.¹⁸ This finding is particularly interesting because, together with smoking, type 2 DM is the largest associated risk factor for PAOD.³² Also, PAOD is more aggressive in patients with DM, with earlier involvement of large vessels. Owing to the sensory neuropathy, amputation rates are 5 to 10 times higher.³² Even without type 2 DM, insulin resistance increases the approximate risk for PAOD by 40% to 50%.³³ Thus, possible new therapies could be developed when there is a better understanding of the underlying mechanisms of the association between type 2 DM and myosteatorsis. For example, Benetti et al³⁴ reported promising results for the role of vitamin D on

insulin resistance and myosteatorsis in mice, showing that vitamin D reverted myosteatorsis and restored impaired muscle insulin signaling.

The European Working Group on Sarcopenia in Older People (EWGSOP) recommends using sex-specific cut-off points of two standard deviations below the mean reference value of healthy young adults for muscle mass.³⁵ The most used values are 7.26 kg/m² for men and 5.5 kg/m² for women attained by dual-energy x-ray absorptiometry. We did not use dual-energy x-ray absorptiometry and thus could not acquire these values. Martin et al²⁶ provided sex-specific cutoff points for SMI also using the cross-sectional muscle area at the level of the third lumbar vertebra using optimal stratification in (obese) cancer patients. However, because cutoff points provided by optimal stratification depend on several factors, including patient characteristics, cutoff values between PAOD and (obese) cancer patients are not comparable.²⁵ Van der Werf et al³⁶ reported cutoff values of 41.6 cm²/m² for men and 32.0 cm²/m² for women based on the fifth percentile in a healthy Dutch reference group of potential kidney donors.

We provided our own sex-specific cutoff values for patients with PAOD using optimal stratification. Our SMI values of 41.2 cm²/m² for men and 31.5 cm²/m² for women are closely related to those reported by van der Werf et al and thus seem applicable. The EWGSOP does not have any recommendations for quantifying myosteatorsis using mean HU. Because we were only interested in the accumulation of intramuscular and intermuscular fat, we decided to make BMI-specific cut-off points. Obviously, patients with larger areas of visceral adipose tissue will have a lower mean HU by default owing to the increase of partial volume effect. This means that, if the mean HU is not being corrected by BMI, patients with low areas of visceral adipose tissue will be underrepresented.

This study has some limitations. Owing to the retrospective nature of this study, it is prone to missing values. For one, accurate data on medication could not be retrospectively assessed. In accordance with local, as well as national, guidelines all patients were expected to have been prescribed antiplatelet medication and statins. However, there is a wide range in adherence to guideline-recommended therapies in patients with PAOD.³⁷ A local population-based study of 70,000 individuals living in the Northern region of The Netherlands showed moderate to poor adherence to statin therapy in (primary and secondary) prevention of cardiovascular disease, although PAOD was not individually included in this study.³⁸ Consequently, we were not able to correct for medication usage in our multivariable analysis, which is a potential major confounding factor as is known that antiplatelet therapy, statins, and angiotensin-converting enzyme inhibitors are all independently associated with an

Table II. Univariable and multivariable Cox proportional hazards model for overall survival in the whole population

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.06	1.05-1.08	<.001	1.04	1.02-1.06	<.001
Sex						
Male	Ref					
Female	1.23	0.92-1.65	.173			
BMI, kg/m ²	0.98	0.95-1.00	.164			
Sarcopenia	2.82	2.05-3.86	<.001	1.40	0.97-2.01	.073
Myosteatosi	4.13	3.03-5.63	<.001	2.09	1.46-2.99	<.001
Smoking	0.69	0.51-0.92	.011			
DM type 2	1.58	1.16-2.14	.004			
Hypertension	1.32	0.96-1.82	.092			
Hypercholesterolemia	0.77	0.54-1.09	.143			
COPD	1.47	1.07-2.00	.017			
Coronary artery disease	1.56	1.16-2.08	.003			
Malignancy	2.10	1.51-2.29	<.001	1.52	1.04-2.21	.031
Congestive heart failure	2.77	1.90-4.02	<.001	2.16	1.46-3.20	<.001
Hemodialysis	5.99	3.67-9.78	<.001	2.94	1.68-5.14	<.001
TIA	1.42	0.72-2.78	.312			
Ischemic stroke	1.75	1.13-2.70	.013			
Type of intervention						
Surgical	Ref					
Endovascular	0.98	0.68-1.40	.895			
Hybrid	1.44	0.84-2.47	.189			
BMT	1.25	0.84-1.88	.272			
CRP, mg/dL						
<5	Ref			Ref		
5-30	2.52	1.66-3.81	<.001	2.17	1.39-3.37	.001
>30	4.05	2.58-6.36	<.001	2.15	1.31-3.51	.002
Missing	1.30	0.85-2.00	.229	1.24	0.79-1.96	.370
Classification						
Fontaine 2a	Ref			Ref		
Fontaine 2b	0.98	0.54-1.78	.948	0.93	0.50-1.72	.816
Fontaine 3	2.17	1.18-3.99	.013	1.67	0.89-3.14	.112
Fontaine 4	3.87	2.21-6.78	<.001	1.87	1.02-3.44	.044
Acute limb ischemia	2.05	0.90-4.70	.089	2.46	1.06-5.72	.036

BMI, Body mass index; BMT, best medical treatment; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HR, hazard ratio; TIA, transient ischemic attack.
Boldface entries indicate statistical significance.

improved survival.³⁹ We could not include muscle strength or low physical performance, two criteria that, together with low muscle mass, are defined as sarcopenia according to the EWGSOP.³⁵ Consequently, sarcopenia had to be defined by low muscle mass alone. Of the included variables, CRP had a relatively high number of missing values. To still be able to investigate the variable in the multivariable Cox proportional hazards model, the categorical subvariable of "missing value" was added. Because this variable is overall insignificant and seems to be divided

proportionally, we believe the potential bias is negligible. This was a single-center study with predominantly white patients, and translation of the results to other ethnicities should be done with caution.

Results presented in this study provide more topics for future research. Sarcopenia is associated with age, sex, malnutrition, disuse, cachexia, and (low-grade) inflammation.⁴⁰ Similarly, myosteatosi is associated with age, glucocorticoid treatment, disuse, sex steroid deficiency, and leptin deficiency.¹⁷ The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)

Table III. Univariable and multivariable Cox proportional hazards model for overall survival for surgically or endovascularly intervened patients

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.06	1.04-1.07	<.001	1.034	1.02-1.05	<.001
Sex						
Male	Ref					
Female	1.22	0.87-1.70	.253			
BMI, kg/m ²	0.98	0.95-1.02	.357			
Sarcopenia	3.04	2.12-4.36	<.001	1.483	0.99-2.23	.058
Myosteatosis	4.49	3.13-6.44	<.001	2.476	1.64-3.74	<.001
Smoking	0.67	0.48-0.93	.017			
DM type 2	1.50	1.06-2.12	.023			
Hypertension	1.29	0.90-1.86	.167			
Hypercholesterolemia	0.79	0.53-1.18	.242			
COPD	1.56	1.10-2.22	.012			
Coronary artery disease	1.56	1.12-2.17	.009			
Malignancy	1.92	1.31-2.82	.001			
Congestive heart failure	2.81	1.86-4.23	<.001	2.402	1.57-3.69	<.001
Hemodialysis	5.65	3.31-9.67	<.001	3.401	1.92-6.04	<.001
TIA	1.01	0.41-2.47	.988			
Ischemic stroke	1.44	0.81-2.55	.212			
Type of intervention						
Surgical	Ref					
Endovascular	0.97	0.67-1.39	.852			
Hybrid	1.43	0.83-2.46	.198			
CRP, mg/dL						
<5	Ref			Ref		
5-30	2.99	1.87-4.77	<.001	2.332	1.43-3.80	.001
>30	4.11	2.47-6.86	<.001	1.847	1.06-3.21	.010
Missing	1.47	0.88-2.45	.140	1.279	0.75-2.17	.362
Classification						
Fontaine 2a	Ref			Ref		
Fontaine 2b	1.06	0.46-2.47	.885	1.033	0.44-2.42	.941
Fontaine 3	2.61	1.14-5.99	.024	1.879	0.80-4.39	.145
Fontaine 4	4.81	2.19-10.5	<.001	2.278	1.01-5.16	.048
Acute limb ischemia	2.84	1.05-7.63	.039	3.423	1.26-9.32	.016

BMI, Body mass index; BMT, best medical treatment; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HR, hazard ratio; TIA, transient ischemic attack.
Boldface entries indicate statistical significance.

currently only recommends treadmill or track walking exercises in patients with intermittent claudication.³² Owing to the multifactorial nature of sarcopenia and myosteatosis, it is uncertain whether these patients will benefit from treadmill or track walking exercises alone. Further research is required to determine whether these patients may benefit from standard care combined with a multimodal therapy aimed at preventing or limiting the development of muscle depletion, for example, consisting of supervised physical therapy or home-based self-assisted exercise, nutritional supplementation in

case of macronutrient deficiency, and anti-inflammatory medication, comparable with the ongoing Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia (MENAC) trial in patients with advanced cancer.⁴¹

CONCLUSIONS

Muscle depletion is independently associated with a poorer overall survival in patients with PAOD. Myosteatosis is a stronger predictor than sarcopenia, which

indicates that quality is more important than quantity. Results should be interpreted with caution owing to missing data on medication usage.

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AUTHOR CONTRIBUTIONS

Conception and design: IV, SL, RD, CZ, JV, AV, RB

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Supplementary Table (online only). Interobserver and intraobserver agreement

	Intraclass correlation coefficient	
	Skeletal muscle index	Mean HU
Interobserver	0.998 (95% CI, 0.997-0.999)	1.000 (95% CI, 0.999-1.000)
Intraobserver	0.999 (95% CI, 0.998-0.999)	1.000 (95% CI, 0.999-1.000)
<i>CI</i> , Confidence interval; <i>HU</i> , Hounsfield units.		