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Original Article / *Özgün Makale*

Impact of sarcopenia in aortoiliac occlusive disease in Mediterranean population

Akdeniz popülasyonunda aortoiliyak tıkayıcı hastalıkta sarkopeninin etkisi

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ABSTRACT

Background: This study aims to validate the psoas muscle area and psoas muscle density as morphometric predictors in cardiovascular and cerebrovascular endpoints in patients with extensive aortoiliac peripheral arterial disease.

Methods: A total of 57 patients (55 males, 2 females; mean age 60±8.2 years; range, 35 to 83 years) with Trans-Atlantic Inter-Society Consensus type D lesions who underwent revascularization at two Portuguese tertiary hospitals between January 2013 and July 2019 were retrospectively analyzed. The patients with a recent (<6 months) computed tomography scan prior to the revascularization procedure were included in the study. Both centers offered to their patients open and endovascular repair of aortoiliac peripheral arterial disease. Major adverse cardiovascular and cerebrovascular events and major adverse limb events were evaluated.

Results: The median follow-up was 20 months. The mean survival rate was 93±3.4% at 30 days and 62.7±8.6% at 48 months. The discriminative thresholds found in this population were 2,175.8 mm^2 for total psoas area and 51.75 Hounsfield unit for psoas muscle density. There was a statistically significant difference in the one-year survival rate (p=0.003 and p=0.291, respectively) and major adverse cardiovascular and cerebrovascular events (p=0.005 and p=0.206, respectively) for total psoas area compared to psoas muscle density.

Conclusion: Total psoas area shows a prognostic value for survival and major adverse cardiovascular and cerebrovascular events in this patient population.

Keywords: Aortoiliac arterial occlusive disease, major adverse cardiovascular and cerebrovascular event, major adverse limb event, sarcopenia.

ÖZ

Amaç: Bu çalışmada yaygın aortoiliyak perifer arter hastalığı olan hastalarda kardiyovasküler ve serebrovasküler sonlanım noktalarında morfometrik öngördürücüler olarak psoas kas alanı ve psoas kas dansitesinin doğrulanması amaçlandı.

Çalışma planı: Ocak 2013 - Temmuz 2019 tarihleri arasında Portekiz merkezli iki üçüncü basamak hastanede revaskülarizasyon yapılan Transatlantik Toplulukları Fikir Birliği tip D lezyonlu toplam 57 hasta (55 erkek, 2 kadın; ort. yaş 60±8.2 yıl; dağılım, 35-83 yıl) retrospektif olarak incelendi. Çalışmaya revaskülarizasyon işleminden önce yakın zamanda (<6 ay) bilgisayarlı tomografi sonucu olan hastalar alındı. Her iki merkezde de, hastalara aortoiliyak periferik arter hastalığının açık ve endovasküler tamiri önerildi. Majör advers kardiyovasküler ve serebrovasküler olaylar ve majör advers ekstremite olayları değerlendirildi.

Bulgular: Medyan takip süresi 20 ay idi. Ortalama sağkalım oranı 30. günde %93±3.4 ve 48. ayda %62.7±8.6 idi. Bu popülasyonda tespit edilen ayırıcı eşik değerler, total psoas alanı için 2,175.8 mm^2 ve psoas kas dansitesi için 51.75 Hounsfield unit idi. Bir yıllık sağkalım oranı (sırasıyla p=0.003 ve p=0.291) ve majör advers kardiyovasküler ve serebrovasküler olaylar (sırasıyla p=0.005 ve p=0.206) açısından, psoas kas dansitesine kıyasla, total psoas alanı için istatistiksel olarak anlamlı bir fark izlendi.

Sonuç: Total psoas alanı, bu hasta popülasyonunda sağkalım ve majör advers kardiyovasküler ve serebrovasküler olaylar için prognostik değere sahiptir.

Anahtar sözcükler: Aortoiliyak arteriyel tıkayıcı hastalık, majör advers kardiyovasküler ve serebrovasküler olay, majör advers ekstremite olayı, sarkopeni.

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The aortoiliac (AI) sector represents one of the major decisional and therapeutic challenges of the peripheral arterial disease (PAD). Since several options are available for AI-PAD treatment currently, contemporary therapeutic decision considers several factors further than anatomic ones. Frailty and sarcopenia are risk predictors emerging in several areas including vascular surgery which are frequent conditions among vascular patients.[1,2]

Sarcopenia is a progressive and generalized skeletal muscle disorder involving the accelerated loss of muscle mass and function which is associated with increased adverse outcomes including falls, functional decline, frailty, and mortality.[3] Despite commonly being regarded as an age-related process, it is very frequent as a life-threatening pathology.[3] The psoas muscle area and its density represent an analytic morphometry and an effortless way to define sarcopenia. Low total psoas area (TPA) has been associated with major complications and mortality in vascular, trauma, cancer, and transplant surgery.[4-12] Low psoas muscle density (PMD) is also described as a predictor of mortality in cardiac,[13] cancer[14-17] and trauma surgery,[18] as well as in other pathologies.[19,20]

Identifying patients at risk is an important step in the decision process of whether a patient would benefit from an intervention or even if there is any sarcopenic reversibility and preoperative optimization that can be provided. However, the ongoing research and subsequent clinical utility is being challenged by different definitions and the still undisclosed optimal frailty tool to use in vascular surgery and its subpopulations. In the present study, we aimed to validate these morphometric predictors in survival and in cardiovascular and cerebrovascular endpoints on extensive AI-PAD patients.

PATIENTS AND METHODS

A cohort of consecutive patients undergoing revascularization of AI-PAD with lesions classified as the Transatlantic Inter-Society Consensus type D lesions (TASC D)[21] were retrospectively included between January 2013 and July 2019 at two Portuguese centers, a referral center and a peripheral hospital. The main inclusion criterion was as follows: having a recent (<6 months) computed tomography (CT) before the revascularization procedure. Both centers offered to their patients open and endovascular repair and the choice was left to surgeon-patient preference and experience. Patients with aneurysmal disease or other etiology rather than atherosclerosis were excluded. Finally, a total of 57 patients (55 males, 2 females; mean age 60±8.2 years; range, 35 to 83 years) with TASC D AI-PAD who underwent revascularization were included. A written informed consent was obtained from each patient. The study protocol was approved by the local Ethics Committee (Comissão ética para a Saúde - CHUSJ/FMUP; Protocol 246-18). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data was obtained by an ongoing vascular registry and from detailed review of the patient's clinical records. All data regarding patients and procedure were defined according to the Society for Vascular Surgery reporting standards for lower extremity ischemic PAD.[22]

Definitions

A major adverse cardiovascular and cerebrovascular event (MACCE) was defined as a composite outcome of stroke, myocardial infarction, coronary reintervention, acute heart failure, and all-cause mortality. A major adverse limb event (MALE) was defined as loss of primary patency (interventions for assisted primary patency, secondary patency or loss of patency without reintervention), and major amputation.

The TPA and PMD were assessed on CT using the program Sectra 7® (Sectra Medical Systems AB, Linköping, Sweden). For measurement purposes, a single cross-sectional slice at the upper level of 4th lumbar vertebrae was used. The borders of the left and right psoas muscle were hand-marked using the region of interest tool in mm^2 and the TPA constituted the sum of both areas.[9] The PMD was calculated by the average of bilateral Hounsfield Units (HU) of the psoas muscle cross-sectional area. All measurements were obtained by the average of the measurements by two independent trained researchers using standard graphics tools available in Sectra workstation IDS7®. The protocol was strictly followed and both researchers were blinded to previous measurements and clinical data.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. Baseline characteristics were compared using the chi-square test, Student's t-test, and Mann-Whitney U test, where appropriate. Outcome variables were expressed in Kaplan-Meier curves. Differences in baseline features were tested upon outcomes variables using

log rank test. Assessment of cut-off values for TPA and PMD was conducted using the receiver operating characteristic (ROC) curve analysis and Youden's J statistic. Accordingly, the sensitivity and specificity of the test were also calculated. The area under the ROC curve (AUC) is defined with its value, 95% confidence interval (CI), and p value. Using the prespecified thresholds, both morphometric variables were transformed in categoric variables and longitudinal statistics was applied. A *p* value of <0.05 was considered statistically significant.

The necessary sample for a two-sided test for survival was calculated resorting to WinPepi® version 11.65 software (PEPI-for-Windows, Brixton Health, London, UK) aiming for a statistical power (β) of 80% and an $\alpha<0.05$.[23] The described survival rate at one-year follow-up is above 90%[24] for an event rate difference of 30% between the groups with an estimated sample size of 52 patients.[25]

RESULTS

The most prevalent cardiovascular risk factors were smoking (current or former smoker) (96.0%), arterial hypertension (64.9%), and dyslipidemia (64.9%). Thirty-five (61.4%) patients presented with limb threatening ischemia. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

Open surgery was the preferred method of intervention with 32 (56.1%) open surgeries versus 25 (43.9%) patients who underwent endovascular treatment. Technical success in the first procedure was achieved in 51 (89.5%) patients. In five patients with a failed endo-first approach, a later open surgery (aortobifemoral) was performed, yielding a total of 56 (98.2%) successfully revascularizations. The mean ankle-brachial index value increased from 0.30±0.11 to 0.77±0.18 after successful treatment.

The mean PMA was 2,447±491.4 (range, 1,285 to 3,459) mm^2, while the mean PMD was 50.2±11.23 (range, 28.5 to 87.5) HU.

The median follow-up was 20 months (95% CI, 0-42.6). The mean survival was 93±3.4% at 30 days, 78±6.4% at one year, and 62.7±8.6% at 48 months. At the end of follow-up, 16 patients died.

According to the ROC curve analysis for one-year mortality, TPA performed better compared to PMD, obtaining an AUC of 0.721 (95% CI, 0.477-0.966; Figure 1), while PMD had an AUC of 0.596 (95% CI, 0.405-0.788; Figure 1). The best discriminative threshold was obtained based on the ROC curves and Youden index. The threshold was set at 2,175.8 mm^2 with 70% sensitivity and 89.3% specificity for TPA and at 51.75 HU with 80% sensitivity and 50% specificity for PMD.

Using the prespecified thresholds, both morphometric variables were transformed in categoric variables and longitudinal analysis was applied. A statistically significant difference for TPA (p=0.003; Figure 2) was demonstrated, but not for PMD (p=0.291; Figure 2). The mean TPA below threshold had one-year survival of 35.5±15.6% and above threshold of 92.9±4.0% (p=0.003) (Figure 2). The mean PMD below threshold had one-year survival of 68.9±9.5% and above threshold of 89.3±7.2% (p=0.08) (Figure 2).

Table 1. Baseline demographic and clinical characteristics of patients (n=57)

Variables	n	%	Mean±SD
Demographics			
Age (year)			60±8.2
Sex			
Male	55	96	
Cardiovascular risk factors			
Hypertension	37	64.9	
Smoking	55	96	
Creatinine (>1.5 mg/dL)	7	12.3	
Diabetes mellitus	19	33.3	
Dyslipidemia	37	64.9	
Comorbidities			
Coronary arterial disease	14	24.6	
Chronic heart failure	4	7	
COPD	5	8.8	
Functional status			
Dependent	0	0	
Partially dependent	4	7	
Independent	53	93	
ASA			2.6±0.59
Limb status			
Rutherford			
3	17	29.8	
4	27	47.4	
5	9	15.8	
6	3	5.3	
Limb threatening ischemia	35	61.4	
Intervention			
Open	32	56.1	
Endo	25	43.9	

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists Classification.

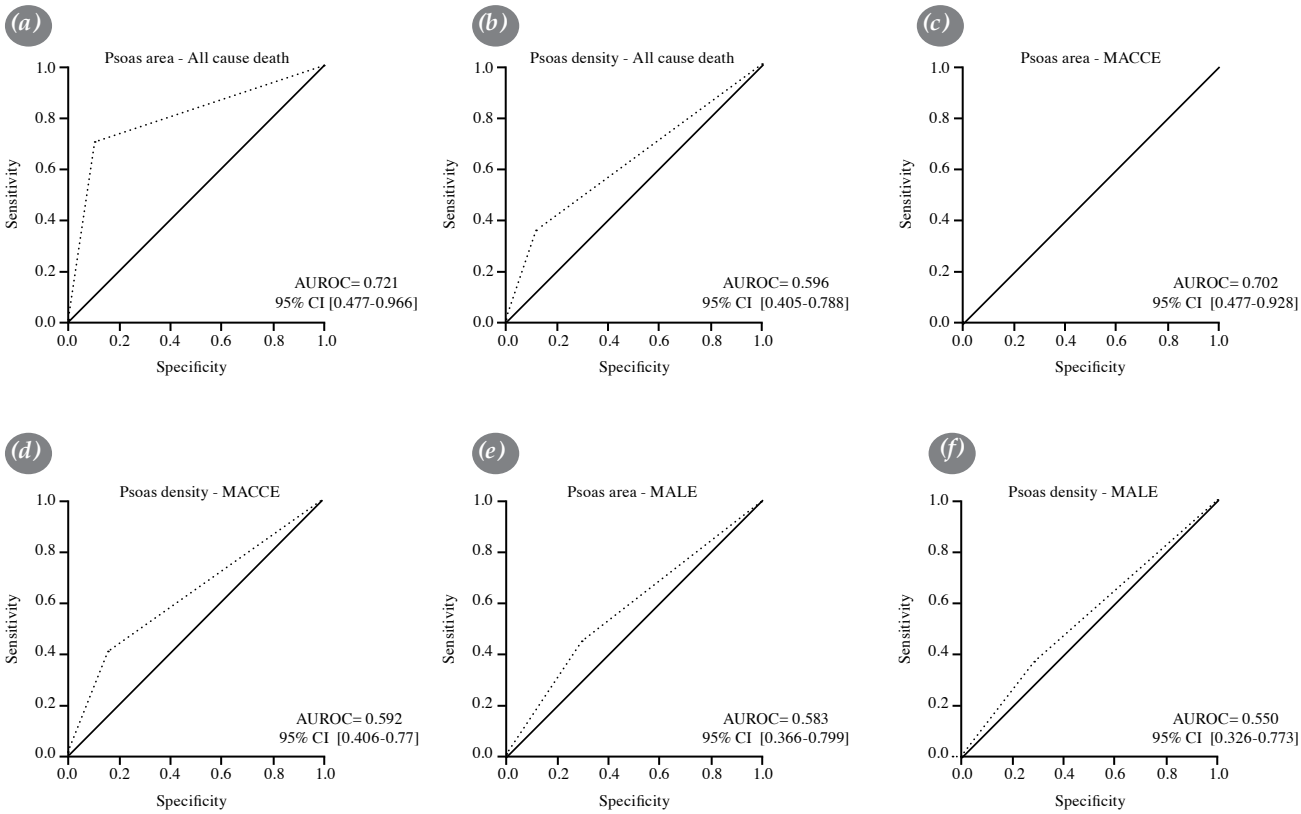


Figure 1. (a) ROC curves for one-year mortality for TPA. **(b)** ROC curves for one-year mortality for PMD. **(c)** ROC curves for MACCE for TPA. **(d)** ROC curves for MACCE for PMD. **(e)** ROC curves for MALE for TPA. **(f)** ROC curves for MALE for PMD.

AUROC: Area Under the Receiver Operating Characteristics; CI: Confidence interval; MACCE: Major adverse cardiovascular and cerebrovascular event; MALE: Major Adverse Limb Event; ROC: Receiver operating characteristic; TPA: Total Psoas Area; PMD: Psoas Muscle Density; MACE: Major Adverse Cardiovascular Event.

During follow-up, 19 patients developed a MACCE. According to the ROC curve analysis for one-year MACCE, TPA was superior to PMD as a morphometric predictor, obtaining an AUC of 0.702 (95% CI, 0.477-0.928; p=0.045), while the PMD had an AUC of 0.592 (95% CI, 0.406-0.77; p=0.360) (Figure 1).

The mean TPA cut-off value was once again 2,175 mm^2 with 67% sensitivity and 89.3% specificity. For the PMD, the mean threshold was 51.7 HU with 75% sensitivity and 53.6% specificity. A statistically significant difference for TPA (p=0.005) was demonstrated, but not for PMD (p=0.206) (Figure 2).

The mean TPA below threshold had an 18-month survival of 32.6±14.7% and above threshold of 90.5±4.5%. The mean PMD below threshold had an 18-month survival of 67.1±9.4% and above threshold of 85.6±7.8%.

Furthermore, there were 14 MALE events in the study. The ROC curves for one-year MALE showed a poor prediction ability for both TPA (AUC of 0.583 [95% CI, 0.366-0.799]) (Figure 1) and PMD (AUC of 0.55 [95% CI, 0.326-0.773]) (Figure 1).

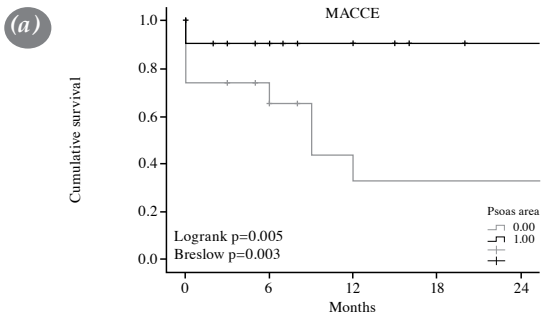
Using the MALE thresholds, ROC analysis was also performed. For TPA, 2,449 mm^2 demonstrated the best performance with 63.9% sensitivity and 54.5% specificity, while 45.5 HU was the best cut off point with 54.5% sensitivity and 63.6% specificity for PMD.

Using the Kaplan-Meier method with the categorical variables obtained by the ROC curve analysis, no statistically significant difference was observed either for TPA (p=0.516) or PMD (p=0.313) (Figure 2).

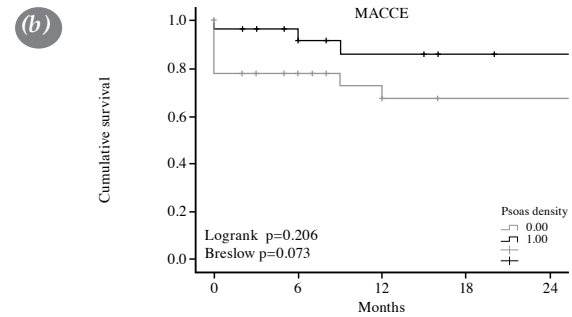
Neither TPA (p=0.557 and p=0.734, respectively) nor PMD (p=0.331 and p=0.447, respectively) were associated with the length of stay in ward or intensive care unit.

DISCUSSION

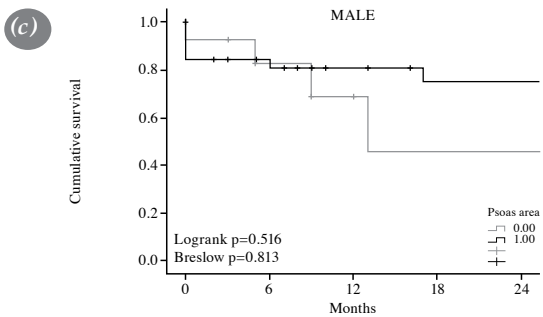
In this study, TPA and PMD were analyzed for the advantage of being less time-consuming and more pragmatic for clinical application. Despite being



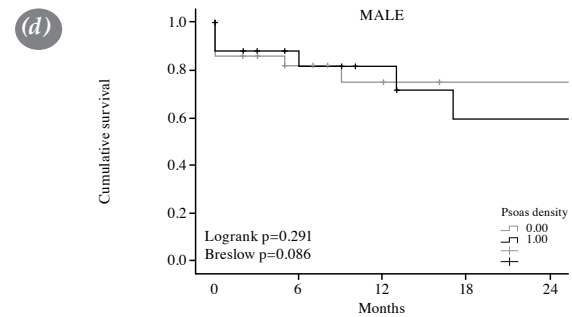
Time (months)		1	6	12	18
Total psoas area <2,175 mm²	Survival (%)	73.3	65.2	32.6	32.6
	SE (%)	11.4	12.7	14.7	14.7
	Under FU (n)	11	7	3	3
	Cumulative events (n)	4	5	8	8
Total psoas area >2,175 mm²	Survival (%)	90.5	90.5	90.5	90.5
	SE (%)	4.5	4.5	4.5	4.5
	Under FU (n)	37	37	37	37
	Cumulative events (n)	4	4	4	4



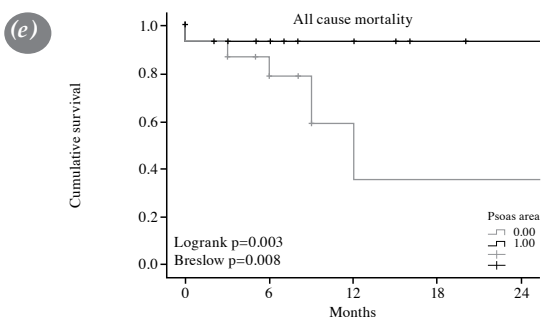
Time (months)		1	6	12	18
Psoas muscle density <51.7 HU	Survival (%)	77.4	77.4	67.1	67.1
	SE (%)	7.5	7.5	9.4	9.4
	Under FU (n)	23	18	12	11
	Cumulative events (n)	7	7	9	9
Psoas muscle density >51.7 HU	Survival (%)	96.2	91.3	85.6	85.6
	SE (%)	3.8	5.9	7.8	7.8
	Under FU (n)	25	19	15	11
	Cumulative events (n)	1	2	3	3



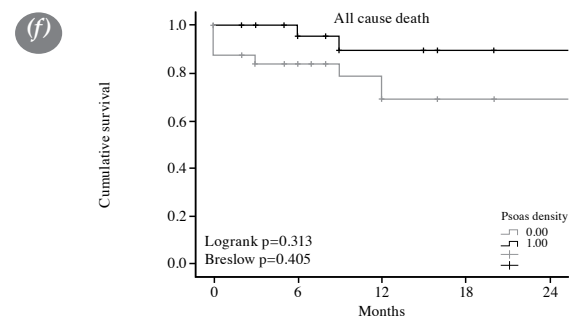
Time (months)		1	6	12	18
Total psoas area <2,175 mm²	Survival (%)	89.3	78.4	71.3	62.4
	SE (%)	5.8	8.8	10.5	12.4
	Under FU (n)	23	13	8	7
	Cumulative events (n)	3	5	6	7
Total psoas area >2,175 mm²	Survival (%)	84	84	84	74.7
	SE (%)	7.3	7.3	7.3	11
	Under FU (n)	20	14	11	8
	Cumulative events (n)	4	4	4	5



Time (months)		1	6	12	18
Psoas Muscle density <51.7 HU	Survival (%)	83.3	76.4	67.9	67.9
	SE (%)	8.8	10.4	12.3	12.3
	Under FU (n)	14	9	8	7
	Cumulative events (n)	3	4	5	5
Psoas Muscle density >51.7 HU	Survival (%)	88.6	84.1	84.1	68
	SE (%)	5.4	6.7	6.7	11.6
	Under FU (n)	29	18	11	8
	Cumulative events (n)	4	5	5	7



Time (months)		1	6	12
Total psoas area < 2,175 mm²	Survival (%)	93.3	78.8	35.5
	SE (%)	6.4	11.0	15.6
	Under FU (n)	14	10	3
	Cumulative events (n)	1	3	7
Total psoas area >2,175 mm²	Survival (%)	92.9	92.9	92.9
	SE (%)	4.0	4.0	4.0
	Under FU (n)	38	28	24
	Cumulative events (n)	3	3	3



Time (months)		1	6	12	18
Psoas muscle density <51.7 HU	Survival (%)	87.1	83.6	68.9	68.9
	SE (%)	6.0	6.7	9.5	9.5
	Under FU (n)	36	21	13	12
	Cumulative events (n)	4	5	8	8
Psoas muscle density >51.7 HU	Survival (%)	95.2	95.2	89.3	89.3
	SE (%)	4.6	4.6	7.2	7.2
	Under FU (n)	25	17	14	11
	Cumulative events (n)	0	1	2	2

Figure 2. Survival plots. 12- and 18-month follow-up Kaplan Meier survival plots for different clinical events post- Aortoiliac revascularization, for Total Psoas Area and Psoas Muscle Density. **(a)** MACCE for total Psoas Area; **(b)** MACCE for Psoas Muscle Density; **(c)** MALE for total Psoas Area; **(d)** MALE for Psoas Muscle Density; **(e)** All-cause Death for Psoas Muscle Area; **(f)** All-cause Death for Psoas Muscle Density.
MACCE: Major Adverse Cardiovascular and Cerebrovascular Event; MALE: Major Adverse Limb Event.

important prognostic markers, the literature presents a gap concerning the threshold of morphometric parameters to define sarcopenia consistently or the risk patients. In this study, a TPA of <2,175 mm^2 was validated as a diagnostic cut-off value for this Mediterranean population, mainly composed of male patients, demonstrating prognostic value for survival and MACCE concerning patients with AI TASC D lesions.

While TPA reflects frailty and a propensity toward lower functional status, PMD reflects frailty with a close relationship to patient nutritional status.[26] In addition, higher densities are related with lower inflammatory markers.[27] Literature about PMD is scarce compared to TPA, inclusively in vascular surgery. A lack of universal thresholds for defining low PMA and PMD and substantial differences in the measurements across the included studies are the main challenges to PMA and PMD use as mentioned previously.

Chowdhury et al.[28] investigated different morphometric predictors including TPA and PMD in older vascular surgery patients and concluded that TPA was significantly associated with readmission-free survival, but no statistically significant result concerning PMD was obtained. Of note, TPA is validated for abdominal aortic aneurysms[5,29] and, with growing literature, for PAD.[1,9] Currently, it is considered a frailty tool with moderate quality and capable of predicting long-term survival after major vascular surgery.[30] These findings are consistent with the previous evidence available in other surgical fields, indicating a higher risk of mortality for lower TPA.[6,11,14,16]

In our study, neither TPA nor PMD revealed statistical significance for MALE (p=0.516 and p=0.313, respectively). In previous studies, PMD also failed to achieve statistical significance with PAD severity or amputation-free survival.

Sarcopenia cut-off values are still to be universally defined, while it is also unclear whether these values can be applied throughout different ethnicities and cultures.[31] Even sarcopenia itself has been measured and defined with different criteria in the literature and, therefore, the European Working Group on Sarcopenia in Older People (EWGSOP) attempted to establish more specific criteria and a staging scheme, proposing the diagnosis of sarcopenia in older people to be set in the presence of low muscle mass plus poor physical performance or muscle strength, the last ones usually defined by gait speed and hand grip strength, respectively.[32] Nonetheless, all three domains have several methods to be measured, although universality is lacking. Concerning these variables, gait speed has been shown to be associated with objective and subjective measurements of physical function in patients with symptomatic PAD.[33] However, in elderly patients (≥60 years old) with cardiovascular disease, it is an independent predictor of all-cause mortality.[34] In regard to hand grip, besides being a useful tool to identify frailty among vascular patients,[1] it revealed an association with all-cause mortality among PAD patients.[35] More interestingly, each 10-cm^2 increase of the psoas area has been linked to a 5.7-kg increase in hand grip strength in a multivariable model adjusting for age and sex (p<0.0001).[1]

Several clinical applications are evident from the results of this study. First, TPA was validated as survival and MACCE predictor concerning patients with AI TASC D lesions in a Mediterranean population. Sarcopenia does not imply non-operability, but rather tailored planning for this group with careful perioperative interventions. Therefore, frailty should be regarded as a therapeutic target with perioperative management and close monitoring and follow-up. To slowdown frailty and sarcopenic progression, multiple interventions are advised such as nutritional intervention, physical rehabilitation and planned discharge with home assistance, despite still poor supporting evidence.[36,37] Second, these predictors, mainly TPA, present the advantage of being ready collectable alongside with the increase number of CTAs as part of medical investigation. It is possible that they become independently or part of a still-to-define frailty score, adding not only prognostic, but also possible therapeutic monitoring.[38,39]

There are some limitations to the present study. It is a retrospective study conducted in only two institutions. Selection bias may have been present, since the frailest patients might have been deemed non-eligible for revascularization. Another major limitation arising from selection bias is the fact that, in this cohort, patients with iliac stent had smaller areas, leading to an empiric selection of sarcopenic patients to endovascular treatment. External validity is limited, due to the specificity of this subset of patients. Although efforts were made to minimize missing data, 44% of patients were excluded due to missing CT scans, largely from peripheral hospitals which referred the patients to the tertiary setting centers that were not uploaded to the electronic system. Furthermore, it is possible that different cut-off values regarding sex can be applied,[40] although this was not addressed in this

study, since the sample is manly composed of males. Also, in this study, we were unable to assess other dimensions of sarcopenia such as muscle strength and physical performance to add a prognostic value to the muscle mass. Nonetheless, the main strength of this study is that it provides a useful evaluation of growing literature on sarcopenia as a predictor of outcomes in vascular surgery.

In conclusion, our study results showed that total psoas area had a prognostic value for survival and major adverse cardiovascular and cerebrovascular events for patients with aortoiliac Trans-Atlantic Inter-Society Consensus type D lesions, while allowing a rapid straightforward assessment with reproducibility. However, neither total psoas area nor psoas muscle density reached statistical significance for major adverse limb events. Based on these results, we believe that this study contributes to the growing literature on sarcopenia as a predictor of outcomes in vascular surgery and should be seen as a stimulus for further researches to achieve the full potential of these markers in the guidance for clinical decision, patient counseling on operative risk, and management of perioperative interventions by multidisciplinary teams to improve outcomes.

Declaration of conflicting interests

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