

Psoas muscle area index as a predictor of major adverse cardiovascular and limb events in patients with infrarenal aortic occlusions

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ABSTRACT

Objectives: In this study, we aimed to investigate whether the total psoas muscle area index (TPAI) was a predictive factor of major adverse cardiovascular and limb events (MACLEs) in patients with infrarenal aortic occlusion (IAO).

Patients and methods: Between January 2011 and December 2019, a total of 72 patients with IAO (56 males, 16 females; mean age: 58.8±7.0 years; range, 46 to 75 years) were retrospectively reviewed. The TPAI was measured by dividing total psoas muscle area to squared patient height. The primary outcome measure was MACLEs. To estimate the effect of TPAI and clinical factors on prognosis, hazard ratios (HRs) with 95% confidence intervals (CIs) were used.

Results: The median follow-up was 32 months (interquartile range 15.9-44). The patients were divided into two groups as MACLE-positive (n=30, 41.6%) and MACLE-negative (n=42, 58.4%). The mean TPAI for MACLE-negative and MACLE-positive patients was 615±171 mm²/m² and 521±129 mm²/m², respectively (p=0.036). The presence of increased TPAI values was associated with the decreased MACLE rate (HR: 0.19; 95% CI: 0.09-0.42; p=0.008).

Conclusion: Our study results indicate that the TPAI measured by computed tomography scans is an independent prognostic factor for MACLEs in patients with chronic IAO.

Keywords: Frailty, infrarenal aortic occlusion, major adverse cardiovascular and limb events, peripheral arterial disease, psoas muscle area, survival.

The obstructive disease of the infrarenal aorta may affect both the aortic bifurcation and the common iliac arteries to varying degrees.^[1] Infrarenal aortic occlusion (IAO) accounts for 3 to 8.5% of patients with existing aortoiliac occlusive disease.^[2] The prognosis of IAO patients is poor, and the risk of cardiovascular and cerebrovascular events is high.^[3,4] Thus, patients with IAO undergo major vascular surgery or complex endovascular procedures and have an increased risk of premature mortality.

Although most of the patients have risk factors for increased mortality, including smoking, diabetes and hypertension, it has been shown that this increased risk is beyond what is attributed to these risk factors.^[5] Analytic morphometry, initially used to define the decrement of lean muscle mass, including psoas muscles associated with ageing, is currently a documented property of systemic circumstances, including cachexia, cancer, inflammatory states, and chronic malnutrition.^[6] The psoas muscle area (PMA)

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is relatively simple to diagnose by pre-procedural computed tomography (CT) imaging. Additionally, PMA has been recently documented as a prognostic factor in lower limb revascularization and aortic aneurysmal diseases.^[7,8] Therefore, if PMA could predict the prognosis of IAO patients, it might assist clinicians to choose the most convenient follow-up treatment plan. To the best of our knowledge, however, no study has explicitly investigated PMA in patients diagnosed with IAO, yet. In the present study, we aimed to investigate the effect of PMA on major adverse cardiovascular and limb events (MACLEs) of patients undergoing surgical or endovascular treatment for IAO.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital between January 2011 and June 2019. A total of 72 patients (56 males, 16 females; mean age: 58.8 ± 7.0 years; range, 46 to 75 years) with chronic primary occlusions of the infrarenal abdominal aorta with the involvement of aortic bifurcation and iliac arteries were included in the study. Diagnosis was made by CT angiography and/or conventional peripheral angiography. The patients were included, irrespective of whether they underwent an endovascular treatment procedure or open surgery. Exclusion criteria were as follows: acute coronary syndrome (ACS) ≤ 3 months before the IAO diagnosis ($n=1$), malignant disease ($n=1$), prior lower extremity amputation ($n=2$), previous cerebral infarction or paraplegia resulting in lower extremity paresis ($n=3$), acute IAO ($n=3$), IAO without extension into aortic bifurcation ($n=6$), in-hospital mortality ($n=2$), and follow-up duration less than 12 months ($n=3$). The indication and selection of whether the endovascular revascularization or open surgery was suitable for each patient were decided at the discretion of a group of vascular specialists, including cardiologists, vascular surgeons, and radiologists. All patients were informed about the diagnostic and therapeutic procedures and a written informed consent was obtained. The study protocol was approved by the Kartal Koşuyolu Yüksek Training and Research Hospital Clinical Investigations Ethics Committee (No: 514/192/19, Date: 30/12/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

Data were collected retrospectively by medical record review from prospectively maintained data sets.

The outcome was MACLE, including cardiovascular death, rehospitalization due to ACS, heart failure, stroke, or amputation during the follow-up period. The patients were divided into two groups: MACLE (-) and MACLE (+). The patients' weight, height, age, sex, and associated risk factors of angiographically proven coronary artery disease (CAD), diabetes mellitus (DM defined according to the American Diabetic Association's diagnostic criteria,^[9] or anti-diabetic medication use), hypertension (HT defined according to the 2018 guidelines on hypertension of the European Society of Cardiology [ESC],^[10] or anti-hypertensive medication use), dyslipidemia (defined according to the 2016 guidelines on dyslipidemia of the ESC),^[11] smoking history, as well as restenosis and survival time, were retrieved from the patient's medical records. The patients were followed using medical records or phone interview twice yearly. There was no loss to follow-up. All patients were managed according to follow-up treatment guidelines.

The body mass index (BMI) was calculated by dividing the patient's weight (kg) to square height (m^2). The ankle-brachial index (ABI) and Rutherford classification were recorded to evaluate the symptom severity. For patients treated for IAO, the resting ABI (highest absolute ankle pressures were documented) was typically obtained at pre-operation or pre-intervention. Medical records of the patients were assessed to generate a frailty score using the modified Frailty Index (mFI) of the Canadian Study of Health and Aging (CSHA).^[12] The mFI is a retrospective measure that assesses frailty as an accumulation of deficits and can be performed in a couple of minutes. The American Society of Anesthesiologists (ASA) score of physical fitness (ASA Class) was measured both pre-operatively and pre-interventionally, due to the primary surgical conversion probability.^[13]

CT analysis

The CT scans of the patients were reviewed by two trained researchers on a workstation using the hospital INFINITT system (Infinit HealthCare Co., NJ, USA), and psoas muscles measurements were performed. A single, cross-sectional imaging slice corresponding to the superior level of L4 was viewed, and the borders of the left and right psoas muscles were outlined using a polygon region of interest tool (Figure 1). The PMA was expressed in mm^2 . The sum of both PMAs was constituted the total psoas muscle cross-sectional area (TPA). Besides, the TPA was divided by the patient's

squared height (m²) to measure the total psoas muscle index (TPAI), which is adjusted according to differences in body size.^[14]

Statistical analysis

Statistical analysis was performed using the R Project for Statistical Computing version 4.0.1 software (R Project for Statistical Computing, Vienna, Austria). Continuous variables were expressed in mean ± standard deviation (SD) or median (interquartile range [IQR] 25th-75th), while categorical variables were expressed in number and percentage. Clinical variables were compared using the Student's t-test for normally distributed data, using the chi-square test or Fisher's exact test for categorical data, and using the Mann-Whitney U test for non-normally distributed continuous data and ranked data, as appropriate. Independent predictor variables were chosen according to the results of previous studies and the stepwise backward univariate analysis of the present study. The univariate Cox regression analysis was performed for all variables to assign significant predictors of MACLEs. Multivariable Cox proportional hazard regression analysis was performed including TPAI, ASA, creatinine, and mFI variables. The results of the Cox regression analyses were presented in hazard ratios (HRs) with 95% confidence intervals (CIs). Model performance measurement was performed based on R2 values. The TPAI was further examined via a receiver operating characteristic (ROC) curve to determine the optimal cutoff according to the Youden index. The MACLE curves were constructed using the Kaplan-Meier method and compared with the log-rank test. A *p* value of <0.05 was considered statistically significant.



Figure 1. Assessment of transverse computed tomography angiogram at the level of the fourth lumbar vertebra (L4). The area of each psoas muscle was measured individually and both were summed for each patient.

Table 1. Clinical characteristics of patients with and without MACLEs

	All patients (n=72)					MACLE (-) (n=42)					MACLE (+) (n=30)					p
	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	
Age (year)			58.8±7.0					59.1±7.4					58.3±6.4		0.650	
Sex																
Male	56	77.8				32	76.2				24	80			0.750	
Body mass index (%)			25.9±4.4					26.1±5.5					25.7±2.2		0.729	
Diabetes mellitus	18	25				12	28.6				6	29			0.401	
Hypertension	26	36.1				14	33.3				12	40			0.568	
Smoking ever	60	83.3				34	81				26	86.7			0.527	
Previous coronary artery disease	40	55.6				20	47.6				20	66.7			0.122	
Previous peripheral artery disease	26	36.1				10	23.8				16	53.3			0.013	
Left ventricle ejection fraction (%)								59±7.9		94-119			58±12.1	103	90.3-146	
Glucose (mg/dL)			58.6±9.8	104	94-128				104						0.954*	
Creatinine (mg/dL)			0.9±0.2					0.9±0.2					0.9±0.3		0.821	
Low density lipoprotein (mg/dL)			127±66.1					138±53.6					159±78.7		0.188	
Total cholesterol (mg/dL)			221±62.9					218±63.8					224±63.5		0.724	
Albumine (g/dL)			38.1±6.5					37.5±7.1					38.8±5.5		0.417	
Index hemoglobin (g/dL)			12.4±2.0					12.1±1.8					12.9±2.1		0.124	
Hemoglobin difference (g/dL)				1.3	0.67-1.88				1.3	0.7-1.8			1.3	0.65-3.08	0.243	
White blood cell count (10 ⁹ /μL)			9.9±4.5					8.9±2.5					11.2±5.9		0.039	

MACLE: Major adverse cardiovascular and limb events; SD: Standard deviation; * Median 25th-75th percentiles (IQR).

Table 2. Clinical characteristics of IAO patients with and without MACLEs

	All patients (n=72)					MACLE (-) (n=42)					MACLE (+) (n=30)					p
	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	
Treatment																
Endovascular therapy	49	68				29	69				20	66.7			0.773	
Bypass therapy	23	32				13	31				10	33.3				
Modified frailty index															0.230	
1	13	18				12	28.5				1	3.3				
2	17	23.6				8	19				9	30				
3	20	27.8				10	23.8				10	33.3				
4	18	25				10	23.8				8	26.7				
5	4	5.6				2	4.9				2	6.7				
Rutherford															0.089	
III	31	43.1				23	54.8				8	26.7				
IV	30	41.7				15	35.7				15	50				
V-VI	11	15.2				4	9.5				7	23.3				
ASA Class															<0.001	
I	2	2.8				2	4.8				0	0				
II	32	44.4				28	66.7				4	13.3				
III	34	47.2				10	23.8				24	80				
IV	4	5.6				2	4.8				2	6.7				
Total psoas muscle area (mm ²)			1,710±569					1,783±627					1,609±455		0.232	
Total psoas muscle area index (mm ²)			595±163					615±171					521±139		0.009	
Index ABI			49.8±4.95					52±4.87					46±4.5		0.164	
Follow-up (months)				32	15.9-44				34.4	19-39				27	7.75-38	0.164

MACLE: Major adverse cardiovascular and limb events; SD: Standard deviation; ASA Class: American Society of Anesthesiologists score of physical fitness; ABI: Ankle-brachial index. NS: Not studied.

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Table 3. Predictors of MACLEs in patients of infrarenal aortic occlusion

	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
TPAI (550.9 to 858.8)	0.37	0.19-0.72	0.003	0.19	0.09-0.42	0.008
ASA Class (II to III)	2.72	1.50-4.93	0.001	4.76	2.07-10.9	0.007
Creatinine (0.63 to 0.98)	1.60	0.92-2.78	0.090	4.23	2.26-7.95	0.010
mFI (2 to 4)	1.32	0.68-2.58	0.125	1.51	0.71-3.20	0.274
Age (52 to 63.5)	0.79	0.41-1.50	0.472			
Sex (reference female)	1.28	0.52-3.16	0.588			
Diabetes mellitus	0.54	0.21-1.37	0.195			
Hypertension	0.86	0.41-1.82	0.683			
Coronary artery disease history	1.82	0.85-3.95	0.123			
Low density lipoprotein (101 to 163)	1.21	0.90-1.63	0.274			

MACLE: Major adverse cardiovascular and limb event; CI: Confidence interval; TPAI: Total psoas muscle area index; ASA Class: American Society of Anesthesiologists score of physical fitness; mFI: Modified Frailty Index.

RESULTS

There were 30 (41.6%) MACLE during the follow-up period, including 11 cardiovascular deaths, 19 rehospitalizations (n=5 heart failure, n=4 ACS, n=4 cerebrovascular events, and n=6 for amputations). The median follow-up was 32 months (IQR 15.9-44). The median follow-up of MACLE (-) and MACLE (+) was 34.4 (range, 19 to 39) months and 27 (range, 7.75 to 38), respectively (p=0.164). There was no statistically significant difference in the age (p=0.650), sex (p=0.750), and BMI values (p=0.729) between the MACLE (+) and (-) groups. However, there was a statistically significant difference in the history of

previous peripheral arterial disease (p=0.013) and white blood cell count (p=0.039). Two groups had a similar incidence of comorbidities, including DM, HT, and smoking (Table 1).

There was no significant difference between the groups in terms of treatment, mFI, and Rutherford category. The mean TPA of patients without MACLE was $1,783 \pm 627 \text{ mm}^2$ and $1,609 \pm 455 \text{ mm}^2$ in the MACLE (+) group, although it did not reach statistical significance (p=0.232). The mean TPAI for MACLE (-) and MACLE (+) patients was $615 \pm 171 \text{ mm}^2/\text{m}^2$ and $521 \pm 139 \text{ mm}^2/\text{m}^2$, respectively (p=0.036; Table 2).

Univariate and multivariate Cox regression analysis were performed to identify prognostic factors for occurrence of MACLE. The univariate analysis showed that the presence of increased TPAI was independently associated with the decreased MACLE

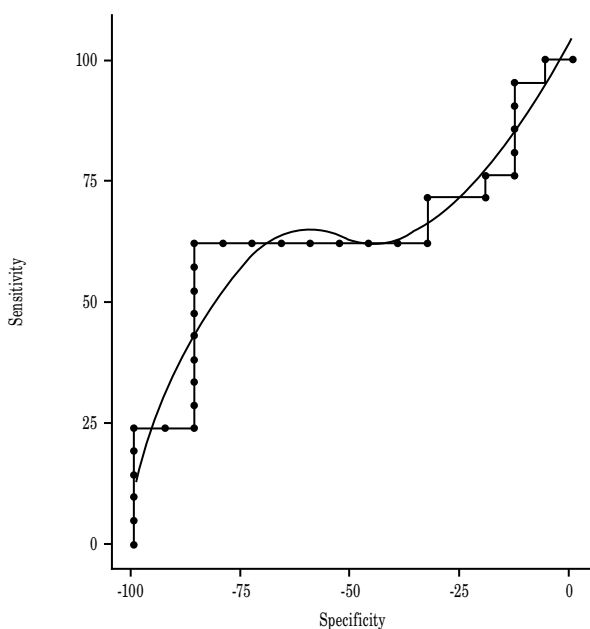


Figure 2. Receiver operating characteristic curves of the total psoas area index for prediction of MACLE.

MACLE: Major adverse cardiovascular and limb event.

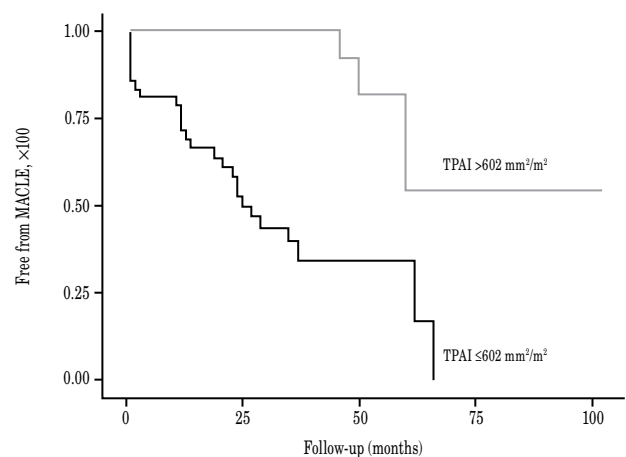


Figure 3. Kaplan-Meier curves show free from MACLE rate for patients with a TPAI of $\leq 602 \text{ mm}^2/\text{m}^2$ and of $> 602 \text{ mm}^2/\text{m}^2$ (p<0.001 by log-rank test).

MACLE: Major adverse cardiovascular and limb event; TPAI: Total psoas area index.

(HR: 0.37; 95% CI: 0.19-0.72; $p=0.003$). Also, the increase in the ASA Class (HR: 2.72; CI: 1.50-4.93; $p=0.001$) was significantly associated with the MACLEs. The multivariate analysis showed that TPAI and ASA Class were independently associated with the occurrence of MACLEs (Table 3).

The ROC curve furnished a plausible univariate TPAI cut-off value of 602 mm²/m² for MACLEs, with 61.9% sensitivity and 86.67% specificity (Figure 2). The Kaplan-Meier analysis was performed by dividing the patients into two groups according to the 602 mm²/m² cut-off values. Higher free from MACLE rates were found in the group with a TPAI of >602 mm²/m² (log-rank $p<0.001$; Figure 3).

DISCUSSION

In the present study, all patients had IAO with the involvement of aortic bifurcation and iliac arteries. Therefore, considerably equivalent disease burden of thrombosis and atherosclerotic plaque due to a longer lesion length and larger artery size were present among the patients.

Regarding the population's increasing age and risk factors, the prevalence of peripheral arterial disease and, consequently, the frequency of IAO increases, which necessitates a more valuable tool for identifying prognostic factors in these vulnerable patients. In the current study, we investigated MACLE outcomes in the most complex peripheral arterial disease group and demonstrated that TPAI was as an independent prognostic factor of MACLE after adjustment for confounding factors. To date, there have been only three studies examining the association between the core muscle mass and outcomes of lower limb lesions.^[7,15,16] All three studies concluded that sarcopenia measured by CT images reflected frailty and was as a predictor of poor prognosis. Similarly, our results demonstrated a link between TPAI and MACLEs. Considering these aforementioned studies, Matsubara et al.^[15] and Sugai et al.^[16] had high proportions of hemodialysis patients (23.4% and 18.6%, respectively); however, the patients with advanced chronic kidney disease (CKD) had a well-documented protein loss, resulting in muscle wasting. Also, CKD patients had a much higher risk of major adverse events. In our study, we had no Grade 4-5 CKD patients; therefore, the impact of these patients on our results was minimal. Another discrepancy between the researches is the Fontaine/Rutherford stage. Matsubara et al.^[15] studied core muscle mass in critical limb ischemia and had 100% Fontaine Stage III-IV patients, which would

indicate their high prevalence of mortality rates. Sugai et al.^[16] studied 22% Fontaine Stage 3-4 patients, which explains their acceptable Kaplan-Meier curves. Juszcak et al.^[7] and our current study had 65% and 57% Fontaine Stage III-IV (Rutherford III-VI), respectively. Higher severity stages were associated with higher-risk interventions, prolonged hospital stay, and short- and long-term complications. In contrast, Chowdhury et al.^[17] did not prove the association of reduced TPA with prognosis, although the patient group in their study was more heterogenous and not procedure- or diagnosis-specific.

On the other hand, our study failed to confirm any significant relationship between the groups according to mFI. This can be attributed to the relatively young and non-significant age of the study groups and the exclusion of patients with chronic neurological deficit. Therefore, points regarding impaired functional status, impaired sensorium, history of transient ischemic attack, and cerebrovascular accident were scarce. This resulted in a relatively low number of points scored in our study compared to Fang et al.'s^[18] study of lower-extremity amputation and mFI. Furthermore, evaluation of frailty in our study was performed only with the CSHA index;^[12] the results may be, therefore, different in other assessment indexes. Sarcopenia expressed by PMA has the benefit of being an objective and quantitative assay of frailty with no impact of disability, illness acuity, immobility, or day-to-day changes in functional status.^[19] In this study, we concluded that decreased TPAI in IAO suggests that patients with IAO may be a frail group.

Sarcopenia is a biomarker for overall debilitation and poor general condition associated with a variety of factors, including age, comorbidities, activities of daily living, and nutrition. A combination of factors, each with a small effect individually, may act together and result in sarcopenia.^[20] We believe that this increase in overall debilitation and poor general condition could have influenced the MACLE. Additionally, a recent study on critical limb ischemia found that sarcopenia and low physical function were the predictors of outcomes.^[21] Taken together, we can conclude that the low muscle mass plus low muscle strength can lead to a low physical performance, strongly highlighting the importance of not only skeletal muscle size, but also physical function. Moreover, mechanism by which sarcopenia may affect the prognosis of patients with IAO might be the reduced effects of adiponectin and carnitine. Skeletal muscle has been recently reported to be an

endocrine organ^[22] and adiponectin and carnitine which target skeletal muscle have shown to improve arteriosclerosis. Sarcopenia, therefore, can reduce the effects of adiponectin and carnitine, exacerbating whole-body arteriosclerosis, which may contribute to the poor prognosis of IAO patients.^[23] These mechanisms may indicate that low core muscle mass is a sensitive indicator of mid-term MACLE after treatment of IAO.

In the present study, we observed no significant association between serious comorbidities (DM, HT, CAD, and smoking) and MACLEs, which were reported as significant in previous studies.^[24,25] Instead, the ASA Class was associated with the outcome. These comorbidity variables were included in our univariate analysis, and we did not observe any correlation, either. This may be due to the small size of the study. The ASA classification system is beneficial; however, as a subjective measure of baseline patient illness, its participation with mortality may differ between studies; therefore, interpreting its predictive value is unreliable. A recent review on risk scoring models for predicting perioperative morbidity and mortality concluded that there is both a lack of multinational validation, and need of more potent predictive precision of risk scores.^[26]

In our study, the IAO severity by measuring ABI and Rutherford classifications and treatment choices were also analyzed for any relationship between TPAI. Although we found no significant association between the TPAI and IAO severity and treatment choices, the relatively low sample size may have led to this result. Further large-scale studies are needed to draw a firm conclusion on this subject.

The psoas muscles arterial supply comes mainly from the iliolumbar artery, to some extent from the obturator artery, external iliac artery, and common femoral artery. With occlusion of the infrarenal aorta, the psoas muscle may be under perfused, and its area may be small. Consequently, relative ischemia may put a boundary to the direct link between sarcopenia and MACLEs. However, all our cohort were homogenous on diagnostic specificity; therefore, relative ischemia affected all patients.

In addition to relative ischemia, there are several limitations to this study. First, we measured TPAI only once during the initial diagnosis. Therefore, we cannot evaluate the changes after treatment or exercise therapy. Further studies are needed to understand the relationship between TPAI and treatment in patients with IAO. Second, frailty was assessed using only

mFI scale of the CSHA, and the other widely adopted tools were not utilized. Third, the post-treatment ABI values were missing for some patients, which preclude a robust interpretation of the post-ABI data.

In conclusion, our study results indicate that the TPAI measured by CT scans is an independent prognostic factor for MACLEs in patients with chronic IAO. The severity of IAO symptoms and classifications do not appear to correlate with the degree of frailty as measured by TPAI.

Declaration of conflicting interests

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