



TOMOGRAPHIC SARCOPENIA PREDICTS ANASTOMOTIC LEAKS AND LONG-TERM SURVIVAL IN GASTRIC CANCER PATIENTS OPERATED WITH CURATIVE INTENT

SARCOPENIA TOMOGRÁFICA PREVÊ FÍSTULAS DE ANASTOMOSES E SOBREVIDA A LONGO PRAZO EM PACIENTES COM CÂNCER GÁSTRICO OPERADOS COM INTENÇÃO CURATIVA

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ABSTRACT – BACKGROUND: The preoperative nutritional state has prognostic postoperative value. Tomographic density and area of psoas muscle are validated tools for assessing nutritional status. There are few reports assessing the utility of staging tomography in gastric cancer patients in this field. **AIMS:** This study aimed to determine the influence of sarcopenia, measured by a preoperative staging computed tomography scan, on postoperative morbimortality and long-term survival in patients operated on for gastric cancer with curative intent. **METHODS:** This retrospective study was conducted from 2007 to 2013. The definition of radiological sarcopenia was by measurement of cross-sectional area and density of psoas muscle at the L3 (third lumbar vertebra) level in an axial cut of an abdominopelvic computed tomography scan (in the selection without intravascular contrast media). The software used was OsirixX version 10.0.2, with the tool “propagate segmentation”, and all muscle seen in the image was manually adjusted. **RESULTS:** We included 70 patients, 77% men, with a mean cross-sectional in L3 of 16.6 cm² (standard deviation+6.1) and mean density of psoas muscle in L3 of 36.1 mean muscle density (standard deviation+7.1). Advanced cancers were 86, 28.6% had signet-ring cells, 78.6% required a total gastrectomy, postoperative surgical morbidity and mortality were 22.8 and 2.8%, respectively, and overall 5-year long-term survival was 57.1%. In the multivariate analysis, cross-sectional area failed to predict surgical morbidity (p=0.04) and 5-year long-term survival (p=0.34), while density of psoas muscle was able to predict anastomotic fistulas (p=0.009; OR 0.86; 95%CI 0.76–0.96) and 5-year long-term survival (p=0.04; OR 2.9; 95%CI 1.04–8.15). **CONCLUSIONS:** Tomographic diagnosis of sarcopenia from density of psoas muscle can predict anastomotic fistulas and long-term survival in gastric cancer patients treated with curative intent. **HEADINGS:** Tomography. Stomach Neoplasms. Fistula. Survival. Sarcopenia.

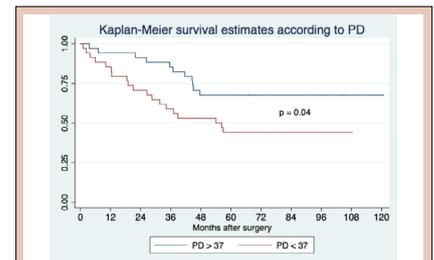


Figure 3 – Long-term survival according to density of psoas muscle, the difference between curves is statistically significant with p=0.04; OR 2.9; 95%CI 1.04–8.15. PD: density of psoas muscle.

Central Message

Radiological diagnosis of sarcopenia in patients with gastric cancer submitted to surgery with curative intent predicts anastomotic leaks and long-term survival.

Perspectives

Knowing if a patient has sarcopenia in the staging CT allows us to prehabilitate them, to eventually reduce the anastomotic leakage risk and improve long-term survival.

RESUMO – RACIONAL: O estado nutricional pré-operatório tem valor prognóstico pós-operatório. A densidade tomográfica e a área do músculo psoas é uma ferramenta validada para o estado nutricional. Existem poucos estudos avaliando a utilidade da tomografia de estadiamento em pacientes com câncer gástrico neste campo. **OBJETIVOS:** Determinar a influência da sarcopenia, medida por tomografia computadorizada de estadiamento pré-operatório, na morbimortalidade pós-operatória e sobrevida em longo prazo em pacientes operados de câncer gástrico com intenção curativa. **MÉTODOS:** Estudo retrospectivo de 2007 a 2013. A definição de sarcopenia radiológica foi pela medida da área (PA) e densidade do músculo psoas (PD) a nível de L3 (Terceira vertebra lombar), em um corte axial de tomografia computadorizada abdominopélvica (na seleção sem meio de contraste intravascular). O Software utilizado foi o OsirixX v 10.0.2, com a ferramenta “propagar segmentação”, ajustando manualmente todos os músculos vistos na imagem. **RESULTADOS:** Foram incluídos 70 pacientes, 77% homens, PA média em L3: 16,6 cm² (desvio padrão+6,1), PD média em L3: 36,1 mean muscle density (desvio padrão+7,1). Os cânceres avançados foram de 86, 28,6% tinham células em anel de sinete, 78,6% necessitaram de gastrectomia total, a morbidade e mortalidade cirúrgica pós-operatória foi de 22,8 e 2,8%, respectivamente, a sobrevida global de 5 anos a longo prazo (SV5) foi de 57,1%. Na análise multivariada, PA falhou em prever morbidade cirúrgica (p=0,4) e sobrevida global de 5 anos (p=0,34), enquanto PD foi capaz de prever fistulas anastomóticas (p=0,009; OR 0,86; IC95% 0,76–0,96) e SV5 (p=0,04; OR 2,9; IC95% 1,04–8,15). **CONCLUSÕES:** O diagnóstico tomográfico de sarcopenia por desvio padrão é capaz de predizer fistulas anastomóticas e sobrevida a longo prazo em pacientes com câncer gástrico tratados com intenção curativa. **DESCRIPTORIOS:** Tomografia. Câncer Gástrico. Fístulas. Sobrevida. Sarcopenia.

INTRODUCTION

According to GLOBACAN in 2018, gastric cancer is the fifth most common neoplasm and the third most deadly neoplasm in the world⁵. Thanks to surgical technology, oncological drugs, and medical advances in critical care units; surgical morbimortality and long-term survival have improved significantly in the past 50 years^{3,10,15,16}. Prognostic factors of postoperative evolution are well described, and the nutritional state has proven to be a relevant short- and long-term independent factors^{12,15,18,20}.

Sarcopenia is defined as a loss of muscle strength, quality/quantity, or reduced physical performance⁹; these variables can be assessed in several ways^{6,7,13}. Tomographic measurements of sarcopenia using the cross-sectional area (PA) and density (PD) of the psoas muscle are a validated practical approach due to their low cost and frequent use, especially in oncological patients⁹.

The aim of this study was to determine the influence of sarcopenia, measured by a preoperative staging CT (computed tomography) scan, on postoperative morbimortality and long-term survival in patients operated on for gastric cancer with curative intent.

METHODS

Design

A retrospective analysis of the oncological database of a Chilean University Hospital (Universidad de Chile Clinical Hospital) from May 2007 to May 2013.

Considering the retrospective nature of the study and the privacy and anonymous analysis of all records, there was no need for institutional IRB approval.

Patients

All adult patients with gastric adenocarcinoma surgically treated with curative intent with in-hospital tomographic records (ICISview^{MR}) of the preoperative staging CT scan were included. Subtotal, total, and extended gastrectomies were included. All the patients were presented to the hospital oncology committee.

Exclusion criteria included gastrectomies due to benign lesions, Stage IV cancers according to the 7th edition TNM classification, R1 resections, type I and II Siewert esophagogastric junction cancers, palliative procedures, complete esophagogastrectomies, and emergency surgeries.

Definitions

- The TNM classification was standardized using the AJCC 7th edition¹⁸.
- Surgical mortality was defined as occurring from the moment of surgery up to postoperative day 90.
- Global survival was defined by patients' discharge from hospitals, eliminating surgical mortality.
- Long-term survival was defined as survival greater than 5 years postoperatively.
- Zero time for determining prognostic association was defined as gastrectomy.

Computed tomography measurement

All preoperative staging CTs were assessed by an expert radiologist with more than 5 years of experience. The mean cross-sectional area (cm²) and mean muscle density (HU) were measured at the L3 (third lumbar vertebra) level in an axial cut of an abdominopelvic CT scan (in the selection without intravascular contrast media). The software used was OsirixX version 10.0.2, with the tool "propagate segmentation" adjusting manually all muscles seen in the image (Figure 1).



Figure 1 - Axial cut of abdominopelvic computed tomography scan without endovascular contrast media. All psoas muscle area is highlighted in red for cross-sectional area and median density measurement.

Follow-up

The present study has 100% follow-up. The database was completed in a prospective manner; the survival update was carried out annually using the database of our hospital and the Chilean Civil Registry.

Statistical analysis

The distribution of variables was determined by the Shapiro-Wilk test. In accordance with this test, the continuous variables with parametric or nonparametric distribution were expressed as average and standard deviation (SD) or median and interquartile (IC_{25%-75%}) ranges, respectively. The categorical variables were described in percentages. The Fisher's, chi-square, Student's t, and Wilcoxon rank-sum tests were used based on the characteristics and distribution of the variables. For the analytical statistical analysis, the Stata^R 14 program was used, and $p < 0.05$ was considered statistically significant. Univariate and multivariate analyses were performed, calculating the odds ratio (OR) with a 95% confidence interval (CI). The Kaplan-Meier and Cox regression were used to calculate survival curves. ROC curves were used to compare prognostic efficacy. The patients signed the informed consent form of the institution.

RESULTS

A total of 70 patients were included; their median age was 60.5 years (SD±13.6); 77% were men; 83.3% had comorbidities; smoking, hypertension, and diabetes were the most common conditions with 41.4, 34.2, and 17.1%, respectively.

Analysis of the psoas muscle at the L3 level in the staging CT scan showed a mean PD of 36.1 HU (SD±7.1) and a mean PA of 16.6 cm² (SD±6.1).

Notably, 86% of cancers were locally advanced, 58% had intestinal histology according to Lauren's classification, 28.6% had signet ring cells, 78.6% required total gastrectomy, and the mean lymph node dissection was 33.7 (SD±13.9). Staging details are explained in Table 1.

Postoperative morbidity and mortality were 22.8 and 2.8%, respectively. The details are explained in Table 2.

Overall long-term survival after five surgeries was achieved in 57.1% of patients (Figure 2).

In the tomographic analysis of sarcopenia, the PA did not achieve statistical significance for any variable measured,

Table 1 - Distribution of patients according to American Joint Committee on Cancer 7th edition¹⁸.

	n (%)
T	
T1a	8 (11.4)
T1b	4 (5.7)
T2	13 (18.6)
T3	20 (28.5)
T4a	25 (35.7)
N	
N0	22 (31.4)
N1	9 (12.9)
N2	12 (17.1)
N3a	18 (25.7)
N3b	9 (12.9)
TNM Stage (7th ed.)	
IA	12 (17.1)
IB	2 (2.8)
IIA	9 (12.9)
IIB	8 (11.4)
IIIA	12 (17.1)
IIIB	14 (20.0)
IIIC	13 (18.6)

Table 2 - Postoperative surgical adverse event.

Adverse event (*)	n (%)
Surgical	
Overall	16 (22.8)
Intra-abdominal abscess	8 (11.4)
Esophagojejunostomy leak	5 (9.4)
Duodenal stump leak	2 (2.8)
Medical	
Overall	15 (21.4)
Respiratory distress	3 (4.3)
Pleural effusion	2 (2.9)
Atrial fibrillation	3 (4.3)
Supraventricular tachycardia	2 (2.9)
Others	5 (7.1)

*Some patients had ≥2 postoperative morbidities at the same time.

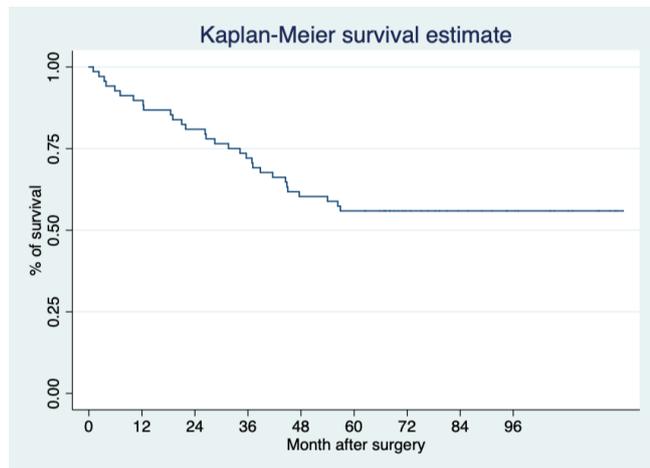


Figure 2 - Survival curve of the entire cohort.

whereas PD was associated with esophagojejunostomy (EJJ) leaks and SV5 (Table 3). The optimum stratification analysis for cutoff points of PD in terms of prognostic value in EJJ leaks was 32 HU, with 71.4% sensitivity and 81% specificity, with an ROC area under the curve of 0.77 (RR 4.6; 95%CI 0.56–0.97), while for SV5, it was 37 HU with 63% sensitivity and 63.3% specificity, with an ROC area under the curve of 0.63 (RR 0.94; 95%CI 0.5–0.76). Using this cutoff value, 20 and 50% of our population were in the risk group for EJJ leakage and reduced long-term survival, respectively (Figures 3, 4, and 5).

Table 3 - Association between different postoperative surgical morbidities and long-term survival, with PA and PD.

	PA	PD
SPOAE	p=0.63	p=0.18
EJJ leaks	p=0.88	p=0.006 (95%CI 2.3–37.9)
Duodenal stump leaks	p=0.82	p=0.18
Surgical mortality	p=0.052	p=0.31
SV5	p=0.45	p=0.02 (95%CI 0.9–0.99)

PA: cross-sectional psoas area; PD: psoas muscle density; SPOAE: surgical postoperative adverse event; EJJ: esophagojejunostomy; SV5: overall 5-year long-term survival.

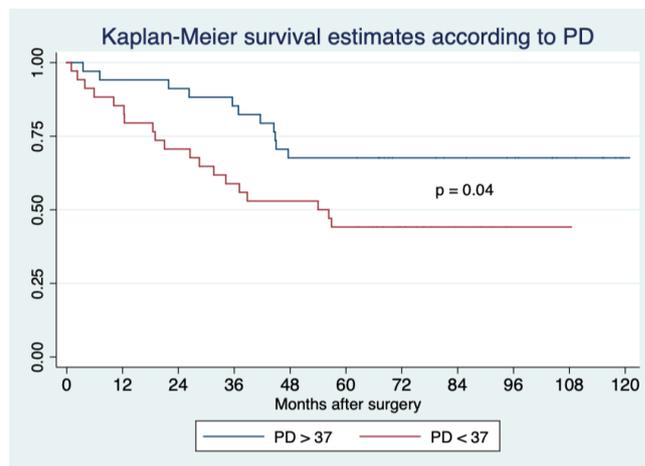
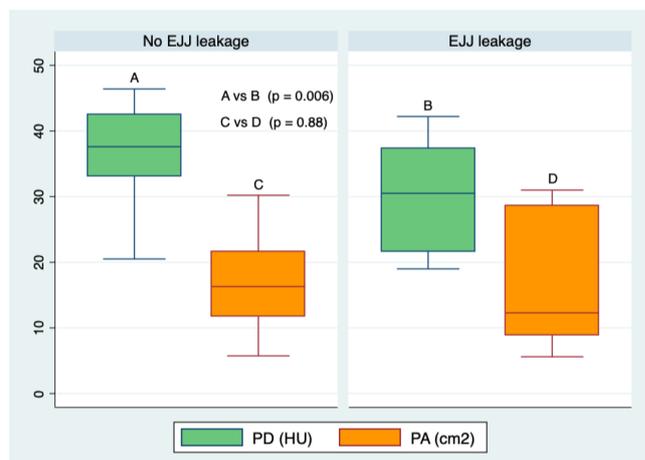


Figure 3 - Long-term survival according to density of psoas muscle, the difference between curves is statistically significant with a p=0.04; OR 2.9; 95%CI 1.04–8.15. Density of psoas muscle.



EJJ: esophagojejunostomy; PD (HU): mean psoas muscle density; PA: psoas muscle cross-sectional area (cm²).

Figure 4 - Box plot comparing EJJ leakage according to PD and PA.

The multivariate analysis predicting EJJ leakages showed that PD was the only independent variable with prognostic power ($p=0.009$; OR 0.86; 95%CI 0.76–0.96). In contrast, analyzing long-term survival, the independent variables were age ($p=0.04$; OR: 0.65; 95%CI 0.91–0.99), locally advanced stage according to the TNM classification system ($p=0.02$; OR 0.08; 95%CI 0.009–0.7), and PD ($p=0.04$; OR 2.9; 95%CI 1.04–8.15) (Table 4).

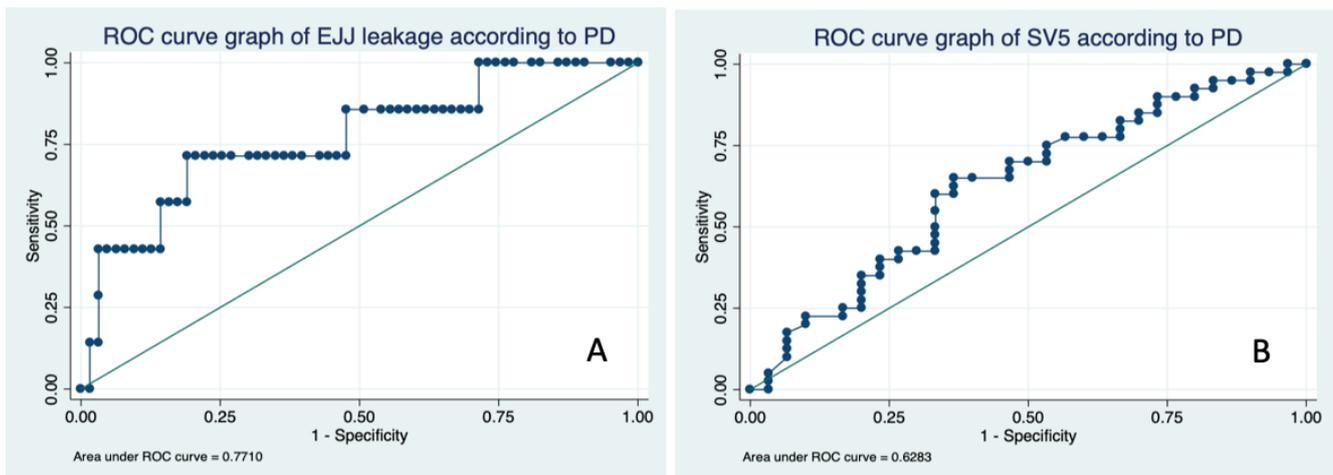
DISCUSSION

Sarcopenia is a well-known prognostic factor for short- and long-term postoperative outcomes; this pathology has different diagnostic methods and affects a specific group of patients, including oncological ones^{9,26}.

Since the introduction of skeletal muscle index (SMI) with CT scan by Prado in 2008²⁵, measurement of cross-sectional area and now density of the psoas muscle has proven to predict whole-body muscle accurately independent of body mass index (BMI), achieving short- and long-term prognostic value in different types of cancer^{2,14,19,26,27,28}. Recently, a meta-analysis including more than 20,000 patients concluded that preoperative incidence of sarcopenia increases the likelihood of postoperative complications ($p<0.001$; RR 1.188; 95%CI 1.083–1.303) and overall mortality ($p<0.001$; HR 1.602; 95%CI 1.369–1.873)²⁸.

The use of this practical and accurate tool in gastric cancer patients has been the subject of a few international reports, mostly from Asia^{8,21,22,28-31} and none from Latin American countries to the knowledge of the authors, this report should be the first coming from that region.

Even though diagnostic criteria and cutoff values for sarcopenia vary depending on country, sex, technology [magnetic resonance imaging (MRI) or CT], variables employed [skeletal muscle area (SMA), index (SMI), and mean attenuation (SMRA)], the European Working Group on Sarcopenia in Older People recommends the use of two standard deviations below the mean reference value of young, healthy adults⁹. The cutoff value for sarcopenia in the US population according to SMA, SMI, and SMRA are 92.2 cm², 34.4 cm²/m², and 34.3 HU in women, and 144.3 cm², 45.4 cm²/m², and 38.5 HU in men, respectively¹³. With these parameters, the patients' rate with sarcopenia in our study was 44.6% (15.0% in women and 57.8% in men), which is higher than the average 34.7% rate in different types of gastrointestinal cancer patients in an international non-Latin American countries¹⁶ but comparable to other specific gastric cancer reports^{21,24,31}. This is an important factor in the discussion; the great heterogeneity of diagnostic criteria and indexes in the Caucasian and Asian literature, sometimes arbitrary, and the lack of this evidence in countries with developing economies, like the present study, makes it difficult to compare results and makes clear the need for scientific evidence.



A: EJJ leakage according to PD, the area under the curve is 0.77, B: SV5 according to PD, the area under the curve is 0.62.

EJJ: esophagojejunostomy; PD: psoas muscle density; SV5: overall 5-year long-term survival.

Figure 5 - ROC curves.

Table 4 - Multivariate analysis predicting esophagojejunostomy leakage and long-term survival, according to psoas muscle density and cross-sectional psoas area.

	EJJ leakage			Long-term survival		
	p-value	OR	95%CI	p-value	OR	95%CI
Sex	0.24	–	–	0.39	–	–
Age	0.07	–	–	0.04	0.65	0.91–0.99
Signet ring cells	0.42	–	–	0.21	–	–
Locally advanced*	0.36	–	–	0.02	0.08	0.009–0.7
Peri-lymphatic invasion	0.20	–	–	0.35	–	–
Peri-vascular invasion	0.89	–	–	0.61	–	–
PD	0.009	0.86	0.76–0.96	0.04	2.9	1.04–8.15
PA	0.40	–	–	0.34	–	–

EJJ: esophagojejunostomy; PD: psoas muscle density; PA: psoas muscle cross-sectional area; OR: odds ratio; CI: confidence interval.

*Locally advanced tumors were defined according to TNM stage system 7th edition¹⁸.

Postoperative morbidity has been assessed by different studies^{8,22,29,30,31}. This is exposed in Table 5. Most of these studies compared SMI with different criteria, and none of them analyzed mean PD; furthermore, most of them do not analyzed long-term survival, except a Chinese prospective study involving 937 patients admitted to radical gastrectomy for gastric cancer whose rate of postoperative morbidity and long-term result were comparable to the present report²⁹.

Considering the heterogeneity in the diagnostic criteria of radiological sarcopenia, finding the best cutoff points to predict long-term postoperative outcomes is a key factor. In a Japanese²⁴ retrospective study of 177 patients with gastric cancer stages II-III admitted to oncological gastrectomy, five cutoff points of SMI (cm^2/m^2) were assessed, and the prevalence of sarcopenia varied from 3 to 64%. The best SV5 predicting criteria were achieved with Martin's²³ cutoff point (SMI 53.0 for BMI >25 or 43.0 for BMI <25 in men, and 41.0 in women), with an SV5 of 48 vs. 68 months ($p=0.005$; HR 2.0; 95%CI 1.24–3.24). Compared to that report, the present study interestingly achieved a better result with density than with muscle area. These results cannot be totally compared because the abovementioned article did not evaluate PD.

Considering that most patients with gastric cancer will need postoperative adjuvant therapy, it is vital to understand the impact of chemotherapy on the patient's nutrition status²⁸. This topic has been studied; a muscle loss $\geq 9\%$ during chemotherapy is associated with a shorter OS ($p < 0.001$; HR 4.47; 95%CI 2.21–9.05)⁴, which, when added to preoperative sarcopenia, may have a synergic effect. This is especially important in therapeutic strategy if sarcopenia is diagnosed preoperatively, and additional effort in improving performance and nutritional status (prehabilitation) could benefit not only postoperative outcomes but also tolerance to chemotherapy and long-term survival. This hypothesis should be studied in future protocols.

In a palliative context, skeletal sarcopenia, diagnosed by Ct, has proved to be a valuable tool for predicting overall survival. Lee²¹ reported a multivariate analysis of a cohort of 140 consecutive patients who underwent palliative chemotherapy for gastric adenocarcinoma; in that study, sarcopenia was defined as an L3 SMI $< 49 \text{ cm}^2/\text{m}^2$ for men and $< 31 \text{ cm}^2/\text{m}^2$ for women, using cutoff points specific for the Korean population. Radiological sarcopenia showed poor overall survival (6.8 vs. 10.3 months; $p=0.033$), which was confirmed in the multivariate analysis ($p=0.029$; HR 1.51; 95%CI 1.04–2.18); interestingly, no difference in response to chemotherapy was found between patients with and without sarcopenia ($p=0.583$).

Some articles have analyzed the presence of myokines, which are proteins produced by skeletal muscle with potential anticancer effects. This hypothesis could have a major impact in terms of prehabilitation and postoperative management if a targeted therapy could be found^{1,17}.

The present article has the following limitations:

1. Small sample size: The main reason was the lack of CT scans done in our institution; most gastric patients operated on during that period had topographies from different radiological centers. This limitation may have some role in the multivariate analysis and the magnitude of prognostic power.
2. Lack of complementary nutritional studies: Even though tomographic assessment for sarcopenia has been validated, the aim of this study was not to compare this tool with other nutritional diagnostic methods. The additional information would have been valuable to define, whereas the condition of sarcopenia was used not only as the tomographic tool but also as a prognostic variable in this population.
3. Lack of SMI: The database used did not have weight measurements to calculate body surface in more than 80% of patients so that index was impossible to assess.

CONCLUSION

The findings in this report suggest that PD has a strong prognostic value in predicting leakage of the EJJ and overall 5-year long-term survival, with 32 and 37 HU being the optimal cutoff points, respectively.

More efforts should be needed in Caucasian, North American, and Latin American countries to study tomographic sarcopenia, in order to assess not only the efficacy of prognostic value but also the optimal cutoff points for that specific population.

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Table 5 - Studies of gastric patients operated with curative intent, analyzed by tomographic sarcopenia.

Author	n	Year	CT p.	Morbidity (%)	Leaks (%)	SV5 (%)
Wang ²⁹	255	2015	SMI	43.8 vs 14.3	NS	–
Zhuang ³¹	937	2016	SMI	28.5 vs 21.2	–	42.6 vs 69.4
Zhou ³⁰	240	2017	SMI	49.3 vs 24.6	NS	–
Lou ²²	206	2017	SMI	64.3 vs 23.9	NS	–
Chen ⁸	313	2019	SMI	35.1 vs 14.8	NS	–
Figuerola-Giralt ¹⁶	70	2021	PD (HU)	22.8*	15.4 vs 5	44.1 vs 69.4

CT p: tomographic parameter used in the study; SMI: skeletal muscle index measured in cm^2/m^2 ; PD(HU): mean psoas muscle density measured; SV5: overall 5-year long-term survival; NS: non-significant. Morbidity (%): All groups of postoperative morbidity (surgical and medical); Leaks (%): Only esophagojejunostomy leaks.

*As the univariate analysis showed that neither psoas muscle cross-sectional area nor psoas muscle density had any prognostic value on morbidity, the rate expresses the frequency of morbidity in the whole group.

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