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ORIGINAL ARTICLE

Sarcopenia and Patient's Body Composition: New Morphometric Tools to Predict Clinical Outcome After Ivor Lewis Esophagectomy: a Multicenter Study

Andrea Cossu[1] · Diego Palumbo[2] · Silvia Battaglia[1] · Paolo Parise[3] · Stefano De Pascale[4] · Monica Gualtierotti[5] · Massimo Vecchiato[6] · Giulia Maria Scotti[7] · Chiara Gritti[2] · Andrea Bettinelli[2] · Francesco Puccetti[1] · Lavinia Barbieri[1] · Manrica Fabbi[4] · Luigi Funicelli[8,9,10] · Giuseppe Roberto Bonfitto[4] · Paolo De Martini[5] · Antonio Martino[6] · Antonio Ziccarelli[6] · Stefano Fapranzi[6] · Lidia Ravizzini[1] · Alessandro Uzzau[11] · Uberto Fumagalli Romario[4] · Giovanni Ferrari[5] · Roberto Petri[6] · Ugo Elmore[1] · Francesco De Cobelli[2] · Riccardo Rosati[1] · on behalf of SISME – Società Italiana per lo Studio delle Malattie dell'Esofago –Italian Society of disease of the esophagus

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Abstract

Background The impact of preoperative body composition as independent predictor of prognosis for esophageal cancer patients after esophagectomy is still unclear. The aim of the study was to explore such a relationship.

Methods This is a multicenter retrospective study from a prospectively maintained database. We enrolled consecutive patients who underwent Ivor Lewis esophagectomy in four Italian high-volume centers from May 2014. Body composition parameters including total abdominal muscle area (TAMA), visceral fat area (VFA), and subcutaneous fat area (SFA) were determined based on CT images. Perioperative variables were systematically collected.

Results After exclusions, 223 patients were enrolled and 24.2% had anastomotic leak (AL). Sixty-eight percent of patients were sarcopenic and were found to be more vulnerable in terms of postoperative 90-day mortality ($p = 0.028$). VFA/TAMA and VFA/SFA ratios demonstrated a linear correlation with the Clavien-Dindo classification ($R = 0.311$ and 0.239, respectively); patients with anastomotic leak (AL) had significantly higher VFA/TAMA (3.56 ± 1.86 vs. 2.75 ± 1.83, $p = 0.003$) and VFA/SFA (1.18 ± 0.68 vs. 0.87 ± 0.54, $p = 0.002$) ratios. No significant correlation was found between preoperative BMI and subsequent AL development ($p = 0.159$). Charlson comorbidity index correlated significantly with AL ($p = 0.008$): these patients had a significantly higher index (≥ 5).

Conclusion Analytical morphometric assessment represents a useful non-invasive tool for preoperative risk stratification. The concurrent association of sarcopenia and visceral obesity seems to be the best predictor of AL, far better than simple BMI evaluation, and potentially modifiable if targeted with prehabilitation programs.

✉ Andrea Cossu
cossu.andrea@hsr.it

1 Department of Gastrointestinal Surgery, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

2 Experimental Imaging Center, Radiology Department, IRCCS San Raffaele Scientific Institute, Milan, Italy

3 Division of General Surgery, Policlinico Di Abano Terme", Padua, Italy

4 Department of Surgery, European Institute of Oncology IRCCS, Milan, Italy

5 Department of General and Oncological Minimally-Invasive Surgery, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

6 Division of Surgery, Department of Surgery, ASUFC "Santa Maria Della Misericordia", Udine, Italy

7 Center for Omics Sciences, IRCCS San Raffaele Scientific Institute, Milan, Italy

8 Division of Medical Imaging and Radiation Sciences, European Institute of Oncology, IEO, IRCCS, Milan, Italy

9 Italian Society of Medical and Interventional Radiology, SIRM, Italian College of Computed Tomography, Milan, Italy

10 Italian Society of Medical and Interventional Radiology, SIRM, Italian College of Oncology, Milan, Italy

11 Division of Surgery, Department of Surgery, DAME, University of Udine, Udine, Italy

Introduction

Ivor Lewis esophagectomy is nowadays the gold standard technique to treat localized carcinoma of the medium-distal esophagus and EGJ cancers, undoubtedly in case of Siewert 1 tumors while considering the current ongoing discussion on the indications for Siewert 2.[1] Although in the last years many improvements in the surgical approach, devices, and anesthesiology care have been achieved,[2] the procedure is still troubled for high morbidity and mortality;[3,4] in fact, different complications can occur after esophagectomy and, among them, the most feared one is the leakage of the esophagogastric anastomosis. This still counts from 10 to 40%,[5,6] depending on the experience of surgeons and the volume of the centers.[5,7,8]

Anastomotic leak (AL) represents an unpredictable occurrence resulting in long hospital stay, increased morbidity, and sometimes mortality, with no standardized treatment currently available.[9,10] Pathogenesis of AL is not well understood: it is multifactorial, mainly attributed to mechanical or ischemic causes. Many factors are thought to trigger this pathogenetic pathway and thus to predispose to leakage, one of which is an altered metabolic status caused by the depletion of energy stores within muscle and the imbalance of body's metabolic requirements.[11–16]

Previous studies proved that preoperative nutritional status influences clinical outcome after oncologic surgery;[17] however, its role after Ivor Lewis esophagectomy and its association with AL has been scarcely investigated.

Data regarding distribution of body tissues can be easily acquired from computed tomography (CT) which is part of patients' routine care. Analyzing specific slices of tomographic studies is possible to detect measurements of skeletal muscle and adipose tissues that may give further insight into clinical outcome to the existing scores of nutritional assessments.

Our aim was to analyze the impact of preoperative CT-based anthropometric measurements on the development of AL after IL esophagectomy. Our secondary endpoint was to assess any correlation with 90-day mortality.

Materials and Methods

Study Population

This is a multicenter retrospective study conducted in four Italian high-volume esophageal units[8] (San Raffaele Scientific Institute (Milan, Italy), European Institute of Oncology (Milan, Italy), ASST Niguarda Hospital (Milan, Italy), Udine University Hospital (Udine, Italy)).[18] The protocol received Ethics Committee approval by local Institutional Review Boards and was endorsed by the Italian society for the study of diseases of the esophagus (SISME).

All consecutive patients with esophageal cancer (both adenocarcinoma and squamous cell carcinoma) who underwent esophagectomy with intrathoracic anastomosis (*Ivor Lewis* technique) between April 2014 and May 2020 were identified ($n = 383$). Within this database, patients who were evaluated with at least one multiphase, contrast-enhanced computed tomography (CT) scan within 45 days before index surgery ($n = 223$), were enrolled into our study.

A detailed flowchart of this study design (comprehensive of inclusion and exclusion criteria) is shown in Fig. 1.

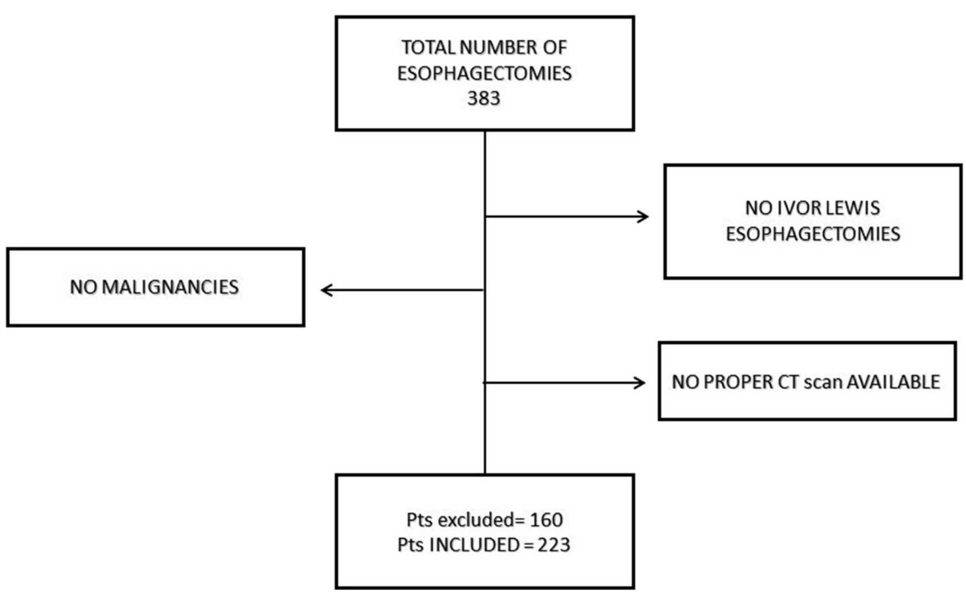

Fig. 1 Inclusion and exclusion criteria

Preoperative Anthropometric Measurements and Image Analysis

Anthropometric data (sex, age, weight, height), nutritional score such as body mass index (BMI) and nutritional risk score (NRS), were considered for each patient.

An independent, blinded radiologist using the software Slice—O-Matic 5.0 (Tomovision, Montreal, Canada), performed the analysis of the CT images. For comparison compliance, the frame including the lumbar vertebra L3 with full visualization of the vertebral transverse processes was considered and a specific marker for the tissues (Hounsfield unit (HU)) was used. The total abdominal muscle area was therefore identified (TAMA in cm^2) including the muscles of the paraspinal and abdominal wall, with an interval between − 29 and + 150 HU. Muscle mass is normalized for height (TAMA cm^2/m^2) and rationalized for sex: by convention, sarcopenia is defined for TAMA values lower than 52.4 cm^2/m^2 in males and 38.5 in females.[19–21] The visceral adipose area (VFA in cm^2) is identified between − 150 and − 50 HU, while the subcutaneous fat area (SFA in cm +) between − 190 and − 30 HU (Fig. 2).

The relationship between visceral fat and muscle mass (VFA/TAMA) and between visceral and subcutaneous fat (VFA/SFA) was calculated for each patient and analyzed independently.

Operative Management

Ivor Lewis esophagectomy is a two-stage surgical procedure, consisting in the resection of both the distal part of the esophagus as well as the gastroesophageal junction; abdominal and mediastinal lymphadenectomy is usually performed.[22–24] The operation starts with an abdominal approach, followed by a thoracic approach. Minimally invasive esophagectomy using laparoscopic and thoracoscopic technique is now the favored option since it is associated with a lower rate of major complications and shorter hospital stay than conventional open resection.[25,26] Specifically, after mobilization of distal esophagus, gastric conduit is created using a surgical linear stapler; the distal esophagus, the gastroesophageal junction, and the gastric conduit are then pulled into the thoracic cavity through the hiatus. Type of anastomosis between proximal esophagus and gastric conduit depends on the surgeon preference and there is currently no standardization. The surgical approach (open, minimally invasive, or hybrid) and the type of anastomosis (end to side circular mechanical (ESc), side to side semi mechanical (SSsm), side to side mechanical (SSm)) were evaluated (Table 1).

Before closure, chest, and/or mediastinal drains (adjacent to the anastomotic site) are placed; a nasogastric tube is routinely placed into the gastric conduit.

Clinical Data Collection

Retrospective review based on institutional prospective database was used to obtain information on demographics (gender, age, BMI), perioperative risk assessment (American Society of Anesthesiologists (ASA) score), neoadjuvant treatment, perioperative variables (patient and surgery related), comorbidities expressed according to Charlson comorbidity index (CCI) and the oncological stage according to TNM classification. The selected clinical variables are summarized in Table 1.

Postoperative complications were analyzed according to Clavien-Dindo classification[27] with particular emphasis on the anastomotic leakage further defined according to ECCG classification.[28]

Assessment of Postoperative Complications and Definition of Outcomes

Anastomotic leak was defined as a full thickness GI defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification according to ECCG classification.[28]

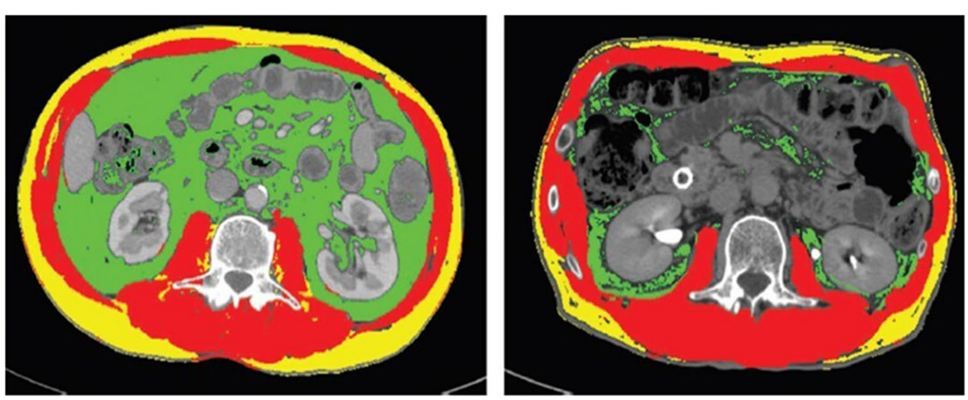

Fig. 2 Comparison of two CT scan at the lumbar vertebra L3 between a sarcopenic patient (left) and no sarcopenic one (right) (red area: TAMA, green area: VFA, yellow area: SFA)

Table 1 Demographic and surgical data

	Number of patients ($n=223$)	Anastomotic leak ($n=54$)	No anastomotic leak ($n=169$)	p value
Age (years)*	62.7 [29–85]	69 [28–82]	62.5 [29–85]	0.024
Sex (male)	182 (81.6)	48 (88.8)	136 (80.4)	0.162
BMI (kg/m^2)*	25.1 [14.8–52]	25.3 [19.1–52]	24.3 [14.8–48.1]	0.154
NRS ≥ 4	40 (17.9)	11 (20.3)	30 (17.7)	0.328
ASA III	83 (37.2)	30 (55.5)	55 (32.5)	0.105
CCI ≥ 5	*85 (38.1)*	*35 (64.8)*	*50 (29.5)*	0.001
TNM				0.465
T1–T2	109 (48.8)	27 (50)	82 (48.5)	
T3–T4	114 (51.1)	27 (50)	87 (51.4)	
N0	115 (51.5)	32 (59.2)	84 (49.7)	
N+	114 (51.1)	22 (40.7)	85 (50.2)	
M0	214 (95.9)	52 (96.2)	163 (96.4)	
M+	9 (4)	2 (3.7)	6 (3.5)	
Neoadjuvant therapy	183 (82.1)	45 (83.3)	138 (81.6)	0.504
Anastomosis				0.320
ES circular	171 (76.6)	38 (70.3)	134 (79.2)	
SS semi mechanic	51 (22.8)	15 (27.7)	36 (21.3)	
SS mechanic	1 (0.4)	0 (0)	1 (0.6)	
VFA (cm^2)§	154.5 ± 198.9	223.7 ± 368.7	133.9 ± 91.6	0.021
SFA (cm^2)§	173.7 ± 233.6	232.7 ± 467.8	156.9 ± 77.1	0.262
TAMA (cm^2/m^2)§	51.6 ± 72.6	66.4 ± 147.6	46.9 ± 9.2	0.319
VFA/TAMA§	2.93 ± 1.87	3.56 ± 1.86	2.75 ± 1.83	0.003
VFA/SFA§	0.93 ± 0.59	1.18 ± 0.68	0.87 ± 0.54	0.002
Sarcopenia	152 (68.1)	41 (75.9)	111 (65.6)	.100

The bold highlights significant differences between patients with and without anastomotic leakage (p value < 0.05)

Unless otherwise indicated, data are numbers of patients and data in parentheses are percentages. *BMI*, body mass index; *ASA*, American Society of Anaesthesiologists; *NRS*, Nutritional Risk Score; *CCI*, Charlson Comorbidity Index; *ESc*, end to side circular mechanic; *SSsm*, side to side semimechanical; *SSm*, side to side mechanical; *VFA*, visceral fat area; *SFA*, subcutaneous fat area; *TAMA*, total abdominal mass area

*Data are medians; data in parentheses are ranges

§Data are means with standard deviations

Postoperative mortality was established as death occurred within 90 days of surgery or any in-hospital death.

Statistical Analysis

The correlation between radiological data from CT analysis and the occurrence of anastomotic leakage was studied with univariate analysis. Binary and categorical variables were compared by means of a chi-squared test. Student's *T* test and Mann–Whitney *U* test were instead used to compare groups of patients with and without anastomotic leak, when the reference variables were continuous (parametric or not, respectively). A ROC-type analysis made it possible to identify cutoff values and define their diagnostic accuracy values. Subsequently, all the variables identified as significant in the univariate analysis ($p < 0.05$) were used as regressors in a multivariate logistic model on the odds of the outcome. Pearson's correlation was calculated within each pair of regressors and, in case of correlated variables, only one of the two was included in the final model, to avoid multicollinearity. The statistical analysis was done by means of SPSS (version 21.0, IBM Corp., Armonk, NY, USA) and R (version 3.6.3, https://www.R-project.org/).

Results

Patients' Characteristics

Three hundred eighty-three patients underwent esophagectomy over the study time period. After exclusions, 223 patients (41 females [18.3%], 182 males [81.6%]; median age: 62.7 years [range: 29–85]; median preoperative BMI: 25.16 kg/m^2 [range: 14.8–52]) who underwent preoperative

CT scan were enrolled (median time interval between preoperative CT scan and index surgery: 21 days [range: 2–42]). Patients' preoperative characteristics as well as perioperative variables and postoperative outcomes are summarized in Table 1.

Preoperative CT-Based Anthropometric Measurements

Body composition parameters are shown in Table 1. According to predetermined sex-specific cutoffs, 152 patients (68.1%, 25 females [55.5%] and 127 males [66.1%]) were classified as sarcopenic. Of note, no statistically significant differences exist in terms of body composition parameters between patients who underwent neoadjuvant chemoradiotherapy and those who did not ($p > 0.05$).

Postoperative Death (Supplementary Table 1)

Eleven patients out of 223 (4.6%) died within 90 days from index surgery; of these, six (54.5%) suffered from AL during hospital stay. Sarcopenic patients were found to be more vulnerable in terms of postoperative death (9.2% (sarcopenic group) vs. 2.3% (non-sarcopenic group), $p = 0.028$). When considering preoperative BMI values, there were instead no statistically significant differences in terms of postoperative death (23.7 ± 3.32 kg/m^2 in those who died *vs.* 25.5 ± 4.97 kg/m^2 in those who did not, $p = 0.159$).

Anastomotic leakage —univariate analysis (Fig. 3)

In our study population, 54 patients (24.2%) suffered from AL during their hospital stay (4 [7.4%] type I, 22 [40.8%] II, 28 [51.8%] III). Patients with AL had significantly higher VFA/TAMA (3.56 ± 1.86 vs. 2.75 ± 1.83, $p = 0.003$) and VFA/SFA (1.18 ± 0.68 vs. 0.87 ± 0.54, $p = 0.002$) ratios (Table 1). Furthermore, among patients suffering from AL, the highest VFA/TAMA ratio values were found in those experiencing type III leakage (4.19 ± 1.97, $p = 0.044$).

Among clinical variables considered (Table 1), only age and CCI demonstrated a statistically significant correlation with the occurrence of AL: specifically, older patients (66 ± 10.6 years vs. 62.2 ± 10.9 years [$p = 0.024$]) with high CCI values (5.1 ± 1.43 vs. 4.3 ± 1.45 [$p = 0.001$]) were found to be at high risk for AL. The optimal cutoff value for CCI in predicting subsequent leakage development was found to be 5. No statistically significant correlation was found

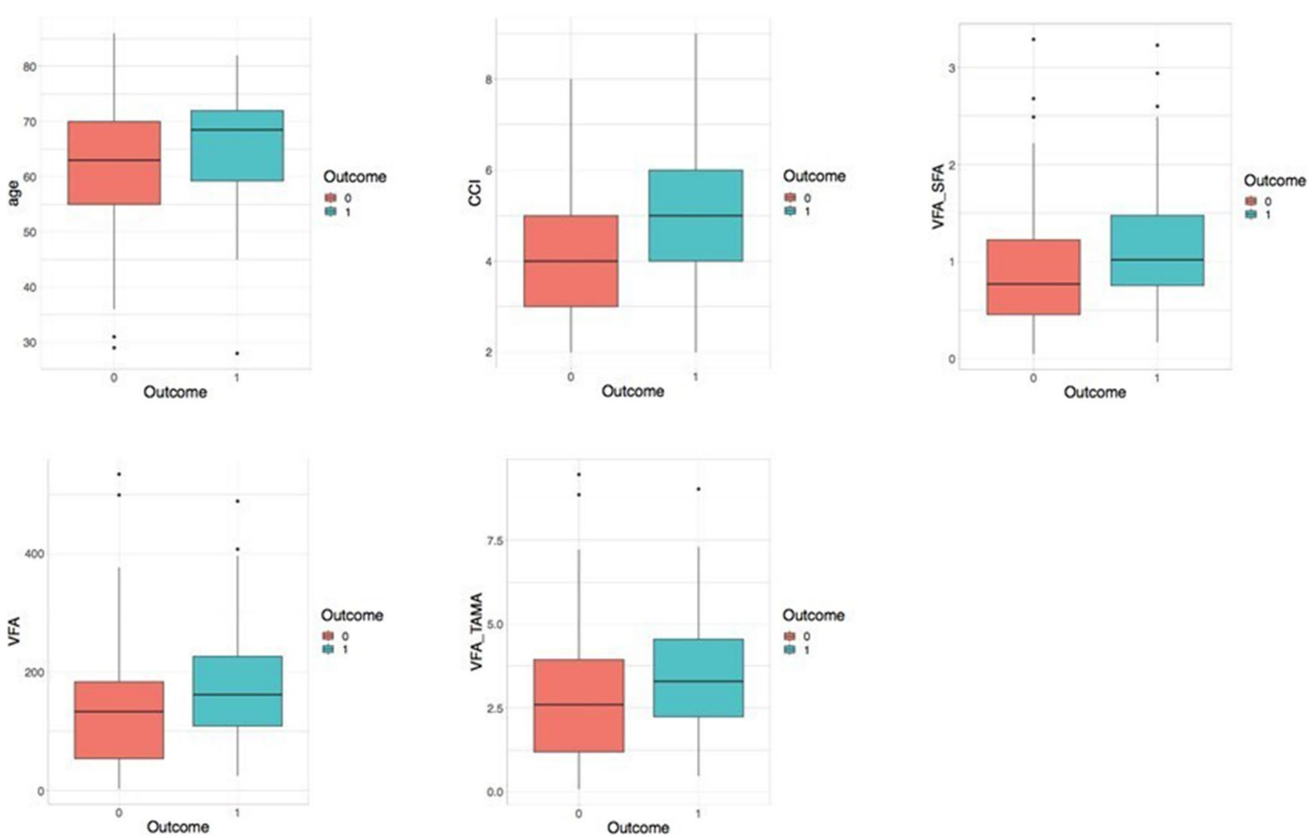

Fig. 3 Comparison of age, CCI, VFA/SFA, VFA, VFA/TAMA distributions between patients who did and did not experience the outcome

between preoperative BMI and subsequent AL development ($p=0.154$).

Anastomotic leakage—multivariate analysis

After collinearity assessment, independent predictors of postoperative mortality identified by multiple logistic regression analysis were VFA/TAMA ratio ($p=0.038$) and CCI ($p=0.0076$). The ROC curve showing the discriminative power of the multivariate model demonstrated an AUC of 0.67 (Fig. 4). Finally, to avoid over fitting, the dataset was split into training and validation sets and 500 iterations (with random sampling for train/test datasets) were performed: mean AUC from iterations was 0.66.

Discussion

Patients affected by esophageal cancer often present different shades of dysmetabolism at the diagnosis, including sarcopenia and sarcopenic obesity, due to the natural history and biology of the disease. The high prevalence of sarcopenic patients in the present study population (68.1%) confirms this evidence.

While these nutritional settings were previously investigated in different series of oncologic patients,[16,17] their role in esophageal surgery outcomes is still contradictory.

Elliott et al. observed that sarcopenia is associated with adverse oncologic outcomes and risk of progression during multimodal therapy. Moreover, muscle mass could also decline during neoadjuvant therapy and preoperative sarcopenia correlates with an increase in overall postoperative complications.[29]

A recent meta-analysis conducted on 2387 patients confirmed the adverse impact of preoperative sarcopenia on postoperative short-term outcomes and evidenced that there was not a substantial difference in terms of mortality between sarcopenic and non-sarcopenic patients.[30]

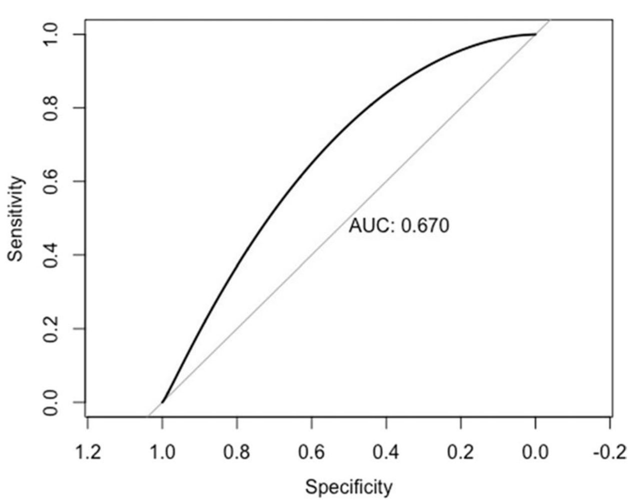

Fig. 4 ROC curve obtained for the final logistic model

Otherwise Boshier et al. showed correlation of sarcopenia with significantly higher rates of mortality and decrease in overall survival.[31]

Our pieces of evidence suggest that significant clinicopathologic features could identify high-risk pattern of sarcopenic population on which could be possible select the adequate management of the condition.

According to CT-based analytical assessment, we used a morphometric tool to assess the patients based on their nutritional status and body composition. We considered the muscle mass, the visceral and subcutaneous adipose tissue and the correlation between these components.

Our data show a significant correlation between sarcopenia and 90-day mortality ($p=0.028$) but no significant correlation with the occurrence of AL was found. These results were consisted with previous studies[32] highlighting that pathophysiology underlying AL is multifactorial and does not relied upon a single factor (sarcopenia). One possible explanation could be that sarcopenia, as previously proved by other authors, can weaken patient's immune response, impacting both the innate and adaptive immunity. Therefore sarcopenic patients could be more vulnerable to septic states as well as less responsive to inflammatory processes after surgery and decrease of respiratory function due to a depletion of respiratory muscles since pulmonary complications are responsible of an increase of mortality themselves.[33–36] We also know that the visceral adipose tissue produces metabolic factors which lead to the development of a chronic low-grade inflammation that can lead to vascular dysfunctions and a poor perfusion of the esophageal anastomosis.[37]

We therefore tested alternative scores that directly correlate muscle and adipose tissue: VFA/TAMA and VFA/SFA ratios demonstrated a significant correlation with AL development (3.56 ± 1.86 vs. 2.75 ± 1.83, $p=0.006$ and 1.18 ± 0.68 vs. 0.87 ± 0.54, $p=0.003$ respectively).

This result may appear in contrast when compared with previous papers. Fehrenbach et al., for instance, in a retrospective monocentric study involving 85 patients undergoing Ivor Lewis esophagectomy after neoadjuvant chemotherapy, found no statistically significant correlation between VFA/TAMA and sarcopenia.[38] We think that the small sample size of their study could be the reason of such a discrepancy. Moreover, the same ratio (VFA/TAMA) has been found to represent a good preoperative predictor of complications as an indicator of patient fragility in other types of surgery.[17]

Furthermore, among patients suffering from AL, the highest VFA/TAMA ratio values were found in those experiencing type III leakage (4.19 ± 1.97, $p=0.044$)[28] (Table 2).

Another crucial point resulting from our data is that both patients' body composition and comorbidities contribute to

Table 2 Summary of anastomotic complications

Anastomotic leak (ECCG)[1]	54 (24.2)
Type 1	7 (12.9)
Type 2	20 (37.0)
Type 3	26 (48.1)

[1]ESOPHAGECTOMY COMPLICATIONS CONSENSUS GROUP (ECCG)[28]

AL development. However, something else is missing, and indeed, the ROC curve showing the discriminative power of our multivariate model demonstrated an AUC of 0.67. It means that there are other factors (different from the above-mentioned patients' body composition and comorbidities) contributing to the occurrence of anastomotic leakage. Taken together, these observations promote the hypothesis of anastomotic leakage as a multifactorial event: in this respect, our study provides an insight into this complexity, but other studies are needed to fully explain it.

The nutritional status, unlike the CCI, is a potential modifiable factor if recognized in advance.

For this reason, body composition assessment (VFA/TAMA ratio) may be targeted with prehabilitation strategies with the aim to reverse the sarcopenic status in selected frail patients focusing on muscle strengthening and/or loss in adipose tissue, in order to decrease the ratio. This score seems to be promising and clinically relevant as predictor of AL if we consider that, in our series, the most traditional and common nutritional scores as body mass index (BMI) and nutrition risk screening (NRS)[39] are interestingly not related to this complication.

Prehabilitation is nowadays a key point of new perspectives in ERAS programs and pieces of evidence support advantages in improving acceptable level of functional activity after surgery.[2] In particular, targeting inspiratory muscle training aims to achieve a reduction in pulmonary complications and hence has a considerable theoretical rationale.[40] Therefore, boosting the respiratory function is strongly recommended; appropriate exercise with adequate protein supplementation can be beneficial.[41]

In summary, the concurrent association of sarcopenia and visceral obesity seems to be a significant predictor of AL, far better than simple BMI evaluation. We are aware of the demanding challenge in fighting the catabolic process during cancer progression and neoadjuvant treatments, which represents a complex of physiopathological events related to the disease; this is the main limitation of the study. Retrospective sample and the lack of sub analysis further investigating the possible role of body composition abnormalities in determining other than AL complications represent other limitations. Despite this, analytical assessment of the body composition represents a useful non-invasive tool for preoperative risk stratification and can represent an advantage in perioperative management, as element that can increase the level and intensity of care in selected high-risk patients. Further studies are expected to establish more effective diagnostic criteria and nutritional status severity classifications in perioperative management with potential implications in improving prehabilitation criteria.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11605-023-05611-1.

Declarations

Conflict of Interest The authors declare no competing interests.

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