"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST DOCTORAL SCHOOL FIELD OF MEDICINE

ABSTRACT DOCTORAL THESIS

The impact of sarcopenia in oncological digestive pathology

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Cuprins

Introduction

This paper, as its title indicates, evaluates the impact of a muscle pathology, called "sarcopenia", characterized by a decrease in muscle quality and quantity, when it is associated with digestive cancers.

The motivation for choosing this topic is that in recent years, the treatment of cancers in general, not just digestive cancers, has become a treatment with a multidisciplinary approach, where the success of curing oncological pathologies is directly dependent on understanding the complexity of these cases, their correct assessment, the multisystemic approach, multifactorial and multidisciplinary.

In this concept of multidisciplinary care of oncological cases, the research of the impact of sarcopenia in digestive oncology has appeared especially in the last 10 years, according to the specialized literature, with the permanent attempt to optimize the results obtained in the treatment of digestive cancers. More precisely, from the point of view of the novelty and topicality of the topic, searching in the specialized literature, we noticed that the flow of scientific articles on this topic, of sarcopenia in digestive cancers, began to increase from 2017 and is a topical topic, where there are no uniform conclusions regarding the impact of sarcopenia in hepato-bilio-pancreatic and colorectal neoplasia. By selecting the search terms sarcopenia, cancer and digestive, from the year 2017 to the year 2022, 135 articles are found. 1

"The term "sarcopenia" derives from the ancient Greek. It is, in fact, the fruit of the union of the two words of the ancient Greek language "σάρξ - sarx", which means "flesh" (or "muscle") and "πενία - penia" which means "poverty". Thus, the literal meaning of sarcopenia is "meat poverty" or "muscle poverty". 2 3

Sarcopenia was initially described as a disease of elderly patients. 4 It was associated with a precarious functional, immunological, metabolic and stress response status. 5 6

Sarcopenia can be present in people with normal or even high body weight, as in sarcopenic obesity. 7

Sarcopenia may be included in the phenotype of patients with cancer cachexia syndrome, a condition that results in skeletal muscle wasting, with or without loss of adipose tissue. There are data that say that 80% of patients with advanced cancer are affected by cancer cachexia and about 30% of cancer deaths result from the syndromes developed in cancer cachexia. 8 9 10 11 12

Not only aging and cancer, but also other diseases such as organ failure can contribute significantly to the loss of lean body mass and adipose tissue. 12 13

For the diagnosis of sarcopenia, a reliable method that is widely applicable and with high specificity, also high sensitivity and reproducibility is recommended to perform measurements of skeletal muscle mass. Computed tomography (CT) and magnetic resonance imaging (MRI) are known for their specificity and accuracy in body imaging and can lead to the diagnosis of sarcopenia. 14

The use of computed tomographic images to determine body composition was first reported in 1979 and 1981 by Heymsfield et al. 15

In 1986, Kvist assessed adipose tissue volume tomographically. 16 Shen showed an increased correlation between two-dimensional abdominal muscle areas and adipose tissue, measured only on a single tomographic section in 2004. 17

In most of the later studies, the third lumbar vertebra (L3) was chosen as the level to perform these measurements as a standard landmark. 7 18

At this level, the skeletal muscles, rectus abdominis, external oblique, internal oblique, transversus, psoas major, quadratus lumboris, and erector spinae muscles, are visible and can be selected and measured manually, or using programs specifically designed for these measurements.

In 2008, Prado et al. were the first to show that a low skeletal muscle mass index at the level of the L3 vertebra was associated with impaired outcome in patients suffering from upper respiratory and digestive tract malignancies. 18 They introduced the term "sarcopenia in oncology". Although, strictly speaking, only low muscle mass index is not consistent with the European Working Group on Sarcopenia in the Elderly (EWGSOP) definition of sarcopenia, because the definition of sarcopenia also includes low muscle function. 19 However, this term, sarcopenia, is generally used in the surgical and oncological literature to describe low skeletal muscle mass.

Although perioperative care and outcomes have greatly improved in recent decades with the introduction of new surgical techniques and Enhanced Recovery After Surgery (ERAS), preoperative risk assessment remains extremely important to further improve outcomes and adaptation of treatment strategies for oncological patients. 20 21

Given the increasing age of the population, increasing incidence of cancer, and increasing surgical and medical treatment options, skeletal muscle

mass could be an important addition, used for risk assessment or as a therapeutic target to improve the outcomes of oncology treatment.

Therefore, the aim of this paper was to investigate the applicability of tomographic skeletal muscle mass measurements and to define the relevance of low skeletal muscle mass in the therapy of digestive cancers. For this purpose, we conducted a retrospective study, in the Center for Oncological Digestive Surgery of the Fundeni Hospital, in 2019.

The chosen theme is interdisciplinary, being on the border between oncology, surgery, gastroenterology and even intensive care, with nutrition and perioperative care specific to digestive cancer patients.

The limits of the research carried out are primarily given by the fact that the current study is retrospective and was carried out during the Covid - 2019 pandemic, when the number of patients in surgery clinics decreased by more than 60% of the usual one.

The prospects for further research are interesting and perhaps promise new results. In this sense, a prospective interventional study would be welcome, where to evaluate the postoperative results in the short and long term in patients who receive sarcopenia treatment versus those who are treated conservatively, without specific intervention on sarcopenia concurrently with cancer treatment.

I. General part – known aspects about sarcopenia

I. 1) Definition and classification; associations-interactions

Sarcopenia is characterized by a decrease in skeletal muscle mass, plus decreased muscle strength and/or decreased physical performance. 19

Sarcopenia is "a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes, including falls, fractures, physical disability, and mortality." 19

The first definition of sarcopenia was developed in 2010 by the European Working Group on Sarcopenia in Older People (EWGSOP), the updated definition of sarcopenia according to EWGSOP was modified by the same society in 2018. 19 22

Sarcopenia is officially called a muscle disease and has an ICD-10-MC diagnostic code. 23 24.

The new definition of sarcopenia in 2018 included low muscle function as a new and main feature of the disease. 19 22

As exemplified below (see Table 1), sarcopenia is likely when low muscle strength is detected. A diagnosis of sarcopenia is confirmed by the presence of reduced muscle quantity or quality. If low muscle performance is added, then sarcopenia is severe. So that, within the diagnostic algorithm, there is also a classification from the point of view of the severity of sarcopenia.19

Tabel 1 Sarcopenia diagnosis algorithm and severity classification

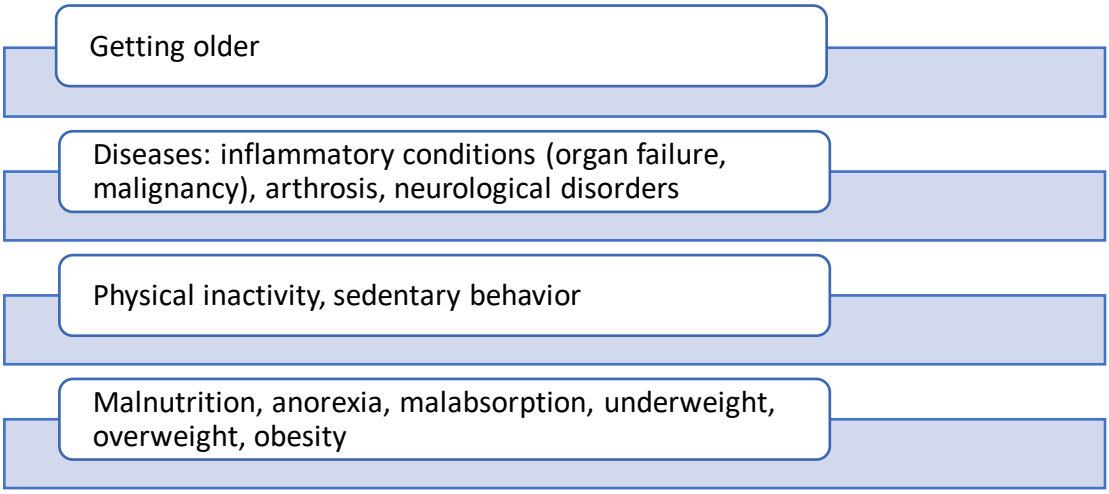
Sarcopenia diagnosis algorithm
Definition of sarcopenia
Probable sarcopenia identified according to criterion 1.
Diagnosis of sarcopenia confirmed by additional investigations, compatible with criterion 2.
If criteria 1,2,3 are met simultaneously, sarcopenia is considered severe
1. Reduced muscle strength
2. Reduced muscle quantity or quality
3. Low physical performance

Classification from the etiological point of view

Primary and secondary sarcopenia

Sarcopenia is considered "primary" (or age-related) when no other specific cause is evident, while sarcopenia is considered "secondary" when causative factors other than (or in addition to) aging are evident. Sarcopenia can occur secondary to a systemic disease, when inflammatory processes are activated, as in malignancy or organic failure. The factors that determine and aggravate muscle quantity and quality are also those that have led to an etiological classification of sarcopenia (see figure 1). 25 26

Figure 1 Factors that determine and aggravate muscle quantity and quality



Evolutionary classification

Acute and chronic sarcopenia

EWGSOP2 (definition updated 2018) recently identifies subcategories of sarcopenia from a developmental perspective as acute and chronic. Sarcopenia that has lasted less than 6 months is considered an acute condition, while sarcopenia that has lasted more than 6 months is considered a chronic condition. Acute sarcopenia can be associated with any acute pathology with limited evolution, including trauma, while chronic sarcopenia is associated with chronic and progressive conditions and increases the risk of mortality. In order to

diagnose, classify, treat and monitor sarcopenia, specific investigations must be carried out in the course of the disease. 26

Interactions

Sarcopenia associated with obesity is called sarcopenic obesity. Also, sarcopenia is included in the frailty syndrome phenotype, it is associated with malnutrition (which is defined as a morbid state, secondary to an excess or deficit of macro/micro nutrients, relative or absolute, which is associated with increased morbidity and mortality27) and cachexia.

I. 2) Screening and diagnosis of sarcopenia

In clinical practice, identification of sarcopenia occurs when a patient shows symptoms or signs of sarcopenia (decreased muscle strength), such as: falls, decreased walking speed, difficulty rising from a chair, or weight loss / mass loss muscular. 28

In such cases, tests for the identification and diagnosis of sarcopenia, outlined below, are recommended.

Identification of sarcopenia/ Screening

EWGSOP2 recommends the use of the SARC-F questionnaire (strength, assistance with walking, rising from a chair, climbing stairs and falls), a 5-question questionnaire (see Table 2), which assesses the risk of sarcopenia, as a simple way to identify patients with characteristic signs of this disease.

Tabel 2 SARC Questionnaire – F 29 – positive at ≥ 4

SARC – F Questionnaire		
Component parts	**Question**	**Score**
Endurance/Strength	What is the difficulty in carrying or lifting 10 kg?	None = 0 Easy = 1 Large/Incapable = 2
Walking assistance	What difficulty do you have walking into a room?	None = 0 Easy = 1 Large/Incapable = 2
Rising from the chair	What difficulty do you have in getting up from a chair?	None = 0 Easy = 1 Large/Incapable = 2
Climbing the stairs	What difficulty do you have in climbing 10 steps?	None = 0 Easy = 1 Large/Incapable = 2
Falling	How many times have you fallen in the last year?	None = 0 1-3 = 1 ≥4 = 2
Malmstrom TK, Miller DK, Simonsick EM et al. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle 2016; 7: 28–36. [29]		

Other screening tests for detecting sarcopenia are: the Ishii test, measuring muscle strength by squeezing the hand (handgrip strength), the bag test. 30 31 32

Sarcopenia diagnostic confirmation and severity classification

To confirm the diagnosis of sarcopenia, the quantity and/or quality of the reduced muscle mass must be highlighted. Assessment of physical performance through various existing methods can establish the severity of sarcopenia. 33

The amount of muscle, or muscle mass, can be estimated by a variety of techniques and there are several methods of adjusting the result for height or body mass index (BMI). 33 34

The amount of muscle can be reported as Skeletal Muscle Mass (SMM), or as muscle area, measured at a specific pre-set section of the body (Appendicular Skeletal Muscle Area - ASA).

Muscle quality is a relatively new term that encompasses aspects related to muscle composition (lipid inclusions), muscle fiber structure and function. 35

Diagnostic imaging tools such as MRI and CT can be used to assess muscle "quality" by determining muscle fat infiltration and measuring muscle radiodensity. 36 37

To date, there is no universal consensus on sarcopenia assessment methods for routine clinical practice, nor specific indications with a high degree of recommendation for the assessment of sarcopenia in patients with certain pathologies.

Diagnostic methods used for sarcopenia are as follows: computed tomography, magnetic resonance imaging, dual energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA).

The classification in a mild or severe form of sarcopenia is made from the perspective of physical performance. Physical performance was defined as objectively measured whole body function related to locomotion. This is a multidimensional concept that involves not only muscles, but also central and peripheral nervous function, including balance. 38

Physical performance can be measured in different ways: walking speed assessment, Short Physical Performance Battery (SPPB) and Timed-Up and Go (TUG), among other tests. 39

I. 3) Epidemiology/Etiopathogenesis

The causes of sarcopenia are divided into two and determine the etiological classification: primary, which represent age-related changes, which determine this disease, and secondary causes, which consist of factors other than aging, which can cause the disease, such as: inflammatory diseases, insufficient organ, cancers, gastrointestinal diseases accompanied by malabsorption, endocrine diseases, neurological pathology (inactivity, disabilities). Thus we find in the specialized literature primary sarcopenia and secondary sarcopenia. 19

Regarding the prevalence of secondary sarcopenia, we have selected some data from the literature as a generality: the prevalence of sarcopenia among digestive cancers varies between 11-74%. The prevalence of sarcopenia in patients with chronic kidney disease is 5.9–14% during the predialysis stages and 12.7–33.7% during the dialysis stage, and

sarcopenia develops with the evolution of the underlying disease. The prevalence of sarcopenia in patients with chronic obstructive pulmonary disease and HIV is 14.5% and 5–24.2%, respectively. 40

I. 4) Cellular metabolism in malignancy

It is well known that muscles have an important metabolic role, they are the place where glucose is absorbed and stored, they are also the main reservoir of amino acids and proteins, they are the main source of ATP (adenosine triphosphate), so the body's main energy reservoir. Also, for inter-organ communication, in cellular and energy metabolism, the musculature is the main regulator. 41 42 These sources of ATP and amino acids are consumed in acute and chronic diseases. 43 Cancer cells excessively consume glucose molecules precisely because they only partially break down glucose molecules. Cancer cells use glycolysis, not oxidative phosphorylation. This results in only 2 molecules of ATP (adenosine triphosphate) for each molecule of glucose, metabolized, instead of the 36 molecules of ATP produced by healthy cells. As a result, cancer cells must use many more glucose molecules, resulting in enough energy to survive. This is the best-known example of metabolism in cancers and is called the Warburg effect or anaerobic glycolysis, it is the classic example of a reprogrammed metabolic pathway in cancer. 44

I. 5) The impact of malnutrition and cachexia in oncological pathology

Malnutrition in cancer is a result not only of inflammatory muscle wasting, but also of inadequate nutritional intake that can lead to and perpetuate the depletion of the body's fat and lean mass stores and ultimately lead to reduced physical function. . 45 Lack of appetite is the first cause of malnutrition most of the time, hence a vicious circle that will be maintained in various forms, depending on the type of cancer and the adjacent symptoms, sarcopenia and/or even cachexia appearing in oncological diseases producing negative effects in in addition to those of the disease itself. 46

I. 6) Sarcopenia as a risk factor in oncological pathology

Sarcopenia is part of the cachectic syndrome in cancer patients, in this case the definitions of the two should be intertwined, given that we are discussing secondary sarcopenia, which occurs as a result of metabolic and inflammatory changes in cancers.

I. 7) How can sarcopenia be combated?

Effective treatment of cachexia and sarcopenia requires a more complex approach than increasing caloric intake. Adequate caloric intake and nutritional supplementation alone are often unsuccessful in restoring muscle mass in patients suffering from sarcopenia or cachexia. 47

Appetite stimulants (eg, megestrol, steroids, and cannabinoids), which have been studied in patients with cachexia for decades, helped weight gain but failed to improve other outcomes, such as physical performance and survival. 48 49 50

II. SPECIAL PART – OWN CONTRIBUTIONS

II. 1) Objectives

Is sarcopenia a pathology associated with oncological diseases of the digestive system, has a significant negative impact and influence on their treatment and evolution? Considering that the data in the literature regarding sarcopenia are contradictory and controversial, this paper aims to evaluate the relevance that sarcopenia had in patients with digestive cancers, in a selected group of patients.

II. 2) Methodology

Data collection:

With the consent of the "Ethical Committee" of the "Fundeni Clinical Institute", including the use and publication of these retrospectively analyzed data, we evaluated a number of 155 patients between January 2019 and December 2019 to establish the diagnosis of sarcopenia and its impact on the evolution of cancers digestive

A total of 464 cases with digestive cancers hospitalized during 2019 were selected following the search in the internal electronic database of patients from the "Department of Oncological Surgery and Transplantation" of the "Fundeni Clinical Institute". Exclusion criteria were: lack of abdominal tomographic assessment, need for emergency surgery and lack of histopathological diagnosis of cancer.

The main inclusion criterion for the study was the availability of an abdominal CT evaluation at the time of diagnosis. According to this criterion, 200 cases remained.

After the images were searched and analyzed in the database of the "Radiology and Imaging Department of the Fundeni Institute" 155 images were valid and validated. Some CT scans were performed in other radiology centers and the images were not uploaded to the local system or some of them were of poor quality.

In this study we present the data evaluated for 155 patients. It should be noted that this group of patients was heterogeneous in terms of cancer type.

The protocol for acquisition and evaluation of tomographic images is described below. Measurements were taken during the hospitalization, preoperatively, in which the diagnosis of digestive cancer was established.

We performed an observational, cohort, retrospective study with the aim of identifying the prevalence and impact of sarcopenia in patients with gastrointestinal and hepato-bilio-pancreatic cancers who underwent curative and palliative interventions or who after biopsy had were referred for radiotherapy/chemotherapy.

The patients were followed from the time of diagnosis/hospitalization, throughout the period of hospitalization during which the curative or palliative treatment was established and applied.

The prevalence of sarcopenia and the relationship between sarcopenia and bio-humoral values during hospitalization, postoperative complications, general complications, length of hospitalization, and histopathological results were analyzed.

The medical data were extracted for each patient from the observation sheets from the hospital archive and from the discharge sheets from the electronic archive, from the "Hippocrates" computer system of the Institute. The tomographic images were selected and processed from the archive of the "Clinical Laboratory of Radiology, Medical Imaging and Interventional Radiology of the Fundeni Clinical Institute".

Demographic and clinico-pathological data were extracted: age, sex distribution, BMI, bio-humoral values (hemoglobinemia, leukocytes, albuminemia, total proteinemia, creatinine, liver transaminases, etc.), anesthetic-surgical risk degree (ASA) , comorbidities, tumor location, tumor histopathological type, TNM classification/staging, resection type, reconstruction type, postoperative complications.

Diagnostic method for sarcopenia.

The diagnosis of "sarcopenia" was established by the computed tomography method.

Given that the tomographic evaluation is part of the evaluation and staging protocol of patients with digestive cancers and is also currently the "gold standard" in the diagnosis and confirmation of sarcopenia, it was used as the only diagnostic tool of this pathology to be able to obtain a standardization of the diagnostic method.

CT has become a routinely used diagnostic tool, especially in oncological pathology.

When interpreting routine scans of cancer patients, appropriate emphasis is placed on lesion detection, assessment and staging of loco-regional and distant lesions.

Body composition data that is routinely collected but not routinely analyzed is assessed, measured, and recorded during tomographic evaluations. This data could help personalize patient care.

We used a pilot group of 60 patients, in which we measured and calculated the Total Psoas Index at L3 and the Skeletal Muscle Index at L3, compared the threshold values, performed the ROC curve analysis, to evaluate the sensitivity and specificity of the Total Psoas Index to establish the diagnosis of sarcopenia. The purpose of determining a threshold value for the muscle mass index of the psoas muscles and comparing it with the skeletal muscle index at L3 was to validate a diagnostic marker for sarcopenia that is easier to

calculate and use, without requiring special computer programs, other than attached to the tomograph computer that was used.

The areas, perimeters and muscle radiodensities were measured and evaluated at the cross-section level of lumbar vertebra 3 (L3), which were later used for various calculation formulas.

How did we measure sarcopenia?

Tomographic images of hospitalized patients with cancers in the digestive sphere were evaluated, selected transverse sections at the level of the L3 vertebra, examinations performed natively and with contrast substance, but the measurements were performed on the native images, without contrast substance.

Tomographic scans were performed and selected transverse sections at the level of the L3 vertebra, in patients diagnosed with gastric, pancreatic, biliary tract, liver, colon and rectal cancer. Patients with a curative, palliative visa (surgical, endoscopic treatment, chemoembolizations) were evaluated, as well as the inoperable ones who, following tumor biopsies, were referred to chemotherapy/radiotherapy.

The scans were performed according to the local evaluation protocol for patients with digestive tract cancer. For the current study, non-contrast CT scanning with a section thickness of 3–5 mm was selected. Other scan parameters were as follows: 64-slice tomograph (Optima CT660 General Electric Medical Sytem); rotation time 0.6 s; tube current (range, 80–400 mA), helical acquisition mode – high quality and high speed; reconstruction algorithms were similar for all scans. Scanners were calibrated every 3 months using air-water phantoms. All scans were performed in the supine position.

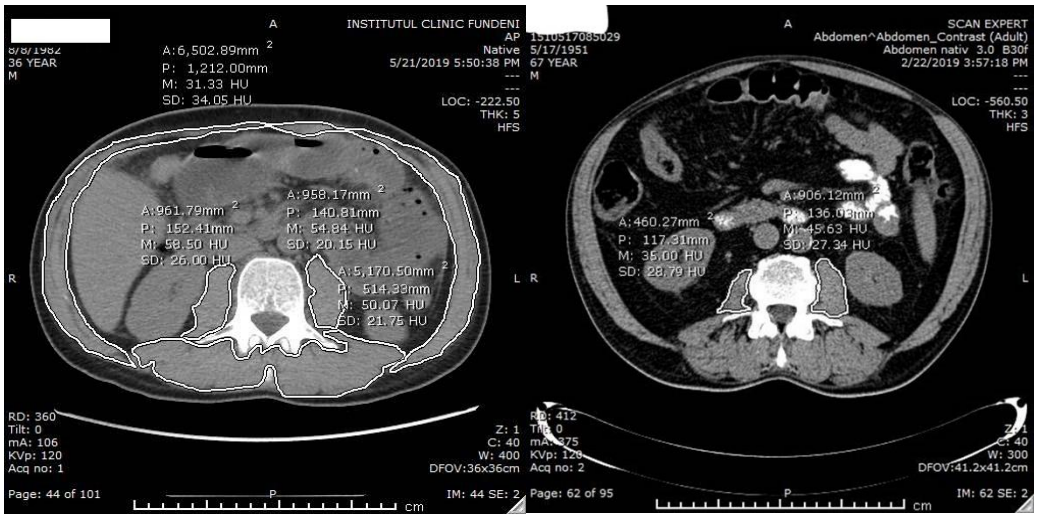
The L3 transverse image that most clearly displays both transverse vertebral processes was selected. The selected image had to be of sufficient quality for muscle analysis, meaning: no artefacts; without muscle breaks and clear differentiation between muscle and surrounding tissue.

The limits of the skeletal muscles at the level of the L3 lumbar vertebra were manually outlined: erector spinae muscles, square lumbar muscles, psoas muscles, transverse, internal oblique, external oblique and rectus abdominis, bilaterally.

After manual selection of the mentioned muscles, the CT workstation software (Advantage Workstation 4.7) elaborated the values of the selected muscles: area, perimeter, mean and SD of skeletal muscle radiation attenuation (see Figures 2, 3). The images that were taken in another medical unit were transferred to the database of the Fundeni Institute,

analyzed and processed with the help of the CT workstation software (Advantage Workstation 4.7), according to the protocol mentioned above.

Figure 2/Figure 3 Tomographic image exemplifying muscle selection at L3, cross section



II. 3) Results

As mentioned in the methodology, we initially worked with a pilot group of 60 patients, in which we calculated the total muscle area index at L3. This index, SMAI (skeletal muscle area index), was then used as a benchmark to establish the threshold value of the total muscle area index of the psoas. This threshold value of TPAI (total psoas area index) was calculated using ROC-AUC curves.

Characteristics of the pilot group (60 patients) for determining the threshold value of TPAI for sarcopenia (TPAI vs. SMAI) studied: Number of men 37 (61.66%) and women 23 (38.33%). Mean age 64.93, SD 10.54. Male average age 65.97, female average age 63.26. Average BMI 22.27; SD 5.37, mean weight (kg) 65.25, SD 17.35; mean height (m) 1.70, SD 0.058.

Mean, median and SD values for area, perimeter, right and left psoas muscle density, together with the index (areas relative to height) for these, are shown in (table 3).

Tabel 3 Area, perimeter, right and left psoas muscle radiodensity

	Average			Median			SD		
	Total	Bărbați	Femei	Total	Bărbați	Femei	Total	Bărbați	Femei
Right psoas									
Right psoas area cm²	6,43	7,10	5,36	5,80	6,60	4,88	2,36	2,51	1,65
Right psoas index cm²/m²	2,21	2,40	1,89	2,04	2,25	1,83	0,80	0,88	0,55
Right psoas perimeter cm	11,9	11,96	11,79	11,5	11,57	11,84	1,74	1,70	1,84
M Right psoas HU	38,73	39,06	38,18	38,89	39,75	38,49	7,24	6,89	7,89
SD Right psoas HU	27,13	26,95	27,41	27,63	26,82	27,95	5,23	5,45	4,95
Psoas stâng									
Left psoas area cm²	6,61	7,33	5,44	6,40	6,65	5,03	2,42	2,47	1,84
Left psoas area cm²/m²	2,27	2,48	1,92	2,17	2,31	1,89	0,83	0,86	0,64
Left psoas perimeter cm	11,99	12,29	11,50	11,81	12,33	11,61	2,17	2,38	1,72
M left psoas HU	37,60	39,04	35,29	37,58	39,93	36,32	8,87	8,97	8,37
SD left psoas HU	28,36	27,87	29,15	27,10	25,60	29,81	5,95	6,62	4,72
Total psoas area cm²	13,05	14,44	10,80	12,11	14,24	10,42	4,66	4,86	3,32
TPAI cm²/H²	4,48	4,89	3,81	4,15	4,62	3,82	1,59	1,71	1,14
ASM									
Area ASM cm²	116,51	120,87	109,50	114,45	115,30	101,47	26,04	24,66	27,22
SMAI cm²/m²	40,15	41,05	38,70	40,31	40,85	35,76	9,54	9,65	9,39
Perimeter ASM cm	220,77	241,13	188,02	198,81	201,67	181,62	11,47	14,12	28,83
M ASM HU	153,34	160,75	141,44	146,47	152,07	144,02	44,36	48,65	34,11
SD ASM HU	14,47	13,98	15,28	13,14	12,40	14,76	4,16	4,53	3,41

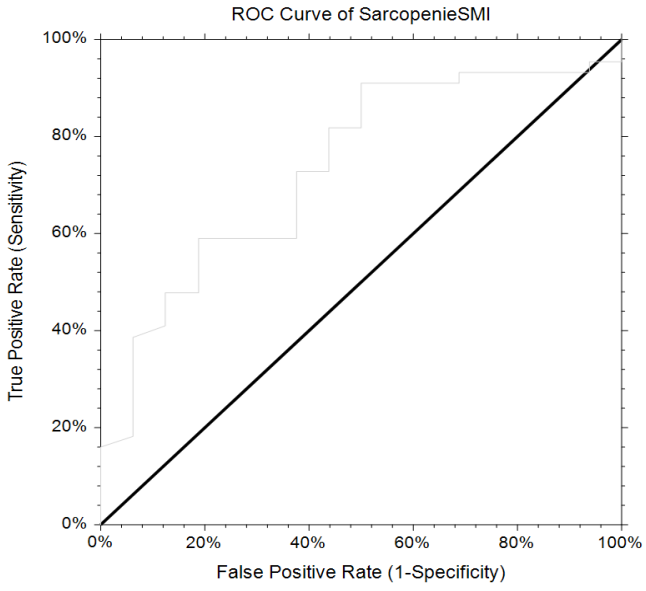
To evaluate to what extent, we can use the TPAI in establishing the diagnosis of sarcopenia, we performed an ROC analysis, in which we compared the ability of the TPAI to establish the diagnosis relative to the SMAI values established by the EWGSOP.

Also, the threshold values of TPAI to diagnose sarcopenia in women and men were established using ROC and AUC (Receiver Operating Curve/Area Under the Curve), taking as a benchmark the SMAI values proposed by the EWGSOP in 2008, for women, SMAI < 38.5 cm2 /m2; for men, SMAI < 52.4 cm2/m2. We chose as a reference the EWGSOP values from 2008, these being the most common in the specialized literature, most of the studies conducted on sarcopenia, referring to these values, from 2008 until now.

Following the analysis of the ROC curves (TPAI compared to SMAI) for 60 patients we obtained the following information:

TPAI predicts sarcopenia with AUC of 0.8358, p-value 0.0006, 95% CI 0.6589 to 0.9486 (see figure 4).

Figură 4 ROC-AUC curve for TPAI relative to SMAI



The estimated prevalence of sarcopenia in that group was 73.33% (44/60).

ROC analysis (TPAI relative to SMAI) for men revealed the following values: area under the ROC curve - AUC was 0.9125, standard error 0.0495, 95% CI 0.7452 to 0.9717, p-value (area=0.5) <0.0001. Youden index 0.9063. Sensitivity 90.62 % and specificity 100 % (see figure 14).

The threshold value obtained for male TPAI in patients from the studied group is 6.27 cm^2/m^2.

After establishing the threshold value for TPAI in men, the prevalence of sarcopenia was calculated based on it. Out of 37 men, 32 (86.49%) were sarcopenic, 5 (13.51%), non-sarcopenic.

ROC analysis (TPAI relative to SMAI) for women revealed the following values: area under the ROC curve (AUC) was 0.8977, standard error 0.0714, 95% CI from 0.7090 to 0.9848, p- value (area=0.5) <0.0001. Youden index J 0.7273. Sensitivity 100% and specificity 72.73%.

The threshold value obtained for female TPAI in patients from the studied group is 3.97.

Also, after obtaining the threshold value of TPAI for women, the prevalence of sarcopenia was calculated. Out of 23 women, 12 (52.17%) were sarcopenic, 11 (47.83%), non-sarcopenic

Analysis of the ROC-AUC curves were also performed for the right and left psoas muscles, separately, in relation to the SMAI, to assess their ability and accuracy individually to diagnose sarcopenia.

Values obtained for the ability of the right psoas muscle (right psoas area index) PDAI (relative to SMAI) to predict the diagnosis of sarcopenia.

AUC 0.7528, standard error 0.0668, p-value 0.0001, CI 95%, from 0.5897 to 0.8569.

The values obtained for the ability of the left psoas muscle (left psoas area index) PSAI (relative to SMAI) to predict the diagnosis of sarcopenia.

AUC 0.7003, standard error 0.0785, p-value 0.0054, CI 95%, from 0.5124 to 0.8242.

According to the values obtained with the help of the ROC-AUC curves, it results a higher capacity, with sensitivity and specificity over 90%, of the TPAI (right and left psoas total area index) measured tomographically to determine the diagnosis of sarcopenia, than of the right or left psoas muscles, individual.

From ROC curve analyzes for the psoas muscles, the diagnostic accuracy of the total psoas muscle area index (TPAI) is good and close to the diagnostic accuracy of the skeletal muscle area index (SMAI).

We evaluated the presence of sarcopenia in the group of 155 patients with digestive cancers using TPAI, which is easier to calculate and less time-consuming, does not require special calculation programs, and is available to any clinician who treats a patient with an oncological disease in the digestive sphere and has a quality tomographic image at the level of the L3 vertebra, transverse section.

The prevalence of sarcopenia was 123/155, 79.35%. AUC 0.9002; standard error 0.0274; p-value 0.00001; 95% CI from 0.8306 to 0.9421.

Male sarcopenia: estimated prevalence 75/92, 76.19%. AUC 0.9886; standard error 0.0059; p-value 0.00001; 95% CI from 0.9687 to 0.9959.

Sarcopenia women: estimated prevalence 48/63, 81.52%. AUC 0.9812; standard error 0.0136; p-value 0.00001; 95% CI from 0.9239 to 0.9955.

The average age of sarcopenic patients was 64 years, of non-sarcopenic patients 65 years. The mean value of TPAI in sarcopenic patients was 3.8 cm2/m2, with SD 1.17 cm2/m2, in non-sarcopenic patients it was 6.26 cm2/m2 SD of 1.48 cm2/m2. The difference between the BMI of sarcopenic and non-sarcopenic patients was not significant (see Table 4).

The frequency of tumor locations was as follows: pancreas and rectum with 20% each, colon 19%, stomach and esophageal-gastric junction 16%, liver 14% and extrahepatic bile ducts 11%. TNM stages III and IV, totaled a percentage of 70%. From the histopathological point of view, grade II was the most frequent, 43%, and for hepatocarcinomas, grades II-III, according to the Edmonson Steiner classification, prevailed (see table 5).

The number of total hospital days and the number of postoperative hospital days between sarcopenic and non-sarcopenic did not differ much, this difference being 1 day. Sarcopenic patients stayed 1 day longer in the hospital than non-sarcopenic patients, without statistical significance (see Table 6).

Tabel 4 Age/TPAI/BMI for the 155 patients

	SARCOPENIC			NON-SARCOPENIC		
Characteristics	Total patients	Men	Women	Total patients	Men	Women
Age, average, SD	64,65; 11,86	64,73; 11,80	65,54; 12,08	65,25; 9,57	65,52; 8,93	64,93; 10,55
TPAI(cm^2/m^2) medium value	3,80; 1,17	4,36; 1,07	2,93; 0,68	6,26; 1,48	7,45; 0,81	4,91; 0,66
BMI kg/m^2	21,73; 5,56	22,09; 5,08	21,17; 5,17	21,65; 4,83	22,62; 5,25	20,56; 4,21

Tabel 5 Tumor location in sarcopenic and non-sarcopenic patients

Tumor locations	**No. total patients**	**SARCOPENIC**	**NON-SARCOPENIC**
Stomach and esogastric junction	24 (16%)	19 (79,16%)	5 (20,84%)
Pancreas	31 (20%)	23 (74,19%)	8 (25,81%)
Extrahepatic bile ducts	17 (11%)	14 (82,35%)	3 (17,65%)
Liver	22 (14%)	18 (81,81%)	4 (18,19%)
Colon	30 (19%)	25 (83,33%)	5 (16,67%)
Rect	31 (20%)	24 (77,41%)	7 (22,59%)
TNM			
I	16 (10%)	12 (75%)	4 (25%)
II	31 (20%)	23 (74,19%)	8 (25,81%)
III	72 (47%)	56 (77,77%)	16 (22,23%)
IV	36 (23%)	32 (88,88%)	4 (11,12%)
Histopathologic grades			
I	50 (32%)	40 (25,80%)	10 (6,45%)
II	67 (43%)	51 (32,90%)	16 (10,32%)
III	24 (16%)	19 (12,25%)	5 (3,22%)
Classification Edmonson-Stainer			
II-III	13 (8%)	13 (8,38%)	
III-IV	1 (1%)		1 (0,64%)

Tabel 6 Duration of hospitalization of patients

	No. Total patients (Mean)	Sarcopenic (Mean)	Non-sarcopenic (Mean)	p-value
Duration of hospitalization, no. total days	14,97	15,16 (SD 7,72)	14,03 (SD 6,29)	0,057
No. of days of postoperative hospitalization	10,61	10,88 (SD 7,19)	9,58 (SD 4,11)	0,069

In both sarcopenic and non-sarcopenic patients, cardiovascular comorbidities predominated.

Notably, in terms of comorbidities, sarcopenic patients had an 11% higher prevalence of antecedent malignancies other than those at the time of study assessment, i.e., metachronous cancers, while non-sarcopenic patients had a prevalence of neoplasia in history of 3%. Metachronous cancers are tumors diagnosed more than 6 months after the diagnosis of another cancer, regardless of site.

Also, sarcopenic patients had 9% of liver infections with virus B and C, compared to non-sarcopenic patients, where there was only one case of hepatocarcinoma with virus C in the antecedents.

Patients with no history of comorbidities were 20% among sarcopenic and 41% among non-sarcopenic.

We applied the statistical tests mentioned in the methodology for the own threshold value of TPAI (F/B) obtained and applied to the group studied and described by patients, following whether the development of graded complications according to the Clavien Dindo classification, the appearance of postoperative fistulas, moderate or severe anemia at discharge, major bleeding, defined by a decrease in hemoglobin of more than 2 g/dl, hypoalbuminemia at discharge, and a decrease in albumin of more than 1 g/dl postoperatively, correlates with sarcopenia defined by TPAI values below the threshold value.

Continuous variables with normal distribution were expressed as mean ± standard deviation. Continuous variables with non-normal distribution were expressed as median [interquartile range]. Qualitative variables were expressed as absolute numbers and percentages. Univariate analysis was used to correlate TPAI as a continuous variable with

selected outcomes. The corrected Chi-square test was used to correlate sarcopenia defined by the TPAI value.

Tabel 7 Sarcopenia - Predictor of postoperative results in all patients according to sex.

	TPAI Sarcopenia N=155	**Men patients N=92**	**Women patients N=63**
	AUC (95%CI)	AUC (95%CI)	AUC (95%CI)
Complications	0.562 (0.471 – 0.653) p=0.191	0.508 (0.390– 0.627) p=0.891	0.598 (0.451 – 0.746) p=0.193
Postoperative fistulas	0.601 (0.469 – 0.734) p=0.163	0.610 (0.424 – 0.796) 0.335	0.481 (0.283 – 0.679) p=0.842
Complications I-II Clavien-Dindo	0.580 (0.487 – 0.673) p=0.091	0.554 (0.430 – 0.678) p=0.378	0.644 (0.507 – 0.781) p=0.54
Complications III-IV Clavien-Dindo	0.530 (0.416 – 0.643) p=0.630	0.518 (0.353 – 0.682) p=0.844	0.433 (0.272 – 0.595) p=0.439
Deacresed hemoglobin > 2g/dl	0.538 (0.445 – 0.630) p=0.421	0.471 (0.350 – 0.592) p=0.635	0.622 (0.484 – 0.761) p=0.096
Anemia at discharge	0.606 (0.491 – 0.721) p=0.127	0.492 (0.346 – 0.638) p=0.916	0.667 (0.453 – 0.881) p=0.333
Moderate/severe anemia at discharge	***0.599 (0.509 – 0.689) p=0.034***	0.531 (0.411 – 0.652) p=0.612	0.639 (0.501 – 0.776) p=0.060
Hypoalbuminemia at discharge	***0.607 (0.497 – 0.716) p=0.046***	***0.640 (0.508 – 0.773) p=0.049***	0.545 (0.359 – 0.730) p=0.622
Deacreased albumin > 1mg/dl	0.514 (0.421 – 0.606) p=0.773	0.439 (0.320 – 0.558) p=0.315	0.605 (0.463 – 0.747) p=0.155

It results those patients with sarcopenia defined by TPAI values, regardless of gender classification, had a significantly higher risk of developing moderate/severe anemia during hospitalization, as well as hypoalbuminemia. Sarcopenic men had a greater tendency to develop hypoalbuminemia in the postoperative period than women and non-sarcopenic men (see Table 7).

Evaluation of the impact of sarcopenia according to TAPI threshold values obtained by other authors, in other medical centers in the world

Given that sarcopenia did not present a negative impact with statistical significance in the studied group of patients mainly on Clavien Dindo complications, I wanted to evaluate the impact of diagnosed sarcopenia, using the TPI and according to the threshold values presented in the international specialized literature.

The main difference with our patient group, which is a mixed group in terms of neoplasia, was that the patient groups in the literature are performed on a single type of neoplasia. One of the reasons why sarcopenia did not prove its negative impact with clinical significance among Clavien Dindo complications could have been the heterogeneous group of patients we had.

We identified in the literature a variety of TPI threshold values, for homogeneous groups of patients, used to define sarcopenia.

So, in the same way that we evaluated the impact of sarcopenia, diagnosed using our own TPI threshold value, we applied the same statistical tests for TPI threshold values in the literature, looking at whether the development of graded complications according to the Clavien Dindo classification, the occurrence of postoperative fistulas, Clavien Dindo complications I-II versus III-IV, moderate or severe anemia at discharge, major bleeding, defined by hemoglobin drop of more than 2 g/dl, hypoalbuminemia at discharge and albumin drop of more than 1 g/dl postoperatively, correlate with sarcopenia defined by different TPI threshold values from the literature.

Continuous variables with normal distribution were expressed as mean ± standard deviation. Continuous variables with non-normal distribution were expressed as median [interquartile range]. Qualitative variables were expressed as absolute numbers and percentages. Univariate analysis was used to correlate TPAI as a continuous variable with selected outcomes. The corrected Chi-square test was used to correlate sarcopenia defined by different TPI values (Threshold value 1 - Dodson et al. (243), Threshold value 2 - Jung et al. (244), Threshold value 3 - Kasahara (245), Threshold value 4 - Kayano et al. (246),

Threshold value - Nakayama et al. (247), Threshold value 6 - Williet et al. (248), Threshold value 7 - Xu et al. (249)) with selected results (see table 8).

Tabel 8 Threshold values of TPAI from the literature

TPAI threshold values	Women (cm^2/m^2)	Men (cm^2/m^2)
Threshold value 1	3.38	4.77
Threshold value 2	4.43	8.18
Threshold value 3	2.07	2.49
Threshold value 4	2.89	4.75
Threshold value 5	3.92	6.36
Threshold value 6	4.37	5.73
Threshold value 7	3.46	4.78

General complications			
TPI threshold values for sarcopenia in the literature	Any complicatons	Complicații Clavien-Dindo III/IV	Fistulae
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Sarcopenia according to threshold value 1	1.14 (0.93 – 1.40) p=0.28	0.98 (0.85 – 1.13) p=0.95	1.03 (0.93 – 1.16) p=0.71
Sarcopenia according to threshold value 2	1.09 (0.79 – 1.50) p=0.86	0.93 (0.68 – 1.26) p=0.86	0.95 (0.75 – 1.21) p=0.66
Sarcopenia according to threshold value 3	1.17 (0.75 – 1.82) p=0.64	0.87 (0.74 – 1.04) p=0.49	1.14 (0.86 – 1.50) p=0.44
Sarcopenia according to threshold value 4	1.07 (0.87 – 1.32) p=0.63	0.94 (0.82 – 1.08) p=0.56	1.003 (0.89 – 1.13) p=0.96
Sarcopenia according to threshold value 5	1.06 (0.84 – 1.34) p=0.77	0.97 (0.81 – 1.16) p=0.91	1.01 (0.88 – 1.15) p=0.91
Sarcopenia according to threshold value 6	1.19 (0.97 – 1.46) p=0.21	1.02 (0.86 – 1.20) p=0.82	1.09 (0.99 – 1.22) p=0.29
Sarcopenia according to threshold value 1	1.12 (0.91 – 1.37) p=0.38	0.97 (0.84 – 1.12) p=0.84	1.03 (0.92 – 1.15) p=0.79
	Development of anemia in relation to sarcopenia		
	Deacresed Hb ≥ 2g/dL	Anemia at discharge	Moderat/Severe anemia at discharge
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Threshold value 1	1.13 (0.84 – 1.51) p=0.51	1.18 (0.52 – 2.68) p=0.87	***1.37 (1.02 – 1.84) p=0.05***
Threshold value 2	1.15 (0.73 – 1.81) p=0.79	1.21 (0.32 – 4.66) p=0.78	1.02 (0.60 – 1.73) p=0.94
Threshold value 3	1.57 (0.76 – 3.22) p=0.24	N/A	1.93 (0.83 – 4.49) p=0.10
Threshold value 4	1.21 (0.89 – 1.63) p=0.27	1.17 (0.51 – 2.71) p=0.89	1.22 (0.89 – 1.66) p=0.26
Threshold value 5	1.03 (0.74 – 1.44) p=0.85	0.58 (0.18 – 1.87) p=0.51	1.21 (0.88 – 1.66) p=0.35
Threshold value 6	1.06 (0.76 – 1.47) p=0.86	0.79 (0.28 – 2.24) p=0.88	1.09 (0.79 – 1.53) p=0.73
Threshold value 7	1.18 (0.89 – 1.58) p=0.31	1.02 (0.45 – 2.32) p=0.96	1.31 (0.97 – 1.76) p=0.11
	Development of hypoalbuminemia in relation to sarcopenia		
	Decrease in albumin > 1 mg/dL	Hypoalbuminemia at discharge	
	OR (95%CI)	OR (95%CI)	
Threshold value 1	1.02 (0.75 – 1.38) p=0.89	1.81 (0.99 – 3.28) p=0.07	
Threshold value 2	1.03 (0.61 – 1.75) p=0.91	1.75 (0.82 – 3.74) p=0.31	
Threshold value 3	1.39 (0.69 – 2.82) p=0.45	1.01 (0.36 – 2.86) p=0.98	
Threshold value 4	1.05 (0.78 – 1.43) p=0.74	1.71 (0.91 – 3.24) p=0.09	
Threshold value 5	1.08 (0.77 – 1.52) p=0.79	1.71 (0.95 – 3.08) p=0.13	
Threshold value 6	0.98 (0.68 – 1.39)	***2.03 (1.16 – 3.58)***	

	p=0.89	***p=0.02***
Valoare prag 7	1.07 (0.79 – 1.45) p=0.76	***1.91 (1.05 – 3.46)*** ***p=0.04***

Tabel 9 Sarcopenia (defined according to the threshold values of TPAI obtained by international authors) - Predictor of postoperative results

It is observed at threshold values for sarcopenia 1, 6 and 7 in sarcopenics, the development of moderate-severe anemia, respectively hypoalbuminemia at discharge (see table 9).

It is observed that the frequency/incidence of digestive, colorectal and hepato-bilio-pancreatic tumors is between 3-5 times higher in sarcopenics than in non-sarcopenics.
Also, the frequency of TNM stages III and IV is 3 to 8 times higher in sarcopenic patients. Histopathological grade II was the most common in both sarcopenic and non-sarcopenic patients, with a 3-fold higher incidence in sarcopenic patients.

TNM disease stages III and IV accounted for 70% of all cases, a possible reason for such an increased prevalence of sarcopenia and more. Most patients with digestive cancers, in advanced stages of the disease, are cachectic. I have already highlighted in the general part of the thesis that in the definition of sarcopenia and that of cachexia, there are common diagnostic criteria. This may be a reason why neither the difference in the type and frequency of Clavien Dindo complications was clinically significant higher in sarcopenics. In advanced stages of neoplasia, complications arise from multiple causes, patients are exhausted, and the emphasis on nutritional care and increasing muscle performance is not maximal or is missing in some centers.

The number of total and postoperative hospitalization days was only one extra day higher, on average, in sarcopenic patients. In advanced stages of the disease it is difficult to accurately extract the role of sarcopenia in the evolution of these patients.
The mean TPAI of sarcopenic men and women was 3.80 cm2/h2 with 4.36 cm2/h2 in men and 2.93 cm2/h2 in women.

The mean TPAI of non-sarcopenic men and women was 6.26 cm2/h2 with 7.45 cm2/h2 in men and 4.91 cm2/h2 in women.

A higher prevalence of comorbidities was observed in sarcopenic patients, especially of associated neoplasias in the antecedents. The highest frequency of comorbidities was that of cardiovascular diseases and the association of cardiovascular diseases with diabetes.

Among non-sarcopenic patients, 41% were observed to have no associated comorbidities.

II. 4) Discussions

In a personal review published in the Romanian Journal of Internal Medicine, on a heterogeneous population of patients with digestive cancers, the prevalence of sarcopenia was over 43%. The highest incidence of sarcopenia was among patients with esophageal cancer and the lowest among those with gastric cancer. 51 In the group of patients studied for this thesis, the prevalence of sarcopenia was over 70%.

The highest prevalence of sarcopenic patients in the studied literature was in esophageal cancer (70.4%) and liver (60.3%), followed by colorectal cancer (56.79%), pancreatic (53.05), biliary cancer (49.3%) and gastric cancer (32.05%), with the lowest prevalence.51

In the group of patients studied in this thesis, the prevalence of sarcopenia was as follows: 39% in colorectal cancer, 20% in pancreatic cancer, stomach and eso-gastric junction 16%, liver 14% and biliary tract 11%. There is an overlap of the prevalence with the data from the literature among colorectal and pancreatic cancers in our own case studies, with liver cancer at the opposite poles, which in the literature in terms of prevalence occupies a leading place, in its own group it is located on penultimate place. I cannot refer to the increased prevalence of sarcopenia in patients with esophageal cancer, because in my personal group we evaluated only cancers of the esophagogastric junction, not having a sufficient number of esophageal cancers to include in the study.

It is difficult to separate sarcopenia from cachexia, for example, in an oncological patient and to determine exactly to what extent which of the two pathologies (sarcopenia/cachexia) have a negative impact in the evolution of these patients and in determining certain complications, especially due to the fact that the definitions of these pathologies associated with neoplasias and the clinical signs overlap, especially in advanced stages of the disease.

In the same personal review regarding the prevalence of sarcopenia among digestive cancers, only two studies showed an increased share of postoperative complications in relation to sarcopenia. 51

Thus, it appears that both in the current thesis, on the studied group of patients, and in the specialized literature, a high prevalence of sarcopenia was demonstrated in patients with digestive cancers, however, this was not correlated with postoperative complications.

II. 5) Conclusions

- TPAI predicted sarcopenia in the pilot group, with AUC of 0.8358, p-value 0.0006, 95% CI from 0.6589 to 0.9486, relative to the threshold values of SMI, defined by EWGSOP in 2008, for women, SMI < 38.5 cm2/m2; for men, SMI < 52.4 cm2/m2, with sensitivity and specificity above 90 %.
- The estimated prevalence of sarcopenia in the pilot group was 73.33% (44/60).
- The threshold value obtained for TPAI in men, in the pilot group, is 6.27 cm^2/m^2.
- The threshold value obtained for TPAI in women, in the pilot group, is 3.97 cm^2/m^2.
- The left and right psoas muscles separately, individually, did not show a good diagnostic capacity in relation to SMAI.
- Following the analysis of the ROC curves for the psoas muscles, the diagnostic accuracy of the total psoas area index (TPAI) is good and approaches the diagnostic accuracy of the skeletal muscle area index (SMAI).
- In our study, sarcopenia did not have a significant impact on the length of hospitalization. A possible explanation may result from the higher percentage of advanced cancers.
- There was no significant difference in the distribution of cardiovascular comorbidities between sarcopenic and non-sarcopenic patients, but in the latter, the lack of pathological antecedents is more common.
- The prevalence of metachronous tumors was three times higher among sarcopenic patients.
- Complications assessed according to the Clavien-Dindo score are more frequent in sarcopenics compared to non-sarcopenics, although in this study the difference did not have statistical power.
- In patients with sarcopenia, the highest prevalence of complications was among gastric and gastro-esophageal tumors 23.52%, followed by colon tumors 20.58%, bile duct tumors 17.64%, rectal and pancreas, each with 14.7% and the liver with 8.82%.
- In patients undergoing surgery for digestive neoplasia, TPAI as the only parameter to define sarcopenia, did not prove a predictor for postoperative complications stratified according to Clavien Dindo classification.

- In our study, although the prevalence of sarcopenia was very high in patients with digestive cancers, it did not prove to be an independent negative predictive factor in the immediate postoperative evolution of these patients.
- Sarcopenia is an independent predictor for the development of postoperative hypoalbuminemia and anemia.
- Sarcopenia, as defined by TPAI, is not an independent predictive factor for postoperative fistulae.
- In our cohort, sarcopenia has a higher prevalence in digestive cancers due to advanced stages of oncological disease. This aspect is consistent with other studies in patients with digestive cancers.
- The impact of sarcopenia on postoperative complications is controversial in the literature. Even our study could not draw a firm conclusion in this direction, although there is a "trend" in favor of increasing these complications.

II. 6) Final remarks

Different formulas and programs are used to measure sarcopenia. An important point of this thesis is the fact that it demonstrates the validity, simplicity and speed with which TPAI can be calculated, using an image, a tomographic cross-section at the level of the L3 vertebra, considering that any patient evaluated for a digestive neoplasia, will perform this imaging investigation.

A prospective study, which we propose, could clarify whether certain interventions on sarcopenia in oncological patients result in improved prognosis in the medium term.

The study dedicated a significantly greater effort to the evaluation and validation of the diagnostic criteria, considering that the real impact of sarcopenia can only be demonstrated after its accurate diagnosis.

This paper wants a clinical tool, which can be the basis of future research on this topic, starting from an easy diagnostic method, less time-consuming and with determined threshold values.

Despite its significance and impact, the issue studied by us is little addressed at the national level. Using the search terms "sarcopenia" and "digestive cancers" on "PubMed" in August 2022, 584 articles from 2008 to the present resulted. The only articles by Romanian authors, being the ones resulting from the present study.

II.7) Limits of the study

- This study is retrospective and was conducted during the Covid-19 pandemic.
- Another limitation of the study derives from the fact that the selected group of patients is heterogeneous from the point of view of tumor locations.
- The diagnosis of sarcopenia was established based on muscle mass only, the study being retrospective, muscle strength could not be quantified, as recommended by EWGSOP2.

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