The prevalence and the impact of sarcopenia in digestive cancers. A systematic review

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Introduction: Sarcopenia is characterized by a decrease in skeletal muscle mass, associated with low muscle strength and/or poor physical performance. Assessing the prevalence of sarcopenia among digestive cancers and establishing the impact that sarcopenia has on the postoperative evolution of digestive tumors may be a central pillar in improving postoperative outcomes by caring for perioperative sarcopenia.

This brief review aimed to evaluate the prevalence of sarcopenia in digestive cancer patients.

Method and materials: PubMed database was searched for “sarcopenia” AND “digestive cancers” from January 1st, 2010, through September 30th, 2020. PRISMA guideline was used for this systematic review. After the selection process, 31 complete studies were included in our review.

Assessment of sarcopenia diagnosis for the studies included in this systematic review was based on a computed tomographic calculation of the skeletal muscle index at the third lumbar vertebra.

Results: Among a total of 11,651 patients with digestive cancers, the prevalence of sarcopenia was 43.68%.

The highest prevalence of sarcopenic patients was in esophageal (70.4%) and hepatic (60.3%) cancer, following by biliary tract (49.3%), pancreatic (45.70%), colorectal (42.83%) cancer, and gastric cancer (32.05%) with the lowest prevalence.

The results of the studies conducted by now regarding the prevalence of sarcopenia in digestive cancers and its relevance in the evolution of these cancers are discordant and uneven.

Some studies show that the presence of sarcopenia in patients with digestive cancers is associated with an increased rate of postoperative complications, increased toxicity of chemotherapeutics and increased mortality. Other studies do not find sarcopenia as an independent risk factor associated with negative consequences in the course of patients with digestive cancers.

Conclusions: Sarcopenia is prevalent in digestive cancers. There is still no consensus about the impact of sarcopenia on the treatment of digestive cancers. Further studies are needed to evaluate the real consequences of sarcopenia in digestive cancers..

Key words: sarcopenia, prevalence, tomography, malnutrition, chemotherapy, abdominal muscles.

INTRODUCTION

According to the updated definition of the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is a muscle disease defined as a progressive decrease in the quality and quantity of skeletal muscle and deterioration of physical function and performance [1]. Sarcopenia is probable when low muscle strength is detected, but the diagnosis is confirmed by the presence of low muscle quantity or quality. When low muscle strength, low muscle quantity/quality, and low physical performance are all detected, sarcopenia is considered severe [1].

The loss of muscle mass and strength accompanying aging is called primary sarcopenia

and could be regarded as a normal and physiological phenomenon. Sarcopenia which occurs and worsens concomitantly with oncologic and inflammatory systemic diseases, some type of chronic diseases, or following polytrauma is considered secondary sarcopenia (SeS).

Among the first who analyzed the primary sarcopenia was McDonald Critchley, a neurologist at Kings College Hospital in London, in 1931. In 1970, Nathan Shock published a series of articles about this topic. The term sarcopenia was suggested by Irwin Rosenberg at a meeting in Albuquerque, New Mexico, in 1988 [2].

Between 1979 and 1981, Heymsfield and collab. were the first who reported the use of

computed tomography (CT) images to evaluate skeletal muscle mass and adipose tissue. [3] In 2008, Prado *et al.* showed that a low L3 muscle index was associated with muscular impairment in patients with malignant disorders of the upper respiratory tract and digestive tract [4].

The recommended method as a “gold standard” for the diagnostic of sarcopenia in digestive cancers is the calculated skeletal muscle index (SMI) by computed tomography method [1,5]. Using specialized software, the appendicular skeletal muscle mass (ASM) at lumbar L3/L4 is calculated, then SMI, using the formula $ASM/height^2$. The cut-off points for men and women are: ASM <20 kg, and respectively 15 kg and SMI <7.0 kg/m², and respectively <5.5 kg/m² [1].

Skeletal muscle mass (SMM) is accounting for 30–40% of total body weight [6], [7]. Approximately 75% of SMM is located in the appendicular region [8].

The **appendicular** skeleton includes the bones of the shoulder belt, the upper limbs, the pelvic belt, and the lower limbs [9]. Reduction of appendicular skeletal muscle mass (ASMM) as a surrogate for sarcopenia is accompanied by negative health consequences such as weakness, disability, deteriorated quality of life (QOL), and mortality resulting in increased health care costs [10].

Using CT evaluation at lumbar L3, Prado *et al.* proposed for the diagnosis of sarcopenia a new formula based on the skeletal muscle area (SMA), which correlates with the whole-body skeletal muscle mass. The formula used is $SMI = SMA/height^2$ and the normal values are $\leq 52.4 \text{ cm}^2/\text{m}^2$ for males, and $\leq 38.5 \text{ cm}^2/\text{m}^2$ for females [4].

Dual-energy x-ray absorptiometry (DXA) are used to measure the SMM with high accuracy, but are expensive and not widely accessible and usually have high radiation exposure [11].

In recent years interest in sarcopenia associated with cancers has increased. As proof, the number of publications on the topic of secondary sarcopenia increased progressively, from 5 in 2010 to 61 papers in 2019 and 46 in 2020 [12].

Considering the increased prevalence of sarcopenia among digestive cancers [4,5], and the negative impact of preoperative sarcopenia on the post-operative outcomes in gastrointestinal cancers [13,14], a guideline for the diagnosis and management of sarcopenia in these patients may be useful.

The present systematic review aims to analyze the prevalence of sarcopenia in patients with digestive cancers.

This systematic review intended to summarize the literature sparse data on the prevalence of sarcopenia in digestive cancers, without being limited to a specific segment of the digestive tract or organ and without being limited by stage disease.

MATERIALS AND METHODS

For this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used [15].

Search strategy

We performed a systematic literature search on PubMed, Web of Knowledge, and Scopus databases from January 2010 to September 2020. The last search was on 30th September 2020.

The search query terms were: “sarcopenia” [MeSH Terms] OR “sarcopenia” [All Fields] AND “neoplasms” [MeSH Terms] OR “neoplasms” [All Fields] OR “cancers” [All Fields]/ AND “gastrointestinal neoplasms” [MeSH Terms] OR “gastrointestinal neoplasms” [All Fields]/ AND “gastrointestinal cancer” [MeSH Terms] OR “gastrointestinal cancers” [All Fields]/AND “pancreatic cancer/hepatic cancer/cholangiocarcinoma” [MeSH Terms] OR “pancreatic cancer/hepatic cancer/cholangiocarcinoma” [All Fields].

We considered for inclusion the full-text publications, in English. We subsequently included articles identified in other reviews, which were not found by the search strategy.

Eligibility criteria

The main criteria used for selecting the articles were: 1. reporting the prevalence of sarcopenia 2. the diagnosis of sarcopenia to be assessed by computed tomography method 3. a definite diagnosis of a gastrointestinal neoplasm (esophageal, gastric, colorectal, pancreatic, hepatic, or cholangiocarcinoma) of any stage, according to the TNM classification.

For the diagnosis of sarcopenia, we considered the computed tomography at the level of the third lumbar vertebra (L3) method and the calculated SMI based on total abdominal muscle area (TAMA), total psoas area (TPA), skeletal muscle mass (SMM), or appendicular skeletal muscle mass (ASM) adjusted by height. The cut-off values for the SMI were considered those recommended by the European Working Group on Sarcopenia in Older People (EWGSOP)[[1]] and the Asian Working Group for Sarcopenia (AWGS) [16].

We excluded the publications reporting the prevalence of secondary sarcopenia using other methods different from CT scan at the level of L3 vertebra.

Two authors (CH and LEM) independently analyzed the studies for eligibility. The differences were discussed with other authors until a consensus was reached.

Data collection

For each study included we collected the data regarding the type of study and publication year, the population (number of patients, sex, mean

age), the prevalence, and method of assessment of sarcopenia, the type of cancer, the distribution of patients on the different types of cancer, data regarding morbidity and mortality.

Quality assessment

The Newcastle-Ottawa assessment scale for case-control studies was used to assess the study quality [17]. The studies were classified as low quality (score <5 points), fair quality (6–7 points), and good quality 8–9 points) (Figure 1).

Figure 1. Quality assesment scale chart.

RESULTS

251 papers were identified through database searching. After screening of the title and abstract, 76 full-text articles were considered eligible. Of

these, 31 publications fulfilled the inclusion criteria (Figure 2). 12 studies were considered with fair quality, and 19 with good quality according to the quality assessment.

Figure 2. PRISMA chart. 25 were retrospective cohort studies, and 6 were prospective cohort studies. A summary of the main characteristics of the included studies is provided in Table 1.

Table 1
Characteristics of the studies included in the systematic review

Study	Year	Study type	Cancer type	Endpoint
Dijksterhuis <i>et al.</i> [18]	2019	Retrospective	Esophageal and esophagogastric cancer	Association between sarcopenia and survival, toxicity in a patient receiving palliative chemotherapy
Grotenhuis <i>et al.</i> [13]	2016	Prospective	Esophageal	Association between sarcopenia and postoperative short-term outcome (morbidity and mortality) and long-term survival in patients undergoing esophagectomy for cancer after neoadjuvant chemoradiotherapy
Järvinen <i>et al.</i> [19]	2018	Retrospective	Esophageal	Impact of sarcopenia on survival of advanced EC patients who received a stent for palliation of malignant obstruction.
Lee <i>et al.</i> [20]	2018	Retrospective	Gastric	The prognostic role of sarcopenia in patients with advanced gastric cancer
Lin <i>et al.</i> [21]	2018	Prospective	Gastric	The relationship between sarcopenia and systemic inflammatory response (neutrophil/lymphocyte ratio [NLR], platelet/ lymphocyte ratio [PLR], and large platelet/lymphocyte ratio [LPLR]) before radical gastrectomy for gastric cancer.
Zhuang <i>et al.</i> [14]	2016	Retrospective	Gastric	The prevalence of sarcopenia and assess its impact on postoperative complications and long-term survival in patients undergoing radical gastrectomy for gastric cancer.
Cespedes-Feliciano <i>et al.</i> [22]	2018	Retrospective	Colorectal	Sarcopenia as a predictor of mortality in non-metastatic colorectal cancer
Dolan <i>et al.</i> [23]	2019	Retrospective	Colorectal	The relationship between the systemic inflammatory response, skeletal muscle index (SMI), skeletal muscle density (SMD), and overall survival in patients with colorectal cancer.
Xiao <i>et al.</i> [24]	2019	Retrospective	Colorectal	The associations of medical and demographic characteristics with sarcopenia and low muscle radiodensity in patients with nonmetastatic colorectal cancer
Vashi <i>et al.</i> [25]	2019	Retrospective	Colorectal	Sarcopenia as a predictor of colorectal cancer
Kurk <i>et al.</i> [26]	2019	Prospective	Colorectal	Skeletal muscle mass loss and dose-limiting toxicities in metastatic colorectal cancer patients
Dolan <i>et al.</i> [27]	2019	Prospective	Colorectal	The relationship between sarcopenia and long-term outcomes in patients undergoing elective bowel resection for colorectal cancer.
Broughman <i>et al.</i> [28]	2015	Retrospective	Colorectal	The prevalence of sarcopenia in older adults with early-stage colorectal cancer.
Choi <i>et al.</i> [29]	2018	Retrospective	Colorectal	The influence of skeletal muscle and visceral fat on short-term and long-term outcomes in locally advanced rectal cancer patients treated with neoadjuvant.
Lieffers <i>et al.</i> [30]	2012	Retrospective	Colorectal	Sarcopenia related primary colorectal cancer resection outcomes in stage II–IV patients

Table 1 (continued)

Richards <i>et al.</i> [31]	2012	Retrospective	Colorectal	The Relationships between Body Composition and the Systemic Inflammatory Response in Patients with Primary Operable Colorectal Cancer
Takeda <i>et al.</i> [32]	2018	Retrospective	Lower rectal	Skeletal muscle loss is an independent negative prognostic factor in patients with advanced lower rectal cancer treated with neoadjuvant chemoradiotherapy
nishi <i>et al.</i> [33]	2018	Retrospective	Pancreatic	The prevalence of sarcopenia and its relationship with nutritional state and quality of life (QoL) in patients with digestive diseases.
Sakamoto <i>et al.</i> [34]	2020	Retrospective	Pancreatic	The prognostic significance of sarcopenia in patients with recurrent pancreatic cancer.
Naumann <i>et al.</i> [35]	2019	Retrospective	Pancreatic	Impact of sarcopenia on outcomes in locally advanced pancreatic cancer treated with chemoradiation
Gruber <i>et al.</i> [36]	2019	Retrospective	Pancreatic	Sarcopenia related postoperative complications and overall survival
Amrani <i>et al.</i> [37]	2018	Retrospective	Pancreatic	Sarcopenia-related postoperative pancreatic fistula, severe morbidity (Clavien $\geq$ 3), and survival.
van Dijk <i>et al.</i> [38]	2017	Prospective	Pancreatic	Sarcopenia related surgical site infections and survival rate
Ninomiya <i>et al.</i> [39]	2017	Retrospective	Pancreatic	Sarcopenia and clinicopathological features and prognosis on patients with resected pancreatic ductal adenocarcinoma
Peng <i>et al.</i> [40]	2012	Retrospective	Pancreatic	Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma.
Choi <i>et al.</i> [41]	2015	Retrospective	Pancreatic	Skeletal Muscle Depletion Predicts the Prognosis of Patients with Advanced Pancreatic Cancer Undergoing Palliative Chemotherapy
Ha <i>et al.</i> [42]	2018	Prospective	Hepatic	Impact of sarcopenia on overall survival in patients with newly diagnosed hepatocellular carcinoma.
Begini <i>et al.</i> [43]	2017	Retrospective	Hepatic	Impact of sarcopenia on overall survival in patients with hepatocellular carcinoma at first diagnosis.
Takagi <i>et al.</i> [44]	2016	Retrospective	Hepatic	Impact of sarcopenia on overall survival in patients with hepatocellular carcinoma undergoing hepatectomy
Zhou <i>et al.</i> [45]	2015	Retrospective	Biliary tract	The correlation between sarcopenia and prognosis of hepatectomy for hepatolithiasis-associated intrahepatic cholangiocarcinoma
Van Vught <i>et al.</i> [46]	2019	Retrospective	Biliary tract (perihilar cholangiocarcinoma)	Low Skeletal Muscle Density Is Associated with Early Death in Patients with Perihilar Cholangiocarcinoma Regardless of Subsequent Treatment

Regarding patient age and gender distribution, these data were available for 6,148 patients (54.48%), 53.3% males and 46.7% females. Eleven studies included in the final analysis did not report the distribution of different stages of the TNM classification. Ag the studies that provided this information, TNM stage IV was reported in 19.73% of patients with esophageal cancer, 21.17% with gastric cancer, and 3.7% with colorectal cancer. The main findings of each included study are presented in Table 2.

Table 2
Main findings in the studies included in the systematic review (References according to Table 1)

Study	Patients n (M/F)	Mean age, years	Tumor/Stage	Sarcopenia n (%)	Treatment	Results
Dijksterhuis <i>et al.</i>	88 (75 % M/F 25%)	63 y	Esophageal and esophagogastric cancer/TNM III/IV	49% Sarcopenic 20% Sarcopenic obesity	Palliative systemic treatment Capecitabine and Oxaliplatin	Pre-treatment sarcopenia was associated with the occurrence of grade 3-4 toxicity [odds ratio (OR) 0.94; 95% CI 0.89–1.00] in both univariable and multivariable logistic regression analyses, and sarcopenic obesity with grade 2 or more peripheral sensory neuropathy (OR 3.82; 95% CI 1.20–12.18) Sarcopenia (pre-treatment), sarcopenic obesity, low skeletal muscle density (SMD), and BMI did not impact progression-free survival and overall survival
Grotenhuis <i>et al.</i>	120 M = 88 (73%) F = 32 (27%)	62 y	Esophageal Stage I–III	54 (45%) Sarcopenic	Esophagectomy	Overall morbidity rate did not differ between sarcopenic (78 %) and non-sarcopenic (68 %) patients ($p = 0.24$); also, in-hospital mortality was not different between the two groups: sarcopenia 6 % versus non-sarcopenia 5%, $p = 0.80$. The type of complications (e.g., pulmonary, or cardiac complications and infections or anastomotic leakage) did also not differ between the groups. There was no significant difference in overall survival between the patients with or without sarcopenia ($p = 0.77$) or in disease-free survival ($p = 0.69$).
Järvinen <i>et al.</i>	238 M 159 (66.8%) F 79 (33.2%)	NR y	Esophageal Stage II–IV	199 (85%) Sarcopenic	Surgery / chemoradiation/ Palliative treatment – stent insertion	Median survival was 146 (range: 76–226) days in the sarcopenia group and 152 (range: 71–249) days in the non-sarcopenic group ($P = 0.61$). Complication rates between the groups were not significantly different ($P = 0.85$). In Cox regression analysis, the skeletal muscle index was inversely correlated with overall survival (hazard ratio 0.98, 95% confidence interval 0.97–0.99; $P = 0.033$)
Lee J.S. <i>et al.</i>	140 M 106 (75.7%)	69 y	Gastric Stage III/IV	67 (47.9%) Sarcopenic	Palliative chemotherapy	Patients with sarcopenia had a significantly shorter OS than those without sarcopenia (median, 6.8 months vs. 10.3 months, respectively; $p = 0.033$). In the multivariable analysis, sarcopenia was an independent prognostic factor of poor OS (hazard ratio, 1.51, $p = 0.029$); no response to chemotherapy ($p < 0.001$), no second-line chemotherapy ($p < 0.001$), metastatic sites ($p < 0.001$), and low serum albumin level ($p = 0.033$) were also independent prognostic factors of poor OS.

Table 2 (continued)

Lin J. <i>et al.</i>	670 M 504 F 166	NR	Gastric Stage I–IV	104 (15.5%) Sarcopenic	NR	Neutrophil/lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR) were independent predictors for sarcopenia ($P<0.05$).
Zhuang C.L. <i>et al.</i>	937 M 730 (77.9%) F 207 (22.1%)	64 y	Gastric Stage I–III	389 (41.5%) Sarcopenic	Gastrectomy	Sarcopenia was an independent risk factor for severe postoperative complications (OR=3.010, $P<0.001$), but not for total complications. Sarcopenia did not show a significant association with operative mortality. Sarcopenia was an independent predictor for poorer overall survival (HR=1.653, $P<0.001$) and disease-free survival (HR=1.620, $P<0.001$).
Céspedes-Feliciano. <i>et al.</i>	807 M 404 F 403	61 y	Colorectal Stage I–III	321 (39.77%) Sarcopenic	Surgery	The hazard ratio and 95% CI for death associated with a low linear area were hazard ratio = 1.66; 95% CI: 1.22, 2.25.
Dolan D.R.	650 M 354 F 296	Majority over 65 years of age	Colorectal Stage I–III	279 (42.9%) Sarcopenic	Surgery	A low SMI and SMD were significantly associated with an elevated mGPS (<0.05). On multivariate analysis, SMI (Martin) [hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.04–2.18, $P = 0.031$], SMD (Xiao) (HR 1.42, 95% CI 0.98–2.05, $P = 0.061$), and mGPS (HR 1.44, 95% CI 1.15–1.79, $P = 0.001$) were independently associated with overall survival.
Xiao J. <i>et al.</i>	3262 M 50.1% F 49.9%	62.6 ± 11.4 y	Colorectal Stage I–III	1383 (42.4%) Sarcopenic	Surgery	Compared with patients aged <50 y, the ORs for sarcopenia were higher in older age. groups: patients aged 70–80 y had the highest odds of sarcopenia (OR: 6.19; 95% CI: 4.72, 8.11). In simple linear regression analyses, SMI decreased 0.27 cm ² and SMD decreased 0.44 HU for every 1-y increase in age; on average, females had 11.05 cm ² lower SMI and 3.05 HU lower SMD than that of their male counterparts.
Vashi P.G. <i>et al.</i>	112 M/F - NR	53.3 y	Colorectal	46 (41.1%) Sarcopenic	NR	On multivariate analysis, after adjusting for age, gender, tumor stage, BMI, treatment history and SGA, patients with sarcopenia had 3 times greater risk of mortality compared to those without sarcopenia ($p = 0.001$).
Kurk S. <i>et al.</i>	557 M 63% F 37%	63 y	Colorectal Stage IV	361 (54%) Sarcopenic	Surgery and Chemotherapy	In this large longitudinal study in metastatic colorectal cancer patients during palliative systemic treatment, sarcopenia and/or muscle loss was associated with an increased risk of dose-limiting toxicities (DLTs). BMI was not associated with DLTs and could not detect sarcopenia or SMI loss.

Table 2 (continued)

Dolan R.D. <i>et al.</i>	163	NR	Colorectal Stage I–IV	32 (19.6%) Sarcopenic	Surgery	Sarcopenia was present in 19.6% of the study participants and was significantly related to body mass index ($p = 0.007$), 30-day mortality ($p = 0.042$) and 1-year mortality ($p = 0.046$). In univariate analysis, American Society of Anesthesiologists grade ($p = 0.016$), tumor stage ($p = 0.018$), and sarcopenia ($p = 0.043$) were found to be significant independent predictors of 1-year mortality.
Broughman JR <i>et al.</i>	87 M 42 F 45	77 y	Colo-rectal Stage I–III	25–60% (M) Sarcopenic 24–54% (F) Sarcopenic	Surgery	There was a positive correlation between BMI and SMI for both men ($r = 0.44$) and women ($r = 0.16$).
Choi MH O. S. <i>et al.</i>	188	NR	Colo-rectal	74 (39.4%) Sarcopenic	Neoadjuvant chemotherapy and Surgery	Sarcopenia and high levels of preoperative carcinoembryonic antigen were significant prognostic factors for overall survival ($P = 0.013$, 0.014 , respectively) in the Cox regression multivariate analysis.
Lieffers JR. <i>et al.</i>	234	NR	Colo-rectal Stage II–IV	91 (38.9%) Sarcopenic	Surgery and Chemotherapy	Length of stay was longer for sarcopenic patients overall (15.9 ± 14.2 days vs 12.3 ± 9.8 days, $P0.038$) and especially in those 65 years (20.2 ± 16.9 days vs 13.1 ± 8.3 days, $P0.008$). Infection risk was greater for sarcopenic patients overall (23.7% vs 12.5%; $P0.025$), and especially those 65 years (29.6% vs 8.8%, $P0.005$). In a multivariate model in patients 65 years, sarcopenia was an independent predictor of both infections (OR 4.6, (95% CI 1.5, 13.9) $P < 0.01$) and rehabilitation care (OR 3.1 (95% CI 1.04, 9.4) $P < 0.04$).
Richards CH <i>et al.</i>	174 M 95 (55%) F 79 (45%)	≤ 64 y 51 (29%) 65–74 y 63 (36%) ≥ 75 y 60 (35%)	Colo-rectal Stage I–III	59 (33.90%) Sarcopenic	Curative surgery	There was a significant relationship between low skeletal muscle index and an elevated systemic inflammatory response, as measured by the Glasgow Prognostic Score (mGPS) ($p = 0.001$). This was confirmed by linear relationships between skeletal muscle index and both C-reactive protein ($r = 20.21$, $p = 0.005$) and albumin ($r = 0.31$, $p, 0.001$). There was no association between skeletal muscle index and tumor stage.
Takeda Y <i>et al.</i>	144 M 102 F 22	60 y Non- sarcopenic 65 y Sarcopenic	Lower rectal Stage II–III	37 (25.7%)	Neoadjuvant chemoradiotherapy followed by curative resection between	Low skeletal muscle mass was independently associated with poor overall survival (hazard ratio = 2.93; 95%CI: 1.11–7.71; $p = 0.031$) and relapse-free survival (hazard ratio = 2.15; 95%CI: 1.06–4.21; $p = 0.035$) but was not associated with the rate of postoperative complications.
Onishi S. <i>et al.</i>	303 M 187 F 116 93 ??	70 y	Pancreatic Stage NR	129 (36.6%) Sarcopenic	NR	QoL was more impaired in physical component subscales in sarcopenia patients than non-sarcopenia ones.

Table 2 (continued)

Sakamoto T. <i>et al.</i>	74	NR	Pancreatic Patients with postoperative recurrence of pancreatic cancer after undergoing pancreatectomies	65 (87.8%) Sarcopenic	NR	The 2-year post-recurrence survival curve in the sarcopenia group was significantly worse than that in the non-sarcopenia group ($P = 0.034$). Multivariate analysis revealed that sarcopenia at the time of recurrence was an independent prognostic factor ($P = 0.043$) along with a high neutrophil-to-lymphocyte ratio ($P = 0.004$), early recurrence ($P = 0.001$), and chemotherapy after recurrence ($P = 0.005$) in patients with recurrent pancreatic cancer. Furthermore, the area under the curve (AUC) of the combination of sarcopenia and time to recurrence for predicting 2-year survival was 0.763, which was much higher than that of sarcopenia alone (AUC = 0.622).
Naumann P. <i>et al.</i>	147 M 79 (53.7%) F 68 (46.3%)	63.6 y	Pancreatic Stage III	98 (67%) Sarcopenic	Neoadjuvant chemotherapy and/or chemoradiation	Sarcopenia was not a prognostic factor. Surgical resection was one of the most important prognostic factors, regardless of R-status ($p < 0.001$, HR 0.4 and 0.3, respectively).
Gruber ES <i>et al.</i>	133 M 32% F 68%	NR	Pancreatic	78 (58.6%)	Neoadjuvant treatment and Surgery	Sarcopenia showed a negative impact on overall survival (OS; 14 vs. 20 months, $p = 0.016$). Sarcopenic patients suffering from obesity showed poorer OS compared to non-sarcopenic obese patients (14 vs. 23 months, $p = 0.007$). Sarcopenic obese patients showed a higher incidence of major postoperative complications ($p < 0.001$).
Amrani M. <i>et al.</i>	107 M 51 (48%) F 56 (52%)	61 y	Pancreatic	50 (47%)	Pancreatectomy	Despite comparable histological types and stages, the median overall and disease-free survivals were lower in sarcopenic patients (16 months vs not reached, $P = 0.02$ and 11.1 months vs 22.5 months; $P = 0.04$, respectively). The multivariate analysis revealed that, sarcopenia tended to increase the risk of death (HR = 2.04, $P = 0.07$). Sarcopenia negatively impacted short- and long-term outcomes in patients undergoing pancreatectomy.
van Dijk DP <i>et al.</i>	186 M 102 (54.8%)	66.5 y	Pancreatic (pancreatic head) Stage I–III	Myosteatorsis 62 (33.33%)	Classical pancreaticoduodenectomy (Whipple) or pylorus-preserving pancreaticoduodenectomy.	Low muscle radiation attenuation was associated with shorter survival in comparison with moderate and high muscle radiation attenuation [median survival 10.8 (95% CI: 8.8–12.8) vs. 17.4 (95% CI: 14.7–20.1), and 18.5 (95% CI: 9.2–27.8) months, respectively; $P < 0.008$]. Muscle radiation attenuation was inversely correlated with intermuscular adipose tissue ($r_p = -0.697$, $P < 0.001$).
Ninomiya G. <i>et al.</i>	265 M 164 F 101	65 y	Pancreatic Stage I–IV	170 (64.2%) Sarcopenic	Curative surgery (pancreatectomy) for pancreatic ductal adenocarcinoma and Chemotherapy	The median survival time (MST) was 23.7 months for sarcopenia patients and 25.8 months for patients without sarcopenia. MST for obesity sarcopenia: 19.2 vs. 35.4 months, $P = 0.025$. There was a significant difference between patients with and without sarcopenia who did not receive chemotherapy (5-year survival rate: 0% vs. 68.3%, $P = 0.003$).

Table 2 (continued)

Peng P. <i>et al.</i>	557 M 296 (53.1 %) F 261 (46.9%)	65.7 y	Pancreatic Stage I–IV	276 (49.5%) Sarcopenic	Pancreaticoduodenectomy (86.0 %) or distal pancreatectomy (14.0 %).	Sarcopenia was associated with increased risk of 3-year mortality (HR = 1.68; $P < 0.001$). Tumor-specific factors such as poor differentiation on histology (HR = 1.75), margin status (HR = 1.66), and lymph node metastasis (HR = 2.06) were associated with risk of death at 3-years (all $P < 0.001$). After controlling for these factors, sarcopenia remained independently associated with an increased risk of death at 3 years (HR = 1.63; $P < 0.001$).
Choi Y <i>et al.</i>	484 M 295 F 189	60.4 y	Pancreatic Stage III–IV	103 (21.3%) Sarcopenic	Palliative chemotherapy	A decrease in SMI during chemotherapy was observed in 156 (60.9%) male and 65 (40.6%) female patients. A decrease in body mass index (BMI) was observed in 149 patients (37.3%), with no gender difference. By multivariate analysis, sarcopenia ($P < 0.001$), decreased BMI, and SMI during chemotherapy ($P = 0.002$, $P = 0.004$, respectively) were poor prognostic factors for overall survival (OS). While the OS of male patients was affected with sarcopenia ($P < 0.001$) and decreased SMI ($P = 0.001$), the OS of female patients was influenced with overweight at diagnosis ($P = 0.006$), decreased BMI ($P = 0.032$), and decreased SMI ($P = 0.014$). The change of BMI during chemotherapy did not have an impact on OS within the patients with maintained SMI ($P = 0.750$), a decrease in SMI was associated with poor OS within the patients with maintained BMI (HR 1.502; $P = 0.002$).
Ha Y. <i>et al.</i>	178 M 43 (69.4%) F 98 (84.4%)	62.5 y	Hepatic	62 (34.8%) Sarcopenic	Surgery	Sarcopenia was significantly associated with overall survival after the inverse probability of treatment weighted (IPTW) adjustment (HR, 1.63; 95% CI, 1.03 to 2.57; $p=0.038$)
Begini P. <i>et al.</i>	92 M 65 (70.6%) F 27 (29.4%)	71.9 y	Hepatic	37 (40.2%) Sarcopenic	Surgery	Univariate Cox regression analysis showed that the presence of , bilirubin level, performance status, presence of liver decompensation (Child-Pugh $\leq$ B7 vs $\geq$ B8), TNM staging, and Barcelona Clinic Liver Cancer (BCLC) class were also significantly associated with survival. In a multivariate analysis, all these parameters, except for the performance status, were confirmed to be independently associated with increased mortality risk ($p < 0.0001$).
Takagi K. <i>et al.</i>	254 M 207 F 47	65.7 y	Hepatic	118 (46.5%) Sarcopenic	Surgery	The sarcopenic group had a significantly lower 5-year overall survival rate than the non-sarcopenic group (58.2 vs. 82.4, $p=0.0002$). In multivariate analyses of prognostic factors, sarcopenia was an independent predictor of poor survival (hazard ratio [HR]=2.28, $p=0.002$) and poor ASA status (HR=3.17, $p=0.001$)

Table 2 (continued)

Zhou G. <i>et al.</i>	67 M 22 F 45	61 y	Biliary tract/ Intrahepatic Cholangio- carcinoma Stage I–IV	33 (49.25%)	Surgery (Pancreatotomy)	Sarcopenic patients had a shorter OS compared with non-sarcopenic patients ($P < 0.001$). On univariate analyses, sarcopenia was significantly associated with overall survival (OS) and recurrence-free survival (RFS; both $P < 0.05$). On multivariate analysis, sarcopenic patients suffered poor overall survival ($P < 0.001$) and recurrence-free survival ($P = 0.011$) compared with non-sarcopenic patients.
van Vugt JLA G. M. <i>et al.</i>	233 M 140 (60.1%) F 93 (39.9%)	66 y	Biliary tract/ Cholangio- carcinoma	103 (44.20%) Sarcopenic	Chemotherapy and/or Surgery	Median OS in 233 included patients did not differ between those with and without low skeletal muscle mass ($p = 0.203$), whereas a significantly different median OS (months) was observed between patients with low (HR 7.0, 95% CI 4.7–9.3) and high (HR 12.1, 95% CI 8.1–16.1) skeletal muscle density ($p = 0.004$). Low skeletal muscle density was independently associated with decreased OS (HR 1.78, 95% CI 1.03–3.07, $p = 0.040$) within the first 6 months but not after 6 months (HR 0.68, 95% CI 0.44–1.07, $p = 0.093$), after adjusting for age, tumor size and suspected peritoneal or other distant metastases on imaging.

The prevalence of sarcopenia among all patients with digestive cancer was 43.68%, with the highest prevalence in the patients with esophageal cancer, followed by hepatic cancer, and biliary tract cancer (Table 3).

Table 3
Prevalence of sarcopenia and types of cancer

Type of cancer	Patients n	Sarcopenic patients n (%)	Non-sarcopenic patients n (%)	References
Esophageal cancer	446	314 (70.4)	132 (29.6)	[13,18,19]
Gastric cancer	1,747	560 (32.05)	1,187 (67.95)	[14,20,21]
Colorectal cancer	6,378	2,732 (42.83)	3,646 (57.17)	[22,23,24,25,26,27,28,29,30,31,32]
Pancreatic cancer	2,256	1,031 (45.70)	1,225 (54.3)	[33,34,35,36,37,38,39,40,47]
Hepatic cancer	524	316 (60.3)	208 (39.7)	[42,43,44]
Biliary tract cancer	300	136 (49.3)	164 (50.7)	[45], [46]
All digestive cancer	11,651	5,089 (43.68)	6,562 (56.32)	All of the above

Most patients (93.8%) underwent curative surgery or surgery and adjuvant chemotherapy. From studies that reported data on gender distribution, the curative treatment was seen slightly more frequently in males (53.3%).

Only sparse studies reported the prevalence of malnutrition in association with sarcopenia. One study reported the prevalence of sarcopenia in malnourished and well-nourished patients with colorectal cancer. In these patients, sarcopenia was found more often in the malnourished patients compared to well-nourished patients (55.8% vs 31.9%, respectively) [25].

Two studies found a postoperative complications risk higher for sarcopenic patients than for non-sarcopenic patients [14,30], whereas three

studies did not find a significant difference in this regard between sarcopenic and non-sarcopenic patients [19,40,48].

Despite the heterogeneity of reported data regarding the mortality, nine studies with digestive cancers, with stages ranging from I to III showed that overall survival and disease-free survival were lower in sarcopenic patients, follow up from 1 year to 5 years postoperatively (Table 4) [23], [26,27,29,37–39,42–46]. Interestingly, one study showed that the median survival time in patients with pancreatic cancer was lower for sarcopenic obesity but not for sarcopenic without obesity [39].

Recurrence rates after operated pancreatic cancer were significantly higher in sarcopenic patients [34].

Table 4
Mortality and sarcopenia in patients with digestive cancer

Study	Disease-free survival		Median survival time		Mortality	
	Sarcopenia	Non-sarcopenia	Sarcopenia	Non-sarcopenia	Sarcopenia	Non-sarcopenia
Grotenhuis <i>et al.</i> [13]	45%	55%			6%	4%
Dijksterhuis WPM [18]	No: 54	No: 66			18%	4%
Dolan <i>et al.</i> [23]	36.61% at 5 years	49.53% at 5 years				
Choi <i>et al.</i> [29]					21.6% at 5 years	7.8% at 5 years
El Amrani <i>et al.</i> [37]	11.1 months	22.5 months				
van Dijk <i>et al.</i> [38]	10.8 months	18.5 months				
Ninomiya <i>et al.</i> [39]			23.7 months	25.8 months		
Begini <i>et al.</i> [43]			66 weeks	123 weeks		
Takagi <i>et al.</i> [44]	58.2%	82.4%				

The rest of the studies expressed the relationship between sarcopenia and mortality through multivariate analyzes, CI and HR or had other endpoints, such as: the relationship between sarcopenia and chemotherapy toxicity, the relationship between sarcopenia and systemic inflammatory response and the relationship between sarcopenia and postoperative complications.

DISCUSSIONS

In our systematic review, we demonstrated a high prevalence of secondary sarcopenia (43.68%) in patients with any form of gastrointestinal cancer. A strength of our study

resides in the selection of studies with pre-specified cut-off points for defining SeS, based on EWGSOP recommendations. This approach may provide a prevalence closer to reality compared to analysis including studies with cut-off points relying on the data within.

Our analysis showed SeS is not uniformly distributed among different types of digestive cancer. The highest incidence was seen in esophageal cancer which may be explained by the fact this type of cancer is usually accompanied by difficulties of feeding. The lowest prevalence of SeS was seen in patients with gastric cancer. We were not able to perform a reliable analysis of the prevalence of SeS based on different TNM stages

because of a lack of reporting necessary data in the included studies. However, the present study signal for anon-uniform distribution may provide a starting point for future risk stratification for SeS based on the type of cancer and grading.

The relationship between SeS and post-operative complications remains unclear, only two studies from our selection demonstrating a higher incidence of such complications in sarcopenic patients. However, a recent meta-analysis showed SeS as a predictor for postoperative complications in patients with gastrointestinal neoplasms [49]. Further trials should assess more clearly the impact of sarcopenia on curative outcomes not only concerning the type of cancer but probably also other factors, like TNM staging, to elaborate effective pre-operative management of these patients.

Nine studies demonstrated increased mortality in patients with digestive cancer and SeS. In one study the mortality was up to 3 times higher in sarcopenic patients [25]. The assessment of the role of SeS on the survival rate of these patients is difficult, as there are different factors, more or less known, that may contribute to the prognosis. For example, in the case of esophageal cancer, it is characteristic to associate eating disorder that may lead to malnutrition and cachexia, making difficult to analyze the direct impact of sarcopenia in the evolution of such patients. Among patients with esophageal cancer, stage IV (TNM), toxicity-related chemotherapy, and survival were not associated with sarcopenia [18]. Also, in stage III TNM esophageal cancer treated with neoadjuvant chemoradiotherapy followed by esophagectomy, the presence of sarcopenia was not associated with negative short- and long-term outcome [13,50]. Conversely, one study showed that patients with gastric cancer who had preoperative sarcopenia and were converted to non-sarcopenic status did not present major postoperative complications [51]. Also, the phenotype of sarcopenia may play a role. In patients with pancreatic cancer, the sarcopenia associated with obesity had lower survival time compared to non-obese sarcopenia [39].

Given the impact of sarcopenia, the accuracy of diagnosis is of utmost importance. We included in our analysis only studies that diagnosed sarcopenia based on the CT scan method. This is a reliable method regardless of the software (like FatSeg, OsiriX, ImageJ, and sliceOmatic) used for measurements [52]. Various

calculation formulas for sarcopenia are found in the literature. For obtaining comparable results it would be ideal to use a unique calculation formula. Therefore, we included in our study only trials that used the most recommended formulas for the diagnosis of SeS, meaning SMI based on skeletal muscle mass or skeletal muscle area parameters [1,4]. However, the CT method is difficult and time-consuming, requiring specialized equipment and personnel, thus not always available. Further research for a new less time-consuming and cheaper diagnostic tool for SeS, simpler and reproducible, is necessary.

Lastly, the early diagnosis of sarcopenia and timing of therapeutic intervention may reflect on costs, as the hospitalization costs are significantly higher in sarcopenic patients [47].

LIMITATIONS

Our review has several limitations. The distribution of the number of patients among types of digestive cancers is significantly different. Many studies did not provide data related to cancer staging and the impact of sarcopenia in surgical and chemo/radiotherapy treatment. Thus, the data regarding the relationship between sarcopenia and curative treatments or severity of the disease is limited.

There is a risk of bias regarding the diagnosis of sarcopenia. Even if the diagnosis of sarcopenia was made using the CT scan method at the level of the lumbar vertebra 3, the SMI was calculated using different formulas. Also, the prevalence of SeS may differ if diagnostic methods other than CT are used.

CONCLUSIONS

1) *Secondary sarcopenia* is highly prevalent among patients with digestive cancer.

2) It was most frequently associated with esophageal cancer, followed by hepatic and biliary tract cancer. The least prevalence was in gastric cancer.

3) It seems the presence of sarcopenia has a negative impact on outcomes of curative treatments and survival rate, but a definite role is unclear.

4) For clarifying this issue, a uniform method of diagnosis and detailed data regarding staging and outcomes in patients with digestive cancer and sarcopenia are needed from future studies.

Introducere. Sarcopenia se caracterizează printr-o scădere a masei musculare scheletice, asociată cu forță musculară scăzută și/sau performanță fizică slabă. Evaluarea prevalenței sarcopeniei printre cancerele digestive și stabilirea impactului pe care sarcopenia îl are asupra evoluției postoperatorii a tumorilor digestive pot reprezenta un pilon central în îmbunătățirea rezultatelor postoperatorii prin îngrijirea sarcopeniei perioperatorii.

Această scurtă trecere în revistă a avut drept scop evaluarea prevalenței sarcopeniei la pacienții cu cancer digestiv.

Materiale și metodă. Baza de date PubMed a fost căutată pentru „sarcopenie” și „cancere digestive” de la 1 ianuarie 2010, până la 30 septembrie 2020. Ghidul PRISMA a fost utilizat pentru această revizuire sistematică. După procesul de selecție, 31 de studii complete au fost incluse în analiza noastră.

Evaluarea diagnosticului de sarcopenie pentru studiile incluse în această revizuire sistematică s-a bazat pe un calcul tomografic computerizat al indicelui mușchilor scheletici la a treia vertebră lombară.

Rezultate. Dintr-un total de 11 651 pacienți cu cancer digestiv, prevalența sarcopeniei a fost de 43,68%.

Cea mai mare prevalență a pacienților sarcopenici a fost în cancerul esofagian (70,4%) și hepatic (60,3%), urmat de tractul biliar (49,3%), pancreatic (45,70%), colorectal (42,83%) și cancer gastric (32,05%) cu cea mai mică prevalență.

Rezultatele studiilor efectuate până acum cu privire la prevalența sarcopeniei în cancerele digestive și relevanța acesteia în evoluția acestor tipuri de cancer sunt discordante și inegale.

Unele studii arată că prezența sarcopeniei la pacienții cu cancer digestive este asociată cu o rată crescută de complicații postoperatorii, o toxicitate crescută a chimioterapiei și o mortalitate crescută. Alte studii nu găsesc sarcopenia ca factor de risc independent asociat cu consecințe negative la pacienții cu cancer digestive.

Concluzii. Sarcopenia este răspândită în cancerele digestive. Încă nu există un consens cu privire la impactul sarcopeniei asupra tratamentului cancerelor digestive. Sunt necesare studii suplimentare pentru a evalua consecințele reale ale sarcopeniei în cancerele digestive.

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