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Original article

Nutritional status and functional status of the pancreatic cancer patients and the impact of adjacent symptoms
Estado Nutricional e Funcional dos Doentes com Cancro Pancreático e o Impacto da Sintomatologia Adjacente

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SUMMARY

Rationale & aims: Pancreatic cancer (PC) is the third most common type of gastrointestinal tract cancer in Europe and the fourth leading cause of death by cancer. Its initial stage is asymptomatic Therefore, the diagnosis tends to be late leading to locally advanced stages that presuppose late and debilitating symptoms, which consequently makes the Nutritional Status (NS) get worse. The weight loss (WL), malnutrition, and oncologic cachexia, which are quite prevalent in PC patients, reflect a poor prognosis. We aimed to track and evaluate the NS and Functional Status (FS) of PC patients (hospitalized patients – HP and Day Hospital patients – DHP) and associate NS with symptoms with nutritional impact and FS.
Methods: Observational cohort study in PC patients from Garcia de Orta Hospital. NS was tracked and evaluated using Nutritional Risk Screening (NRS-2002) and Patient-Generated Subjective Global Assessment (PG-SGA). To assess FS we used the Eastern Cooperative Oncology Group (ECOG), Karnofsky Performance Scale Index (KPSI) and Handgrip Dynamometer (HGD).
Results: 41 PC patients (30-HP and 11-DHP). 29 patients in stage IV of the tumor. 24 with a WL >10% in the last 6 months. 37 manifest symptoms with nutritional impact. 30 to 34 malnourished according to the GLIM criteria and PG-SGA, respectively. 11 in ECOG level 2 and corresponding KPSI, 10 in level 3 and 8 in level 4. 28 patients had a value of HGD below the 10th percentile. NRS-2002, PG-SGA and GLIM criteria were positively correlated with the symptoms ($p < 0.01$), % WL ($p < 0.01$) and ECOG ($p < 0.01$) and negatively correlated with HGS ($p < 0.05$ – NRS-2002; $p < 0.01$ – PG-SGA and GLIM criteria).
Conclusions: PC patients manifest debilitating symptoms with nutritional impact, namely severe WL and anorexia, which in turn lead to deterioration of the NS and FS. It is an oncology population with high nutritional risk and a higher prevalence of malnutrition, associated with severe % WL and symptoms and a sharp decline in FS.

1. Introduction

Pancreatic cancer (PC) is the third most common type of cancer of the gastrointestinal tract in Europe and represents the fourth leading cause of cancer death among all types of cancer [1,2]. In the latest data (2018) the estimated values for PC in Portugal, there are around 1619 new cases and 1594 deaths with PC being the sixth leading cause of cancer mortality [3].

The diagnosis of PC is usually delayed, given that premalignant pancreatic lesions and the initial stage of PC are asymptomatic, resulting in a rapid and aggressive evolution, which deals with locally advanced and metastatic stages that presuppose late and debilitating symptoms [4].

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PC patients associated with exocrine pancreatic insufficiency have malabsorption of nutrients, accompanied by jaundice, asthenia, unintentional weight loss (WL), anorexia, epigastric and lumbar pain, early satiety and gastrointestinal symptoms such as nausea, incoercible vomiting, dehydration, diarrhea and steatorrhea and, consequently, energy-protein malnutrition [1,5–7].

Unintentional weight loss is usually the first symptom of cancer patients. Several studies have reported it affects 50–80% of cancer patients and it is a factor dependent on the location, stage and type of tumor, being strictly related to malnutrition and oncological cachexia [8–10]. Pancreatic cancer belongs to the group of cancer with a higher prevalence of weight loss, around a percentage higher than half of the patients [11–13]. Furthermore, WL is a criterion commonly used in clinical practice, included in numerous screening, assessment, diagnosis and classification tools of malnutrition and as one of the diagnostic criteria for cachexia [9,11,13].

The etiology of malnutrition in cancer patients is complex because it is correlated to secondary symptoms from antineoplastic treatments, symptoms with nutritional impact, functional status (FS) and the nutritional therapeutic intervention implemented [12].

Oncological malnutrition is multifactorial and arises from decreased energy-protein intake and increased nutritional needs, with an unfavorable outcome and unintentional WL associated with a loss of muscle (MM) and bone mass and, consequently, a decrease in cognitive and functional functions and an increase in comorbidities [11,14]. Oncological cachexia is defined as a multifactorial syndrome that is characterized by a continuous loss of skeletal MM, with or without loss of fat mass, which cannot be reversed by conventional nutritional support and leads to progressive functional disability [11]. Therefore, the anorexia–cachexia syndrome represents the direct cause of at least 20% of deaths and can affect 80% of cancer patients, being associated with more advanced stages and higher morbidity and mortality [8,15,16]. Furthermore, these also have implications for the functional status of patients [11,14,17].

2. Aims

This study is aimed to track and evaluate the nutritional status of pancreatic cancer patients (hospitalized patients (HP) and Day Hospital patients (DHP)) through Nutritional Risk Screening (NRS-2002) and Patient-Generated Subjective Global Assessment (PG-SGA); evaluate the functional status of these patients using the Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Scale Index (KPSI) scales and Handgrip Dynamometer (HGD); and associate NS with symptoms with nutritional impact and FS.

3. Patients and methods

3.1. Study design and patients

This study was designed and conducted according to the declaration of Helsinki and approved by the Hospital Ethics Committee.

An observational cohort study in HP or DHP from Garcia de Orta Hospital. Data were collected between February 2019 and June 2020. HP includes patients that, at the time of the evaluation, had been hospitalized for less than 48 h in the Hematoncology or Medical service. DHP refers to patients with outpatient health care, where patients remain only the time needed to complete their daily chemotherapy treatment.

Inclusion criteria: adults (age $\geq$ 18 years) with a confirmed diagnosis of pancreatic cancer about 1 year or less, who may be doing chemotherapy, radiotherapy, surgery and combination therapy or had completed treatment and agreed to participate in the study. Exclusion criteria: patients in a coma, mentally handicapped, unable to independently respond to the PG-SGA, refused to be included in the study, patients with repeated readmissions or patients with more evaluations during hospitalization and chemotherapy treatment.

Each patient's general features (age, sex, etc.), comorbidities and the number of medications they were taking were obtained through face-to-face interviews. The information about each patient's cancer stage (TNM classification), histological classification and treatment were gathered from the patient's medical file. Data collection, anthropometric measurements, Handgrip Strength (HGS), as well as the application of NRS-2002 and PG-SGA were assessed and registered by the researcher.

3.2. Nutritional risk screening

The NRS-2002 tool was used for nutritional screening according to the European Society for Clinical Nutrition and Metabolism (ESPEN) [11,18], and the Dispatch n° 6634/2018 published in the Diário da República n° 129/2018, Series II of 2018-07-06, that indicates this is the tool to be used in patients admitted to the National Health Service establishments for a period longer than 24 h in the case of an adult Portuguese patient [19].

The NRS-2002 evaluates the change in nutritional status along with disease severity, intending to quickly and effectively identify individuals who are at nutritional risk (score $\geq$ 3 points) [20].

3.3. Nutritional status assessment

The nutritional status assessment consists of a global assessment of the patient status [21].

3.3.1. Assessment tools of nutritional status

PG-SGA, developed by Ottery specifically for the oncology population [22], is recommended by the guidelines [18,23,24], as the non-invasive, simple and fast gold standard tool [25].

The PG-SGA includes recent weight history, food intake, symptoms with nutritional impact, activities/function capacity, %WL, disease and relation to nutritional requirements, metabolic stress and physical examination (loss/deficit of subcutaneous fat and muscle, presence of edema or ascites). The patient can be classified as well nourished (A), moderately malnourished or suspected malnutrition (B) and severely malnourished (C) [26,27].

3.3.2. Anthropometric measurements

BMI was calculated according to World Health Organization (WHO) with weight in kilograms and height in meters: BMI = kg/m^2. The measurement of the Mid-Upper Arm Circumference (MUAC) was made at the midpoint of the non-dominant arm, obtained by the average distance between the acromion and the olecranium, with the arm flexed at 90° at the elbow level and with the palm facing the body. It was measured with the arm relaxed and in a parallel position to the body using a flexible, non-extensible tape measure perpendicular to the longitudinal axis of the arm. Tricipital Skin Fold (TSF) was measured using a skinfold caliper, the reading was performed on the rear portion of the arm at the midpoint between the acromion and the olecranon. The measurements were performed in triplicate and the average value was adopted as the final result [28]. With these measurements we calculated the Mid-Upper Arm Muscle Perimeter (MUAMP) and the Mid-Upper Arm Muscle Area (MUAMA), using the formulas: [28,29].

$$\text{MUAMP (cm)} = \text{MUAC (cm)} - 3.14 \times [\text{TSF (mm)}/10]$$

$$\text{MUAMA}\left(\text{cm}^2\right) = \frac{\left[\text{AC} - \left(\pi \times \frac{\text{TSF}}{10}\right)\right]^2}{4\pi} = \frac{[\text{MUAMP}]^2}{4\pi}$$

3.4. Diagnostic criteria and classification of severity of malnutrition

Recently, the Global Leadership Initiative on Malnutrition (GLIM), developed an approach with global consensus criteria to standardize the diagnosis of malnutrition in a clinical context [30]. This approach was used in this study, following the steps recommended by GLIM: the nutritional risk was first identified through validated tools [30], in this case NRS-2002 [11,18] and, subsequently, the diagnosis and classification of severity was performed [30].

For the diagnosis of malnutrition, the combination of at least one phenotypic criterion (unintentional weight loss, BMI and depletion of MM) and an etiological criterion (reduced food intake, inflammation of the disease) is recommended [30]. After this, the severity is classified as moderate (stage 1) or severe (stage 2) [30].

3.5. Functional status assessment

Functional status was assessed using the ECOG and KPSI scales and HGD [18,23,24].

Both scales, ECOG and KPSI, classify the patient according to functional impairment, self-care ability, daily activity and physical ability. Both allow an association with survival prognosis, response to chemotherapy toxicity and QOL [31,32]. ECOG is a scale from 0 (fully active) to 5 (dead), also used for choosing the treatment antineoplastic. The KPSI consists of a scale from 0 (dead) to 100 (normally active with no evidence of disease) [33].

HGS reflects the maximum strength resulting from the combined contraction of the extrinsic and intrinsic muscles of the hand, being a validated, non-invasive, fast and easy-to-perform method of assessing skeletal muscle function [34–36]. Also, it is more sensitive to changes induced by malnutrition in muscle function that usually precedes changes in NS, particularly in terms of body composition [34,35]. As recommended by the guidelines [18,23,24] to evaluate the FS for cancer patients [34,36].

HGS was measured using a Jamar® Hydraulic HGD and it was performed by pre-adjusting the size of the patient's hand. The patient was sitting in a standardized position adapted to the clinical context, with the elbow flexed at 90° and with support [37]. Each patient performed the test three times at intervals of 10–30 s, with the researcher encouraging the patient to exercise his maximum strength and the maximum HGS value was used [34,37,38].

HGS is even included in the GLIM criteria for the assessment, diagnosis and classification of malnutrition. Specifically in the phenotypic criterion of MM depletion, when it cannot be readily assessed by body assessment methods because, regardless of the etiology, the considerable loss of muscle mass is usually accompanied by reduced muscle function [30].

3.6. Statistical analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics), version 25.0 was used. The results were considered significant at a 5% significance level. Descriptive statistics were used to describe the patient's characteristics. To study the relationship between NRS-2002, PG-SGA, GLIM criteria, Symptoms, ECOG, KPSI, HGS, % WL, BMI and Tumor Staging, the Spearman correlation was used.

4. Results

This study included 41 pancreatic cancer patients (30-HP and 11-DHP), 23 men (56.1%) and 18 women (43.9%), with a mean age of 69 (SD = 11) ranging from 40 to 87 years.

At the time of inclusion, the diagnosis of CP had been known for 1 year in only 3 patients. In 25.6% (n = 10) the evaluation was performed 7–11 months after diagnosis, 12.8% (n = 5) 3–6 months after diagnosis, 35.9% (n = 14) 1 to 2 after diagnosis and 17.9% (n = 7) less than 1 month after diagnosis. As for the stage of the tumor (Table 1), the percentage of patients with stage IV cancer was 85.3% (n = 29), with stage III was 5.9% (n = 2) and with stage I was 8.8% (n = 3), while the remaining patients had no tumor staging at the time of the assessment.

4.1. Nutritional and functional status

56.1% (n = 23) of the total patients (66.7%; n = 20-HP and 27.3%; n = 3-DHP) had low BMI and only 4.9% (6.6%; n = 2-HP) had obesity (Table 1). In total, 50.0% (n = 18) of patients had a fat mass (FM) deficit (TSF < 15th percentile) and 41.7% (n = 15) had a FM within normal values (15th percentile < TSF < 75th percentile), described in Table 1. 52.7% (n = 19) had muscle mass deficit (MUAMA < 15th percentile), with a higher percentage in HP (69.2%; n = 18) than in DHP (10.0%; n = 1) and 41.7% (n = 15) had a MM within normal values (15th percentile < MUAMA < 75th percentile), described in Table 1.

68.3% (n = 28) of patients had lost weight in the last 6 months, of which 53.7% (n = 24) had a loss of more than 10% of body weight and 29.3% (n = 12) of the patients (30.0%; n = 9-HP and 27.3%; n = 3-DHP) had a loss of more than 20% of body weight (Table 1).

90.2% (n = 37) of patients (100% (n = 19)-HP; 63.6% (n = 7)-DHP) had symptoms with nutritional impact (Table 2). The most prevalent symptoms were anorexia (75.6%; n = 31), xerostomia (61.0%; n = 25), early satiety and/or pain (51.2%; n = 21) and nausea (46.3%; n = 19). In HP, we found 86.7% (n = 26) of that manifest anorexia, 70.0% (n = 21) pain, 60.0% (n = 18) xerostomia and/or early satiety and 50.0% (n = 15) nausea. In DHP, prevailed xerostomia (63.6%; n = 7), anorexia and/or dysgeusia (45.5%; n = 5) and nausea (36.4%; n = 4). We, also, found that 73.1% (n = 30) manifested more than three symptoms (58.5%; n = 24 – 4 to 6 symptoms and 14.63%; n = 6 – 7 to 8 symptoms). In HP, 63.3% (n = 19) manifested a combination of 4–6 symptoms and 20.0% (n = 6) manifest 7 to 8 symptoms. In HDP, 45.4% (n = 5) manifest a combination of 4–6 symptoms and 36.4% (n = 4) had no symptoms.

About nutritional status (Table 3), according to the NRS-2002, 82.9% (n = 34) of the patients (93.3%; n = 28-HP and 54.5%; n = 6-DHP) were at nutritional risk. According to the PG-SGA, 82.9% (n = 34) of the patients (93.4%; n = 28-HP and 54.5%; n = 6-DHP) were malnourished (PG-SGA B + C), of which 39.0% (n = 16) were moderately malnourished – PG-SGA B (36.7%; n = 11-HP and 45.5%; n = 5-DHP) and 43.9% (n = 18) were severely malnourished – PG-SGA C (56,7%; n = 17-HP and 9.0%; n = 1-DHP). According to the recent GLIM criteria, 73.2% (n = 30) of the patients had malnutrition (83.3%; n = 25-HP and 45.5%; n = 5-DHP), which 48.8% (n = 20) had severe malnutrition (63.3%; n = 19-HP and 9.1%; n = 1-DHP) and 24.4% (n = 10) had moderate malnutrition (20.0%; n = 6-HP and 36.4%; n = 4-DHP) (n = 12). We found that 73.3% (n = 22) of HP had cachexia, of which 60.0% (n = 18) had refractory cachexia, 10.0% (n = 3) had cachexia and 3.3%; n = 1 had pre-cachexia. In DHP, 55.5% (n = 6) of patients had cachexia (27.3%; n = 3 – refractory cachexia, 18.2%; n = 2 – cachexia, and 9.1%; n = 1 – pre-cachexia). In total, 68.3% of patients had oncologic cachexia.

Regarding functional status (Table 3), using ECOG and KPSI scales there was a higher percentage ECOG level 2 and

Table 1
Clinical and nutritional characteristics of pancreatic cancer patients.

		Hospitalization (n = 30)		Day Hospital (n = 11)		Total (n = 41)	
		n	%	n	%	n	%
Genre	Female	11	36.7	7	63.6	18	43.9
	Male	19	63.3	4	36.4	23	56.1
Tumor staging	1	2	7.7	1	12.5	3	8.8
	2	0	0.0	0	0.0	0	0.0
	3	1	3.8	1	12.5	2	5.9
	4	23	88.5	6	75.0	29	85.3
BMI	Low weight	20	66.7	3	27.3	23	56.1
	Eutrophy	5	16.7	5	45.5	10	24.4
	Pre-obesity	3	10.0	3	27.3	6	14.6
	Obesity	2	6.6	0	0.0	2	4.9
TSF	<P5	11	42.3	4	40.0	15	41.7
	P5–P15	3	11.5	0	0.0	3	8.3
	P15–P75	11	42.3	4	40.0	15	41.7
	P75–P85	0	0.0	0	0.0	0	0.0
	>P85	1	3.9	2	20.0	3	8.3
MUAMA	<P5	11	42.3	1	10.0	12	33.3
	P5–P15	7	26.9	0	0.0	7	19.4
	P15–P75	7	26.9	8	80.0	15	41.7
	P75–P85	1	3.9	0	0.0	1	2.8
	>P85	0	0.0	1	10.0	1	2.8
Weight loss (6 months)	0%	8	26.6	5	45.5	13	31.7
	0–5%	2	6.7	1	9.1	3	7.3
	5–10%	2	6.7	1	9.1	3	7.3
	10–20%	9	30.0	1	9.1	10	24.4
	>20%	9	30.0	3	27.3	12	29.3

Note: P, Percentile; BMI, Body Mass Index; MUAC, Mid-Upper Arm Circumference; TSF, Tricipital Skin Fold; MUAMA, Mid-Upper Arm Muscle Area.

Table 2
Symptoms of pancreatic cancer patients.

		Hospitalization (n = 30)		Day Hospital (n = 11)		Total (n = 41)	
		n	%	n	%	n	%
Symptoms	Asymptomatic	0	0.0	4	36.4	4	9.8
	Symptomatic	30	100.0	7	63.6	37	90.2
	Anorexia	26	86.7	5	45.5	31	75.6
	Nausea	15	50.0	4	36.4	19	46.3
	Vomiting	11	36.7	2	18.2	13	31.7
	Constipation	11	36.7	2	18.2	13	31.7
	Diarrhea	5	16.7	3	27.3	8	19.5
	Mucositis	5	16.7	1	9.1	6	14.6
	Xerostomia	18	60.0	7	63.6	25	61.0
	Dysgeusia	4	13.3	5	45.5	9	22.0
	Dysosmia	0	0.0	0	0.0	0	0.0
	Dysphagia	9	30.0	0	0.0	9	22.0
	Early satiety	18	60.0	3	27.3	21	51.2
	Asthenia	14	46.7	0	0.0	14	34.1
	Pain	21	70.0	0	0.0	21	51.2
Number of symptoms	0	0	0.0	4	36.4	4	9.8
	1–3	5	16.7	2	18.2	7	17.1
	4–6	19	63.3	5	45.4	24	58.5
	7–8	6	20.0	0	0.0	6	14.6

corresponding KPSI (26.8%; n = 11). When the percentage of patients decreases, the higher the severity level (24.4% (n = 10) – level 3; 19.5% (n = 8) – level 4) and only 7.3% (n = 3) in ECOG level 0 and corresponding KPSI. It should be noted that patients with ECOG 0 (n = 3) are only included in DHP and that patients with ECOG 4 (n = 8) in HP. In HP the level 2 (30.0%; n = 9), 3 and 4 of ECOG (each one with 26.7%; n = 8) prevailed, and in DHP prevailed the level 1 (36.4%; n = 4). 73.7% (n = 28) of the patients had a value of HGS below the 10th percentile. 75% (n = 21) of the HP and 70.0% (n = 7) of the DHP had a value of HGS below the 10th percentile. Only 5.3% (n = 2) were classified within normal HGS values (between 30th and 70th percentile).

4.2. Relationship between nutritional status and symptoms with nutritional impact

In patients with PG-SGA B + C (Table 4), indicative of moderate or severe malnutrition, we found that 100.0% (n = 28-HP; n = 6-DHP) of the patients manifested symptoms with nutritional impact. 88.2% (n = 30) of patients manifested anorexia (92.6%; n = 26-HP and 66.7%; n = 4-DHP), 67.6% (n = 23) xerostomia (60.7%; n = 17-HP and 100.0%; n = 6-DHP), 61.8% (n = 21) early satiety (64.3%; n = 18-HP and 50.0%; n = 3-DHP), 58.8% (n = 20) pain (71.4%; n = 20-HP) and 52.9% (n = 18) nausea (50.0%; n = 14-HP and 66.7%; n = 4-DHP), these being the most prevalent

Table 3
Nutritional and functional status indicators of pancreatic cancer patients.

		Hospitalization (n = 30)		Day Hospital (n = 11)		Total (n = 41)	
		n	%	n	%	n	%
NRS-2002	No nutritional risk (score < 3)	2	6.7	5	45.5	7	17.1
	Nutritional risk (score ≥ 3)	28	93.3	6	54.5	34	82.9
PG-SGA	A – well nourished	2	6.6	5	45.5	7	17.1
	B – moderately or suspected malnutrition	11	36.7	5	45.5	16	39.0
	C – severely malnourished	17	56.7	1	9.0	18	43.9
Malnutrition (GLIM criteria)	Without criteria for malnutrition	5	16.7	3	15.8	11	26.8
	Malnutrition	25	83.3	5	45.5	30	73.2
	Moderately malnutrition	6	20.0	4	36.4	10	24.4
	Severely malnutrition	19	63.3	1	9.1	20	48.8
Oncologic cachexia	Absent	8	26.7	5	45.5	13	31.7
	Pre-cachexia	1	3.3	1	9.0	2	4.9
	Cachexia	3	10.0	2	18.2	5	12.2
	Refractory cachexia	18	60.0	3	27.3	21	51.2
ECOG/KPSI	0/100–90	0	0.0	3	27.3	3	7.3
	1/80–70	5	16.6	4	36.4	9	22.0
	2/60–50	9	30.0	2	18.2	11	26.8
	3/40–30	8	26.7	2	18.2	10	24.4
	4/20–10	8	26.7	0	0.0	8	19.5
	5/0	0	0.0	0	0.0	0	0.0
HGS	<P10	21	75.0	7	70.0	28	73.7
	P10–P30	6	21.4	2	20.0	8	21.0
	P30–P70	1	3.6	1	10.0	2	5.3
	P70–P90	0	0.0	0	0.0	0	0.0
	>P90	0	0.0	0	0.0	0	0.0

Note: P, Percentile; NRS-2002, Nutritional Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; GLIM, Global Leadership Initiative on Malnutrition; ECOG, Eastern Cooperative Oncology Group; KPSI, Karnofsky Performance Scale Index; HGS, Handgrip Strength.

symptoms. We also found that 88.2% (n = 33) of these patients manifested more than three symptoms, of which 70.6% (n = 24) manifested 4–6 symptoms (67.9%; n = 19-HP and 83.3%; n = 5-DHP) and 17.6% (n = 6) manifested a combination of 7–8 symptoms (21.4%; n = 6-HP).

The PG-SGA score, as well as NRS-2002 and GLIM criteria, were significantly positively correlated (Table 5) with the symptoms with nutritional impact ($r = 0.763$; $p < 0.01$–PG-SGA; $r = 0.696$; $p < 0.01$–NRS-2002 and $r = 0.710$; $p < 0.01$–GLIM criteria) and the % WL ($r = 0.496$; $p < 0.01$–PG-SGA; $r = 0.557$; $p < 0.01$–NRS-2002 and $r = 0.676$; $p < 0.01$–GLIM criteria).

4.3. Relationship between nutritional status and functional status

Associating the nutritional status (according to PG-SGA) with the functional status (according to ECOG and KPSI scales and HGS), described in Table 4, we found in patients with PG-SGA B + C the level 2,3 and 4 of ECOG and corresponding KPSI (32.4% level 2 (n = 11) – 32.1%; n = 9-HP and 33.3%; n = 2-DHP; 29.4% level 3 (n = 10) – 28.6%; n = 8-HP and 33.3%; n = 2-DHP). However, in patients with PG-SGA A (indicative of being well-nourished) we only found the level 0 and 1 of ECOG and corresponding KPSI that, consequently, are less severe. 23.5% (n = 8) of patients were in level 4 of ECOG and 14.7% (n = 5) in level 1, although level 4 of ECOG was only present in HP (29.4%; n = 5). At the HGS level associated with PG-SGA A, it was found that 28.6% (n = 2) of patients had HGS values within the normal percentile (between 30th and 70th percentile) and 42.9% (n = 3) had HGS values < P10. In malnourished patients, HGS < P10 (80.6%; n = 25) values prevailed, in HP (76.9%; n = 20) as well as in DHP (100%; n = 5).

Moreover, PG-SGA, NRS-2002 score and GLIM criteria were significantly positively correlated (Table 5) with ECOG ($r = 0.787$; $p < 0.01$–PG-SGA; $r = 0.613$; $p < 0.01$–NRS-2002 and $r = 0.622$; $p < 0.01$–GLIM criteria) and significantly negatively correlated with HGS ($r = -0.490$; $p < 0.01$–PG-SGA; $r = -0.379$; $p < 0.05$–NRS-2002 and $r = -0.433$; $p < 0.01$–GLIM criteria).

5. Discussion

Pancreatic cancer, as mentioned above, is common in Europe and Portugal. It has a very high mortality rate, being the fourth leading cause of cancer death [1,2]. Furthermore, it has a low 5-year survival rate, with an average survival time of 6–8 months after diagnosis.

That being said, pancreatic cancer is mostly diagnosed at a late stage [4], as we found in the present study, 85.3% (n = 29) of the patients classified as stage IV, of which the majority had been diagnosed less than 2 months ago. Consequently, causing debilitating symptoms [4], we found 90.2% (n = 37) of the patients manifested symptoms with nutritional impact and all hospitalized patients had symptoms. It is known that the most common symptoms in patients with pancreatic cancer include anorexia, epigastric pain, early satiety and gastrointestinal symptoms [1,5–7]. We found similar results, with the most prevalent symptoms being anorexia (75.6%; n = 31), xerostomia (61.0%; n = 25), early satiety and/or pain (51.2%; n = 21) and nausea (46.3%; n = 19). These symptoms are associated with an accentuated decrease in food intake that presupposes an elevated unintentional weight loss and evident nutritional deficiencies, namely malnutrition and cancer cachexia [7,11–13,18]. Thus, nutritional intervention is crucial to prevent and address nutritional deficits. During the nutritional assessment, hospitalized patients had personalization of diet according to their energetic and protein needs and present symptoms, using oral nutritional supplements if necessary. During the anti-neoplastic treatment session, patients in a day hospital had nutritional counseling to optimize food intake, according to the symptoms and to prevent or recovery weight loss.

These patients have a higher prevalence of unintentional weight loss [8,9], 68.3% (n = 28) had lost weight in the last 6 months, of which 29.3% (n = 12) had lost more than 20% of body weight, which translates into worse nutritional and functional status [11–13]. 73.2% (n = 30) to 82.9% (n = 34) were malnourished according to the GLIM criteria and PG-SGA, respectively, of which 40% (n = 12) to

Table 4
Nutritional and functional indicators according to PG-SGA.

		PG-SGA											
		A						B + C					
		HP (n = 2)		DHP (n = 5)		Total (n = 7)		HP (n = 28)		DHP (n = 6)		Total (n = 34)	
		n	%	n	%	n	%	n	%	n	%	n	%
BMI	Low weight	0	0.0	0	0.0	0	0.0	20	71.4	3	50.0	23	67.6
	Eutrophy	0	0.0	2	40.0	2	28.6	5	17.9	3	50.0	8	23.5
	Pre-obesity	1	50.0	3	60.0	4	57.1	2	7.1	0	0.0	2	5.9
	Obesity	1	50.0	0	0.0	1	14.3	1	3.6	0	0.0	1	3.0
Weight loss	0%	2	100.0	5	100.0	7	100.0	6	21.4	0	0.0	6	17.6
	0–5%	0	0.0	0	0.0	0	0.0	2	7.2	1	16.7	3	8.8
	5–10%	0	0.0	0	0.0	0	0.0	2	7.2	1	16.7	3	8.8
	10–20%	0	0.0	0	0.0	0	0.0	9	32.1	1	16.7	10	29.4
	>20%	0	0.0	0	0.0	0	0.0	9	32.1	3	50.0	12	35.4
Symptoms	Asymptomatic	0	0.0	4	80.0	4	57.1	0	0.0	0	0.0	0	0.0
	Symptomatic	2	100.0	1	20.0	3	42.9	28	100.0	6	100.0	34	100.0
	Anorexia	0	0.0	1	20.0	1	14.3	26	92.6	4	66.7	30	88.2
	Nausea	1	50.0	0	0.0	1	14.3	14	50.0	4	66.7	18	52.9
	Vomiting	0	0.0	0	0.0	0	0.0	11	39.3	2	33.3	13	38.2
	Constipation	1	50.0	0	0.0	1	14.3	10	35.7	2	33.3	12	35.3
	Diarrhea	0	0.0	0	0.0	0	0.0	5	17.9	3	50.0	8	23.5
	Mucositis	0	0.0	1	20.0	1	14.3	5	17.9	0	0.0	5	14.7
	Xerostomia	1	50.0	1	20.0	2	28.6	17	60.7	6	100.0	23	67.6
	Dysgeusia	0	0.0	0	0.0	0	0.0	4	14.3	5	83.3	9	26.5
	Dysosmia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Dysphagia	0	0.0	0	0.0	0	0.0	9	32.1	0	0.0	9	26.5
	Early satiety	0	0.0	0	0.0	0	0.0	18	64.3	3	50.0	21	61.8
	Asthenia	1	50.0	0	0.0	1	14.3	13	46.4	0	0.0	13	38.2
	Pain	1	50.0	0	0.0	1	14.3	20	71.4	0	0.0	20	58.8
Number of symptoms	0	0	0.0	4	80.0	4	57.1	0	0.0	0	0.0	0	0.0
	1–3	2	100.0	1	20.0	3	42.9	3	10.7	1	16.7	4	11.8
	4–6	0	0.0	0	0.0	0	0.0	19	67.9	5	83.3	24	70.6
	7–8	0	0.0	0	0.0	0	0.0	6	21.4	0	0.0	6	17.6
ECOG/KPSI	0/100–90	0	0.0	3	60.0	3	42.9	0	0.0	0	0.0	0	0.0
	1/80–70	2	100.0	2	40.0	4	57.1	3	10.7	2	33.3	5	14.7
	2/60–50	0	0.0	0	0.0	0	0.0	9	32.1	2	33.3	11	32.4
	3/40–30	0	0.0	0	0.0	0	0.0	8	28.6	2	33.3	10	29.4
	4/20–10	0	0.0	0	0.0	0	0.0	8	28.6	0	0.0	8	23.5
	5/0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
HGS	<P10	1	50.0	2	40.0	3	42.9	20	76.9	5	100.0	25	80.6
	P10–P30	0	0.0	2	40.0	2	28.6	6	23.1	0	0.0	6	19.4
	P30–P70	1	50.0	1	20.0	2	28.6	0	0.0	0	0.0	0	0.0
	P70–P90	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	>P90	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Note: PG-SGA, Patient-Generated Subjective Global Assessment; HP, Hospitalized Patients; DHP, Day Hospital Patients; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; KPSI, Karnofsky Performance Scale Index; HGS, Handgrip Strength.

Table 5
Correlation coefficients and p-values for the symptoms, nutritional and functional assessment.

	Correlations/p-value					
	NRS-2002	PG-SGA	GLIM criteria	Symptoms	ECOG/KPSI	HGS
Tumor staging	0.076/0.671	0.259/0.139	0.042/0.816	0.006/0.974	0.028/0.877	−0.265/0.150
BMI	−0.586/0.000*	−0.693/0.000*	−0.787/0.000*	−0.681/0.000*	−0.644/0.000*	0.526/0.001*
% Weight loss	0.557/0.000*	0.496/0.001*	0.676/0.000*	0.457/0.003*	0.455/0.003*	−0.365/0.024*
NRS-2002	–	0.706/0.000*	0.624/0.000*	0.696/0.000*	0.613/0.000*	−0.379/0.019*
PG-SGA	0.706/0.000*	–	0.696/0.000*	0.763/0.000*	0.787/0.000*	−0.490/0.002*
Oncologic cachexia	0.588/0.000*	0.652/0.000*	0.784/0.000*	0.576/0.000*	0.439/0.004*	−0.431/0.007*
Malnutrition (GLIM criteria)	0.624/0.000*	0.696/0.000*	–	0.710/0.000*	0.622/0.000*	−0.433/0.007*
Symptoms	0.696/0.000*	0.763/0.000*	0.710/0.000*	–	0.727/0.000*	−0.529/0.001*
ECOG/KPSI	0.613/0.000*	0.787/0.000*	0.622/0.000*	0.727/0.000*	–	−0.439/0.006*
HGS	−0.379/0.019*	−0.490/0.002*	−0.433/0.007*	−0.529/0.001*	−0.439/0.006*	–

Note: BMI, Body Mass Index; NRS-2002, Nutritional Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; GLIM, Global Leadership Initiative on Malnutrition; ECOG, Eastern Cooperative Oncology Group; KPSI, Karnofsky Performance Scale Index; HGS, Handgrip Strength.
*There is a significant correlation at the 5% significance level with Spearman correlation analysis.

43.9% (n = 18) were severely malnourished (stage 2, PG-SGA C) and 24.4% (n = 10) to 39.0% (n = 16) were moderately malnourished (stage 1, PG-SGA B). These results corroborate what the scientific evidence states.

We also found a positively correlation between the symptoms with nutritional impact and the PG-SGA score ($r = 0.763$; $p < 0.01$), the GLIM criteria ($r = 0.710$; $p < 0.01$) and also the % weight loss ($r = 0.457$; $p < 0.01$). In the present study, all patients with PG-SGA

B + C (n = 34) manifestly symptoms with nutritional impact, being the most prevalent symptoms the anorexia (88.2%; n = 30), xerostomia (67.6%; n = 23), early satiety (61.8%; n = 21) and pain (58.8%; n = 20). As such, the presence of symptoms is significantly associated ($p < 0.01$) with higher % WL, poorer nutritional status (higher PG-SGA and NRS-2002 score and stage of malnutrition by GLIM criteria) and functional status (higher ECOG/lower KPSI and HGS). Therefore, the more the number of symptoms manifested, the worse are the outcomes previously mentioned.

Moreover, it is known that an unintentional weight loss, malnutrition and oncologic cachexia reflect a poor prognosis with significant complications for the patient, including a decrease of the functional status [11,14,17]. As mentioned previously, the HGS is a validated, non-invasive, fast and easy-to-perform method that has a higher sensitivity to changes induced by malnutrition in muscle function that usually precedes changes in NS [34,35]. It is also considered useful for assessing the risk of malnutrition on hospital admission and predicting clinical outcomes, as low HGS values are strongly correlated with increased risk of complications, length of stay, readmission rate and decreased survival and quality of life [34,36]. Furthermore, the guidelines [18,23,24] recommended these to complete the evaluation of the NS for cancer patients, as there is a significant association between nutritional and functional status, like demonstrated in the study of the PG-SGA score, as well as GLIM criteria and % weight loss, were positively correlated with ECOG ($p < 0.01$) and negatively correlated with HGS ($p < 0.01$ – PG-SGA and GLIM criteria; $p < 0.05$ – %WL). Thus, worse nutritional status (higher PG-SGA and stage of malnutrition by GLIM criteria) and higher unintentional weight loss are associated with worse functional status, i.e., higher ECOG/lower KPSI and HGS, results according to recent studies [17,34,36].

Despite the corroborating evidence from recent studies, this study is different because it reveals, in an innovative way, a correlation between nutritional status using the PG-SGA, also the recent GLIM and the functional state, using the ECOG, HGS and also KPSI scale. Furthermore, it correlates symptoms with nutritional impact and nutritional and functional status.

After this study, it can be stated, corroborating what the evidence tells us, that this is a population with a high prevalence of malnutrition and deterioration of functional status, so the use of appropriate tools to quickly determine the nutritional and functional status and the early detection of nutritional deficiencies, allows us to make the difference and direct the best nutritional intervention strategy to reduce many tumor complications and improve the nutritional and functional status of the patient, the outcomes of treatment and, consequently, reduce the costs associated with health care, morbidity and mortality.

6. Conclusion

Pancreatic cancer is common and has a low survival rate and high mortality. Patients with pancreatic cancer manifest debilitating symptoms with nutritional impact, namely severe weight loss and marked anorexia which, in turn, lead to deterioration of the nutritional and functional status.

In this study, we found a very high prevalence of malnutrition, with more than 70% of patients waring moderate or severe malnutrition, associated with severe % weight loss, symptoms and a sharp decline in functional status. However, when validated tools are applied as early as possible to assess the nutritional and functional status of patients, it is possible to act earlier. Thus, a nutritional intervention with strategies to improve adjacent symptoms is essential to maintain body weight, avoiding loss of muscle mass. It is important optimization of the patients' nutritional and functional status, with a view to the best possible health care and an improvement in the patient's well-being and quality of life.

Statement of authorship

I.S. writing, reviewing, and editing; I.S. and C.S. conceptualization, methodology, investigation, and manuscript revision; L.M and C.S coordinated the working group and revised the final version. H.M revised the final version. All the authors have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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Conflict of interest

No conflict of interests.

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References

[1] Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v56–68. https://doi.org/10.1093/annonc/mdv295.

[2] Cancer Today [Internet]. [cited 2020 Apr 7]. Available from: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents& population=900&populations=908&key=asr&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&i.

[3] WHO. Globocan 2018 - Portugal [Internet]. [cited 2020 Apr 7]. Available from: http://gco.iarc.fr/today/data/factsheets/populations/620-portugal-fact-sheets.pdf; 2019.

[4] Crawford HC, Pasca di Magliano M, Banerjee S. Signaling networks that control cellular plasticity in pancreatic tumorigenesis, progression, and metastasis. Gastroenterology 2019;156(7):2073–84. https://doi.org/10.1053/j.gastro.2018.12.042.

[5] Gupta R, Amanam I, Chung V. Current and future therapies for advanced pancreatic cancer. J Surg Oncol 2017;116(1):25–34. https://doi.org/10.1002/jso.24623.

[6] Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, et al. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumor site and stage. Clin Transl Oncol 2005;7(5):189–97. https://doi.org/10.1007/BF02712816.

[7] Lindkvist B, Phillips ME, Domínguez-Muñoz JE. Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: prevalence and diagnostic use. Pancreatology 2015;15(6):589–97. https://doi.org/10.1038/s41575-018-0005-x.

[8] Ryan AM, Power DG, Daly L, Cushen SJ, Ní Bhuachalla E, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. Proc Nutr Soc 2016;75(2):199–211. https://doi.org/10.1017/S002966511500419X.

[9] Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol 2015;33(1):90–9. https://doi.org/10.1200/JCO.2014.56.1894.

[10] Ryan AM, Prado CM, Sullivan ES, Power DG, Daly LE. Effects of weight loss and sarcopenia on response to chemotherapy, quality of life, and survival. Nutrition 2019;67–68:110539. https://doi.org/10.1016/j.nut.2019.06.020.

[11] Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr 2017;36(5):1187–96. https://doi.org/10.1016/j.clnu.2017.06.017.

[12] de Pinho NB, Martucci RB, Rodrigues VD, D'Almeida CA, Thuler LCS, Saunders C, et al. Malnutrition associated with nutrition impact symptoms

and localization of the disease: results of a multicentric research on oncological nutrition. Clin Nutr 2019;38(3):1274–9. https://doi.org/10.1016/j.clnu.2018.05.010.
[13] Nemer L, Krishna SG, Shah ZK, Conwell DL, Cruz-Monserrate Z, Dillhoff M, et al. Predictors of pancreatic cancer–associated weight loss and nutritional interventions. Pancreas 2017;46(9):1152–7. https://doi.org/10.1097/MPA.0000000000000898.
[14] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischof SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017;36(1):49–64. https://doi.org/10.1016/j.clnu.2016.09.004.
[15] Porporato PE. Understanding cachexia as a cancer metabolism syndrome. Oncogenesis 2016;5(2):e200. https://doi.org/10.1038/oncsis.2016.3.
[16] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12(5):489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.
[17] Bicakli DH, Uslu R, Güney SC, Coker A. The relationship between nutritional status, performance status, and survival among pancreatic cancer patients. Nutr Cancer 2020;72(2):202–8. https://doi.org/10.1080/01635581.2019.1634217.
[18] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2016;36(1):11–48. https://doi.org/10.1016/j.clnu.2016.07.015.
[19] Despacho 6634/2018, 2018-07-06 - DRE [Internet]. [cited 2020 Apr 3]. Available from: https://dre.pt/home/-/dre/115652170/details/2/maximized?print_preview=print-preview.
[20] Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22(4):415–21. https://doi.org/10.1016/S0261-5614(03)00098-0.
[21] Swan WI, Vivanti A, Hakel-Smith NA, Hotson B, Orrevall Y, Trostler N, et al. Nutrition care process and model update: toward realizing people-centered care and outcomes management. J Acad Nutr Diet 2017;117(12):2003–14. https://doi.org/10.1016/j.jand.2017.07.015.
[22] Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition 1996;12(1):S15–9. https://doi.org/10.1016/0899-9007(95)00067-4.
[23] August DA, Huhmann MB. A.S.P.E.N. Clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. J Parenter Enteral Nutr 2009;33(5):472–500. https://doi.org/10.1177/0148607109341804.
[24] Thompson KL, Elliott L, Fuchs-Tarlovsky V, Levin RM, Voss AC, Piemonte T. Oncology evidence-based nutrition practice guideline for adults. J Acad Nutr Diet 2017;117(2):297–310. https://doi.org/10.1016/j.jand.2016.05.010. e47.
[25] Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 2002;56(8):779–85. https://doi.org/10.1038/sj.ejcn.1601412.
[26] Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the patient-generated subjective global assessment. Curr Opin Clin Nutr Metab Care 2017;20(5):322–9. https://doi.org/10.1097/MCO.0000000000000389.
[27] PG-SGA© | Pt-Global [Internet]. [cited 2020 Apr 9]. Available from: http://pt-global.org/?page_id=8074&lang=pt.
[28] Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr 1981;34(11):2540–5. https://doi.org/10.1093/ajcn/34.11.2540.
[29] Gurney JM, Jelliffe DB. Arm anthropometry in nutritional assessment: nomogram for rapid calculation of muscle circumference and cross-sectional muscle and fat areas. Am J Clin Nutr 1973;26(9):912–5. https://doi.org/10.1093/ajcn/26.9.912.
[30] Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. Clin Nutr 2019;38(1):1–9. https://doi.org/10.1016/j.clnu.2018.08.002.
[31] Kelly CM, Shahrokni A. Moving beyond Karnofsky and ECOG performance status assessments with new technologies. J Oncol 2016;2016:6186543. https://doi.org/10.1155/2016/6186543.
[32] West H (Jack), Jin JO. Performance status in patients with cancer. JAMA Oncol 2015;1(7):998. https://doi.org/10.1001/jamaoncol.2015.3113.
[33] Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance status scale: an examination of its reliability and validity in a research setting. Cancer 1984;53(9):2002–7. https://doi.org/10.1002/1097-0142(19840501)53:9%3C2002::AID-CNCR2820530933%3E3.0.CO;2-W.
[34] Alkan ŞB, Artaç M, Rakıcıoğlu N. The relationship between nutritional status and handgrip strength in adult cancer patients: a cross-sectional study. Support Care Cancer 2018;26(7):2441–51. https://doi.org/10.1007/s00520-018-4082-8.
[35] Guerra RS, Fonseca I, Pichel F, Restivo MT, Amaral TF. Handgrip strength and associated factors in hospitalized patients. J Parenter Enteral Nutr 2015;39(3):322–30. https://doi.org/10.1177/0148607113514113.
[36] Hu CL, Yu M, Yuan KT, Yu HL, Shi YY, Yang JJ, et al. Determinants and nutritional assessment value of hand grip strength in patients hospitalized with cancer. Asia Pac J Clin Nutr 2018;27(4):777–84. https://doi.org/10.6133/apjcn.072017.04.
[37] Hillman T, Nunes Q, Hornby S, Stanga Z, Neal KR, Rowlands BJ, et al. A practical posture for hand grip dynamometry in the clinical setting. Clin Nutr 2005;24(2):224–8. https://doi.org/10.1016/j.clnu.2004.09.013.
[38] Schlüssel MM, dos Anjos LA, de Vasconcellos MTL, Kac G. Reference values of handgrip dynamometry of healthy adults: a population-based study. Clin Nutr 2008;27(4):601–7. https://doi.org/10.1016/j.clnu.2008.04.004.