The global leadership into malnutrition criteria reveals a high percentage of malnutrition which influences overall survival in patients with gastroenteropancreatic neuroendocrine tumours

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The global leadership into malnutrition criteria reveals a high percentage of malnutrition which influences overall survival in patients with gastroenteropancreatic neuroendocrine tumours

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Abstract

Patients with neuroendocrine tumours located in the gastroenteropancreatic tract (GEP-NETs) and treatment with somatostatin analogues (SSA's) are at risk of malnutrition which has been reported previously evaluating weight loss or body mass index (BMI) only. The global leadership into malnutrition (GLIM) criteria include weight loss, BMI, and sarcopenia, for diagnosing malnutrition. These GLIM criteria have not been assessed in patients with GEP-NETs on SSA. The effect of malnutrition on overall survival has not been explored before. The aim of this study is to describe the presence of malnutrition in patients with GEP-NET on SSA based on the GLIM criteria and associate this with overall survival. Cross-sectional study screening all patients with GEP-NETs on SSA's for malnutrition using the GLIM criteria. Body composition analysis for sarcopenia diagnosis were performed. Bloods including vitamins, minerals, and lipid profile were collected. Overall survival since the date of nutrition screening was calculated. Uni- and multivariate Cox regression analysis were performed to identify malnutrition as risk factor for overall survival. A total of 118 patients, 47% male, with median age 67 years (IQR 56.8–75.0) were included. Overall, malnutrition was present in 88 patients (75%); based on low BMI in 26 (22%) patients, based on weight loss in 35 (30%) patients, and based on sarcopenia in 83 (70%) patients. Vitamin deficiencies were present for vitamin D in 64 patients (54%), and vitamin A in 29 patients (25%). The presence of malnutrition demonstrated a significantly worse overall survival (p-value = .01). In multivariate analysis meeting 2 or 3 GLIM criteria was significantly associated with worse overall survival (HR 2.16 95% CI 1.34–3.48, p-value = .002). Weight loss was the most important risk factor out of the 3 GLIM

criteria (HR 3.5 95% CI 1.14–10.85, *p*-value = .03) for worse overall survival. A high percentage (75%) of patients with GEP-NETs using a SSA meet the GLIM criteria for malnutrition. Meeting more than 1 GLIM criterium, especially if there is weight loss these are risk factors for worse overall survival.

KEYWORDS
gastroenteropancreatic neuroendocrine tumour, malnutrition, sarcopenia, somatostatin analogue, survival

1 | INTRODUCTION

Neuroendocrine tumours (NETs) are uncommon cancers arising from the enterochromaffin cells.[1] NETs are part of the group of neuroendocrine neoplasms (NEN) which also includes neuroendocrine carcinoma (NECs). NETs and NECs differ in morphology, clinical behaviour, treatment, and prognosis and should be considered as different entities. NETs can arise anywhere in the body but the main locations are the gastroenteropancreatic (GEP) and pulmonary tract.[1,2] Diagnosing a GEP-NET is often difficult and may take up to 3–5 years.[3,4] Due to their location in the GEP tract, patients can have symptoms of abdominal pain, diarrhoea or weight loss. Treatment with surgery or somatostatin analogues (SSA's) are the first options but can also cause diarrhoea and weight loss.

Malnutrition is a state of nutrition in which a deficiency, excess, or imbalance of energy, protein, and other nutrients causes measurable adverse effects on body form and functional or clinical outcomes.[5] Malnutrition is a multifactorial process and can be caused by the GEP-NET, weight loss, diarrhoea, or other factors.

Malnutrition in patients with GEP-NETs has been described in previous studies based on anthropometric data (weight loss and body mass index (BMI)) and used different scoring systems. These studies reported a prevalence of malnutrition between 4% and 38%[6–8] and included heterogeneous populations with previous surgery in 48%–60% of patients and suggesting no tumour present at the moment of study, with use of SSA varying between 30% and 51% of patients.[6–9] Only one of these studies reports the effect of malnutrition on overall survival. In this study patients with a pancreas NET and low BMI have a shorter overall survival compared to patients with a pancreas NET and normal BMI or obesity, however, this was only in univariate analysis, and no multivariate analysis for the BMI were performed.[10]

A phenotype of malnutrition is sarcopenia which is a muscle disease rooted in adverse muscle changes that occur across a lifetime, is common among adults of older age but can also occur earlier in life, for example, in patients with cancer.[11] Sarcopenia can be measured with several techniques but body composition analysis on cross-sectional imaging is considered as the gold standard.[11] These body composition analysis can also diagnose adipopenia which means fat mass depletion[12] and myosteatosis which is fat infiltration in the muscle and is used as surrogate marker for muscle quality.[13] A few small studies describe sarcopenia to be present in 16%–87% of patients with GEP-NETs, however, the clinical consequences of sarcopenia are unknown.[14–16] Adipopenia and myosteatosis have not been described in patients with GEP-NETs.

For a few years the worldwide global leadership into malnutrition (GLIM) criteria have existed to describe the presence of malnutrition. Which is present if there is; weight loss (>5% in past 6 months or>10% beyond 6 months), a low BMI (<20 if age <70 years or <22 if age >70 years), or sarcopenia in the presence of; reduced food intake or assimilation, or inflammation (acute or chronic disease).[17] The prevalence of malnutrition in patients with GEP-NETs based on the GLIM criteria is lacking.

The aim of this study is to describe the presence of malnutrition based on the GLIM criteria in a cohort of patients with GEP-NETs including body composition analysis. A Secondary aim is to evaluate the effect of malnutrition on overall survival.

2 | METHODS

2.1 | Study design and study population

This is a cross-sectional study screening all patients for malnutrition with a GEP-NET treated with monthly SSA's at King's College Hospital, London between August 2018 and February 2019.

Inclusion criteria were adult patients (>18 years) with a histology-confirmed diagnosis of GEP-NET and treatment with monthly SSA. If there were no histology reports available, avidity on Gallium68 DOTATATE PET scan was used to confirm diagnosis.

Exclusion criteria were NET outside the GEP tract, treatment with chemotherapy for a second cancer, presence of ascites or spinal metal implant, and no CT scan available.

2.2 | Outcomes

The primary outcome of this study was the presence of malnutrition according to the GLIM criteria (GLIM+).

The secondary outcomes were the presence of sarcopenia, adipopenia, and myosteatosis. To describe presence of deficiencies in vitamins, minerals, or lipids and its association with GLIM criteria. To assess the severity of malnutrition and to explore the effect of malnutrition on overall survival.

2.3 | Data collection

All patients were screened for malnutrition according to the malnutrition universal screening tool (MUST score) which is based on weight, BMI, and weight loss.[5] To confirm the diagnosis of malnutrition the GLIM criteria were used.

If there was either:

1. weight loss (>5% in past 6 months or >10% beyond 6 months) or
2. low BMI (<20 if age <70 year or < 22 if age >70 year) or
3. sarcopenia (males if the BMI <25 and skeletal muscle index (SMI) <43 cm^2/m^2 or BMI >25 and SMI <53 cm^2/m^2 and for females SMI <41cm^2/m^2), the diagnosis of malnutrition was confirmed (GLIM+ group), as summarised in Figure 1.

The severity of malnutrition according to the GLIM criteria cannot be analysed as no cut-off exists for severe sarcopenia.[17] However, for severity of malnutrition we calculated the number of patients meeting 1 or 2 or all 3 GLIM criteria.

The CT scan performed ± 3 months from the date of malnutrition screening was analysed for body composition analysis. A single slice of the CT scan at lumbar level L3 was used, as this corresponds with total body muscle- and fat mass.[18,19] Slice-O-Matic software (5.0 Rev-8, Tomovision Milletta Canada) was used. Relevant tissues were identified based on their anatomical features and tagged with a colour. The software multiplies preset Hounsfield Units (HU) with pixels for the tagged area to calculate the relevant areas. For skeletal muscle area (SMA) the settings were −29HU to +150HU, the result was corrected for height^2 to get the SMI. Sarcopenia is present in males if the BMI <25 and SMI < 43 cm^2/m^2 or BMI >25 and SMI < 53 cm^2/m^2 and for females SMI <41 cm^2/m^2. The median HU per SMA are used for myosteatosis which is present if BMI <25 HU > 41 or BMI > 25 HU > 33HU (for males and females). For adipose tissue, the subcutaneous adipose tissue area (setting −150HU to −50HU), visceral adipose tissue area (setting −190 to −30HU), and intermuscular tissue area (setting −190 to −30HU) were analysed. These areas were summed to get the total adipose tissue area. If this was below 364 cm^2 for males and 318 cm^2 for females, adipopenia was present.

Bloods were collected as non-fasted blood samples, and taken on the day of the malnutrition screening. A stool sample pot was provided to the patient and collected at the day of malnutrition screening or next visit. Bloods that were collected, haemoglobin level (115–155 g/dL), mean capsular volume level (77–100 fL), albumin (35–50 g/L), vitamin A (1.4–3.84 μmol/L), vitamin D (>50 nmol/L), magnesium (0.7–1.0 mmol/L), zinc (11–19 μmol/L), iron (14–30 μmol/L), total iron binding capacity (50–72 μmol/L), iron saturation (20%–50%), cholesterol (1.0–5.0 mmol/L), triglyceride (0.5–2.0 mmol/L), high-density lipoprotein (HDL) cholesterol (>1 mmol/L), low-density lipoprotein (LDL) cholesterol (1–3 mmol/L). A stool sample for faecal elastase (>200 μg/g) was collected.

Baseline demographic characteristics were collected including, histology details for grading- and staging according to WHO 2019 classification.[20] Primary tumours were categorised as located in small intestine, pancreas, or other. A functional NET was present if there was evidence of hormone overproduction. Carcinoid syndrome was diagnosed if there was diarrhoea and/or flushing in the presence of raised 5-hydroxyindolecactic acid (5-HIAA) in the urine or raised serotonin levels in blood.[21] Tumour nodes metastasis staging was based on Union for International Cancer Control 8th edition (2016). The World Health Organisation (WHO) performance status classification was used for vitality. The Charleston Comorbidity index was used for comorbidity scoring, including diabetes mellitus with or without complications.[22] If patients had symptoms of diarrhoea, loose stools, steatorrhoea, or bloating this was suggestive for pancreatic exocrine insufficiency (PEI) due to SSA use, and pancreatic enzyme replacement therapy (PERT) was commenced.

For the date of diagnosis, the date of histology report or first multidisciplinary meeting was used. For period on SSA's the recorded start date of SSA was compared with the date of malnutrition screening. For the period since diagnosis, the date of diagnosis was compared with the date of malnutrition screening. The overall survival was calculated between date of malnutritional screening and date of death or last follow-up appointment (cut-off data collection May 2022). Disease status was categorised as stable disease or progressive disease. When there was documentation of progressive disease on cross-sectional imaging or adding a type of treatment ± 3 months of malnutrition screening those patients were coded as having progressive disease.

2.4 | Ethics

All data were collected pseudo-anonymized. The study was in accordance with the declaration of Helsinki for experiments involving humans. The health research authority United Kingdom (IRAS number 246990), approved the study.

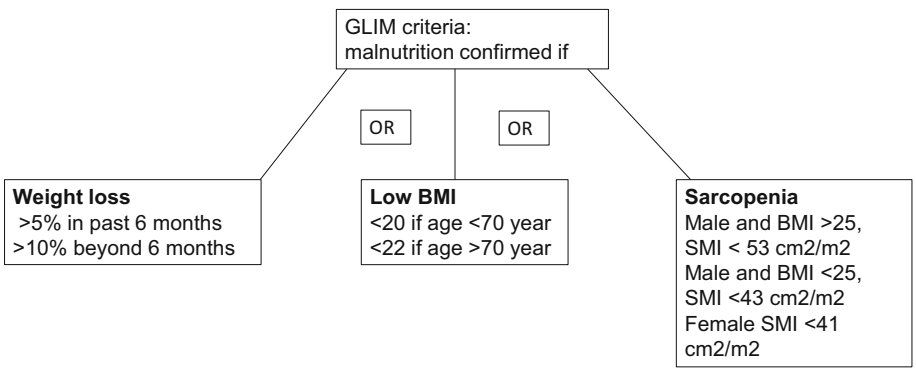


FIGURE 1 Summary GLIM criteria. BMI, body mass index; GLIM, global leadership into malnutrition; SMI. skeletal muscle index.

TABLE 1 Baseline characteristics.

Baseline characteristics	$N = 118$ patients	GLIM − $N = 30$	GLIM + $N = 88$	*p*-value
Sex				.4
Male, *n* (%)	55 (47%)	12 (40%)	43 (49%)	
Female, *n* (%)	63 (53%)	18 (60%)	45 (51%)	
Age (median, IQR)	67 (56.8–75)	62 (51–69.8)	69 (59–75)	**.04**
Ethnicity				.94
White, *n* (%)	86 (73%)	23 (77%)	63 (72%)	
BAME, *n* (%)	21 (18%)	6 (20%)	15 (17%)	
Missing, *n* (%)	11 (9%)	1 (3%)	10 (11%)	
WHO performance score				.82
0, *n* (%)	31 (26%)	8 (26%)	23 (26%)	
1, *n* (%)	71 (60%)	17 (57%)	54 (61%)	
2, *n* (%)	15 (13%)	5 (16%)	10 (11%)	
3, *n* (%)	1 (1%)	0	1 (1%)	
Charlson comorbidity index (median, IQR)	2 (1–4)	2.5 (1–3.3)	2 (1–4)	.59
Location primary tumour				.83
Small intestine, *n* (%)	91 (77%)	25 (83%)	66 (75%)	
Pancreas, *n* (%)	25 (21%)	5 (7%)	20 (23%)	
Other, *n* (%)	2 (2%)	0	2 (2%)	
Disease stage				.7
Stage II, *n* (%)	2 (2%)	1 (3%)	1 (1%)	
Stage III, *n* (%)	17 (14%)	4 (13%)	13 (16%)	
Stage IV, *n* (%)	91 (77%)	22 (73%)	69 (86%)	
Missing, *n* (%)	8 (7%)	3 (10%)	5 (6%)	
Grading				**.03**
G1, *n* (%)	74 (63%)	26 (87%)	48 (55%)	
G2, *n* (%)	30 (25%)	4 (13%)	26 (30%)	
Missing, *n* (%)	14 (12%)	0	14 (15%)	
Functional NET, *n* (%)	46 (40%)	11 (37%)	35 (40%)	.36
Carcinoid syndrome, *n* (%)	41 (35%)	10 (33%)	31 (26%)	.36
Functional panNET, *n* (%)	4 (3%)	1 (3%)	3 (3%)	.74
Other, *n* (%)	1 (0.8%)			
Stable disease, *n* (%)	84 (71%)	26 (87%)	62 (70%)	.76
Months since diagnosis of NET (median, IQR)	40 (14–84)	22.5 (2.3–42.5)	24 (7.8–64.8)	.25
Months on SSA (median, IQR)	23 (5.5–59)	29 (21.5–61.5)	46 (12.3–94.8)	.19
PERT use, *n* (%)	$N = 46$ (39%)	N = 7 (24%)	$N = 39$ (45%)	**.04**
Weight (median, IQR)	70 (59.1–82.3)	85.1 (73–95.2)	66.8 (55.9–75.7)	**<.001**
BMI (median, IQR)	24.8 (21.7–28.7)	30.4 (26.5–34)	23.3 (20.3–25.8)	**<.001**
Sarcopenia *n* (%)	$N = 83$ (70.3%)	$N = 0$	$N = 83$ (94%)	
Myosteatosis *n* (%)	$N = 47$ (40%)	$N = 11$ (37%)	$N = 36$ (41%)	
Adipopenia *n* (%)	$N = 87$ (74%)	$N = 14$ (47%)	$N = 73$ (83%)	

Note: Bold indicates relevant/significant findings.

Abbreviations: BAME black, asian minority ethnicity; BMI, body mass index; IQR, interquartile range; panNET pancreatic neuroendocrine tumour; PERT pancreatic enzyme replacement therapy, SSA, somatostatin analogue.

2.5 | Statistical analysis

Data were analysed using SPSS version 28 (IBM, New York, United States). Data were displayed as median with interquartile range or for categorical data as number and percentage. The Mann–Whitney U test and Chi-square were performed to describe differences between groups. Logistic regression analysis were performed to explore the relationship between malnutrition and deficiencies in

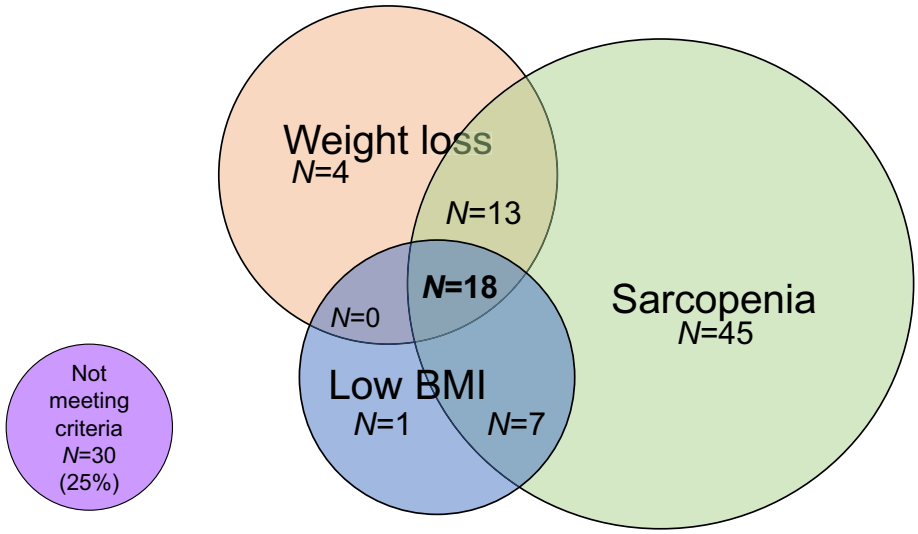


FIGURE 2 Venn diagram relation GLIM criteria, BMI, body mass index.

blood markers. For survival analysis, Kaplan Meier curves were plotted and log-rank test was performed. Cox-regression analysis was performed to correct for confounders including age, sex, grading, and disease status. A *p*-value of <.05 was considered significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 118 patients underwent malnutrition screening and were included in this study. There were 55 male patients (47%) with a median age of 67 years (IQR 56.8–75.0). At the moment of malnutrition screening, the median period since the diagnosis of the GEP-NET was 40 months (IQR 14–84 months) and the median period on SSA's was 23 months (IQR 5.5–59 months). Baseline characters are summarised in Table 1. Details of SSA use were: Lanreotide 60 mg monthly in 4 patients (3%), Lanreotide 90 mg monthly in 14 patients (12%), Lanreotide 120 mg monthly in 49 patients (42%), Lanreotide >120 mg monthly in 2 patients (2%), Sandostatin 20 mg monthly in 9 patients (8%), Sandostatin 30 mg monthly in 31 patients (26%), Sandostatin >30 mg monthly in 9 patients (8%).

Ninety one patients (77%) had metastatic disease, located in one or more of the following locations: liver $n = 83$ (70%), bones $n = 15$ (13%), lymph nodes $n = 7$ (6%), mesentery $n = 5$ (4%), or other $n = 11$ (9%). Prior to inclusion 88 patients (75%) had surgery, 8 patients had embolization of liver metastases (7%), 38 patients had treatment with PRRT (32%), 10 patients had chemotherapy (8%), 5 patients had treatment with everolimus (4%) and 2 patients had treatment with sunitinib (2%).

3.2 | Nutritional outcomes

In total 88 patients (75%) met the GLIM criteria for malnutrition (GLIM+ patients).

The median BMI was 25.0 (IQR 22.5–28.8). There were 7 (6%) patients with BMI <18.5, 52 (44%) patients with BMI 18.51–24.99, 33 (28%) with BMI 25.0–29.99, and 26 (22%) with BMI > 30.0. Twenty six patients (22%) met the GLIM criteria for low BMI. In 35 patients (30%) there was weight loss. Sarcopenia was present in 83 patients (70%).

The correlation between the parameters is summarised in a Venn diagram in Figure 2.

The results of body composition analysis showed, next to sarcopenia, myosteatosis in 47 (40%) and adipopenia in 87 (74%) patients. In patients who did not meet the GLIM criteria for malnutrition myosteatosis was present in 11 (37%) and adipopenia in 14 (47%) patients, as summarised in Table 1.

For severity of malnutrition, there were patients who met 1 GLIM criteria ($n = 50$, 42%), 2 GLIM criteria ($n = 20$, 17%) or all 3 GLIM criteria ($n = 18$, 15%).

3.3 | Blood results

The results of nutritional blood and faeces screening are summarised in Table 2.

Vitamin D levels are normal (>75 nmol/L) in only 15 patients (13%), insufficient (50–75 nmol/L) in 36 patients (31%), deficient (<50 nmol/L) in 54 patients (47%), and severe deficient (<25 nmol/L) in 10 patients (9%). Magnesium is deficient in 22 patients (19%), zinc in 54 patients (51%), and iron in 81 patients (75%). The lipid profile is within normal range in all patients. The faecal elastase was available for 69 patients and low in 45% of patients.

Comparing the blood and faeces results between GLIM+ and GLIM− patients shows no significant differences except, vitamin D levels, total iron binding capacity, and triglyceride levels, as summarised in supplementary Table 1. The vitamin D levels are significantly lower in GLIM+ patients (p-value = .05), however the percentage of patients meeting the criteria for deficiency (<50 nmol/L) is not significantly different (p-value = .07). The total iron binding capacity is significantly lower in GLIM+ patients, (p-value = .007), but

TABLE 2 Blood- and faecal markers.

Parameter	Reference value	Median value (IQR)	% Deficient
Haemoglobin	115–155 g/dL	125 (116–138)	***N* = 25 (21%)**
Mean capsular volume	77–100 fL	94 (89–98)	*N* = 5 (6%)
Albumin	35–50 g/L	44 (41–45)	*N* = 2 (2%)
Vitamin A	1.4–3.84 μmol/L	1.86 (1.39–2.5)	***N* = 29 (25%)**
Vitamin D	>50 nmol/L	47 (35–62)	***N* = 64 (54%)**
Magnesium	0.7–1.0 mmol/L	0.78 (0.71–0.83)	***N* = 22 (19%)**
Zinc	11–19 μmol/L	10.8 (9.5–12.8)	***N* = 54 (51%)**
Iron	14–30 μmol/L	11 (7.7–14)	***N* = 81 (75%)**
Total iron binding capacity	50–72 μmol/L	64 (55–71)	*N* = 18 (17%)
Iron saturation	20%–50%	19 (12–25)	***N* = 57 (55%)**
Cholesterol	1.0–5.0 mmol/L	4 (3.2–4.9)	*N* = 0
Triglyceride	0.5–2.0 mmol/L	1.4 (0.9–1.9)	*N* = 1 (1%)
HDL cholesterol	>1 mmol/L	1.4 (1.1–1.8)	*N* = 19 (18%)
LDL cholesterol	1–3 mmol/L	1.9 (1.4–2.5)	*N* = 13 (13%)
Faecal elastase	>200 μg/g	236 (106–372)	***N* = 31/69 (45%)**

Note: Bold indicates relevant/significant findings.
Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

the percentage of patients meeting the criteria for deficiency differs not significantly (p-value = .13). The triglyceride levels are significantly lower in the GLIM+ patients (p-value = .001).

Logistic regression analysis could not identify a relationship between malnutrition based on the GLIM criteria and any of the blood results.

3.4 | Survival analysis including uni- and multivariate analysis

The median overall survival since nutritional screening for the study group was not reached. There were significant survival differences between GLIM+ or GLIM− patients (p-value = .01). This was also the case for patients who met 1 GLIM criterium, met 2 GLIM criteria, or met all 3 GLIM criteria (p-value = .006). Looking into detail of the separate parameters of the GLIM criteria, weight loss versus stable weight, BMI below cut-off versus normal BMI, and sarcopenia versus no sarcopenia all showed significant survival differences with p-value = .004, p-value = .01, p-value = .035, respectively. For adipopenia, there were significant survival differences (p-value = .037), while the presence of myosteatosis had no effect on survival (p-value = .11) as displayed in Figure 3–F. There were no significant survival differences between patients with and without carcinoid syndrome (p-value = .56), graph not displayed.

Factors associated with overall survival in univariate analysis are reported in Table 3.

Sex, age, grading, and disease status were included in the multivariate analysis, combined with GLIM+, the presence of malnutrition was not statistically significant (p-value = .11) associated with worse overall survival, Table 3 multivariate analysis model 1.

In Table 3, model 2, meeting 1, 2, or all 3 GLIM criteria was added to sex, age, grading, and disease status in the multivariate analysis. This showed meeting 2 or 3 GLIM criteria was associated with worse overall survival (p-value = .002).

Next, each separate parameter of the GLIM criteria were analysed in combination with sex, age, grading, and disease status. Two out of three individual parameters were significantly associated with overall survival, weight loss HR 4.2 (95% CI 1.6–10.9) (p-value = .003), low BMI HR 4.13 (95% 1.63–10.79) (p-value = .003), sarcopenia HR 1.9 (0.62–5.83) (p-value = .26), model not shown.

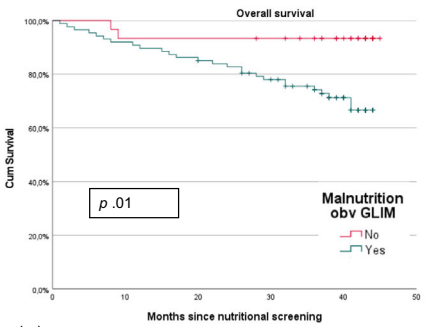
Subsequently, all three separate GLIM criteria were included in model 3 of the multivariate analysis; only weight loss was significantly associated with survival with HR 3.5 (95% CI 1.14–10.85) (p-value = .03) as displayed in Table 3 (model 3).

In model 4 sarcopenia and weight loss were included in the multivariate analysis in combination with sex, age, grading, and disease status, weight loss was significantly associated with worse overall survival with HR 4.66 (95% 1.64–13.20) (p-value = .004), model not shown. In model 5 in the multivariate analysis sex, age, grading, and disease status were combined with sarcopenia and low BMI, only low BMI was significantly associated with worse overall survival HR 3.71 (1.31–10.51) (p-value = .01), model not shown.

In model 6 (not shown) weight loss and low BMI were both included together with sex, age, grading, and disease status; weight loss significant associated with worse overall survival with HR 3.53 (95% CI 1.16–10.76) p-value = .03. Adipopenia was not significantly associated with overall survival after correcting for sex, age, grading, and disease status, HR 3 (95% CI 0.67–13.5), p-value = .15.

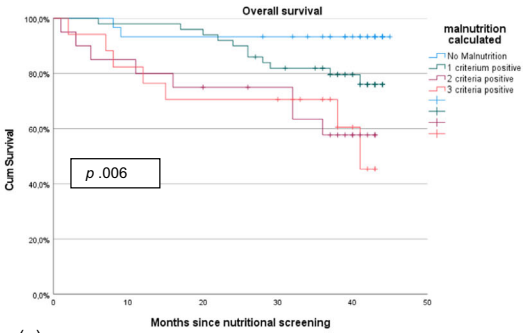
4 | DISCUSSION

This cross-sectional study showed malnutrition based on the GLIM criteria is present in 75% of patients with GEP-NETs using an SSA.



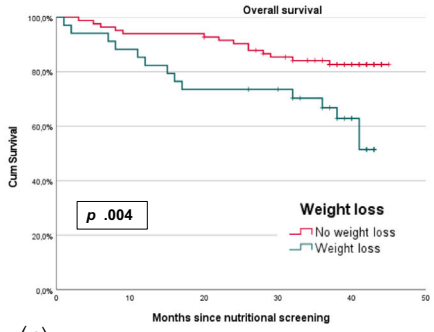
(A) Kaplan Meier curve GLIM- versus GLIM+

Number of patients	Time (months)	0	12	24	36
GLIM-		30	28	28	25
GLIM+		87	79	72	58



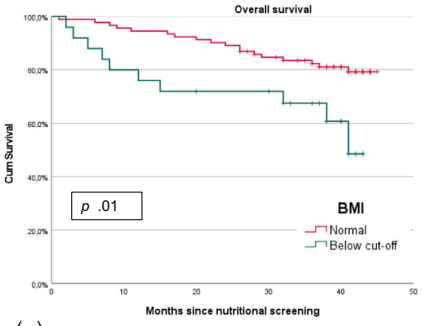
(B) Kaplan Meier curve overall survival severity malnutrition

Number of patients	Time (months)	0	12	24	36
No malnutrition		30	28	28	25
1 GLIM criterium +		50	49	46	38
2 GLIM criteria +		20	16	14	11
3 GLIM criteria +		17	14	12	9



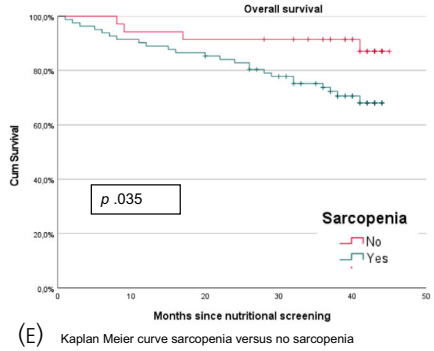
(C) Kaplan-Meier curve weight loss versus stable weight

Number of patients	Time (months)	0	12	24	36
No weight loss		83	78	75	63
Weight loss		34	29	25	20



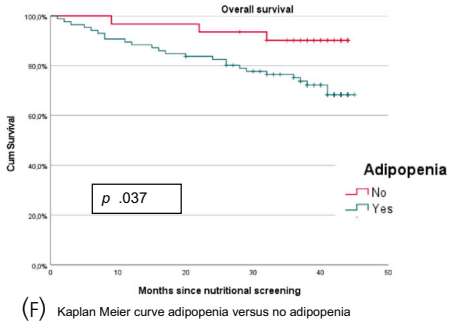
(D) Kaplan Meier curve low versus normal BMI

Number of patients	Time (months)	0	12	24	36
Normal BMI		92	87	83	70
Low BMI		25	20	17	13



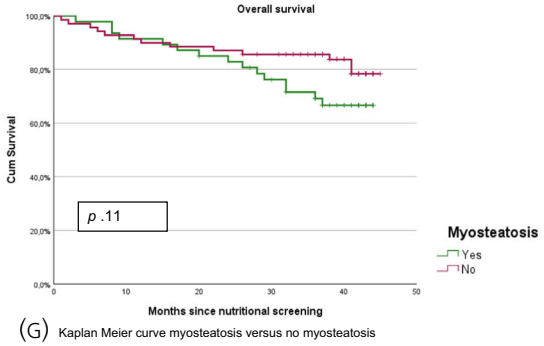
(E) Kaplan Meier curve sarcopenia versus no sarcopenia

Number of patients	Time (months)	0	12	24	36
No sarcopenia		35	33	32	29
Sarcopenia		82	74	68	54



(F) Kaplan Meier curve adipopenia versus no adipopenia

Number of patients	Time (months)	0	12	24	36
No adipopenia		31	30	29	25
Adipopenia		86	77	71	58



(G) Kaplan Meier curve myosteatosis versus no myosteatosis

Number of patients	Time (months)	0	12	24	36
No myosteatosis		70	64	61	53
Myosteatosis		47	43	39	30

FIGURE 3 Legend on next page.

TABLE 3 Uni- and multivariate analysis regarding overall survival.

	Univariate analysis		Multivariate analysis Model 1 GLIM+		Multivariate analysis Model 2 Severity GLIM		Multivariate analysis Model 3 Weight loss or low BMI or sarcopenia	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex	0.55 (0.26–1.15)	.13	0.64 (0.26–1.55)	.32	0.65 (0.27–1.59)	.35	0.63 (0.25–1.55)	.31
Age	1 (0.99–1.1)	.84	1 (0.99–1.01)	.9	1 (0.98–1.01)	.43	1 (0.98–1.07)	.32
Grading	2.4 (1.0–5.5)	**.05**	1.82 (0.74–4.46)	.19	1.98 (0.8–4.90)	.14	2.1 (0.77–5.53)	.15
Location primary	0.88 (0.38–2.02)	.76						
Disease status	2.6 (1.24–5.5)	**.01**	2.78 (1.17–6.61)	**.02**	4.5 (1.7–11.76)	**.002**	5.95 (2.03–17.42)	**.001**
GLIM+	5.2 (1.23–21.8)	**.03**	3.47 (0.77–15.55)	.11				
Severity GLIM	1.8 (1.3–2.6)	**.001**			2.16 (1.34–3.48)	**.002**		
Weight loss	2.85 (1.36–5.97)	**.006**					3.5 (1.14–10.85)	**.03**
Low BMI	2.62 (1.21–5.69)	**.02**					2.47 (0.73–6.89)	.16
Sarcopenia	2.97 (1.03–8.56)	**.04**					1 (0.30–3.42)	.98
Adipopenia	3.32 (1.01–11)	**.05**						

Note: Bold indicates relevant/significant findings.

Second to progressive disease, meeting more than 1 of the GLIM criteria was associated with worse overall survival in uni- and multivariate analysis, and weight loss was the most important GLIM criterium.

This is the first study evaluating the presence of malnutrition according to the GLIM criteria and to associate the GLIM criteria as a whole and as individual criteria with overall survival in patients with GEP-NETs using a SSA. This study population used different doses and prescriptions of SSA's. However, 90% of patients used doses recommended by the current ENETS and ESMO guidelines,[23,24] Sandostatin 10–30 mg every 28 days or Lanreotide 60–120 mg every 28 days. The recommended doses are lower than the doses studied in the CLARINET[25] and PROMID[26] studies which described Lanreotide 120 mg every 28 days or Sandostatin 30 mg every 28 days, respectively.[27] The current study population is slightly older (median age 67 years) compared to the median age of patients in the CLARINET[25] and PROMID[26] studies (median age 63 years). In older patients, we commence patients on a lower dose than the recommended maximum dose of Lanreotide or Sandostatin to await the side effects and titrate the dose to maximum if well tolerated. There were 27 patients (23%) not on the maximum dose of SSA it could be hypothesised this effected the overall survival. However, this is a small subgroup and the numbers are too low for subgroup analysis or to draw conclusions.

The presence of malnutrition according to the GLIM criteria was higher than the prevalence of malnutrition previously described in patients with GEP-NETs of 4%–38%. This could be explained by the difference in definitions used for malnutrition and methods of assessment. The GLIM criteria include weight loss, low BMI with different cut-offs for age above/below 70 years, and the presence of sarcopenia. The studies from Robbins[6] and Qureshi[9] only used the MUST score, which is based on weight loss and BMI and lacks an age-specific cut-off. The studies from Borre[7] and Maasberg[8] used the nutrition risk screening 2002 (NRS) and subjective global assessment (SGA) which are both again based on weight loss and BMI, however, the SGA also includes gastrointestinal (GI) symptoms. The percentage malnutrition in the Borre study[7] is 38% and in the Maasberg[8] study 21% based on NRS and 25% based on the SGA. This is in line with the findings from our study looking at low BMI (22%) and weight loss (30%) only.

The GLIM criteria diagnose malnutrition if sarcopenia is present on CT scan-based body composition analysis as well as weight loss and low BMI.[11,17] However, the body composition analysis in our study highlighted a high percentage (70%) of sarcopenia and this has not been reported before. The only two comparable studies used different techniques to measure sarcopenia and reported a prevalence of 25, respectively, 26%.[7,8] Two other studies examining sarcopenia alone have reported similar findings to our results with sarcopenia present in 67%–87%.[14,15] These two studies cannot be compared to the population in the current study as the Chan group[14] only included patients with progressive disease of their NET and Herrera[15] included patients at diagnosis of their NET.

The prevalence of sarcopenia in our study is higher than in studies with metastatic colorectal cancer with a reported percentage of sarcopenia 27%–44%[28,29] or metasatic gastroIntestinal stromacel tumour (GIST) with a reported percentage of sarcopenia 23%–56%.[30,31] Differences in the prevalence of sarcopenia could be explained by

FIGURE 3 (A) Kaplan–Meier curve GLIM− versus GLIM+. (B) Kaplan–Meier curve overall survival severity malnutrition. (C) Kaplan–Meier curve weight loss versus stable weight. (D) Kaplan–Meier curve low versus normal BMI. (E) Kaplan–Meier curve sarcopenia versus no sarcopenia. (F) Kaplan–Meier curve adipopenia versus no adipopenia. (G) Kaplan–Meier curve myosteatosis versus no myosteatosis.

different techniques to measure the presence of sarcopenia, different cut-offs to confirm the diagnosis of sarcopenia used. Another explanation could be the moment of sarcopenia measurement as in both the colorectal cancer as GIST studies the measurements were performed prior to start with systemic anti-cancer treatment while our measurements were at a random moment.[28–31] Nevertheless, the prevalence of sarcopenia in patients with GEP-NETs is high. This could be explained by multiple factors such as ageing, the presence of the NET and its catabolism, and possible malnutrition due to reduced intake. Sarcopenia was first described in the ageing population as from the age of 50 years loss of muscle mass and strength has been reported.[11] As the median age is 67 years the high prevalence of sarcopenia could be driven by ageing. In patients with cancer the ongoing inflammatory response results in protein catabolism and reduced muscle mass and strength.[32] There are no studies confirming this hypothesis in patients with NETs but as it is considered as a cancer it could be assumed there is some protein catabolism present. Also, the median period since diagnosis of the NET was 40 months in this study, it could be assumed a long period to develop catabolism. Another explanation for the high prevalence of sarcopenia could be reduced nutritional intake or absorption. As 75% of the patients in this study had previous surgery with an alteration to the digestive tract which could result in reduced nutrition uptake.[33–35] All patients were using a SSA which can result in PEI and reduced nutrition uptake.[34,36] When patients developed symptoms of diarrhoea or steatorrhoea they commenced on PERT, faecal elastase was available for only 58% of patients. The role of faecal elastase testing in patients with GEP-NETs is not clear as 2 abstracts and 1 article report conflicting results. In the abstract from Donnelly et al regarding 57 patients with GEP-NETs with symptoms of steatorrhoea, in only 17% the faecal elastase was low.[37] Another abstract regarding 32 patients on an SSA reported steatorrhoea in 82% of patients but the faecal elastase was only low in 19%.[38] While the study from Lamarca et al regarding 50 patients commencing an SSA report faecal elastase is a good marker for diagnosing PEI. Although in this study only 64% of patients returned a stool sample.[39]

Forty percent of patients had a functional NET, mainly carcinoid syndrome with diarrhoea as main symptom due to increased bowel transit which can also contribute to malnutrition and subsequently to the development of sarcopenia.[35] The presence of carcinoid syndrome in the current study (35%) is higher than described in the literature (20%), this could be explained due to different definitions used[40] and different study designs large national database[40] versus single centre study.

Besides disease status and meeting more than 1 of the GLIM criteria, weight loss is the most important parameter in uni- and multivariate analysis associated with overall survival. The percentage of malnutrition based on the GLIM criteria is high due to the high percentage of sarcopenia. It could be hypothesised the first stage of malnutrition is sarcopenia but this might not be related to overall survival. When the phenotypes of malnutrition with weight loss or low BMI develop in the presence of sarcopenia this should be considered as severe malnutrition and was significantly associated with poorer overall survival. Other studies showed the obesity paradox which is a hypothesis that patients with a BMI >30 kg/m^2 have a survival benefit. One study regarding patients with a NET in the USA confirmed this paradox.[41] While a study from Portugal regarding metabolic syndrome in patients with GEP-NETs could not confirm this obesity paradox.[42] However, in our study the obesity paradox is present.

Comparing patients with and without malnutrition significant differences between age, weight, and BMI were observed, this could be explained by the GLIM criteria as there is a different cut-off for BMI for patients above and below 70 years.[17] The difference in grading could be explained by aggressiveness of the tumour, it could be grade 2 tumours are more aggressive resulting in sarcopenia or malnutrition earlier than grade 1 tumours. Another explanation for this could be the large group of patients with a small bowel NET in the study, in our previous study regarding sarcopenia in patients with GEP-NETs grading of a small bowel NET was significantly associated with worse overall survival.[43]

Interestingly, the patients who met the criteria for malnutrition used significantly more PERT compared to the well-nourished patients. It could be hypothesised that PEI is a risk factor for developing malnutrition. Other factors such as location of primary tumour or presence of metastasis does not differ between the well- and malnourished patients, this could be explained by the large group of patients with small bowel NETs or metastatic disease.

The reported fat-soluble vitamin deficiency in this study is in line with previous studies reporting vitamin A and vitamin D deficiency.[44–46] The reported deficiency in the mineral magnesium has not been reported before. It could be suggested that magnesium deficiency is more prevalent in patients who had a terminal ileum resection as magnesium is resorbed here. The reported deficiency of zinc is in line with previous reports. The high percentage of iron deficiency has not been reported before, this deficiency resulted in anaemia in 21% of patients which has not been reported before either. This percentage of anaemia could be explained by reduced absorption of iron due to surgery to the small intestine or due to abnormal pH levels in the case of PEI.[47]

The GLIM criteria, the previously used European Society of parenteral and enteral nutrition (ESPEN), nor American Society of parenteral and enteral nutrition criteria for malnutrition did include vitamin, mineral, or trace element deficiency as a diagnostic criterium for malnutrition, nor it is considered as a phenotype of malnutrition.[17,48,49] It could be questioned what the relevance of the reported deficiencies is. Severe vitamin A deficiency could lead to night blindness and has been published in several case reports.[50–53] Vitamin D deficiency could lead to osteopenia or osteoporosis which has been reported in 1 study regarding 50 patients with small intestinal NETs and vitamin D deficiency, osteopenia was prevalent in 36%–44% of patients and osteoporosis in 24%–32% of patients.[16] Magnesium deficiency could result in several clinical symptoms or problems with other minerals such as potassium or calcium.[54] Zinc deficiency is related with growth retardation and cognitive impairment and children,[55] therefore, it is consequence of low levels in patients with GEP-NETs is unknown. Iron deficiency

can result in anaemia this could be relevant for patients with a GEP-NET as fatigue is a common symptom and affecting quality of life.[56,57]

Body composition analysis demonstrated the presence of myosteatosis in 37% and adipopenia in 47% in patients who do not meet the GLIM criteria for malnutrition. This phenomenon has been described in patients with colorectal cancer where 21%–34% of patients with stable weight had myosteatosis.[58] An explanation for the presence of adipopenia and myosteatosis in patients who are not malnourished could be the presence of PEI which might result in adipopenia and myosteatosis.

For body composition analysis the GLIM criteria suggest multiple different techniques including bio impedance analysis (BIA). A study from Barrea et al. performed BIA analysis in 83 patients with GEP-NETs and found the BIA-phase angle a useful marker for nutritional status.[59] The BIA analysis is based on multiple assumptions such as 73% of fat-free mass is water. It also requires controlled circumstances such as no exercise 12 h prior to the test, no alcohol or coffee prior to the test, and be well hydrated.[60] The current guidelines for sarcopenia suggest body composition analysis on cross-sectional imaging as gold standard.[11,17] Although body composition analysis might be a time-consuming technique and not available in every centre, in that case, the BIA analyses could be a good alternative.

In this study, progressive disease is significantly associated with overall survival in uni- and multivariate analysis. While this is not the case in the only comparable study from Maasberg et al.[8] In this study 177 patients admitted to hospital and 26 out patients were screened for malnutrition and its presence was associated with overall survival in uni- and multivariate analysis. The disease status was based on the RECIST criteria while our study used another definition. The length of time prior to the diagnosis of the NEN was unknown and there were patients with a NET and NEC included. Therefore, these studies are difficult to compare. In studies regarding patients with metastatic colorectal cancer or metastatic GIST the presence of sarcopenia, prior to start with systemic anti-cancer treatment, is also significantly associated with poorer progression-free survival or overall survival.[30,31,61] As progressive disease, regardless of nutritional status, in patients with GEP-NETs is associated with worse overall survival the findings in this study regarding progressive disease could be expected.[1,62-64]

This study highlights the importance of screening for malnutrition in patients with GEP-NETs using an SSA, especially monitoring weight loss is important. There are also some limitations in this study. Malnutrition is a multifactorial process and can be caused by the GEP-NET itself, symptoms related to the GEP-NET, or side-effects of treatment such as diarrhoea.[33] Data regarding aetiology of malnutrition or symptoms were not collected. In 23% of patients there was localised disease but due to comorbidity or performance status curative surgery was not possible. Although a cross-sectional study in a single centre the data are not complete for all patients. The study was performed in 2018–2019 therefore the overall survival data are maximum of 4 years. If there was longer follow up the effect of malnutrition could be different. Another limitation is the severity of sarcopenia and malnutrition could not be established as the GLIM criteria do not provide cut-offs for severity of sarcopenia.[17] However, we tried to correct for this highlighting the differences between patients who meet 1 or more parameters of the GLIM criteria as this has not been described before. One of the explanations of the high percentage malnutrition and sarcopenia could be poor oral intake related to GI symptoms, however, these data were not collected in this study.

Future research should focus on how to treat malnutrition and if reversal of malnutrition effects the overall survival. The DIVIT study included 53 patients with a NET and on an SSA for >6 months, nearly all patients (91%) received nutritional support, and after 18 weeks this resulted in significantly less vitamin deficiencies. However, the effect on outcomes of the patients unknown.[65] Studies regarding patients with pancreatic cancer reported weight gain improved overall survival[66,67] and patients with colorectal cancer had survival benefits following nutritional interventions.[68,69] However there are also studies regarding patients with cancer in the upper GI tract who failed to demonstrate a survival benefit of nutritional interventions.[70,71] To answer the question ideally a randomised controlled trial comparing a standardised nutritional- and exercise programme with the standard of care for all patients commencing with an SSA should be set up. At baseline, the nutritional status based on GLIM criteria, GI symptoms, and quality of life should be measured. The aim for the primary outcome of this RCT should be improvement in nutritional status. Secondary outcomes aim to demonstrate prolonged overall survival, improved quality of life, and less GI-symptoms. In studies regarding colorectal cancer, pancreatic adenocarcinoma, and bladder cancer reversibility of sarcopenia 1–2 years following diagnosis, has been associated with improved survival.[58,72,73]

5 | CONCLUSION

Based on GLIM criteria, malnutrition is common in patients with GEP-NETs using a SSA. When malnutrition is related to weight loss it is associated with poor overall survival. Patients could benefit from regular weight monitoring and possibly from early nutritional intervention.

AUTHOR CONTRIBUTIONS

Dominique S. V. M. Clement: Conceptualization; formal analysis; investigation; methodology; writing – original draft. **Monique E. van Leerdam:** Formal analysis; methodology; validation; writing – review and editing. **Margot E. T. Tesselaar:** Validation; writing – review and editing. **Elmie Cananea:** Investigation; writing – review and editing. **Wendy Martin:** Investigation; writing – review and editing. **Martin O. Weickert:** Resources; writing – review and editing. **Debashis Sarker:** Validation; writing – review and editing. **John K. Ramage:** Supervision; writing – review and editing. **Rajaventhan Srirajaskanthan:** Conceptualization; supervision; writing – review and editing.

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The authors have no conflicts of interest to declare.

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DATA AVAILABILITY STATEMENT

All data generated during this study were included in this manuscript. Further enquiries can be directed to the corresponding author.

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REFERENCES

1. Yao JC, Hassan M, Phan A, et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26:3063-3072.
2. Genus TSE, Bouvier C, Wong KF, et al. Impact of neuroendocrine morphology on cancer outcomes and stage at diagnosis: a UK nationwide cohort study 2013–2015. *Br J Cancer*. 2019;121:966-972.
3. Wolin EM, Leyden J, Goldstein G, Kolarova T, Hollander R, Warner RRP. Patient-reported experience of diagnosis, management, and burden of neuroendocrine tumors: results from a large patient survey in the United States. *Pancreas*. 2017;46:639-647.
4. Basuroy R, Bouvier C, Ramage JK, Sissons M, Kent A, Srirajaskanthan R. Presenting symptoms and delay in diagnosis of gastrointestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology*. 2018;107:42-49.
5. Stratton RJ, Hackston A, Longmore D, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. *Br J Nutr*. 2004;92:799-808.
6. Robbins HL, Symington M, Mosterman B, et al. Supplementation of vitamin D deficiency in patients with neuroendocrine tumors using over-the-counter vitamin D3 preparations. *Nutr Cancer*. 2018;70:748-754.
7. Borre M, Dam GA, Knudsen AW, Grønbaek H. Nutritional status and nutritional risk in patients with neuroendocrine tumors. *Scand J Gastroenterol*. 2018;53:284-292.
8. Maasberg S, Knappe-Drzikova B, Vonderbeck D, et al. Malnutrition predicts clinical outcome in patients with neuroendocrine neoplasia. *Neuroendocrinology*. 2017;104:11-25.
9. Qureshi SA, Burch N, Druce M, et al. Screening for malnutrition in patients with gastro-entero-pancreatic neuroendocrine tumours: a cross-sectional study. *BMJ Open*. 2016;6:1-7. doi:10.1136/bmjopen-2015-010765
10. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. doi:10.1158/1078-0432.CCR-08-0734
11. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48:16-31.
12. Kim EY, Lee HY, Cho EK, et al. Prognostic significance of cachexia score assessed by CT in male patients with small cell lung cancer. *Eur J Cancer Care*. 2017;27:e12695. doi:10.1111/ecc.12695
13. Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. *Curr Opin Clin Nutr Metab Care*. 2010;13:260-264. doi:10.1097/MCO.0b013e328337d826
14. Chan DL, Clarke SJ, Engel A, et al. Computed tomography (CT)-defined sarcopenia and myosteatosis are prevalent in patients with neuroendocrine neoplasms (NENs) treated with peptide receptor radionuclide therapy (PRRT). *Eur J Clin Nutr*. 2022;76:143-149.
15. Herrera-Martínez Y, Teomiro CA, Idougourram SL, et al. Sarcopenia and ghrelin system in the clinical outcome and prognosis of gastroenteropancreatic neuroendocrine neoplasms. *Cancers*. 2022;14:1-13.
16. Lind A, Wängberg B, Ellegård L. Vitamin D and vitamin B12 deficiencies are common in patients with midgut carcinoid (SI-NET). *Eur J Clin Nutr*. 2016;70:990-994.
17. Cederholm T, Jensen GL, Correia MITDITD, et al. GLIM criteria for the diagnosis of malnutrition—a consensus report from the global clinical nutrition community. *Clin Nutr*. 2019;38:1-9.
18. Shen W. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol*. 2004;97:2333-2338.
19. Mourtzakis M, Prado CMM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33:997-1006. doi:10.1139/H08-075
20. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76:182-188.
21. Fottner C, Ferrata M, Weber MM. Hormone secreting gastro-entero-pancreatic neuroendocrine neoplasias (GEP-NEN): when to consider, how to diagnose? *Rev Endocr Metab Disord*. 2017;18:393-410.
22. Charlson ME, Carrozzino D, Guidi J, et al. Charlson comorbidity index: a critical review of Clinimetric properties. *Psychother Psychosom*. 2022;91:8-35.
23. Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31:844-860.
24. Pavel M, O'Toole D, Costa F, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology*. 2016;103:172-185. doi:10.1159/000443167
25. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic Enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371:224-233.
26. Rinke A, Müller H-H, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol*. 2009;27:4656-4663.
27. La Salvia A, Modica R, Rossi RE, et al. Targeting neuroendocrine tumors with octreotide and lanreotide: key points for clinical practice from NET specialists. *Cancer Treat Rev*. 2023;117:102560.
28. Miyamoto Y, Baba Y, Sakamoto Y, et al. Negative impact of skeletal muscle loss after systemic chemotherapy in patients with unresectable colorectal cancer. *PLoS One*. 2015;10:1-12. doi:10.1371/journal.pone.0129742
29. van Vugt JLA, Braam HJ, van Oudheusden TR, et al. Skeletal muscle depletion is associated with severe postoperative complications in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol*. 2015;22:3625-3631. doi:10.1245/s10434-015-4429-z
30. Yi X, Zhou G, Fu Y, et al. CT-based assessment of sarcopenia for differentiating wild-type from mutant-type gastrointestinal stromal tumor. *Sci Rep*. 2023;13:1-9.
31. Chang YR, Huang WK, Wang SY, et al. A nomogram predicting progression free survival in patients with gastrointestinal stromal tumor receiving sunitinib: incorporating pre-treatment and post-treatment parameters. *Cancer*. 2021;13:1-14.

32. Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. *Proc the Nutr Soc*. 2016;75:188-198.
33. Clement DSVM, Tesselaar MET, van Leerdam ME, et al. Nutritional and vitamin status in patients with neuroendocrine neoplasms. *World J Gastroenterol*. 2019;25:1171-1184.
34. Gallo M, Muscogiuri G, Pizza G, et al. The management of neuroendocrine tumors: a nutritional viewpoint. *Crit Rev Food Sci Nutr*. 2017;59:1046-1057. doi:10.1080/10408398.2017.1390729
35. Sagar VM, Cooper SC, Johnson J, Shetty S, Shah T. Gastrointestinal manifestations of neuroendocrine tumours: their investigation and management. *Postgrad Med J*. 2017;93:494-497.
36. Arnold R, Trautmann ME, Creutzfeldt W, et al. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut*. 1996;38:430-438.
37. Donnelly L, Tailor S, Reid K, et al. A prospective service evaluation of systematic gastroenterological assessment and management on patients with neuroendocrine tumours in south East Wales. ENETS Abstract. https://www.enets.org/a-prospective-service-evaluation-of-systematic-gastroenterological-assessment-and-management-on-patients-with-neuroendocrine-tumours-in-south-east-wales.html 2017.
38. Chaudhry R, Newbould R, Williams M, Reid K, Donnelly L, Lewis JKM. Evaluation of faecal elastase 1 in symptomatic patients with neuroendocrine tumours. *Endocr Abstr*, https://www.endocrine-abstracts.org/ea/0046/ea0046p23. 2016;46:23.
39. Lamarca A, McCallum L, Nuttall C, et al. Somatostatin analogue-induced pancreatic exocrine insufficiency in patients with neuroendocrine tumors: results of a prospective observational study. *Expert Rev Gastroenterol Hepatol*. 2018;12:723-731.
40. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18:525-534.
41. Glazer E, Stanko K, Ong E, Guerrero M. Decreased inpatient mortality in obese patients with abdominal Nets. *Endocr Pract*. 2014;1–20:1-20.
42. Santos AP, Rodrigues J, Henrique R, Cardoso MH, Monteiro MP. Visceral obesity is associated with shorter progression-free survival in well-differentiated gastro-entero-pancreatic neuroendocrine neoplasia. *J Clin Med*. 2022;11:1-14.
43. Clement DSVM, van Leerdam ME, de Jong S, et al. Prevalence of sarcopenia and impact on survival in patients with metastatic gastroenteropancreatic neuroendocrine tumours. *Cancers*. 2023;15:1-14. doi:10.3390/cancers15030782
44. Fiebrich H-B, van den Berg G, Kema IP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. *Aliment Pharmacol Ther*. 2010;32:1398-1404.
45. Motylewska E, Gawronska J, Niedziela A, et al. Somatostatin analogs and tumor localization do not influence vitamin D concentration in patients with neuroendocrine tumors. *Nutr Cancer*. 2016;68:428-434.
46. Muhammad Wasif S, Romano A, Smith MH, Patel R, Relias V. Chronic use of long-acting somatostatin analogues (SSAs) and exocrine pancreatic insufficiency (EPI) in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs): an under-recognized adverse effect. *Cancer Med J*. 2020;3(2):75-84.
47. Saboor M, Zehra A, Qamar K, Moinuddin. Disorders associated with malabsorption of iron: a critical review. *Pak J Med Sci*. 2015;31:1549-1553.
48. Cederholm T, Bosaeus I, Barazzoni R, et al. Diagnostic criteria for malnutrition—an ESPEN consensus statement. *Clin Nutr*. 2015;34:335-340.
49. White JV, Guenter P, Jensen G, et al. Consensus statement: academy of nutrition and dietetics and American society for parenteral and enteral nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *J Parenter Enteral Nutr*. 2012;36:275-283.
50. Kassif Y, Rehany U, Rumelt S. Metoprolol responding uveitis: reply. *Eye*. 2005;19:720.
51. Rowe PH, Taylor PR, Shearer MJ, et al. Vitamin a deficiency secondary to pancreatic carcinoid. Case report. *Acta Chir Scand*. 1988;154:487-488.
52. Hansen BA, Mendoza-Santiesteban CE, Hedges TR. Reversible nyctalopia associated with vitamin a deficiency after resected malignant ileal carcinoid and pancreatic adenocarcinoma. *Retin Cases Brief Rep*. 2018;12:127-130.
53. Davis RB, Alexander CS, Adicoff A. Metabolic studies in carcinoid syndrome: observations on use of alpha-methyl DOPA, isonicotinic acid hydrazide and selective tryptophan deficiency. *Metabolism*. 1961;10:1035-1044.
54. al -Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. *Am J Kidney Dis*. 1994;24:737-752.
55. Sigel A. *Metal Ions Fontis Media*; 2004;43.
56. Beaumont JL, Cella D, Phan AT, et al. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas*. 2012;41:461-466.
57. Laing E, Gough K, Krishnasamy M, Michael M, Kiss N. Prevalence of malnutrition and nutrition-related complications in patients with gastroenteropancreatic neuroendocrine tumours. *J Neuroendocrinol*. 2022;34:1-12.
58. Brown JC, Caan BJ, Feliciano EMC, et al. Weight stability masks changes in body composition in colorectal cancer: a retrospective cohort study. *Am J Clin Nutr*. 2021;1-8.
59. Barrea L, Altieri B, Muscogiuri G, et al. Impact of nutritional status on gastroenteropancreatic neuroendocrine tumors (GEP-NET) aggressiveness. *Nutrients*. 2018;10:1-18.
60. Khalil SF, Mohktar MS, Ibrahim F. The theory and fundamentals of bioimpedance analysis in clinical status monitoring and diagnosis of diseases. *Sensors*. 2014;14:10895-10928.
61. Wu T, Xu H, Zou Y, et al. Mid-arm muscle circumference or body weight-standardized hand grip strength in the GLIM superiorly predicts survival in Chinese colorectal cancer patients. *Nutrients*. 2022;14:1-16.
62. Folkestad O, Wasmuth HH, Mjønes P, Fougner R, Hauso Ø, Fossmark R. Survival and disease recurrence in patients operated for small intestinal neuroendocrine tumors at a referral hospital. *Surg Oncol*. 2020;35:336-343.
63. Poleé IN, Hermans BCM, van der Zwan JM, et al. Long-term survival in patients with gastroenteropancreatic neuroendocrine neoplasms: a population-based study. *Eur J Cancer*. 2022;172:252-263.
64. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol*. 2010;21:1794-1803.
65. Stelwagen J, de Hosson L, Sijtema B, van Faassen M, Kema I, de Vries E, Walenkamp A. Vitamin supplementation and a personalized diet in patients with neuroendocrine tumors: the DIVIT study. *Neuroendocrinology*. 2020;110(suppl 1):1-312.
66. Trestini I, Carbognin L, Sperduti I, et al. Prognostic impact of early nutritional support in patients affected by locally advanced and metastatic pancreatic ductal adenocarcinoma undergoing chemotherapy. *Eur J Clin Nutr*. 2018;72:772-779.
67. Davidson W, Ash S, Capra S, Bauer J, Cancer Cachexia Study Group. Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. *Clin Nutr*. 2004;23:239-247.

68. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. *Am J Clin Nutr*. 2012;96:1346-1353.
69. van der Werf A, Langius JAE, Beeker A, et al. The effect of nutritional counseling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy: a randomized controlled trial. *Clin Nutr*. 2020;39:3005-3013.
70. Chen J, Zou L, Sun W, Zhou J, He Q. The effects of nutritional support team intervention on postoperative immune function, nutritional statuses, inflammatory responses, clinical outcomes of elderly patients with gastric cancer. *BMC Surg*. 2022;22:1-9.
71. Bourdel-Marchasson I, Blanc-Bisson C, Doussau A, et al. Nutritional advice in older patients at risk of malnutrition during treatment for chemotherapy: a two-year randomized controlled trial. *PLoS ONE*. 2014;9:1-7.
72. Cloyd JM, Nogueras-González GM, Prakash LR, et al. Anthropometric changes in patients with pancreatic cancer undergoing preoperative therapy and pancreatoduodenectomy. *J Gastrointest Surg*. 2018;22:703-712.
73. Miyake M, Morizawa Y, Hori S, et al. Clinical impact of postoperative loss in psoas major muscle and nutrition index after radical cystectomy for patients with urothelial carcinoma of the bladder. *BMC Cancer*. 2017;17:1-11.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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