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Screening for malnutrition in patients with gastro-entero-pancreatic neuroendocrine tumours: a cross-sectional study

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ABSTRACT

Objectives: To investigate whether screening for malnutrition using the validated malnutrition universal screening tool (MUST) identifies specific characteristics of patients at risk, in patients with gastro-entero-pancreatic neuroendocrine tumours (GEP-NET).

Design: Cross-sectional study.

Setting: University Hospitals Coventry & Warwickshire NHS Trust; European Neuroendocrine Tumour Society Centre of Excellence.

Participants: Patients with confirmed GEP-NET (n=161) of varying primary tumour sites, functioning status, grading, staging and treatment modalities.

Main outcome measure: To identify disease and treatment-related characteristics of patients with GEP-NET who score using MUST, and should be directed to detailed nutritional assessment.

Results: MUST score was positive (≥1) in 14% of outpatients with GEP-NET. MUST-positive patients had lower faecal elastase concentrations compared to MUST-negative patients (244±37 vs 383±20 µg/g stool; p=0.018), and were more likely to be on treatment with long-acting somatostatin analogues (65 vs 38%, p=0.021). MUST-positive patients were also more likely to have rectal or unknown primary NET, whereas, frequencies of other GEP-NET including pancreatic NET were comparable between MUST-positive and MUST-negative patients.

Conclusions: Given the frequency of patients identified at malnutrition risk using MUST in our relatively large and diverse GEP-NET cohort and the clinical implications of detecting malnutrition early, we recommend routine use of malnutrition screening in all patients with GEP-NET, and particularly in patients who are treated with long-acting somatostatin analogues.

Strengths and limitations of this study

- This study investigates the important clinical problem of malnutrition screening in patients with gastro-entero-pancreatic neuroendocrine tumours (GEP-NET).
- Possible implications of the use of somatostatin analogues on the risk of malnutrition in patients with GEP-NET have not been reported in previous studies.
- Strengths of the study include the relatively large size of a well characterised diverse cohort of patients with GEP-NET, including information about tumour grading, staging, functioning status, biomarkers and treatment modalities.
- Limitations include the observational, real-world nature of this study, with attendant limitations on availability of data subsets and power in regression analyses.

INTRODUCTION

Malnutrition is caused by insufficient delivery of nutrients, or increased catabolism, and is linked to major negative outcomes including excess morbidity, mortality and higher treatment costs.[1–4] The prevalence of malnutrition in patients with cancer has been reported to range between 30% and 70%, depending on tumour type, stage and treatment modalities,[5] but might be different in patients with gastro-entero-pancreatic neuroendocrine tumours (GEP-NET).

GEP-NET comprise a complex group of often slow-growing neoplasms that are derived from primitive endocrine and neural cells. The annual incidence of GEP-NET has recently tripled to 40–50 cases per million, which is thought to be at least, in part, related to increased awareness and improved diagnostic modalities.[6] Malnutrition in patients with GEP-NET might be frequent for various reasons which include functioning tumours producing hormones that affect gut transit,[7–9] pancreatic masses, tumour infiltration of the mesentery in midgut

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NET,[10 11] prior abdominal surgery, or treatment with somatostatin analogues.[12–14]

The National Institute for Health and Care Excellence (NICE) recommends malnutrition screening in all adult inpatients and outpatients in at-risk groups.[2] Several screening tools of varying complexity have been developed.[5] The malabsorption universal screening tool (MUST) is one of the more commonly used screening methods in UK NHS Trusts, due to its simplicity and previous validation in multiple settings including use in patients with cancer[2 15–17] (figure 1). However, the potential utility of malnutrition screening in patients with GEP-NET was only reported in a single very recent study to date.[18]

Here, in a cohort of 161 patients with confirmed GEP-NET of varying primary tumour sites, grading, staging, functioning status and treatment modalities, we explored the prevalence of malnutrition, and whether MUST-positive GEP-NET patients showed specific disease or treatment-related characteristics.

MATERIALS AND METHODS

Participants and sample collection

The University Hospitals Coventry and Warwickshire NHS Trust (UHCW) audit department approved the study (audit number 1133/2015; July 2015). Data were obtained from the local data base at the ARDEN NET centre, European Neuroendocrine Tumour Society (ENETS) Centre of Excellence (CoE) in UHCW. All patients with GEP-NET who attend their routine clinical appointments in the ARDEN NET Centre are screened using MUST since May 2015; and were eligible for inclusion.

Patients had physical examination as part of routine clinical care and were characterised according to age, gender, body weight, body height, body mass index (BMI), the location of the primary tumour, staging, histological grading (surgical sample or diagnostic biopsy), presence or absence of functioning symptoms (ie, flushing or diarrhoea), treatment modalities received, for example, treatment with somatostatin analogues, information about prior abdominal surgery GEP-NET-related or for any reason, and GEP-NET-related biomarkers (most recent overnight fasted gut hormone profile from within the previous 6 months including Chromogranin A; other biomarkers such as Chromogranin B, gastrin, vasoactive intestinal polypeptide (VIP), somatostatin, glucagon and pancreatic polypeptide were available but only used for clinical decision-making when appropriate. Samples for 24 h urine were obtained following restriction of known factors that can cause false high measurements of

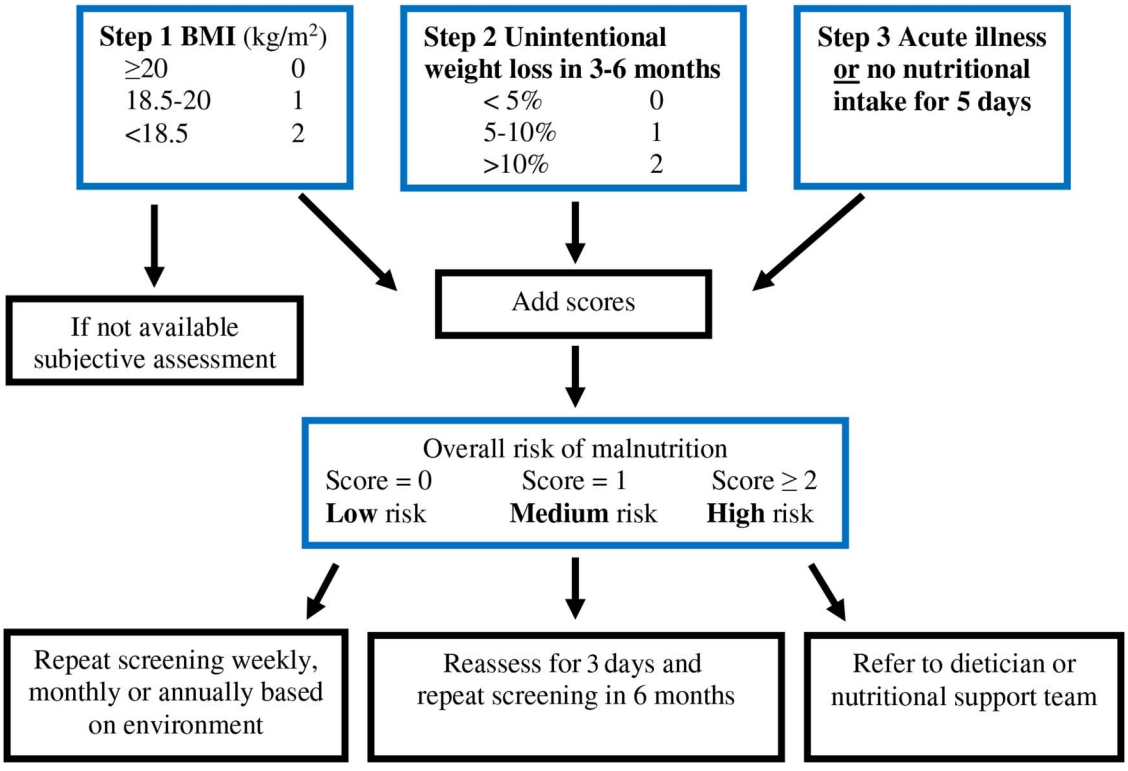


Figure 1 Simplified scheme of use of the MUST score (adapted from BAPEN[15]). MUST was positive in 14.2% of the screened patients (23/161 patients with GEP-NET). The majority of the patients with positive MUST scored 1 (n=14) or 2 (n=7), mostly related to BMI <20 kg/m^2 (n=16) and/or, less frequently, recent weight loss (n=9). Only n=2 of the patients in the entire cohort had a MUST score of ≥3. MUST, malnutrition universal screening tool; GEP-NET, gastro-entero-pancreatic neuroendocrine tumours; BMI, body mass index.

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urinary 5-HIAA. Further characteristics such as biomarkers for screening for exocrine pancreatic insufficiency or heart failure were used if available for clinical reasons. Using the available data a MUST score was calculated. A simplified scheme of the use of the MUST score is depicted in (figure 1).

Measurement of biomarkers

Routine biochemical markers were performed in the biochemistry laboratory at UHCW. Plasma gut hormone profiles were sampled after at least 10 h of overnight fast. Analyses were performed by radioimmunoassay at Hammersmith Hospital. Analyses for 5-HIAA were performed using HPLC at Heartlands Hospital, Birmingham. Faecal elastase-1 concentration in stools was determined using an ELISA (ScheBo Pancreatic Elastase-1 Stool Test), measured at City Hospital, Birmingham, UK. The human faecal elastase-1 antibody used here is immunologically specific and is not affected by enzyme replacement therapies. A faecal elastase concentration<200 µg/g stool indicates moderate, and a concentration<100 µg/g stool indicates severe exocrine pancreatic insufficiency.

Statistical analyses

Data are presented as mean±SE. Metric values were tested for normal distribution using the Kolmogorov-Smirnov test, and further analysed using the paired t test. Non-normally distributed metric variables and ordinally scaled variables were analysed using the Mann-Whitney U test. For nominally scaled variables, χ^2 tests were applied. Ordinal data were correlated using Spearman's analyses (based on 1000 bootstrap samples) to assess the associations between variables. Owing to the relatively small number of patients in the respective subgroups, all MUST-positive patients were pooled for comparison with MUST-negative patients. Breusch Pagan test and auxiliary regressions were used to investigate for heteroscedasticity and significant relationships between fitted predicted values and squared residuals. Bootstrapped ordinal regression analyses (set as 1000 bootstrap samples) were performed with MUST score (positive vs negative) as the dependent variable and age, tumour stage, prior abdominal surgery (separately for any prior abdominal surgery or GEP-NET-related surgery, ie, ileocaecal resection or right hemicolectomy), functioning status, treatment and duration of treatment (in month) with somatostatin analogues and GEP-NET-related biomarkers (normal or pathological) as the independent variables, based on biological plausibility to potentially cause malabsorption; bootstrapped p values are provided. Backward stepwise binary logistic regression analyses were additionally used to assess the influence of individual variables on MUST score. A p value<0.05 was considered statistically significant. Data analyses were performed using IBM SPSS Statistics V.22 (Chicago, Illinois, USA).

RESULTS

Baseline characteristics

MUST data were available in n=161 patients of the GEP-NET cohort in the ARDEN NET centre. The cohort comprised 74 men and 87 women. Age was 63.2 ±1.2 years, body weight 75±1.4 kg, body height 167 ±0.01 cm, BMI 26.7±0.4 kg/m^2, and serum creatinine 85.1±3.5 µmol/L. Previous abdominal surgery for any reason had been performed in n=96 (59.6%) of the patients. Previous ileocaecal resection was done in n=17 (10.6%), and right hemicolectomy in n=14 (8.7%) of the patients. Histological grading was available in n=133 (82.6%) of the patients, if performed for clinical reasons; of those, n=86 (64.7%) had a grade 1 well differentiated (G1) GEP-NET; n=32 (24.1%) had a grade 2 well differentiated (G2) GEP-NET; and n=15 (11.3%) had a poorly differentiated (G3) neuroendocrine carcinoma of gastro-entero-pancreatic origin. Out of the 161 NET patients in this cohort, n=67 (41.6%) were on treatment with somatostatin analogues (Sandostatin LAR 30 mg once monthly; or Somatuline Autogel 120 mg once monthly); of those, n=43 (65.2%) had a well differentiated midgut NET, and n=14 (21.2%) had a well differentiated pancreatic NET. Mean duration of treatment with somatostatin analogues in the n=67 treated patients was 19.5±3.3 months at the time of data collection. Of the 15 patients in the GEP NET cohort with pathological faecal elastase concentrations (<200 µg/g stool; 96.1 ±18.9 µg/g stool), n=12 had previous abdominal surgery (any), n=7 had a pNET, n=3 had previous ileocaecal resection, and n=1 had previous right hemicolectomy. Further tumour characteristics of the cohort are shown in (figure 2A–C).

Patients scoring positive using MUST

Fourteen per cent of the GEP-NET patients (n=23/161) scored ≥1 using MUST, which classifies the patient as 'medium risk for malnutrition', and should trigger a recommendation of 'further observation' of nutrition status according to BAPEN/NICE guidelines;[2 16] and 5.5% of the patients scored ≥2 (n=9/161), which classifies the patient as 'high risk for malnutrition' and should trigger treatment of malnutrition and, ideally, referral to the dieticians or multidisciplinary nutrition team.[16]

Correlation analyses

Spearman analyses (based on 1000 bootstrap samples) showed a moderate but statistically significant negative correlation of total MUST score (positive vs negative) with faecal elastase concentrations (r=−0.32, p=0.005), and a weak but statistically significant positive correlation with treatment with somatostatin analogues (r=0.20, p=0.013). Duration of treatment with somatostatin analogues showed a weak trend with total MUST score (r=0.14; p=0.078). None of the remaining markers significantly correlated with MUST total score in bootstrapped regression analyses, which included age, gender, functioning status, tumour grade, tumour stage,

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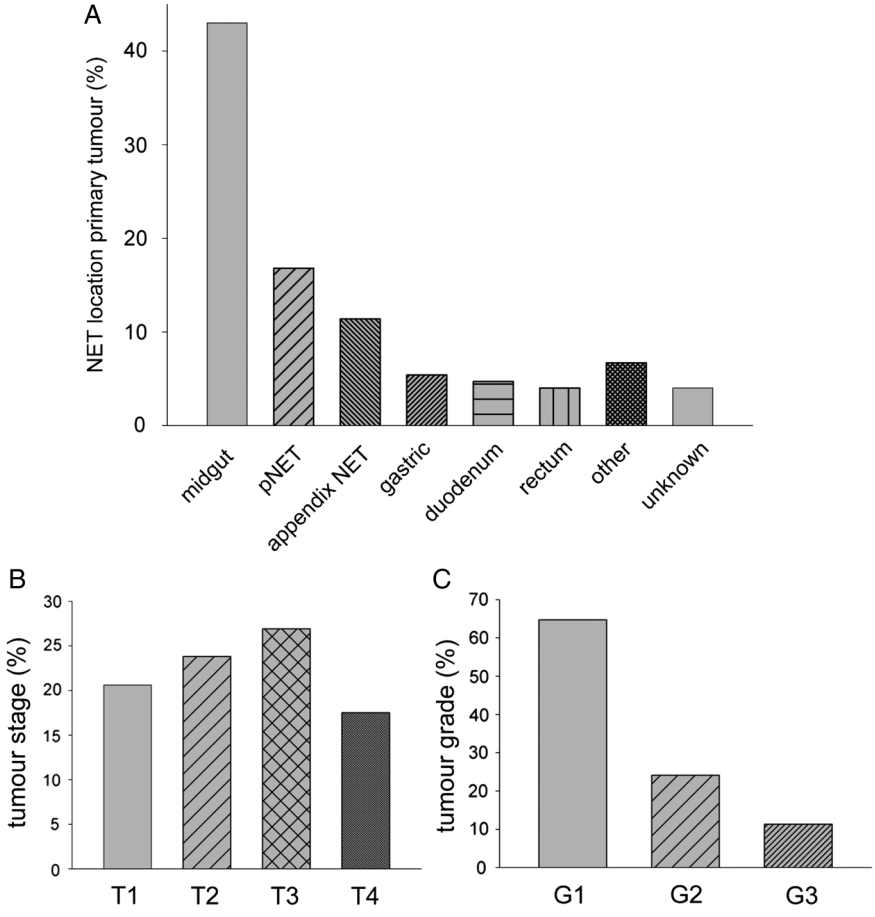


Figure 2 Characteristics of the GEP-NET cohort. (A) location of the primary tumour, (B) distribution of tumour staging, with the remaining 11.2% of the patients being classified as Tx (no signs of primary tumour), (C) histological grading (well differentiated, grade 1 and 2; poorly differentiated, grade 3). GEP-NET, gastro-entero-pancreatic neuroendocrine tumours.

biomarkers in blood and urine, serum creatinine, BNP, prior abdominal surgery (any), and prior ileocaecal resection or right hemicolectomy (all p>0.13).

Regression analyses

Bootstrapped binary logistic regression analyses in the complete model identified use of somatostatin analogues (exp (B)=0.022; 95% CI (0.000 to 1.554); p=0.004), faecal elastase concentrations (exp (B)=0.992; 95% CI (0.984 to 1.001); p=0.009)), age (exp (B)=0.901; 95% CI (0.781 to 1.038; p=0.010) and tumour stage (≥T2; p<0.044); and presence of distant metastatic disease M1 (p=0.037); but not N1) as significant predictors of MUST score. Duration of treatment with somatostatin analogues was not a significant predictor, neither in bootstrapped nor in conventional analyses (p=0.11 and p=0.63, respectively). The regression model was statistically significant (χ^2 26.58; p=0.046). The model explained 57% (Nagelkerke R^2) of the variance in MUST, and correctly identified 95.5% of MUST-negative and 44.4% of MUST-positive subjects.

To obtain additional information about the influence of individual dependent variables, additional backward stepwise binary logistic regression analyses were tested. In step 6 of this stepwise model, again 44.4% of MUST-positive patients and 97% of MUST-negative patients were correctly identified, with use of somatostatin analogues, but not other factors including the duration of treatment with somatostatin analogues remaining a statistically significant predictor (p<0.001; χ^2 test 21.98, p=0.009), and explaining 49% (Nagelkerke R^2) of the variance in MUST. Again, duration of treatment with somatostatin analogues did not influence the variance in the MUST score (p>0.595 in all tested models).

Use of somatostatin analogues (yes vs no) in bootstrapped analyses with location of the primary tumour, tumour grade, tumour stage and functioning status as the independent variables was predicted by functioning status (p=0.011), tumour grade (p<0.032) and presence of distant metastases (M1, p=0.035), with location of the primary tumour showing a trend. The model explained 55% of the variance in use of somatostatin analogues and reasonably correctly predicted both treated (84.2%) and untreated (78.3%) patients (χ^2 66.35, p<0.001).

Characteristics of MUST-positive compared with MUST-negative patients

Specific characteristics of GEP-NET patients with a positive as compared with a negative MUST scores are shown in (table 1). GEP-NET patients who scored ≥1 using MUST were significantly more frequently treated with somatostatin analogues as compared with patients who did not score using MUST (65% vs 38%; p=0.021) (table 1).

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Table 1 Characteristics of MUST-positive compared with MUST-negative patients with gastro-entero-pancreatic neuroendocrine tumours of varying primaries, tumour grading, staging and functioning status

	MUST-positive n=23	MUST-negative n=138	p Value
Treatment with SSA (%)	65	38	0.021
Faecal elastase (µg/g stool)	244±37	383±20	0.018

Data are given as mean±SE.
MUST, malnutrition universal screening tool; SSA, long-acting somatostatin analogues.

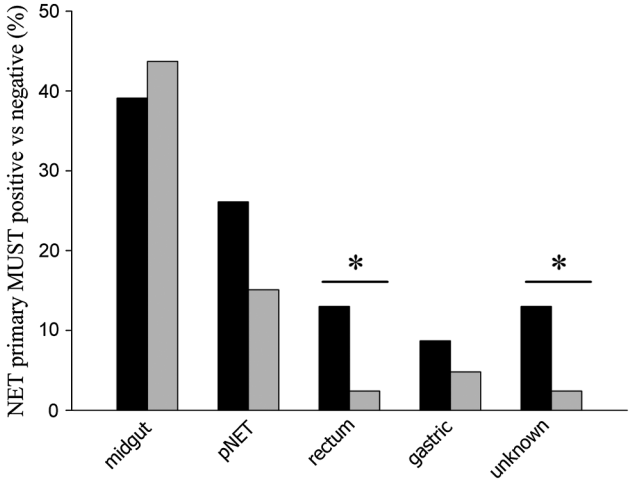


Figure 3 MUST-positive compared with MUST-negative patients with GEP-NET. Patients who scored using MUST were significantly more likely to have rectum NET (p<0.017) or a NET with an unknown primary (p<0.017). Other types of NET were not significantly different between MUST-positive and MUST-negative patients, which included pancreatic NET (p=0.195). Black bars: MUST-positive patients; grey bars: MUST-negative patients. pNET, pancreatic neuroendocrine tumour. MUST, malnutrition universal screening tool; GEP-NET, gastro-entero-pancreatic neuroendocrine tumours; NET, neuroendocrine tumours.

When stratifying the entire cohort according to treatment with somatostatin analogues, 22.4% (n=15 of 67 patients) who were treated with somatostatin analogues scored ≥1 using MUST, as compared to 8.5% (n=8 of 94 patients) who were not on treatment with somatostatin analogues (p=0.013). MUST-positive patients showed significantly lower faecal elastase levels, as compared with MUST-negative patients (table 1). Faecal elastase concentrations also tended to be lower in patients who were on treatment with somatostatin analogues, as compared with patients who were not on treatment with somatostatin analogues (335±26 vs 402±27 µg/g stool; p=0.075). Finally, patients who scored using MUST had significantly more often NET of the rectum or of unknown origin, as compared with patients who did not score (figure 3). Frequencies of midgut NET (p=0.688), pancreatic NET (p=0.195) and gastric NET (p=0.443) were not significantly different between MUST-positive and MUST-negative patients (figure 3).

DISCUSSION

Malnutrition is an adjustable risk factor,[19] but associated with severe adverse clinical outcomes if not addressed.[1 2] Patients with GEP-NET do not typically present with major weight loss or acute illness before reaching the very final stages with extensive metastatic disease or carcinoid heart disease. This is related to the fact that GEP-NET are often slower growing and less aggressive tumours at least when well differentiated, as compared with other types of cancer.[20] Nevertheless, malnutrition in patients with GEP-NET could be present for other reasons, including chronic loose stools, osmotic diarrhoea,[20] and excess secretion of serotonin precursors stimulating small bowel motility.[7–9] Pancreatic mass effects, tumour infiltration of the mesentery[10 11] and GEP-NET-related treatment[12–14] are further potential risk factors.

In our outpatient cohort of patients with various types of GEP-NET, 14% had a MUST score of >1, which should trigger referral to the dietitians and the nutrition support team.[2 16] When comparing the cohort of patients who scored using MUST with the patients who did not score, we identified distinct characteristics of MUST-positive patients with GEP-NET. MUST-positive patients were more likely to have unknown primary or rectal NET, which might be related to delayed diagnosis and widespread disease in these patients. Furthermore, MUST-positive patients showed significantly lower faecal elastase concentrations, although the frequency of pancreatic NET was not significantly different between groups, arguing against possible pancreatic mass effects as the main driving factor. Most importantly, MUST-positive patients were some twofold more likely to be on treatment with long-acting somatostatin analogues. After acute, short-term administration, rapid onset suppression of pancreatic exocrine secretion by somatostatin analogues[21 22] and consequent steatorrhoea[23] have been reported. Further known mechanisms are in agreement with a possible role of somatostatin analogues in conveying malnutrition in patients with GEP-NET, although it is important to mention that most previous reports refer to effects of acute administration of somatostatin analogues[12 13 24 25] or in vitro studies,[26] whereas effects after chronic administration[23] might be differently related to possible adaptive mechanisms. Impairment of hepatic bile acid physiology by somatostatin analogues has been reported after both short-term[27] and more prolonged administration, and is causally involved in gallstone formation.[28] In the acute setting, intravenous somatostatin inhibits glucose, triglyceride, amino acid and calcium absorption by direct effects on the intestinal mucosa;[12 13 24] and decreases gastric acid secretion by

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90% in healthy volunteers.[24] In addition, acute suppression or in vitro effects of various gut hormones, such as cholecystokinin and glucagon-like peptide-1 by somatostatin analogues are well described,[23 25 26] and diarrhoea, steatorrhoea and weight loss are key features of excess hormone-producing somatostatinomas.[29] Possible implications of treatment with somatostatin analogues on other aspects such as loss of fat-soluble vitamins in the faeces have been also reported.[30] It might be argued that patients who were treated with long-acting somatostatin analogues were more prone to score using MUST related to functioning status and advanced disease progression, as well as general risk factors such as age and disease-related depression. However, treatment with somatostatin analogues remained a statistically significant predictor of MUST in all tested models. Importantly, duration of treatment with somatostatin analogues showed no significant influence in our analyses, indicating that acute effects of the administration of somatostatin analogues on the likelihood scoring positive in the MUST score were sustained after longer term treatment, and somewhat arguing against adaptive mechanisms in this context.

Our observed total rate of patients at risk of malnutrition was somewhat lower than the prevalence very recently reported by Maasberg *et al*[18] in a neuroendocrine cohort of comparable size. Authors identified some 21%–25% of the patients at risk,[18] as compared to 14% in our study; however, the cohort in the mentioned study comprised 87% inpatients and also included patients with neuroendocrine tumours of the lung, as compared with our study, which was exclusively assessed in outpatients with GEP-NET. This may explain the lower frequency of patients at risk of malnutrition in our cohort.

The observational nature of this study needs to be mentioned as a limitation, as well as its relatively small sample sizes when including not routinely measured biomarkers in the regression models. Our study confirms the importance of screening for malnutrition in patients with GEP-NET. This is directly clinically relevant, considering that malnutrition in patients with neuroendocrine tumours could be an independent prognostic factor.[18] Confirmation of our findings in multicentre settings with access to large and diverse GEP-NET patient cohorts will be useful.

In summary, somatostatin analogues are key treatment modalities in patients with well-differentiated GEP-NET, but may cause transient or permanent gastrointestinal side effects such as bloating and cramping in up to 30% of the patients;[31–33] and, based on our findings, appear to increase malnutrition risk as identified by MUST. Without systematically screening GEP-NET patients for malnutrition, mild impairment of digestive processes might be missed or attributed to functioning aspects of the GEP-NET, rather than recognised and treated as a possible side effect of the treatment. Referring these patients for early nutritional intervention could lead to improvement of the nutritional status and quality of life.[34]

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Contributors MOW, NB and SAQ were involved in the study concept and design. SK, KG, JLHW, LD, SF, WS and SS were involved in the acquisition of clinical data. CD was involved in the analyses of biochemical markers. SAQ, NB, LD, GKD and MOW were involved in the collection of MUST data. MOW and JGH did the statistical analyses. MOW and MD supervised the MSc project of SAQ. MD provided important intellectual content and critical review of the manuscript. SAQ provided input to the first draft of the manuscript. MOW drafted the manuscript, and all authors critically revised it for important intellectual content. MOW supervised the study and is the guarantor. The authors thank Ms Josie Goodby for support with data collection.

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Competing interests None.

Ethics approval The UHCW audit department had approved this study (audit number 1133/2015; July 2015). All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and, because this study involved analysis of pre-existing, deidentified data, it was exempt from institutional review board approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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