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A new score for screening of malnutrition in patients with inoperable gastric adenocarcinoma

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Abstract

Background: Malnutrition is common in patients with gastric cancer. Early identification of malnourished patients results in improving quality of life. We aimed to assess the nutritional status of patients with inoperable gastric adenocarcinoma (IGA) and finding a precise malnutrition screening score for these patients before the onset of chemotherapy.

Methods: Nutritional status was assessed using patient generated subjective global assessment (PG-SGA), visceral proteins, and high-sensitivity C reactive protein. Tumor markers of carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA-125) and CA 19-9 and their association with nutritional status were assessed. Then a new score for malnutrition screening was defined.

Results: Seventy-one patients with IGA completed the study. Malnourished and well-nourished patients (based on PG-SGA) were statistically different regarding albumin, prealbumin and CA-125. The best cut-off value for prealbumin for prediction of malnutrition was determined at 0.20 mg/dl and using known cut-off values for albumin (3.5 g/dl) and CA-125 (35 U/ml), a new score was defined for malnutrition screening named MS-score. According to MS-score, 92% of the patients had malnutrition and it could predict malnutrition with 96.8% sensitivity, 50% specificity and accuracy of 91.4%.

Conclusion: MS-score has been suggested as an available and easy-to-use tool for malnutrition screening in patients with IGA.

Key words: stomach neoplasms, albumin, prealbumin, nutritional screening, CA-125, antigen

Introduction

Malnutrition and inflammatory response is common in patients with gastrointestinal cancer due to tumor's progression and high metabolism (1–3). Inflammation causes a decrease of lean body mass, increased energy consumption, elevated thermogenesis and increased risk of infection, all resulting morbidity and mortality of the cancer patients (4–6) and malnutrition leads to reduced response rate, short survival, increased risk of treatment-induced complications and higher cost of health care procedures (7,8). Therefore, finding an appropriate score for early identification of gastrointestinal cancer patients with

malnutrition will help to provide an early nutrition support that will in turn, improve tolerance to the treatment modalities, lower rate of toxicities, thereby improving the quality of life.

This study aimed to evaluate the nutritional status of patients with inoperable gastric adenocarcinoma (IGA) using measurements of body mass index (BMI), patient generated subjective global assessment (PG-SGA), as well as serum levels of albumin and rapid turnover proteins (RTPs) of prealbumin and transferrin (visceral protein biomarkers of nutrition status), high-sensitivity C reactive protein (hs-CRP) and total lymphocyte count (TLC). Moreover, the possible relationship between nutritional status and serum tumor markers of carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA-125) and carbohydrate antigen (CA 19-9) was evaluated and then a new score for malnutrition screening of patients with IGA was introduced.

Methods

Study population

Based on a convenient sampling method, a total of 71 patients with IGA visiting Sheikhorraeis University Clinic between February 2013 and March 2014 were recruited in this prospective study before the onset of chemotherapy. Written informed consent was taken from all the study subjects and the Human Ethics Committee of Tabriz University of Medical Sciences approved the study protocol. Exclusion criteria included the past record of other cancers, chronic renal or hepatic disease, thyroid dysfunction, diabetes and taking anti-inflammatory medicine. Tumor staging was done using TNM (tumor-node–metastasis) classification.

Nutritional assessment

To calculate BMI [weight (kg)/height $(m)^2$], height was measured using a mounted tape, with the subject's arm hanging freely by their sides and recorded to the nearest 0.5 cm. Weights were recorded to the nearest 0.1 kg with a Seca scale (patients were barefoot and wore light clothing).

The nutritional status of the patients with IGA was evaluated using PG-SGA which is a valid score for patients with cancer. PG-SGA consists of the history of weight alterations, food intake, gastrointestinal complications (such as diarrhea, nausea, vomiting, mouth sores and pain), changes in physical activity and function, metabolic stress and physical examination for assessing the fluid status, muscle status and fat stores (7).

There is a nutritional triage of recommendations based on the scored PG-SGA. Those with scores of 0–1 need no intervention and those with scores of 2–3 and 4–8 need some degree of nutrition support. Scores of greater and equal to 9 indicated an urgent need for nutritional intervention. PG-SGA also gives a three categorical nutritional assessment: SGA-A (well-nourished or anabolic patients), SGA-B (moderate or suspected malnutrition) and SGA-C (severely malnourished). A trained oncology nurse assisted the patients in completing the PG-SGA questionnaires.

Biochemical analyses

Biochemical analyses were done for each patient before the commencement of chemotherapy. Venous blood samples were taken from each patient after an overnight fast. Serum levels of prealbumin, transferrin and hs-CRP were measured with the Minineph™ Human kits (Birmingham, UK), and a Hitachi 917 automated equipment was used for analyzing albumin concentration. Serum levels of tumor markers (CA-125, CA19-9 and CEA) were measured on the chemiluminescence immunoassay analyzer LIAISON® (Diasorin, Saluggia, Italy) with LIAISON® CEA, LIAISON® CA 19-9™ and LIAISON® CA 125 II™, respectively.

Statistical analysis

Mean (standard deviation [SD]) or median (percentile 25–percentile 75) were used to present quantitative variables according to their distribution and the qualitative variables were shown as frequency (%). Receive operating characteristic (ROC) analysis was carried out to determine the best cut-off point value for prealbumin. The area under curve (AUC) and the likelihood ratios (LRs) were presented as a measure for predicting of malnutrition. Independent-Samples *T* Test or Mann–Whitney *U* Test was used to evaluate the differences between well-nourished and malnourished patients regarding quantitative variables. Spearman's correlation coefficient was used to assess the correlation between the variables. A significant level of 0.05 was set in doing a two-tailed analysis. SPSS software (SPSS Inc., Chicago, IL) was used for the statistical analyses.

Results

Seventy-one patients with IGA were included in the study. The general characteristics of the patients including age, gender, BMI, stage, metastasis status, anatomic location, type of carcinoma, Scored PG-SGA and categorized SGA (SGA-A, B and C) are presented in Table 1. Considering SGA-A as a category for well-nourished

Table 1. General characteristic of the patients

Age (Mean ± SD)	62.13 ± 14.39
Gender (*n*, %)	
Male	56, 79%
Female	15, 21%
BMI[a] (Mean ± SD)	21.08 ± 3.99
SGA[b] A	9 (13%)
SGA B	35 (49%)
SGA C	27 (38%)
PG-SGA[c] (Mean ± SD)	16.07 ± 5.02
Stage (%)	
3	28 (39%)
4	43 (61%)
Anatomic location (%)	
GEJ[d]/proximal stomach	38 (54%)
Distl stomach	33 (46%)
Type[e] (%)	
Diffuse	36 (51%)
Intestinal	35 (49%)
Metastasis	
Metastatic	43 (61%)
Non-metastatic	28 (39%)
Tumor markers	
CEA[f] (above cut-off value, 5.0 ng/ml)	61%[h]
CA19-9[g] (above cut-off value, 37 U/ml)	48%[h]
CA-125[g] (above cut-off value, 35 U/ml)	75%[h]

[a]Body mass index.
[b]Subjective global assessment.
[c]Patient generated-subjective global assessment.
[d]Gastroesophageal junction.
[e]Type of gastric adenocarcinoma.
[f]Carcinoembryonic antigen.
[g]Carbohydrate antigen.
[h]Percent of patients over the normal cut-off value.

patients and both SGA-B and SGA-C for degrees of malnutrition, 87% of the patients with IGA were malnourished and the mean score of 16.07(5.02) for scored PG-SGA, showed a need for nutritional support in patients with IGA before the commencement of the chemotherapy.

The normal cut-off value for CEA, CA-19-9 and CA-125 was taken as 5.0 ng/ml, 37 U/ml and 35 U/ml, respectively, for dividing the patients into two categories and the percentage of patients over the normal cut-off value is presented in Table 1. In 61% of the patients, serum CEA levels were above 5.0 ng/ml and CA 19-9 values of 48% of the patients were above 37 U/ml. Moreover, 75% of the study subjects had serum levels above 35 U/ml for CA-125. Albumin, RTPs (prealbumin and transferrin), hs-CRP and TLC were compared between well-nourished and malnourished patients with IGA. There was statistical difference between these groups regarding prealbumin and albumin (P = 0.013, P = 0.010, respectively) (Table 2). In terms of tumor markers, the well-nourished patients were statistically different from patients with malnutrition for CA-125 (P = 0.033), so that 86.5% of IGA patients with serum CA-125 > 35 U/ml had malnutrition. The correlation analysis between tumor markers, and nutritional status related parameters (RTPs, albumin and BMI) and inflammation indices (hs-CRP and TLC) showed that only CA-125 had statistically significant correlation with the examined variables (Table 3).

There is a cut-off value of 3.5 g/dl for albumin and 35 U/ml for CA-125. The best cut-off value for prealbumin was defined at 0.20 mg/dl for differentiating well-nourished IGA patients from malnourished ones using ROC analysis (Table 4). Albumin, prealbumin and tumor marker CA-125 (variables which were statistically different between well-nourished and malnourished patients with IGA) made a new composite score for malnutrition screening named 'Malnutrition Screening score/MS-score'. According to MS-score, patients with albumin level ≤3.5 g/dl, prealbumin level <0.20 mg/dl and CA-125 level >35 U/ml were allocated a score of 3. Patients with one or two parameters abnormalities were allocated scores of 1 and 2, respectively, and those in whom the albumin level was >3.5 g/dl, prealbumin level >0.20 mg/dl and CA-125 level ≤35 U/ml were allocated a score of zero (Table 5). MS-score could predict malnutrition with 96.8% sensitivity, 50% specificity and accuracy of 91.4% (considering score 0 in one category and scores of 1, 2 and 3 in the second category). Based on MS-score, 92% of the patients had malnutrition. MS-score and nutritional status influencing parameters (albumin, prealbumin and CA-125) were compared regarding diagnostic indices (Table 6). The sensitivity and accuracy of MS-score for malnutrition screening was higher than the albumin, prealbumin and CA-125.

Table 2. Biomarkers of nutritional status and inflammation

	SGA	Mean (SD[a])	MD[b] (95% CI), P value
Transferrin	1[c]	332.77 (160.83)	
	2[d]	241.97 (87.65)	90.80 (−77.45 to 259.05), 0.230
Prealbumin	1	0.22 (0.06)	
	2	0.15 (0.06)	0.07 (0.01 to 0.13), **0.013**
Albumin	1	4.52 (0.83)	
	2	3.64 (0.59)	0.88 (0.23 to 1.54), **0.010**
hs-CRP	1	19.62 (2.28–25.24)[e]	
	2	33.36 (11.65–85.11)	0.123[e]

[a]Standard deviation.
[b]Mean difference (P value based on Independent-Samples T test).
[c]Well-nourished patients.
[d]Patients with malnutrition.
[e]Median (percentile 25–75, P value based on the Mann–Whitney U test).
Statistically significant correlations are bolded.

Discussion

The timely screening of cancer patients with malnutrition is a pivotal step to providing adequate nutrition support as a main part of the

Table 3. Correlation between tumor markers and nutritional status and inflammation related variables

	BMI	Transferrin	Prealbumin	Albumin	hs-CRP
CEA[a]					
Spearman's rho, P value	−0.113, 0.470	0.015, 0.908	−0.124, 0.345	−0.079, 0.564	0.115, 0.392
CA-125[b]					
Spearman's rho, P value	0.114, 0.468	−0.289, **0.024**	−0.370, **0.004**	−0.446, **0.001**	0.433, **0.001**
CA-19-9[c]					
Spearman's rho, P value	0.294, 0.055	0.022, 0.862	−0.229, 0.079	−0.148, 0.278	0.072, 0.589

[a]Carcinoembryonic antigen.
[b]Carbohydrate antigen 125 (CA-125).
[c]Carbohydrate antigen (CA 19-9).
Statistically significant correlations are bolded.

Table 4. ROC analysis and optimum cut-off point of prealbumin for predicting malnutrition in patients with inoperable gastric adenocarcinoma

PA	AUC	SEN	SPE	PPV	NPV	LR^+	LR^-
0.20 (mg/dl)	0.838 (0.68–0.99)*	75.0% (58.9–86.2)	83.3% (43.6–97.0)	96.4% (82.3–99.4)	35.7% (16.3–61.2)	4.50 (0.74–27.2)	0.30 (0.15–0.59)

*95% confidence interval.
ROC, receiver operating characteristic; PA, prealbumin; AUC, area under the curve; LR^+, positive likelihood ratio; LR^-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

patients care program. It results in achieving better outcomes, lower treatment-induced toxicities and improved quality of life (6,7). Therefore, it was hypothesized that the combined use of the biomarkers associated with nutritional status may provide a new easy approach for malnutrition screening in patients with IGA.

Studies have shown that serum level of albumin can be considered as a prognostic factor in different kind of malignancies, including gastrointestinal cancer. Although albumin is not a sensitive biomarker for nutritional status as it is influenced by many factors such as infection, metabolic stress and liver disorders, the easy and inexpensive measurement of albumin has made it a good indicator for non-acute inadequate nutritional status in cancer patients (9–11).

Serum prealbumin, a rapid turnover visceral protein, is a sensitive biomarker for detection of malnutrition (12). The short half-life of ≈ 2days (compared to 20 days for albumin) has made prealbumin a suitable biomarker not only for identification of malnourished patients, but also for monitoring the nutritional support (13). The findings of this study were in line with the previous studies in that serum prealbumin was a significant prognostic factor and/or a biomarker for nutritional status in patients with colon (14), ovarian (15), esophageal (16) and lung cancers (17,18).

Recently we found that higher level of prealbumin is associated with better hospital outcomes (short duration of hospital stay and neutropenic fever) in patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Ho et al. suggested that prealbumin could be an independent prognostic factor for the overall survival of patients with cancer an also as an important factor to be routinely assessed in the palliative care process (19).

On the other hand, response to treatment was influenced by pre-chemotherapy serum levels of prealbumin in patients with ovarian cancer (19) and non-small cell lung cancer (18). Similar to the results obtained from this study, Inoue et al. found that among the RTPs, prealbumin had the most prognostic importance in patients with advanced cancer receiving total parenteral nutrition (20).

Table 5. Classification of malnutrition screening score/MS-score

Albumin (g/dl)	Prealbumin (mg/dl)	CA-125 (U/ml)	MS-score
3.50<	0.20<	≤35	0
	One parameters abnormalities		1
	Two parameters abnormalities		2
≤3.5	<0.20	>35	3

Measurement of serum tumor marker is an easy method for tumor diagnosis. Although there is no sensitive and specific tumor marker for gastric cancer diagnosis, serum levels of CEA, CA19-9 and CA-125 are widely used for assessing the response to chemotherapy and its efficacy in this group of patients (21–23).

Serum CA-125 is commonly used for ovarian cancer diagnosis and prognosis (24) but in recent years, an increased level has been detected in patients with different types of digestive tract tumors including gastric, pancreatic and esophageal adenocarcinoma with prognostic importance (25–27).

It has been proposed that the pre-chemotherapy level of CA-125 is not just an independent prognostic factor but an indicator for tumor burden and its aggressive nature. On the other hand, the overall survival was remarkably shorter in gastric cancer patients who had higher levels of CA-125 and it was also associated with peritoneal metastasis and ascites in these patients, all made it an essential factor to be examined routinely before and during chemotherapy in patients with gastric cancer.

In this study, the nutritional status of patients with IGA was assessed by PG-SGA, serum levels of albumin, prealbumin, transferrin (serum visceral proteins indicator for nutritional status), hs-CRP and TLC (as inflammation can affect nutritional requirements by increasing the loss of lean mass, energy consumption, body temperature and inducing more susceptibility to infection) and tumor markers CEA, CA 19-9 and CA-125. It was found that albumin, prealbumin and tumor markers CA-125 were associated with nutritional status. The best cut-off value for prealbumin was determined at 0.20 mg/dl by ROC analysis. Then a composite score for screening of the malnutrition: MS-score was introduced and this consisted of albumin, prealbumin and CA-125. By MS-score, malnutrition could be predicted with 96.8% sensitivity, 50% specificity and accuracy of 91.4%.

In this study, nutritional status of the patients with gastric cancer was influenced by albumin, prealbumin and CA-125. All these parameters as well as nutritional status have prognostic value and they affect survival in patients with advanced gastric cancer, maybe due to their role in the nutritional status. Although scored PG-SGA is a valid tool for assessment of nutritional status in patients with cancer, filling out the questionnaire is a time-consuming procedure as the patients should be trained to properly complete it. Moreover, professional staff should score several worksheets including weight history, disease affecting nutritional requirements, metabolic stress and physical examination (7), while albumin, prealbumin and CA-125 can be measured routinely at the first time of diagnosis and for malnutrition screening, and for decision to implement a proper

Table 6. Comparison of nutritional status influencing parameters regarding diagnostic indices

	SEN (%)	SPE (%)	ACC (%)	PPV (%)	NPV (%)	LR^+	LR^-
AB	44.1	75	47.3	93.8	13.6	1.76	0.75
	28.9–60.5*	30.1–95.4	–	71.7–98.9	4.7– 33.3	0.31–10.04	0.39–1.41
PA	75	83.3	76.2	96.4	35.7	4.50	0.30
	58.9–86.2	43.6–97.0	–	82.3–99.4	16.3–61.2	0.74–27.20	0.15–0.59
CA 125	86.5	50	81.4	91.4	37.5	1.73	0.27
	72.0–94.1	18.8–81.2	–	77.6–97.0	13.7–69.4	0.77–3.89	0.09–0.85
MS-score	**96.8**	50.0	**91.4**	93.8	66.7	1.94	0.06
	83.8–99.4	15.0–85.0	–	79.9–98.3	20.8–93.9	0.72–5.17	0.01–0.56

*95% confidence interval (CI).

AB, albumin (g/dl); PA, prealbumin (mg/dl); CA 125 (U/ml); SEN, sensitivity; SPE, specificity; LR^+, positive likelihood ratio; LR^-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; MS-score, malnutrition screening score.

nutritional support and monitor the treatment outcomes as well as nutritional status.

One of the limitations of this study was the relatively small sample size, as it was conducted in a single center. In addition, due to lack of an official registration system, there was no follow-up for the patients to assess the outcomes.

Conclusion

MS-score could be an easy-to-implement tool for screening of malnutrition in patients with IGA. For verification of this new score, more studies with larger sample size and on different kind of malignancies are warranted.

Conflict of interest statement

The authors declare that there is no conflict of interests.

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