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Factors Associated with Malnutrition among Newly Diagnosed Esophageal Cancer Patients

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ABSTRACT

The study aimed to investigate the factors associated with malnutrition among newly diagnosed Esophageal Cancer (EC) patients. A cross-sectional study included newly diagnosed EC patients from October 2020 to March 2022. Data on clinical status (diagnosis, comorbidities, and cancer stage), socio-demographic characteristics, functional status (performance status scale using Eastern Cooperative Oncology Group (ECOG)), anthropometric measures (weight, height, and percentage of weight loss (% LOW) past 1-month), biochemical profiles (lymphocyte and serum albumin), malnutrition status (Subjective Global Assessment (SGA)) and total daily energy protein intake were assessed. The study enrolled 227 participants, and 96.5% (n=219) were malnourished. The mean for age, weight, percentage of weight loss past 6-months, SGA score, total daily energy protein intake, and serum albumin were 61.1±11.4 years, 57.7±14.4 kg, -8.6±6.5%, 12.6±3.9, 17±5 kcal/kg/day, 0.7±0.1 g/kg/day, and 35±5 g/L respectively. About 80.6% were stage III and IV, 96% experienced dysphagia, and 67% experienced muscle wasting. The % LOW past 1 month, gender, ECOG status, and lymphocyte levels were found to be the significant factors related to malnutrition among newly diagnosed EC patients ($p<0.05$) by a multi-linear regression test. Esophageal Cancer patients are at high risk of being malnourished as the tumor-related symptoms include dysphagia, inadequate nutritional intake, muscle wasting, and lymphocytopenia. The current study is restricted to only one-time nutritional screening and evaluation. The current proposed model of malnutrition is a simple, useful, and efficient clinical tool to identify EC-related malnutrition followed by the early multidisciplinary-team approach-based nutrition intervention to minimize nutrition depletion, improve functional status, and enhance clinical outcomes before therapy or even higher survival rate.

Keywords: cancer patients, esophageal cancer, malnutrition, newly diagnosed

INTRODUCTION

Esophageal Cancer (EC) is known as the eighth most diagnosed cancer and the sixth most prominent cause of cancer-related deaths globally (GBD 2017 Oesophageal Cancer Collaborators 2020). EC is indeed considered one of the most malignant cancers, with significant global incidence and mortality rates. According to the Global Cancer Observatory (GLOBOCAN), 2020 data, there were more than 0.6 million new cases and 0.54 million deaths attributed to EC globally in 2020 (Kamangar *et al.* 2020). With an adjusted death rate of 1.54 per 100,000 population, Malaysia is ranked 123rd in the world with esophageal cancer mortality (Ferlay *et al.* 2021). According to the World Health Organization and International Association of Cancer Registries, EC is reported as the 21st most common cancer in Malaysia. There were 398 new cases of EC reported, and the total death numbers attributed to EC in Malaysia reached 435 in 2020. It accounted for approximately 0.26% of the total deaths in the population (Ferlay *et al.* 2021).

EC is a gastrointestinal-related cancer that can significantly impact patients' food consumption. The study demonstrated that almost all EC patients who came for medical examination had difficulty in swallowing or even swallowing obstruction (Cao *et al.* 2021; Pham Van *et al.* 2021). Those common symptoms could affect patients' ability to eat and consequently

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lead to rapid and massive weight reduction at diagnosis. It is reported that the incidence of significant weight loss in EC ranges from 32% to 70% at the time of treatment onset (Pham Van *et al.* 2021). Significantly, study shows that the occurrence of loss of weight and malnutrition risk is the highest in EC compared to other cancers (Reim & Friess 2016). Commonly, the early stage of the disease is asymptomatic and it takes several months for patients to experience from minor to major symptoms. Consequently, most patients seek medical investigation in the advanced stage and more than 80% of them had nutritional risk before undergoing treatment (Pham Van *et al.* 2021; Cao *et al.* 2021). Malnutrition is well known to influence the prognosis in cancer patients by affecting treatment tolerance and efficacy, increasing the risk of complications and side effects of treatment (Okamoto *et al.* 2019), increasing the risk for surgical and clinical complications, broadening hospitalization and reducing the quality of life (Triantafyllou & Wijnhoven 2020; Watanabe *et al.* 2020).

Nutritional status assessment in cancer patients is crucial and several validated tools have been widely used for screening and diagnosing (Cao *et al.* 2021; Ho *et al.* 2021). Subjective Global Assessment (SGA) is a common tool to assess nutritional status that comprises several components based on a patient's history and physical examination (Detsky *et al.* 1987; Ho *et al.* 2021). However, despite there were presence of established evidence, the factors that may be associated with malnutrition in EC are limited and yet to be determined. Thus, in this current study, we intend to determine the prevalence of malnutrition and investigate associated factors of malnutrition among newly diagnosed EC patients.

METHODS

Design, location, and time

This was a cross-sectional study that involved newly diagnosed EC patients who were admitted to surgical wards in Institut Kanser Negara (IKN), Putrajaya, Malaysia from October 2020 to March 2022. IKN is a cancer medical institution specially built to provide special facilities in treatment and medicine for cancer patients in Malaysia. This study has been registered in the National Medical Research Registry (NMRR) Malaysia, and ethical approval was obtained from the Medical Research and Ethics Committee (MREC) of the Ministry of Health, Malaysia, with research ID: NMRR ID-22-00792-HKU. The study was also registered under the ClinicalTrials.gov protocol registration and results system with ID NCT05867810.

Sampling

Malaysians aged 18 years old and above with EC admitted for elective operation in IKN were voluntarily selected. All consented participants were seen by a dietitian during admission. Patients who came as outpatients, non-Malaysians, and minors were excluded from this study. Sample size estimation was calculated using the population proportion formulae (Lemeshow *et al.* 1990). Prior data indicate that the proportion of loss of weight was 0.476 (Pham Van *et al.* 2021) and the population size was 650. Since the Type I error probability and precision were 0.05 and 0.05, 194 samples were required. With an additional 20% dropout rate, the sample size was 242 samples.

Data collection

Socio-demographic and clinical characteristic

Socio-demographic and clinical characteristics, such as age, gender, and ethnicity, and clinical data, including primary diagnosis cancer stage, were gathered by using a data collection form.

Nutrition status

Anthropometric measurements. A regularly calibrated SECA weighing scale, which can provide body weight in kg (up to 0.1 kg) in the ward, was used to measure anthropometric measurements (body weight and height). The participant must stand upright with one bare foot on the scale's metal plate, wear just the barest minimum of clothing, and have no possessions in their pockets. Height was measured using a scheduled calibrated SECA Height Measurement (up to 0.1 cm). While taking the measurement, that individual must be barefoot, stand straight, and face the front. Measurements for weight and height were taken 3 times and average measurements were recorded. Body Mass Index (BMI) was calculated using weight in kilograms divided by height in meters squared (WHO 1995).

Biochemical profile. Biochemical profiles, lymphocytes, and serum albumin

blood investigation were routine procedures of admission, and the data was obtained from the Electronic Medical Record (EMR).

Dietary intake. Dietary intake was assessed by a 24-hour dietary recall method via a face-to-face interview with the research dietitian. If the participants were unable to recall their dietary intake for the past 24 hours, caregivers as proxy respondents were interviewed for clarification. Daily energy and protein intake were calculated from the recorded dietary intake by using the Atlas of Food Exchanges & Portion Sizes (Abdul Manaf *et al.* 2015).

Subjective Global Assessment score (SGA). Subjective Global Assessment (SGA) is a nutritional assessment tool that refers to an overall evaluation of a patient's history and physical examination as well as uses structured clinical parameters to diagnose malnutrition (Duerksen *et al.* 2021). It includes the history of dietary intake, weight change, gastrointestinal symptoms, functional impairment, and physical examination. Results were scored. The scoring is categorized as SGA-A (score 0–5), SGA-B (score 6–18), and SGA-C (score 19–39). The definition of nutritional status is stated in three key SGA categories; nourished (SGA-A), mild to moderately malnourished (SGA-B), or severely malnourished (SGA-C) (Detsky *et al.* 1987).

Performance status

Data on functional status (Performance status scale: Eastern Cooperative Oncology Group (ECOG)) were also collected. Performance status was determined by using the Eastern Cooperative Oncology Group scale (ECOG). The ECOG is a 6-point scale (0–5) that ranges from 0 (good performance status) to 5 (deceased). It correlates with cancer morbidity, mortality, and complications from chemotherapy and can assist in direct clinical decisions and prognostication (Neeman *et al.* 2019). ECOG scoring was conducted by observation of the medical officer as a routine care for every patient in the ward.

Data analysis

The IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp.) was used to analyze data. Descriptive statistics were utilized for selected variables. The results of categorical data were shown as frequencies and percentages, whilst those of numerical data were shown as mean and standard deviation. The association between categorical data and categorical data was analyzed by using Pearson's Chi-square test. A multi-linear regression test was used to analyze the factors associated with the SGA score. All probability values used two-sided, and a level of significance of less than 0.05 ($p<0.05$) is considered statistically significant.

RESULTS AND DISCUSSION

The study enrolled 227 participants with a mean age of 61.1±11.4 years, and 80.6% diagnosed stages III and IV (Table 1). About 96.5% were malnourished. The mean weight, percentage of weight loss past 6-months, SGA score, total daily energy protein intake, and serum albumin were 57.7±14.4 kg, -8.6±6.5%, 12.6±3.9, 17±5 kcal/kg/day, 0.7±0.1 g/kg/day, and 35±5 g/L respectively. About 87%, 96%, and 88% experienced vomiting, dysphagia, and

Table 1. Socio-demographic and clinical characteristics of newly diagnosed esophageal cancer patients

Variables (n=227)	n (%)
Age (years) (Mean±SD)	61.1±11.4
Gender	
Male	170 (74.9)
Female	57 (25.1)
Ethnicity	
Malay	116 (51.1)
Chinese	66 (29.1)
Indian	45 (19.8)
Stage	
T	
I	7 (3.1)
II	37 (16.3)
III	109 (48.0)
IV	74 (32.6)
N	
0	50 (22.0)
1	118 (52.0)
2	49 (21.6)
3	10 (4.4)
M	
0	170 (74.9)
1	57 (25.1)
Comorbidity	
Yes	187 (82.4)
No	40 (17.6)

SD: Standard Deviation; T: Primary tumor site and size; N: Lymph node involvement; M: Metastatic

dyspepsia, respectively; 67% experienced muscle wasting; 47% tolerated fluid only (Table 2). The percentage of weight loss past 1 month, gender, ECOG performance status scale, and lymphocyte levels were found to be the significant factors related to malnutrition among newly diagnosed EC patients ($p<0.05$) by a multi-linear regression test (Table 3). Statistically, the multiple regression model significantly predicted SGA scores, $F(3,226)=17.8$, $p<0.001$, adjusted $R^2=0.213$. The current model could clarify 21.3% of the risk of malnutrition among EC patients. All four variables added statistically significantly to the prediction, $p<0.05$.

Patients with esophageal cancer commonly lose significant weight and experience a high risk of malnutrition, as a result of the severity of the disease and the multidisciplinary oncological

Table 2. Nutritional assessment and functional status of newly diagnosed esophageal cancer patients

Variables	Mean±SD	n (%)
Anthropometry		
Weight (kg)	57.7±14.4	
Height (m)	1.63±0.89	
Body mass index (kg/m^2)	21.6±4.9	
Percentage of weight loss past 1-month	8.6±6.5	
Percentage of weight loss past 6-months	19.7±9.5	
Muscle wasting		
Present		152 (67.0)
Absent		75 (33.0)
Fat wasting		
Present		153 (67.0)
Absent		74 (33.0)
Subjective global assessment		
A		8 (3.5)
B		203 (89.4)
C		16 (7.1)
Subjective global assessment score	12.6±3.9	
Biochemical data		
Serum Albumin (g/L)	35.9±5.3	
Lymphocytes (109/L)	1.7±0.7	
Dietary Intake		
Daily energy intake (kcal/kg/day)	17.0±5.0	
Daily protein intake (g/kg/day)	0.65±0.19	
Gastrointestinal symptoms		
Vomit		
Yes		198 (87.2)
No		29 (12.8)
Dysphagia		
Yes		218 (96.0)
No		9 (4.0)
Dyspepsia		
Yes		200 (88.1)
No		27 (11.9)
Functional status		
Eastern cooperative oncology group scale		
0		21 (9.3)
1		130 (57.3)
2		57 (25.1)
3		19 (8.4)

SD: Standard Deviation; A: Nourished; B: Mild to moderately; C: Severely malnourished

Table 3. Factors associated with malnutrition (SGA score) among newly diagnosed esophageal cancer patients

Variables	Univariate analysis			Multivariate analysis		
	Unadjusted coefficient	95% CI	*p*	Adjusted coefficient	95% CI	*p*
Constant				9.220		
Percentage of weight loss past 1-months (%)	0.247	0.175–0.319	<0.001***	0.226	0.157–0.296	<0.001***
Gender (Male)	1.496	0.332–2.660	0.012	1.588	0.555–2.622	0.003**
Lymphocytes (109/L)	- 1.051	-1.717–-0.384	0.002	-0.881	-1.486–-0.276	0.004**
ECOG performance status scale	1.129	0.469–1.790	0.001	0.718	0.114–1.323	0.020*
Serum albumin (g/L)	-0.125	-0.22–-0.030	0.010			
Stage (T)	0.843	0.193–1.493	0.011			
Vomiting (Present)	2.110	0.602–3.618	0.006			
Dysphagia (Present)	3.169	0.579–5.759	0.017			

ECOG: Eastern Cooperative Oncology Group; *p<0.05; **p<0.01; ***p<0.001; Stepwise Multi-linear Regression; R=0.494; R^2=0.244; adjusted R^2=0.213; F=17.8; p=0.000; CI: Confident Interval; SGA: Subjective Global Assessment

treatment (Cao *et al.* 2021; Grace *et al.* 2018). There was an alarming high rate of malnutrition in this study where 96.5% of our EC patients had SGA B or C category. This prevalence is also much higher compared to other studies where malnutrition prevalence ranged from 60% to 85% (Grace *et al.* 2018). EC is a type of aggressive malignancy that originates in the inner esophageal wall and spreads through other layers such as the mucosa, thin muscle layer, sub-mucosa, or thick muscle layer (Ilson & van Hillegersberg 2018). Therefore, early-stage EC typically has no noticeable symptoms until large tumor size and local invasion in the advanced stage of EC leading to dysphagia and reduced oral intake, resulting in late-stage detection and severe weight loss (Visaggi *et al.* 2021). There was almost 20% weight loss in EC patients upon diagnosis in this study. EC is one of the cancer types with the utmost prevalence of weight loss, nearly comparable to that of pancreatic and gastric cancers (Darakhshandeh & Momenzadeh 2020). In advanced EC, weight loss is an independent predictor of poor survival and an increase in treatment-related complications (Zhang *et al.* 2020).

Malnutrition is a result of prolonged inadequate intake or disrupted nutrient absorption (Ho *et al.* 2021; Cao *et al.* 2021). Due to EC is an aggressive disease and is usually diagnosed at an advanced stage (Triantafyllou & Wijnhoven 2020), EC patients are more likely to be malnourished as compared with other gastrointestinal cancers (Watanabe *et al.* 2020). This causes measurable negative repercussions in terms of body weight, composition of the body, and functional and clinical results (Ho *et al.* 2021). Cancer cachexia is a disease-specific inflammatory reaction that causes malnutrition (Visaggi *et al.* 2021), reduced treatment tolerance and efficacy (Ravasco 2019), increased risk for surgical and clinical complications (Cao *et al.* 2021), and increased hospital stays (Ho *et al.* 2021). An estimation of 10%–20% of cancer patients died from malnutrition rather than the cancer itself (Cao *et al.* 2021).

Along with malnutrition, dysphagia is the primary symptom in EC patients at the initial diagnosis. Due to local tumors that usually result in symptoms like dysphagia, vomiting, exhaustion, poor nutritional intake, weight loss, and muscular atrophy, these individuals often appear malnourished at diagnosis (Cao *et al.* 2021). It usually involves dietary changes to avoid foods that aggravate symptoms leading to insufficient calorie intake. Initially, patients experience difficulty swallowing solid food, followed by soft food, and eventually, liquids and saliva (Grace *et al.* 2018). Moreover, along with nutrition depletion, it increases the risk of having poor performance status (GBD 2017 Oesophageal Cancer Collaborators 2020).

As the most abundant protein in human serum, albumin has been used for decades as a malnutrition indicator for those patients who are stable clinically (Keller 2019). Among cancer

patients, serum albumin has been a generally accepted method for assessing nutritional and inflammatory status (Wu *et al.* 2015). Nonetheless, more recent studies revealed that rather than being the indicator of malnutrition or inadequate nutritional intake, hypoalbuminemia reflects disease-induced or treatment-induced inflammation (Hartwell *et al.* 2018). Such inconsistent outcomes may explain our finding in which albumin only showed up as a significant malnutrition predictor in univariate analysis but not multivariate analysis.

Our study revealed that the pre-treatment status, such as weight loss and ECOG performance status, had prognostic significance in esophageal cancer. From this study, a multiple linear regression test discovered that the ECOG performance status is a significant factor associated with malnutrition among newly diagnosed EC patients. This is in contrast to a previous study among locally advanced EC patients by Song *et al.* (2017) that found no significant association between ECOG and nutritional risk. However, this contradiction might be attributed to the different nutritional tools employed in the use of Nutritional Risk Screening 2002 which is a nutritional screening tool, whereas SGA which is a nutritional assessment tool was performed in the current study.

Our study findings showed that male Esophageal Cancer (EC) patients had a considerably higher risk of malnutrition in comparison to females. This concurred with the results by Karami *et al.* (2021) which demonstrated that nearly half of the male cancer patients, particularly those with gastrointestinal cancer, were at risk of malnutrition. According to GLOBOCAN 2020, approximately 70% of EC cases occur in males, which was the majority of our EC patients in the current study. With strong male predominance, the risk of developing EC in men is 2 to 3-fold higher compared to women (GBD 2017 Oesophageal Cancer Collaborators 2020). In terms of staging, the majority of the EC patients (80.6%) in this study were diagnosed at an advanced stage (stage III and IV), and this is similar to a previous finding by Then *et al.* (2020) where most EC patients in the low- and middle-income countries presented at an advanced stage and experience poorer survival. Similarly, a previous study on EC patients in Taiwan also showed that the majority of EC patients were in the advanced stage and strongly associated with malnutrition upon diagnosis (Chen *et al.* 2021).

This study also showed that lymphocyte count is a significant factor associated with malnutrition in multivariate analyses. The association between malnutrition and lymphocytes was introduced in the 1990s when lymphoid atrophy as a dramatic feature of protein-energy malnutrition and zinc deficiency was likely to be linked with decreased lymphocytes (Lehman & Ballow 2020). Adequate protein and nutrients are essential in lymphocyte production, where protein–energy malnutrition often leads to lower lymphocyte counts. Past studies have shown that lymphocyte levels <1,500/mm^3 correlated strongly with malnutrition, while levels <900/mm^3 indicated severe malnutrition (Keller 2019). Grossman *et al.* (2015) showed that baseline or treatment-induced lymphopenia is associated with short-term cancer survival, including EC, highlighting the importance of lymphocyte monitoring in this population (Grossman *et al.* 2015).

Several potential limitations in this study should be acknowledged. Firstly, the assessment of malnutrition in this study relied on the Subjective Global Assessment (SGA), while other studies predominantly utilized the Patient-Generated Subjective Global Assessment (PG-SGA), which focuses more on cancer patients and includes a wider range of symptom evaluation. This difference in assessment tools may affect the accuracy and comprehensiveness of malnutrition identification. Another limitation is the lack of nutrition monitoring in EC patients, especially post-treatment. The absence of comprehensive follow-up and nutritional status monitoring hinders a thorough understanding of the impact of malnutrition on treatment outcomes. Long-term assessments would provide valuable insights into the effectiveness of interventions and the persistence of malnutrition-related issues in EC patients.

CONCLUSION

The advanced stage of EC, particularly when dysphagia is present, causes decreased oral intake and impaired nutrient absorption, increasing the risk of malnutrition. Hence, recognizing and addressing malnutrition in EC patients is crucial to improving treatment

outcomes and overall prognosis. The current proposed model of malnutrition, particularly in cases related to EC, is practical for clinical use and enables the timely identification of malnutrition through early multidisciplinary-team approach-based nutrition intervention that focuses on nutrition. This approach aims to reduce nutritional deficits, and improve the patient's functional status and clinical outcomes. It's also beneficial in enhancing survival rates when implemented before starting therapy.

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DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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