



Nutritional Status of Cancer Patients: A Unicentric Report from Iran

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ABSTRACT

Background: Considering the incidence of malnutrition, a multidisciplinary approach with targeted nutrition is vital to improve the quality of care in cancer patients. This study aimed to investigate the overall nutritional status of Iranian cancer patients. **Methods:** This cross-sectional study in 70 cancer patients was conducted in Shohada-e Tajrish Hospital from February to April 2019. The cancer patients were assessed by demographics and Scored Patient-Generated Subjective Global Assessment (PG-SGA) utilized as a common tool to evaluate the nutritional status of patients with different types of cancer. **Results:** Overall, 20.0% and 70.0% of the patients had normal body mass index (BMI) and overweight/obese, respectively. Moreover, 30.0% and 60.0% of the participants reported poor and normal intake, respectively. Males were more affected by malnutrition. Approximately 8.0% of the participants lost more than 10.0% of their weight; however, a vast majority of the patients maintained their weight. **Conclusion:** The high prevalence of malnutrition among the studied cancer patients demonstrated the necessity of nutritional care to improve possible malnutrition for better treatment results.

Keywords: Malnutrition; Cancer; Patient-generated subjective global assessment

Introduction

Cancer is one of the major causes of death worldwide and the risk of developing cancer is increasing in both developed and developing countries (Akbari *et al.*, 2017, Ferlay *et al.*, 2015). Cancer has become the second-largest group of chronic non-communicable diseases and the third

most common cause of death after heart diseases, accidents, and other natural phenomena (Farhood *et al.*, 2018). Cancer is one of the leading causes of death globally, with about 10 million deaths in 2020 (Ferlay *et al.*, 2020). It has been expected that the number of new cancer cases will rise as

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many as 23.6 million/year by 2030 due to tobacco and alcohol use, unhealthy diet, physical inactivity, air pollution, some chronic infections, and other risk factors of cancers (Boyle and Levin, 2008, World Health Organization, 2021).

Cancer patients undergo several treatments depending on the type and the stage of cancer, including surgery, radiotherapy, and pharmacological therapy, and experiencing various side effects that may negatively affect dietary intakes, such as loss of appetite, change in taste, vomiting, nausea, malabsorption of nutrients, and fatigue (Arends *et al.*, 2017, Rakhsha *et al.*, 2019). These side effects may put patients at risk of inadequate nutrient intakes, resulting in the development of malnutrition during or even after completion of the treatment. Furthermore, the tumor site and its proximity to the alimentary tract may have direct nutritional implications. Malnourished cancer patients have been reported to be 15 – 20 % at the time of cancer diagnosis and increased up to 85 – 90% at the time of the terminal stage (Virizuela *et al.*, 2018). In addition, while approximately 20 – 60% of hospitalized patients have been reported to suffer from malnutrition at the time of admission (Baxter *et al.*, 2014, Saka *et al.*, 2011), cancer patients are more likely to be malnourished compared to non-cancer patients (Arends *et al.*, 2017). The risk of malnutrition has been suggested to increase with metabolic complications and prolonged hospitalization. Since malnutrition may further increase risks of infectious diseases, side effects from treatments, and mortality, its early diagnosis is important (Löser, 2010). A literature review by (Alberti *et al.*, 2020) shows that The Brazilian Survey of Oncological Nutrition found that 45.1% of the evaluated cancer patients had some degree of malnutrition. Also, 19–68.75% of patients following gastrointestinal surgery suffer from malnutrition (Wan *et al.*, 2020). Moreover, the result of this study showed that nutritional status purposefully affects the long-term prognosis and quality of life of gastrointestinal cancer patients.

A multidisciplinary approach to care, including effective nutritional screening, assessment, and

intervention has demonstrated improved outcomes in various terms. The improvements are regarding nutritional requirements, nutritional status, and quality of life in cancer patients (Kristensen *et al.*, 2020). Thus, the importance of investigating the nutritional status of these patients is that early management of malnutrition could improve drug tolerance, and increase the health-related quality of life (Molina-Garrido, 2020).

Despite the importance of nutrition in cancer patients, there is limited evidence among Iranian patients. Understanding the nutritional status of Iranian cancer patients may result in the implementation of strategies to improve malnourished patients. This may result in the reduction of side effects during and after the treatment and also improvement of their quality of life.

The primary aim of this article was to investigate the nutritional status of cancer patients hospitalized in a hospital in Tehran, Iran, to provide tailored recommendations to improve the nutritional status of the cancer patients.

Materials and methods

Study setting: A cross-sectional study was conducted at the oncology department of Shohada-e Tajrish Hospital, one of the main cancer centers in Iran. The study was conducted from February 2019 to April 2019.

Participants: A total of 70 patients participated in the study. All patients diagnosed with cancer regardless of gender, type, and stage admitted to Shohada-e Tajrish Hospital, were included in the study. The participants included cancer patients who were receiving cancer-directed treatments or were on follow-up care after treatment. The exclusion criteria included patients with difficulty with oral nutrition and those who were severely ill to understand or respond and had no accompanying person who could answer the questionnaires. Before the assignment of the treatment groups, written informed consent and a statement confirming to publish was obtained from the patients.

Anthropometric indices: Height and weight were

extracted from the patients' records. The participants with missing data on height and/or weight were measured according to the WHO protocol using calibrated tools. Height was measured by a stadiometer (SECA 213 Portable Stadiometer) and body weight was measured using a weighing scale standardized in the hospital (SECA, 703) (World Health Organization, 1999). This index categorized as underweight was defined as body mass index (BMI) < 18.5, normal weight was defined as BMI 18.5 - <24.9, overweight was defined as BMI 25 - <29.9, and obesity was defined as BMI \geq 30 (World Health Organization, 1998).

Instruments: The participants who returned signed consent forms were requested to complete a questionnaire. Medical and specialized information of the patient, such as the cause of the patient's referral, the time of diagnosis, and the current treatment of the patient were completed with the help of the oncologist, nurse, and information provided in the patients' records. Any information that could not collect from the interview was also obtained from the patients records or insurance card.

The other questionnaires consisted of a socio-demographic questionnaire and the Scored Patient-Generated Subjective Global Assessment (PG-SGA; version Ottery, FD 2001) (Jager-Wittenaar and Ottery, 2017). The questionnaire was completed by a face-to-face interview with a trained registered dietitian. If the participant had difficulty in answering the questions, the questionnaire was completed with the assistance of an accompanying person.

The PG-SGA was utilized as a common tool to evaluate the nutritional status of the patients with different types of cancer (Jager-Wittenaar and Ottery, 2017). It was adapted from the Subjective Global Assessment (SGA), an essential clinical assessment method proposed by Detsky *et al.* in 1987 and recently modified and validated by Ottery *et al.* in 2017 (Detsky *et al.*, 1987, Jager-Wittenaar and Ottery, 2017). The tool was recommended as the standard for nutrition

assessment in cancer patients by the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association and it has been recognized as the standard and best interdisciplinary patient assessment in oncology and other chronic catabolic conditions (Bauer *et al.*, 2002).

PG-SGA consists of seven sections that gather patients' data on 1) *current and past weight status*: with a maximum score equal to 5 points (pts) that up to 4 pts from weight loss + up to 1 point for the past 2 weeks; 2) *changes in food intakes*: the score how the patient self-rates his/her intake during the past month that helps to address recent deficit / current risk. This score is not additive with a maximum score equal to 4 that use the highest score checked; 3) *nutrition impact symptom*: any symptoms that patient reports (checks off) that have kept them from eating enough during the past 2 weeks is scored. The total score of this section is the sum of the patient complaints; 4) *activities and function*: patient rates his/her activity level over the past month regardless of the cause – inadequate intake, metabolic stress (corticosteroids, fever, inflammation, trauma) or significant inactivity; 5) *disease and its relation to nutritional requirements*, such as fever and steroid use, cancer, AIDS, trauma, and age above 65 years and the total score is additive; 6) *metabolic demand*: score for metabolic stress is determined by some of the variables known to increase protein and calorie needs. The score is additive, so that a patient who has a fever of > 38.9°c degrees (3 points) and is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points; 7) *physical exam*: includes a subjective evaluation of 3 aspects of body composition, including fat, muscle, and fluid status. Since this is subjective, each aspect of the exam is rated for the degree of deficit. Muscle deficit impacts point to score more than the fat deficit (definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate 3+ = severe).

Health professionals, including doctors, nurses, and dietitians completed the last section. The maximum point score for a physical exam was only 3 points and there will be no decrease by

more than 1 point.

The scores in the previous seven sections were summarized and interpreted as follows:

- *Global assessment categories* which classified patients into three statuses, including well-nourished, moderate/suspected malnourished, and severely malnourished. This classification was based on some indices, including weight status, food intake, nutrition impact symptoms, functioning, and physical exam

- *Nutritional triage recommendations* that their score was the sum of all seven sections scores. The additive score was used to define specific nutritional interventions, including patient and family education, symptom management, including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). Triage was based on PG-SGA score, so that in the score of 0-1, no intervention was required at this time and re-assessment on a routine and regular basis during treatment. In the score of 2-3, patient and family education was required by the dietitian, nurse, or other clinicians with pharmacologic intervention as indicated by symptom survey. The score of 4-8 necessitated the intervention by the dietitian, in conjunction with nurse or physician as indicated by symptoms and finally, the score of > 9 indicated a critical need for improved symptom management, and/or nutrient intervention options. In the current study, a Persian version, which was translated by a group of nutritionists, surgeons, and oncologists, was utilized (Khoshnevis *et al.*, 2012).

Ethical considerations: This research was approved by the Institute of Nutrition Research and Food Industry of the country (Ethics Identification number: IR. SBMU.NNFTRI.REC.1398.013). Written informed consent was attained from patients to complete the questionnaire and physical exams.

Data analysis: All statistical analysis was conducted using the SPSS program (version 21.0,

SPSS Inc, Chicago, IL). Demographic information was expressed as number and percentage or mean \pm standard deviation (SD). Categorical variables were analyzed using the Chi-squared test. Two-tailed Spearman correlation coefficients were used to assess correlations. Mann-Whitney U test was used to evaluate associations between parameters of nutritional status and clinical characteristics namely weight loss, food intake, nutrition impact symptoms, functioning, and physical exams. Between-group comparisons were performed by one-way analysis of variance for continuous variables, with Bonferroni or Dunn adjustment for multiple comparisons. A multivariate general linear model was used to identify variables related to nutritional status. All associations and correlations were adjusted for potentially confounding variables (e.g., age, sex, and the number of patients). All analyses were based on a significance level of 0.05 for the *p*-value.

Results

The demographic characteristics of the participants are shown in **Table 1**. Thematic and data saturation was issued upon 21 and 32 cases, respectively. Therefore, the sample size was considered adequate for this qualitative study. The majority of participants were females (72.9%) and married. Only 20.0% had BMI within the acceptable range and 70.0% had their BMI either in overweight or obese categories. In addition, while 17.0% of the participants were illiterate and 58.6% were working as a homemaker, more than 65.0% reported that their income is insufficient.

Participants' status regarding cancers, including types and time of diagnosis, are shown in **Table 2**. About half of the participants had female-specific cancers, such as cervical, breast, ovarian cancers (47.1%) followed by cancers in the gastrointestinal tract (27.1%). A vast majority of participants reported that their cancers were diagnosed more than eight weeks of their participation in the project (92.9%) and more than 70% were under chemotherapy (71.4%).

Table 1. Demographic characteristics of the participants.

Variables	Description	Number of patients (Total %)
Body mass index	Underweight	1 (1.4)
	Normal weight	20 (28.6)
	Overweight	35 (50.0)
	Obese	14 (20.0)
Living situation	Alone	4 (5.7)
	With spouse	10 (14.3)
	With spouse and children	38 (54.3)
	With children	11 (15.7)
	With family members	7 (10.0)
Education	Illiterate	12 (17.1)
	Literate	26 (37.1)
	Diploma	21 (30.0)
	University	11 (15.7)
Job status	Employed	7 (10.0)
	Self-employed	2 (2.9)
	Retired	12 (17.1)
	Homemaker	41 (58.6)
	Unemployed	8 (11.4)
Resource of family income	Monthly salary	20 (28.6)
	Retirement pension	21 (30.0)
	Income from personal assets/income without work	4 (5.7)
	Covered by relatives' help	12 (17.1)
	Others	13 (18.6)
Adequacy of income	Insufficient	46 (65.7)
	Low (as much as family expenses)	19 (27.1)
	Sufficient	5 (7.1)
Marital status	Single	6 (8.6)
	Married	49 (70.0)
	Divorced	3 (4.3)
	Widow	12 (17.1)

Table 2. Details of cancers possessed by patients.

Details	Description	Number of patients (%)
Site of cancers	GI tract (e.g. esophagus, stomach, intestine, liver, and pancreas)	19 (27.1)
	Urinary (kidney, Gallbladder, and urinary tract)	4 (5.7)
	Female-specific (e.g. cervix, uterine, ovary, and breast)	33 (47.1)
	Male-specific (e.g. testicles and prostate)	4 (5.7)
	Lung	2 (2.9)
	Hematology (e.g. lymphoma, leukemia)	4 (5.7)
	Others	4 (5.7)
Time of diagnosis	Less than 2 weeks ago	0 (0.0)
	2-3 weeks ago	2 (2.9)
	4-8 weeks ago	3 (4.3)
	More than 8 weeks (2 month)	65 (92.9)
Current treatment	Surgery	4 (5.7)
	Chemotherapy	50 (71.4)
	Radiotherapy	5 (7.1)
	Chemotherapy and radiotherapy	5 (7.1)
	No treatment	6 (8.6)

Nutritional status obtained from the PG-SGA indicated that, while about 8.0% of the participants lost more than 10.0% of their weight, a vast majority of them maintained their weight (**Table 3**). Although about 30.0% of the participants reported that they eat less, more than 60.0% of the participants did not report any problems with their food intake. While more than 40.0% of the participants reported odd taste, dry mouth, and

pain, more than 30.0% expressed nausea and feeling of a full stomach. In addition, more than 40.0% expressed that they spend most of the day bedridden and have a minimum amount of physical activity. Based on the PG-SGA results, less than 30.0% of the participants were considered well-nourished. More males were classified as either suspected or severe malnutrition compared to females (**Figure 1**).

Table 3. Clinical characteristics affecting patients' nutritional status.

Clinical characteristics	Descriptions	Number of patients (Total %)
Weight Loss	0-1.9 %	50 (71.4)
	2-2.9 %	2 (2.9)
	3-4.9 %	4 (5.7)
	5-9.9 %	8 (11.4)
	10% or greater	6 (8.6)
Food Intake	Normal foods but less than usual	45 (64.3)
	Solid foods in small quantities	1 (1.4)
	Only liquid foods	6 (8.6)
	Only nutrient supplements	0 (0.0)
	Any food in small quantities	18 (25.7)
	Tube feeding or total parenteral nutrition	0 (0.0)
Nutrient Impact symptoms	Vomiting	14 (20.0)
	Diarrhea	16 (22.9)
	Dry mouth	31 (44.3)
	Smells bother	26 (37.1)
	Things taste funny or have no taste	15 (21.4)
	Pain	34 (48.6)
	Anorexia	28 (40.0)
	Nausea	20 (28.6)
	Constipation	24 (34.3)
	Mouth sores	10 (14.3)
	Problems swallowing	2 (2.9)
	Feel full quickly	9 (12.9)
Others (such as depression and oral problems)	21 (30.0)	
Functioning	Normal with no limitation	18 (25.7)
	Not my normal self, but able to be up and about with fairly normal activities	12 (17.1)
	Not feeling up to most things, but in bed or chair less than half the day	9 (12.9)
	Able to do limited activities and spend most of the day in bed or chair pretty much bedridden, rarely out of bed	31 (44.3)
Physical exam	No deficiency	33 (47.1)
	Mild deficiency	20 (28.6)
	Moderate deficiency	13 (18.6)
	Severe deficiency	4 (5.7)

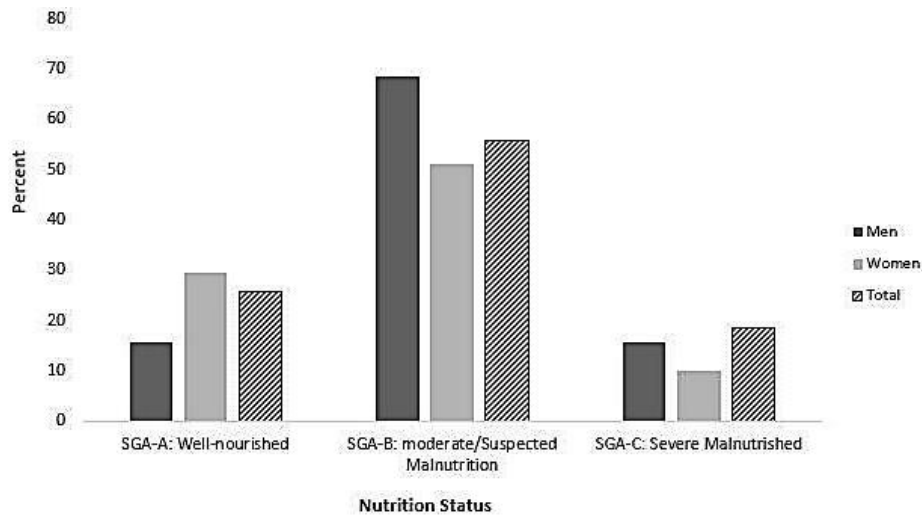


Figure 1. Nutrition status distribution in males and females.

Table 4 reveals that the only factor that significantly affects the nutritional status is the type of treatment. The rate of malnutrition is significantly higher in patients that received both

radiotherapy and chemotherapy. People who needed critical nutritional care included the age group of over 64 years, single people, and those who lived alone.

Table 4. Subjective global assessment (SGA) and nutrition triage recommendation in patients by age, and other demographic characteristics.

Variables	Subjective Global Assessment (SGA)		p-value ^a	Nutrition triage recommendation			P-value
	Well-nourished	Moderate/severe malnutrition		Nutrition education	Symptom management /nutrition counseling	Critical nutrition care	
Age groups (year)							
< 40	2 (14.3)	12 (85.7)	0.52	1 (7.1)	2 (14.3)	11 (78.6)	0.34
40 – 64	13 (29.5)	31 (70.5)		1 (2.3)	13 (29.5)	30 (68.2)	
≥ 60	3 (25.0)	9 (75.0)		0 (0.0)	1 (8.3)	11 (91.7)	
Marital status							
Single	1 (16.7)	5 (83.3)	0.52	0 (0.0)	1 (16.7)	5 (83.3)	0.51
Married	11 (22.4)	38 (77.6)		1 (2.0)	11 (22.4)	37 (75.5)	
Divorced	1 (33.3)	2 (66.7)		0 (0.0)	2 (66.7)	1 (33.3)	
Widow	5 (41.7)	7 (58.3)		1 (8.3)	2 (16.7)	9 (75.0)	
Education							
Illiterate	4 (33.3)	8 (66.7)	0.86	0 (0.0)	3 (25.0)	9 (75.0)	0.55
Literate	7 (26.9)	19 (73.1)		1 (3.8)	5 (19.2)	20 (76.9)	
Diploma	5 (23.8)	16 (76.2)		0 (0.0)	7 (33.3)	14 (66.7)	
University	2 (18.2)	9 (81.8)		1 (9.1)	1 (9.1)	9 (81.8)	
Living condition							
Alone	1 (25.0)	3 (75.0)	0.72	0 (0.0)	1 (25.0)	3 (75.0)	0.93
Not alone	17 (25.8)	49 (74.2)		2 (3.0)	15 (22.7)	49 (74.2)	
Cancer site							
Gastro-intestinal	4 (21.1)	15 (78.9)	0.36	1 (5.3)	3 (15.8)	15 (78.9)	0.60
Urinary tract	2 (50.0)	2 (50.0)		0 (0.0)	1 (25.0)	3 (75.0)	
Female cancer	10 (30.3)	23 (69.7)		1 (3.0)	6 (18.2)	26 (78.8)	
Male cancer	2 (50.0)	2 (50.0)		0 (0.0)	1 (25.0)	3 (75.0)	

Table 4. Subjective global assessment (SGA) and nutrition triage recommendation in patients by age, and other demographic characteristics.

Variables	Subjective Global Assessment (SGA)		p-value ^a	Nutrition triage recommendation			P-value
	Well-nourished	Moderate/severe malnutrition		Nutrition education	Symptom management /nutrition counseling	Critical nutrition care	
Lung	0 (0.0)	2 (100)		0 (0.0)	0 (0.0)	2 (100)	
Leukemia, lymphoma	0 (0.0)	4 (100)		0 (0.0)	2 (50.0)	2 (50.0)	
Others	0 (0.0)	4 (100)		0 (0.0)	3 (75.0)	1 (25.0)	
Time to diagnosis							
Less than 8 weeks	2 (40.0)	3 (60.0)	0.38	0 (0.0)	1 (20.0)	4 (80.0)	0.90
More than 8 weeks	16 (24.6)	49 (75.4)		2 (3.1)	15 (23.1)	48 (73.8)	
Current treatment							
Surgery	2 (50.0)	2 (50.0)	0.63	0 (0.0)	2 (50.0)	2 (50.0)	0.02
Chemotherapy	11 (22.0)	39 (78.0)		1 (2.0)	8 (16.0)	41 (82.0)	
Radiotherapy	1 (20.0)	4 (80.0)		0 (0.0)	4 (80.0)	1 (20.0)	
Chemotherapy and Radiotherapy	1 (20.0)	4 (.080)		0 (0.0)	0 (0.0)	5 (100)	

^a Chi-square test.

Discussion

Nutritional and metabolic derangements are frequent in cancer patients that may affect their prognosis (Akbari *et al.*, 2019, Martin *et al.*, 2015). Advances in the understanding of the status of malnutrition and its related risk factors can result in its improvement among cancer patients. In a meta-analysis of 117 cohort studies, adherence to a high-quality diet and western diet significantly decreased and increased the overall rate of mortality among cancer patients (Schwedhelm *et al.*, 2016).

To the best of the authors' knowledge, this was the first study in Iran to examine the nutritional status of cancer patients regardless of gender, types, and stages, to classify them to decide on different treatments and preventive intervention measures using the PG-SGA tool, which is considered as the best standard questionnaire used in oncologic patients' nutritional status (Bauer *et al.*, 2002, Isenring *et al.*, 2006).

Conducting this hospital-based cross-sectional study on 70 cancer patients with diverse diagnoses showed a high prevalence of an inadequate nutritional status. The participants enrolled in the study comprised cancer patients who had undergone surgery, radiotherapy, pharmacological

therapy or a combination of these or had completed treatment and were on follow-up care. The participants were based on a reference from the oncologists and were included in the study based on a diagnosis from biopsy results. Many tools were proposed for the evaluation of the nutritional status based on objective methods (anthropometrics and body composition assessment) and subjective methods to improve the diagnosis.

As a result, only 20.0% had BMI within an acceptable range, and 70.0% had their BMI either in overweight or obese categories. While about 8.0% of the participants lost more than 10.0% of their weight, a vast majority of them maintained their weight. Although about 30.0% of the participant reported that they eat less, more than 60.0% of the participants did not report any problems with their food intake. More males were classified as either suspected or severe malnutrition. Like elsewhere in the world, a systematic review showed that hospital malnutrition is highly prevalent in Latin America and is associated with several adverse clinical outcomes, such as infectious and non-infectious complications, as well as increased length of hospitalization (Correia *et al.*, 2017, Konturek *et al.*, 2015). This

emphasizes the essential need to assess the nutritional status of patients.

As identified by other authors, cancer patients are especially at risk for malnutrition since they have elevated metabolic requirements due to tumor burden, inadequate or insufficient oral intake due to chemotherapy and inherently altered taste and smell (Hong *et al.*, 2009).

Although malnutrition is a common trouble in hospitals, literature reviews showing the prevalence rate of 40%-80% are often unnoticed and neglected (Bauer and Capra, 2003, Gupta *et al.*, 2005). A study by Bauer *et al.*, 2002, in the Australian Hospital Oncology Division, showed that 24% of patients had a good nutritional status, 59% were at risk of malnutrition, and 17% were severely malnourished (Bauer *et al.*, 2002).

Results of the study by Wu *et al.*, demonstrated that SGA is a reliable assessment tool and helps predict the hospital stay and medical costs of Chinese surgical gastrointestinal cancer patients (Wu *et al.*, 2009).

In 2008 in Iceland, in a study evaluated the malnutrition and nutritional status of patients undergoing chemotherapy for lung, colon, and breast cancer at the Landspítali-University Outpatient Clinic. The results of this study showed malnutrition in 20% of participants. Patients' nutritional decline was also seen as a negative nitrogen balance and unwanted weight loss from the healthy weight, with no reduction in overall energy consumption, recent weight loss or low weight loss. SSM testing showed that 40% of patients were malnourished (Gudny Geirsdottir and Thorsdottir, 2008).

Montaya *et al.* conducted a cross-sectional study in 2009 at an institution in Philippines. This study was performed on 88 cancer patients undergoing chemotherapy. They reported that about half of the patients had malnutrition or were exposed to acute malnutrition. The SGA also found that weight loss of over 10% in the past six months was a common trend among cancer patients (Montoya *et al.*, 2010). Another study on 450 cancer patients with the age range of 18-95 years undergoing radiotherapy, classified by age and sex, showed a high

prevalence of overweight or obesity and malnutrition and their potential role in the histological behavior of cancer (Chaves *et al.*, 2010).

The present study had limitations due to a small number of patients who were participated. In addition, the impact of malnutrition on the clinical course of patients has been described several times. Other limitations of the study included the evaluation of patients from only one medical center and lack of analysis of a long-term follow-up prognosis. Therefore, a larger prospective study is essential to extrapolate better results.

Conclusion

The results of the study showed that the prevalence of malnutrition among the cancer patients was high as moderate and severe classified by PGS-SGA. The study demonstrated the necessity of nutritional care to assess possible malnutrition and improve their nutritional status to perform the treatment process effectively.

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Conflict of interests

The authors have no conflict of interests to declare.

Author's contribution

Roshanmehr F, Kagawa M and Roudsari AH conceived the study. Roshanmehr F and Taghizadeh-Hesary F collected data and conducted analysis. Taghizadeh-Hesary F did medical examination and made final diagnosis. Kagawa M and Roudsari AH supervised the entire study and data interpretation. Roshanmehr F and Milani-bonab A prepared the final draft and all of authors read and approved the final manuscript.

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