

Research Article



Association between TNF- α , Nutritional status and Quality of Life in Syrian Patients with Cancer

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ABSTRACT

An increasingly important issue in oncology is the evaluation of patient outcomes such as nutritional status and quality of life (QoL), which have been important factors to consider in the holistic monitoring of cancer patients. Nonetheless, no study so far has assessed them among Syrian cancer patients. Our study was conducted to highlight this importance, and assess Syrian cancer patients' throughout investigating the prevalence of malnutrition, evaluating QoL of the patients, and looking for an early marker for malnutrition and bad QoL among Syrian cancer patients. The current study was carried out on 72 individuals in three groups: 24 patients of breast cancer, 24 patients of lung cancer and 24 matched age and sex healthy subjects. Patient outcomes were evaluated by well-known questionnaires: Patient-Generated Subjective Global Assessment PG-SGA to evaluate nutritional status, and the European Organization for Research and Treatment of Cancer (EORTC) questionnaire to evaluate QoL. TNF-alpha serum concentrations were measured using an enzyme-linked immune sorbent assay. We observed that in both breast and lung cancer groups malnourished patients had significantly worse QoL scores and higher values of TNF- α . Additionally, we found that TNF-alpha concentration was highly associated to PG-SGA total score and QoL scores, which in turn were significantly associated. We concluded that single laboratory test of TNF-alpha serum concentrations, can give a strong evaluation as the validated questionnaires do, which can save time and efforts. We suggest adding it to the tests used in monitoring Syrian breast and lung cancer patients.

Keywords: Breast cancer, Lung cancer, Malnutrition, Quality of life (QoL), TNF-alpha.

INTRODUCTION

Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) and leads to progressive functional impairment.¹ Common clinical manifestations are fatigue, impaired immune system, metabolic abnormalities, diminished quality of life, and reduced survival.²

The prevalence of cachexia ranges from 50% to >80% according to the type of cancer, and it is considered to cause death in almost 20% of cancer patients.³

The nature of cachexia has not been entirely understood, but it is reported that cachexia is a chronic inflammatory disease associated with the elevated concentrations of pro-inflammatory cytokines, especially tumor necrosis factor alpha (TNF- α).⁴

TNF- α is a multifunctional cytokine which was originally named (cachexin). It is secreted from several cell types, including macrophages, monocytes, B cells, and most tumor cell types.⁵ In experimental cancer models, TNF-alpha is proved to have an essential role in the development of cachexia. However, this cachectic effect of TNF- α can be diminished by specific anti-TNF- α antibodies.⁶

Measuring quality of life in cancer patients has been the focus of clinical practice and research in recent decades. It is important in assessing treatment outcomes.⁷ QoL for cancer patients is personal multidimensional forms that

evaluate the patient's functional status, psychosocial well-being, and disease-related symptoms. In all, QoL assesses health status, which is immensely influenced by nutritional status.⁸

Despite the growing importance of nutritional status and QoL of cancer patients, no study so far has assessed them among Syrian cancer patients, whose number has sharply increased in the last two decades.⁹ This has been the cause beyond our study which assesses Syrian cancer patients throughout investigating the prevalence of malnutrition, evaluating QoL of the patients, and looking for an early marker for malnutrition and bad QoL of Syrian cancer patients.

SUBJECTS AND METHODS

Patients

Informed consent was obtained from all subjects. The study protocol was approved by the scientific research ethics committee of Damascus University, Damascus, Syria.

The current study was carried out on 72 individuals: 24 breast cancer female patients with age 50 \pm 11 range from 30 to 77 years and 12 age matched healthy females and 24 lung cancer patients (Male/Female:22/2) with age 61 \pm 11 range from 44 to 90 years and 12 healthy volunteer (Male/Female:11/1) age matched healthy smokers.

Sera from patient and control groups were stored at -80 $^{\circ}$ C until the assay time.



Evaluating of patient outcomes

Nutritional status was evaluated by recording weight change in the last previous six months and the scored patient-generated subjective global assessment (PGSGA) which provides a standardized approach to nutrition assessment in cancer patients, it includes a clinical and weight history, and a physical examination.⁸ The patient is given a total score, PGSGA total score of 0-1 (no need for nutritional support), 2-3 (patient and family nutritional education), 4-8 (requires medical intervention after examining symptoms), and PGSGA score of ≥ 9 (reveals the crucial need for symptoms management).¹⁰

Quality of life was evaluated with the European Organization for Research and Treatment of Cancer (EORTC) core QOL questionnaire which is a well-known validated instrument for measuring quality of life of cancer patients and includes 30 items that assesses functional scales, symptom scales, a global health/QoL scale and other single items about symptoms.¹¹ All the scales measure range in score from 0 to 100. A higher score for a functional scale represents a higher level of functioning, and a higher score for a symptom scale / item represents a higher level of problems.¹²

Measurement of serum TNF-alpha concentrations

Serum TNF- α concentration was measured by ELISA (TNF- α -EASIA Kit, DIA source, Belgium). The assay was carried out exactly as recommended by the manufacturer.

Statistical Analyses

The results were expressed as mean \pm SD. All statistical analyses were performed using the SPSS program (version 21, IBM SPSS). Student t-test and non-parametric tests were used to assess differences between groups. The cut-point value, sensitivity, and specificity were determined by applying the receiver operating characteristic (ROC) curve. Spearman non-parametric correlation was used to study the correlation between parameters. And $P < 0.05$ was considered statistically significant.

RESULTS

Evaluating patient outcomes

Twenty-four breast cancer patients (100%) recorded a weight loss of 4.62 (range: 1-12) % over the previous six months, 10 (41.7%) patients had lost $< 5\%$, and 14 (58.3%) had lost $\geq 5\%$ of their body weight.

Twenty-four Lung cancer patients (100%) recorded a weight loss of 10.8958 (range: 5-20) % over the previous six months, 10 (41.7%) patients had lost $< 10\%$, and 14 (58.3%) had lost $\geq 10\%$ of their body weight.

Among different groups in terms of weight change over the last previous six months, we found differences in QoL dimension scores, as summarized in Table 1.

Evaluating the nutritional status and requirements of cancer patients using PG-SGA total score is illustrated in Table 2.

Table 1: Median QoL scores differences among different groups in terms of weight loss.

Lung and breast cancer n =48 patients of weight loss				
	< 5% n=10	5-10% n=24	$\geq 10\%$ n=14	
Global health status / QoL	58***	37	25	P=. 000
Functional scales				
Physical functioning	53***	40	7	P=. 000
Role functioning	67***	50	0	P=. 000
Emotional functioning	58***	42	25	P=. 000
Cognitive functioning	83*	67	33	P=. 047
Social functioning	50*	33	17	P=. 035
Symptom scales / items				
Fatigue	33***	61	100	P=. 000
Nausea and vomiting	0**	17	33	P=.007
Pain	33*	67	83	P=. 014
Dyspnea	33	33	100	
Insomnia	33***	67	100	P=. 000
Appetite loss	66***	67	100	P=. 000
Constipation	0	0	33	
Diarrhea	0	0	0	
Financial difficulties	66	83	100	

QoL scores score 0-100: Higher scores on function scales indicate better functioning; Higher scores on symptom scales / single items indicate worse problem; * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$.

Table 2: Evaluating the need for some type of nutritional support among cancer patients using PG-SGA total score.

PG-SGA score	Breast cancer n =24		Lung cancer n =24	
	n	%	n	%
0-1 no need for nutritional support	8	33.2	0	0
≥ 2 need for some type of nutritional intervention:	16	66.8	24	100
2-3 Nutritional education	2	8.3	0	0
4-8 medical intervention	3	12.5	2	8.3
≥ 9 symptoms management	11	45.8	22	91.7

A significant correlation was observed between the PG-SGA score and most of QoL dimensions as shown in Table 3.



Table 3: Spearman rho correlations between PG-SGA score and QoL scores

PG-SGA score		
Lung cancer and breast cancer n =48		
Global health status / QoL	rho= -0.767***	P=. 000
Functional scales		
Physical functioning	rho= -0.810***	P=. 000
Role functioning	rho= -0.762***	P=. 000
Emotional functioning	rho= -0.462**	P=. 001
Cognitive functioning	rho= -0.612***	P=. 000
Social functioning	rho= -0.637**	P=. 007
Symptom scales / items		
Fatigue	rho= 0.822***	P=. 000
Nausea and vomiting	rho= 0.399***	P=. 005
Pain	rho= 0.777***	P=. 000
Dyspnea	rho= 0.537***	P=. 000
Insomnia	rho= 0.710***	P=. 000
Appetite loss	rho= 0.667***	P=. 000
Constipation	rho= 0.293*	P=. 043

*p<0.05; **p<0.01; ***p<0.001

Measurement of serum TNF- α concentration

In both breast and lung cancer the measured average TNF- α serum concentrations of the breast cancer patients was statistically higher than that of the control groups, and TNF- α serum concentrations of the patients with and without weight loss \geq of the average weight loss was high significantly different as illustrated in Table 4.

Table 4: Comparison of serum TNF- α (pg. /ml) concentrations between study groups

Breast cancer			Lung cancer		
	mean \pm SD	p		mean \pm SD	p
Patients group n=24	10.97 \pm 4.52	.000	Patients group n=24	15.17 \pm 6.32	.000
Control group n=12	4.45 \pm 2.90		Control group n=12	5.76 \pm 1.64	
Patients group with weight loss of \geq 5% n=14	13.56 \pm 04.12	.000	Patients group with weight loss of \geq 10% n=14	19.00 \pm 5.30	.000
Patients group without weight loss of \geq 5% n=10	7.33 \pm 1.57		Patients group with weight loss of \geq 10% n=10	9.82 \pm 2.41	

Moreover, we applied (ROC) curve to determine TNF-alpha cut-off value which identify malnourished patients as defined by PG-SGA:

A TNF-alpha cut-off value of 8.75 pg. /ml with sensitivity and specificity of 92.9% and 90% respectively in breast cancer patients Figure 1A.

A TNF-alpha cut-off value of 13 pg. /ml with sensitivity and specificity of 92.3%, 90.9 % respectively in lung cancer patients Figure 1B.

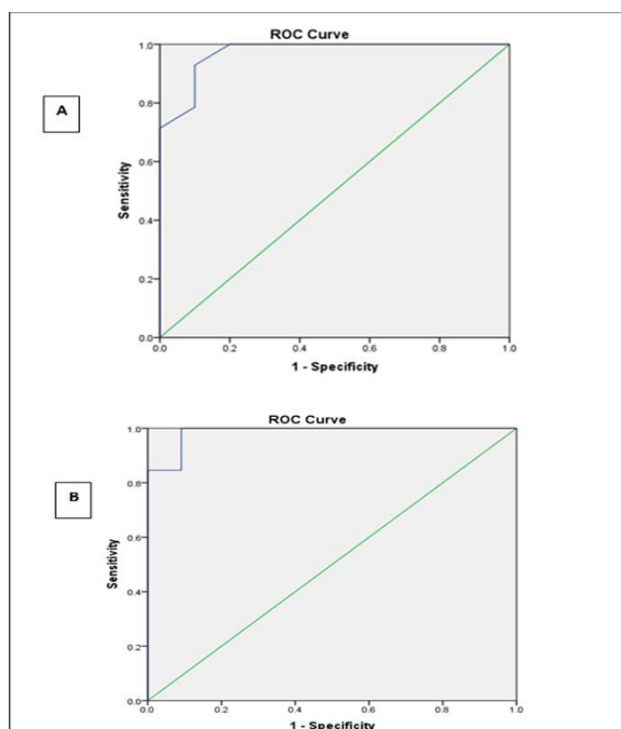


Figure 1: Relation between serum concentrations of TNF-alpha (pg. /ml) with malnutrition classified by PG-SGA in ROC curve. AUC = area under the curve; [A] In breast cancer group. AUC=0.971, P= 000; [B] In lung cancer group. AUC=0.986, P=000.

We have also observed high positive associations between serum concentrations of TNF-alpha and total PG-SGA: rho=0.845*** and rho= 0.896*** in breast and lung cancer groups respectively.

Moreover we observed the significant association between serum concentrations of TNF-alpha and QoL dimensions in both breast and cancer patient groups, as shown in Table 5.

DISCUSSION

The American Society of Clinical Oncology recommends that assessing patient outcomes such as survival and quality of life, is more important than assessing other outcomes as biomarkers in the evaluation of new technologies and the development of cancer treatment guidelines.¹³

In Syria, where cancer is the third cause of death among Syrian people¹⁴, that recommendation has not been taken into consideration yet. So, we are looking forward to highlighting its importance. In our study, we have found that malnutrition is a highly prevalent problem among Syrian cancer patients. The prevalence varies according to

the type of the cancer. It is about 58.3 % and 100% in breast and lung cancer respectively. The average weight

loss also varies. It is about 5% and 10% in breast and lung cancer respectively.

Table 5: Spearman rho correlation between QoL dimensions and serum concentrations of TNF- α

	TNF-alpha			
	Lung cancer n =24		Breast cancer n =24	
Global health status / QoL	rho=- 0.752***	P=. 000	rho= -0.856***	P=. 000
Functional scales				
Physical functioning	rho= -0.677***	P=. 000	rho= -0.692***	P=. 000
Role functioning	rho= -0.708***	P=. 000	rho= -0.536**	P=. 007
Emotional functioning	rho= -0.701***	P=. 000		
Cognitive functioning	rho= -0.855***	P=. 000	rho= -0.642**	P=. 001
Social functioning	rho= -0.503*	P=. 012	rho= -0.463*	P=. 023
Symptom scales / items				
Fatigue	rho= 0.713***	P=. 000	rho= 0.629**	P=. 001
Pain	rho= 0.710***	P=. 000	rho= 0.594**	P=. 002
Insomnia	rho= 0.604**	P=. 002	rho= 0.788***	P=. 000
Appetite loss	rho=0.481*	P=.045	rho= 0.638**	P=. 001

*p<0.05; **p<0.01; ***p<0.001

The age variation between the breast and lung cancer patients (50 and 62, respectively) may also contribute to these variations, since the age of 50 onwards is related to the degenerative loss of skeletal muscle; a condition known as sarcopenia.¹⁵

Therefore, we emphasize the need for evaluating all Syrian cancer patients.

As known, we observed that TNF- α serum level of the patients was significantly higher than of its concentrations in control groups. This is because TNF- α is one of the most commonly studied cytokines and is associated with various cancer types.⁵ The average TNF- α serum level of the patients with weight loss was significantly higher in comparison with those without it. In agreement with studies in pancreatic cancer¹⁶ hepatocellular carcinoma⁶ and prostate cancer.¹⁷

The cachectic effect of TNF- α can be explained as it has been shown to suppress activity of lipoprotein lipase and to stimulate the proteolytic system, both of which may increase the catabolism of body mass, resulting in weight loss.⁶

We have observed that TNF- α serum concentration was highly associated with PG-SGA total score P=.000, and its cut-off value has had high sensitivity and specificity to identifying malnourished patients as defined by PG-SGA with both breast and lung cancer patients. This encourages us to suggest using TNF- α as an indication to PG-SGA total score, and to classify malnourished patients who need nutritional support.

This is highly significant since most of these patients will be subjected to aggressive methods of treatment, mainly surgery, which cause weight loss among a large number of patients.¹⁸

An increasingly important issue in oncology is evaluating quality of life (QoL) of cancer patients. We have included both breast and lung cancer groups in our study in evaluating QoL, as a heterogeneous cancer patient study.

We have revealed that functions and symptoms were worse in those with higher weight loss. This is consistent with other studies¹⁸⁻²¹, we explain that since weight loss as low as 5% can alter immune response and lung and cardiac function, $\geq 10\%$ has a large impact on QoL scores, and $\geq 20\%$ significantly correlates with infections and early mortality.⁸

The PG-SGA total score in turn was significantly correlated to most QoL scores in agreement with other heterogeneous cancer patient study.²²

Thus we reemphasize the importance of early identifying patients who need nutritional support so that we can enhance their nutritional status and also their QoL.

Moreover, we have observed the significant association between concentrations of TNF- α , and QoL scores in both breast and lung cancer patient groups, a similar result has been observed in lung cancer patient groups.¹⁸ Depending on that, we can suggest that serum TNF- α concentrations can be used as a marker for QoL in both breast and lung cancer patients.

Our study has been designed to evaluate Syrian breast and lung cancer patients, using well known instruments like PG-SGA and EROTIC QLQ-C30, and a laboratory test of TNF- α serum concentrations. We have concluded that a single test can give us a strong evaluation as the two questionnaires do. This test is easy to perform using ELISA assay that is affordable, and does not require much time or training as the questionnaires do.

We suggest that TNF-alpha serum concentrations measurement must be included in the tests used in monitoring Syrian breast and lung cancer patients.

We also advise to test its validity among patients of other types of cancer.

CONCLUSION

One laboratory test of TNF-alpha serum concentrations in Syrian patients with breast and lung cancer can give us a strong evaluation for cancer patient outcomes (nutritional status and QoL) as the validated questionnaires PG-SGA and EROTIC QLQ-C30 do, which saves time and effort.

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