Changes in Albumin Level and Cachexia Parameters Over Time and Their Effect on Survival in Patients Who Received Chemotherapy

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Abstract:

Background: Cachexia is an irreversible multifactorial process. One of the most important indicators of nutritional status and a prognostic biomarker in cancer cachectic patients is serum albumin level, its reduction is associated with poor prognosis, we aimed to see effect of improvement over time in albumin on survival and the most independent factors for survival with the contributions of different clinic pathologic parameters to different cachexia parameters.

Methods: a prospective observational single center study. 125 patients were enrolled after their diagnosis as cachectic patients. We collected demographic data, type of nutritional support, anthropometric measures and laboratory data are collected every 3 months for 1 year.

Results: There was significant improvement of total protein and albumin and no significant improvement of body mass index across different time points of measurements despite increasing the percentages of patients attaining normal BMI. Surviving patients completing one year expressed significant improvement of oral intake. The mean OS was 6.4 months, and the median OS was 5 months. OS was positively correlated with serum albumin level. Only age, BMI, NLR, and PLR had significant effect on OS.

Conclusion: Improvement of albumin with progression of time in patients who received their anticancer treatment had significant positive effect on overall survival of cancer cachectic patients.

Keywords: cachexia, albumin, nutrition

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Introduction:

The term cachexia originally comes from the Greek words Kakos hexis which means poor physical state and wasting process occurring in chronic ill patients as cancer patients. Many definitions have evolved over time for cachexia and sarcopenia, they are multifactorial, mostly all definitions agreed that weight loss with loss of skeletal muscle mass is the main and obvious factor in these definitions and are also associated with other parameters as fatigue, anorexia, reduced muscle strength, low fat free mass index, low serum albumin, anemia and increased inflammatory markers as CRP and IL-6 [1-2].

Cachexia has a bad impact on the response of cancer patients including their response to treatment, toxicity profile and quality of life and this therefore leads to increase mortality rates [3]. Cachexia is a process that can't be fully reversed, and its treatment is very difficult. To achieve the goal of increasing muscle mass and improving the state of the body it is important to enhance response to anticancer therapies [3-4].

Patients suffering from cancer that affects ingestion, digestion or absorption of nutrients and patients with advanced stages are the group most susceptible to develop cachexia, so gastric, esophageal, hepatobiliary, pancreatic and hypopharyngeal cancers are the more common cancers associated with cachexia [4-5].

Much research showed the importance of serum albumin level in cachectic patients as it served as an indicator of patient's nutritional status and a prognostic biomarker in those patients, and it has a significant negative linear association with the one-year survival in cachectic patients [6-7].

Although reduced albumin level is associated with bad prognosis in cancer cachectic patients, not much research according to our knowledge answered the following questions: what's the effect of changes in albumin level over time on survival of cachectic

patients who received chemotherapy, what are the most independent factors affecting survival in those patients and what are the contributions of different clinic pathologic parameters to different cachectic parameters?

Patients and Methods:

This was a prospective observational study, that took place at the clinical oncology department at Assiut university hospital from May 2021 to May 2023. Ethical approval of Assiut university committee number is 17101730. Clinical trial.gov number is 05103059.

Patient characteristics:

125 patients were enrolled in our study after their diagnosis as cachectic patients according to Fearon (2012), weight loss more than 5% over past 6 months with loss of skeletal muscle mass with or without loss of fat mass.

We collected demographic data including age, sex, tumor type, tumor staging, metastatic sites, chemotherapy type, weight, height, comorbidities, ECOG Performance Status (PS), Ishii score, family history, anorexia history assessed by anorexia grading scale NCI CTCAE V:4.03, fatigue history and assessment by fatigue assessment scale (FAS), type of nutritional support, we used an in body scale balance. Anthropometric measures and laboratory data are collected every 3 months for 1 year and body mass index (BMI) was calculated by weight in kilograms over height in meters squared.

Ishii score:

the male score was calculated as follows: 0.62 ×(age-64) -3.09 × (grip strength − 50) -4.64 ×(CC-42), and the cut point for sarcopenia was ≥105 points. For female score, it was calculated as follows: 0.8 ×(age-64)- 5.09 × (grip strength − 34)- 3.28 ×(CC-42), and the cut point was ≥ 120 points. Grip strength was measured by adjustable hand gripper device, Mid arm circumference (MAC) was measured by plastic metric tape measure, Tissue skin fold (TSF) was measured by skin fold caliper device, Calf circumference (CC) was measured by plastic metric tape measure, Fat free mass (FFM) and Fat free mass index (FFMI) were calculated by an application called muscle calculator application, Skeletal muscle mass was measured by the in body scale balance.

Serum total protein, Albumin, (HB) hemoglobin, (WBCs) white blood cells, neutrophilic count, lymphocytic count, red blood cells (RBCs), platelet (PLT), NLR dividing neutrophilic count by lymphocytic count, PLR dividing platelet count over lymphocytic count, PNI prognostic nutritional index was calculated by 10 x albumin (g/dl) + 0.005 x total lymphocytic count per mm3.

We evaluated the patients nutritional support including route and type of nutrition given every 3 months for 1 year. Our primary end point is the evaluation of changes in albumin level over time and its relation to survival of cancer cachectic patients and the secondary end point is the relation of different clinicopathologic parameters to different cachectic parameters.

Statistical analysis

All scale variables were not normally distributed with Kolmogorov-Smirnov test <0.05 with the presence of multiple outliers. Inferential statistics were Mann Whitney u-test, Kruskal Wallis test to analyze two and more categorical factors with scale dependent variable, Spearman rho correlation was run for the association between scale variables.

Changes of cachexia parameters, hematologic indices, and BMI across time points were assessed using Freidman and Cochrane Q tests, strength, and significance of different independent variables on baseline cachexia parameters were analyzed by Anova and partial eta squared test.

Cox regression with stepwise method was run in order to remove all collinearity between variables with condition index reached up to 20 and eigen value approached 0, so all highly and moderately correlated variables were excluded, then the highly significant variable introduced in the model was BMI followed by age, then further introduction of variables was not associated with significant increase in p-value, so the model stopped.

Overall survival (OS) was calculated from time of diagnosis to death or end of study (which was predetermined to be one year), the curve was graphed and analyzed by Kaplan-Meier test, all data analyzed by IBM-SPSS version 27 with P-value considered significant at ≤5%, Graph-Pad prism version 8.4.0 was run for drawing different variables and relations. Also the power of the current study with sample size 125 patients was 92.5%, figure (1).

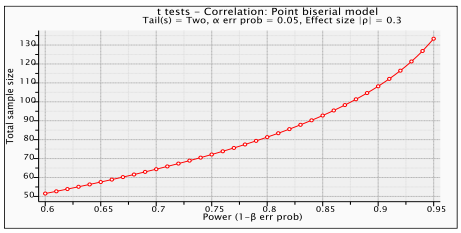

Figure (1): power of the study

Results:

The current study involved 125 patients with different cancer types and characterized by having cachexia at the time of presentation, however they had adequate performance status to receive systemic treatments according to standardized guidelines. The median age was unfortunately lower than expected with median age of 45 years and 52.8% of patients had ages ≤45 years, the majority of patients were females, also

69.6% of patients had underweight, different types of comorbidities were described in 18.4% (23 patients), 76.9% of patients had good performance, and positive family history was reported in 6.4% of patients, table (1).

Table (1): Demographic data of these patients were tabulated below:

Data	Descriptive (n=125)
Age (mean± SD)	45.4± 14.5 years
Median	45 years
Range	20-75
≤45 years	66 (52.8%)
>45 years	59 (47.2%)
Sex (male/female)	55/70 (0.8:1)
Baseline BMI	
Underweight (<18.5)	87 (69.6%)
Normal weight (18.5-24.9)	38 (30.9%)
Comorbidities	
DM	3 (2.4%)
HTN	8 (6.4%)
DM+ HTN	8 (6.4%)
Hypothyroidism	2 (1.6%)
Ischemic heart disease	1 (0.8%)
Myelofibrosis	1 (0.8%)
No comorbidities	102 (81.6%)
ECOG-PS	
PS≤2	101 (80.8%)
PS>2	23 (18.4%)
Family history	
Negative	117 (93.6%)
Positive	8 (6.4%)

Data expressed as mean± SD, median, numbers, and percentages.

All studied patients had anorexia and fatigue; 8.8% (11 patients), 56% (70 patients), and 35.2% (44 patients) had mild, moderate, and severe anorexia respectively, heat map was used to draw the numerical rating scale (NRS) where the intensities of fatigue were scaled from 1-10 and the corresponding frequencies on right-sided scale, they were graded into mild, moderate, and severe fatigue in 9.6% (12 patients), 44.8% (56 patients), and 45.6% (57 patients) respectively, figure (2).

As expected, most cachectic patients had debilitating tumors even in early stages; squamous cell carcinoma of head and neck and gastrointestinal tumors tumors were the most common ones, most patients >80% had advanced diseases (whether locally or distantly) with metastatic rate of 64.8%, table (2).

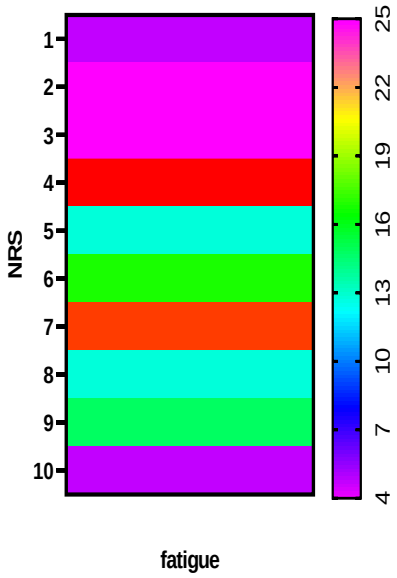

Figure (2): grades of anorexia and fatigue.

Ishii score

For the current study, the male score was 139.0± 26.01 (range 99.8-211.5), and the female score was 159.8± 27.9 (range 92.0-217.3), figure (3).

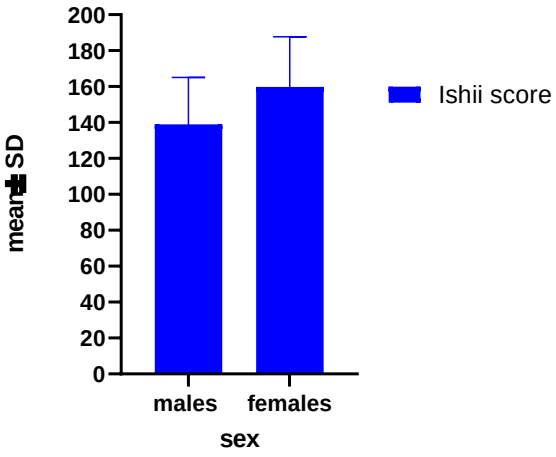

Figure (3): Ishii score difference between males and females,

Fat free mass and fat free mass index

The mean FFM and FFMI were 38.5± 6.0 and 14.5± 1.4 respectively, table (3).

Table (2): Tumor characteristics of 125 patients with cachexia

Characteristics	Descriptive
Tumor types	
SCC of head and neck	23 (18.4%)
UGI	12 (9.6%)
LGI	33 (26.4%)
Hepatobiliary	16 (12.8%)
Lung cancers	10 (8%)
Urinary tract tumors	7 (5.6%)
Hematologic malignancies	6 (4.8%)
MUO	5 (4%)
Breast cancers	4 (3.2%)
Genital organs	4 (3.2%)
Skin cancers	3 (2.3%)
Recurrent desmoid tumors	2 (1.6%)
Tumor stages (123/125)	
I	5 (4%)
II	7 (5.6%)
III	30 (24%)
IV	81 (64.8%)
2 cases were excluded from staging (GBM and desmoid tumor) as they have no staging system.	
Metastatic sites	
1- Non-metastatic	44 (35.2%)
2- Metastatic	81 (64.8%)
A. Multiple sites	6 (4.8%)
B. Single site	75 (60%)
i. Liver	23 (18.4%)
ii. Peritoneum	24 (19.2%)
iii. Lung	12 (9.6%)
iv. Bone	9 (7.2%)
v. BM	4 (3.2%)
vi. Brain	2 (1.6%)
vii. Non-regional LNs	1 (0.8%)
Types of systemic therapy received (116/125)	92.8%
5-FU based regimens	16 (12.8%)
Platinum- based regimens	34 (27.2%)
Combined 5-FU and platinum-based regimens.	51 (40.8%)
Others	15 (12%)
Not received	9 (7.2%)
Dose reduction ≥ 25%	20 (16%)
Grip strength (mean± SD), range	
Males	22.6± 3.5 (11-27.7)
Females	9.1± 2.5 (3-15.6)

Data expressed as numbers, and percentages.
SCC: squamous cell carcinoma, UGI: upper gastrointestinal, LGI: lower gastrointestinal, MUO: malignancy of unknown origin

Table (3): FFM and FFMI among studied patients.

Criterion	Descriptive
FFM	
Mean± SD.	38.5± 6.0
Median	38.2
Min-max	27.9-52.4
FFMI	
Mean± SD.	14.5± 1.4
Median	14.3
Min-max	11.6-18.2

FFM; fat free mass, FFMI; fat free mass index.

Anemia, hypoproteinemia, and hypoalbuminemia were the predominant hematologic and biochemical disturbance detected in the studied patients, no improvement developed in anemia during the course of treatment that could be attributed to toxicity of treatment and short survival of patients, conversely, significant improvement of total protein and albumin were achieved denoting in part improvement of cachexia (<0.001), table (4), figure (4).

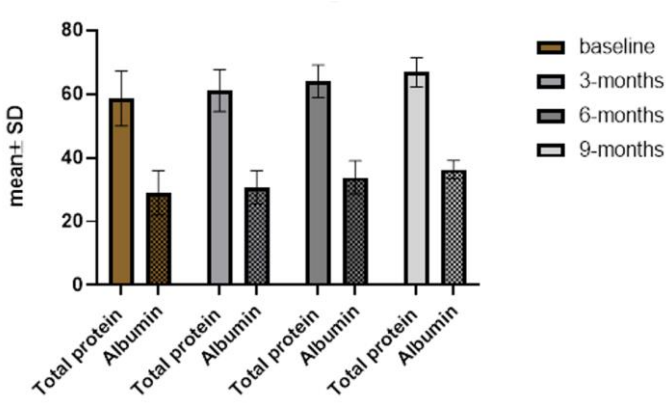

Figure (4): Changes of total protein and albumin across time with treatments, Freidman test, p<0.001.

Table (4): hematologic and biochemical indices across different time points

Hematologic parameter	Mean± SD	Median
Total protein before treatment (n=125)	58.6± 8.6	58.0
Albumin before treatment (n=125)	29.0± 6.9	29.0
HB before treatment (n=125)	10.12± 1.5	10.0
WBCs before treatment (n=125)	8.7± 4.7	7.0
Neutrophilic count before treatment (n=125)	5.2± 3.9	4.0
Lymphocytic count before treatment (n=125)	1.7± 0.9	1.5
RBCs before treatment (n=125)	3.5± 0.7	3.3
PLTs count before treatment (n=125)	231.6± 127.6	200.0
After 3 months of treatment (n=41)		
Total protein	61.1± 6.6	60.0
Albumin	30.7±5.15	30.5
HB	10.0± 1.2	9.5
WBCS	5.54± 2.4	5.0
Neutrophils	3.12± 2.4	2.0
Lymphocytes	1.35± 0.54	1.3
RBCs	3.56± 0.6	3.4
PLTs	246.15± 114.5	200.0
After 6 months of treatment (n=31)		
Total protein	64.0± 5.1	65.0
Albumin	33.8± 5.2	33.0
HB	10.8± 1.4	10.3
WBCs	5.4± 1.8	5.9
Neutrophils	2.44± 1.1	2.0
Lymphocytes	1.6± 0.85	1.3
RBCs	3.6± 0.5	3.5
PLTs	234.5± 74.9	240.0
After 9 months of treatment (n=29)		
Total protein	66.8± 4.6	66.0
Albumin	36.3± 2.9	35.0
HB	10.8± 1.0	10.5
WBCs	5.73± 1.5	5.0
Neutrophils	2.5± 0.8	2.0
Lymphocytes	1.7±0.6	1.7
RBCs	3.84± 0.5	4.0
PLTs	250.6± 71.04	224.0

RBCs; red blood cells, HB; hemoglobin, WBCs; white blood cells, PLT; platelets

Inflammatory indices among cachectic patients

For the current study, the mean values for NLR, PLR, and PNI at baseline, 3 months, 6 months, and 9 months were (3.7± 4.1, 3.4± 4.5, 1.7± 1.1, and 1.9± 2.3), (154.6± 101.7, 237.4± 289.9, 174.0± 84.7, and 171.6± 103.3), and (29.0± 6.9, 30.7± 5.1, 33.8± 5.2, and 36.3± 2.9) with corresponding p-values of 0.9, 0.3, and <0.001 respectively, figure (5).

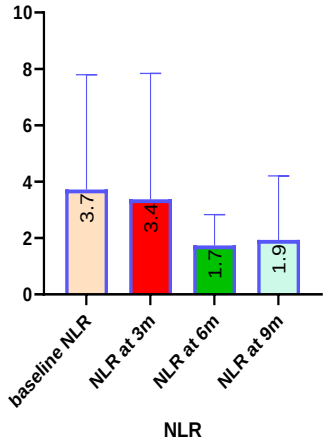

Figure 5(a)

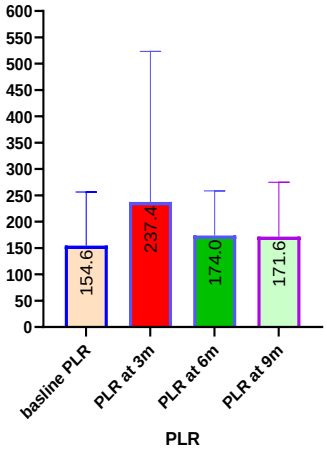

Figure 5(b)

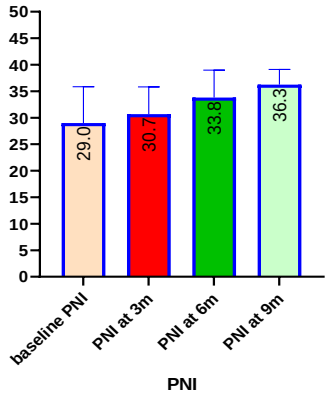

Figure 5(c)

Figure (5): Changes of inflammatory indices during different time points, Friedman test.
5(a): neutrophil to lymphocyte ratio.
5(b): platelet to lymphocyte ratio.
5(c): prognostic nutritional index.

BMI among cachectic patients

The current results revealed no significant improvement of BMI across different time points of measurements despite increasing the percentages of patients attaining normal BMI with subsequent point intervals (53.7% (22/41) at 3-months, 54.8% (17/31) at 6-months, and 62.1% (18/29) at 9-months), figure (6).

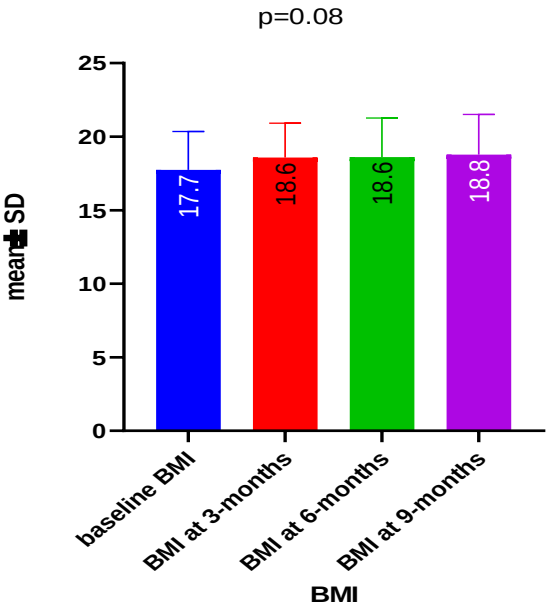

Figure (6): differences of BMI measured at different time points, Freidman test, p=0.08

We detected significant improvements of calf circumference (p=0.02), and skeletal muscle mass (p=0.005) with progressive time points, figure (7).

Surviving patients completing one year expressed significant improvement of oral intake which depended mainly on Ensure and Supportan as the percentages progressively increased with time points (64% at baseline, 43.9% at 3m, 74.2% at 6m, 96.6% at 9m, p=0.001, figure (8).

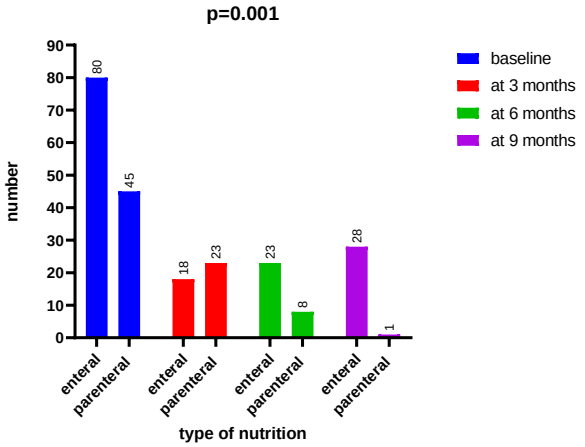

Figure (8): Improvement of nutritional type with time points, Cochran's Q=18.2, p=0.001

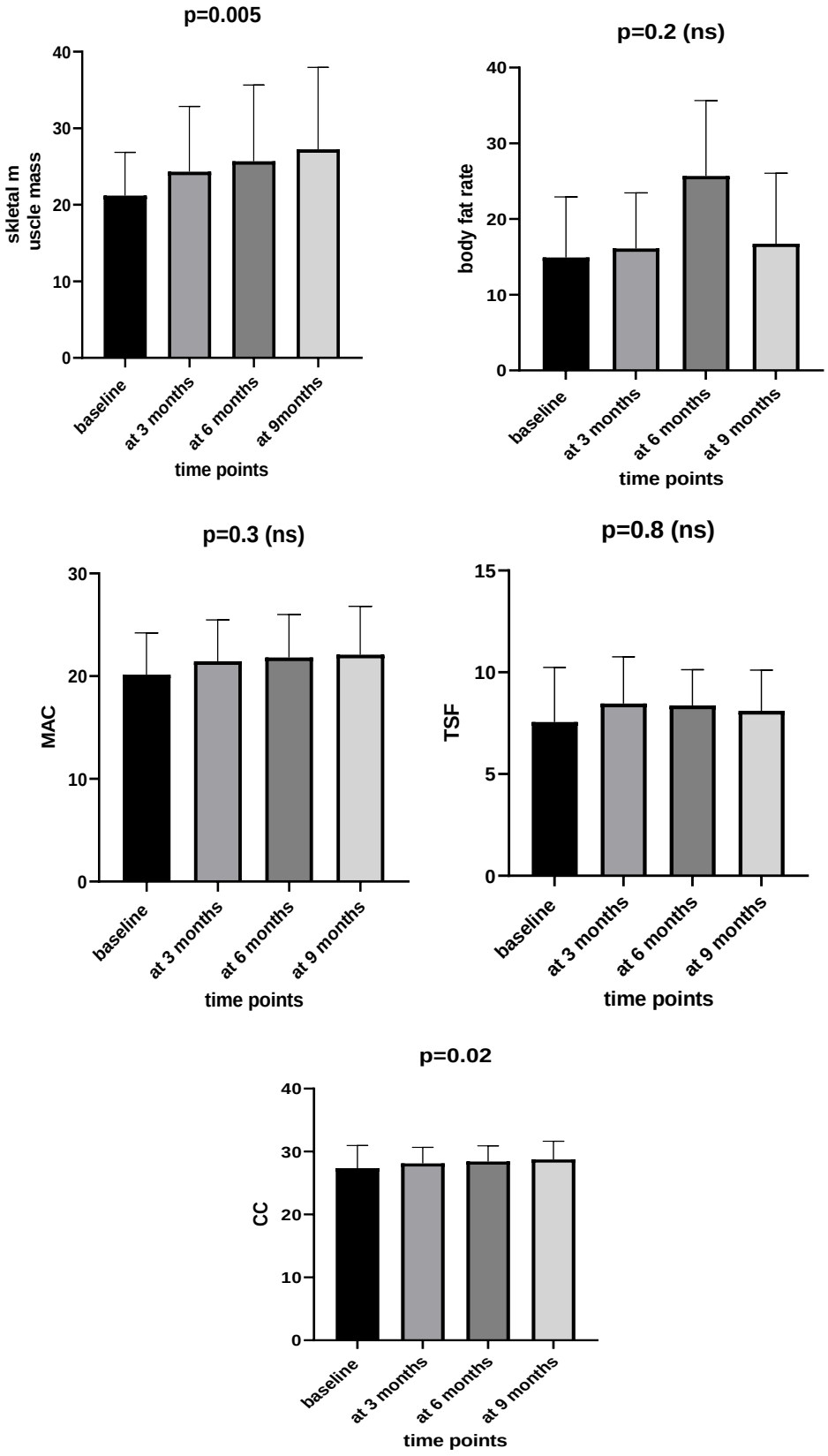

Figure (7): Changes of cachexia and sarcopenia parameters with time points, Freidman test

Association between cachexia and sarcopenia with other clinic pathologic variables

Sex difference was responsible for 4.6%, 6.7%, and 5% of changes in the SMM-MAC-CC. Increasing the stages was responsible for 22%, 6%, 9.6%, 16%, and 10.2% of changes of skeletal MM, body fat rate, MAC, TSF, and CC respectively with significant effect on all except body fat rate. Declining of performance status was associated with 11.5%, 6%, 7%, 15.4%, and 14% of changes in skeletal MM, body fat rate, MAC, TSF, and CC cachexia parameters respectively with significant effect except in body fat rate. Having more than an organ metastasis contributed to the changes of the prementioned cachexia parameters by 12%, 5.5%, 5.1%, 15.3%, and 7.1% with significant impact in all parameters. However, there is no significant relation to age and comorbidities in the prementioned cachexia parameters, table (5).

Survival analysis

Overall Survival was defined in the current study as the time from diagnosis to time of death or end of study (one year after diagnosis). The mean OS was 6.4± o.4 months (95% CI= 5.63-7.1), and the median OS was 5 months, figure (9). The One-year OS was 23.2% (29/125). Overall survival was negatively correlated with Ishii score with significant impact ($p<0.001$), figure (10), OS was positively correlated with serum albumin level ($r=0.35$, $p<0.001$), figure (11).

Univariate and multivariate analysis of OS

In univariate analysis, most predictors had significant impact on OS with younger age, having non-metastatic tumors, increasing BMI, BFR, SMM, TSF, MAC, and CC, also increased PLR and PNI were associated with better survival, on the other hand, decreasing Ishii score and NLR were associated with improved survival, moreover, sex, PS, FFM, and FFMI had no impact on OS.

In cox regression with enter method, where all variables were compared together, only age, BMI, NLR, and PLR had significant effect on OS, also cox regression with stepwise method, the most independent predictors on OS were age, albumin level and BMI where increasing the age by one year increased the hazard of death by 2%, conversely, increasing the level of albumin by one unit was associated with decreased hazard of death by 4.2%, also increased BMI by one integer was associated with decreased hazard of death by 16%, table (6).

Discussion:

The current study involved 125 cancer patients diagnosed as cachectic patients at time of presentation based on weight loss equal to or more than 5% at last 6 months with loss of skeletal muscle mass plus different grading of anorexia and fatigue, 69.6% of patients were underweight and most patients were young with no comorbidities and performance 1 to 2, 116 patients received chemotherapy in which 40.8% were combined 5-Fluorouracil and Platinum based regimens. Most cases are GIT, biliary, pancreatic and head and neck cancer with 64.8% were metastatic.

All patients were anemic with median HB level 10 g/dl and by observing changes over time we noticed no improvement in HB level as patients were receiving chemotherapy and anemia is a common toxicity of the treatment given. There was no significant role of HB level on survival of cancer cachectic patients which is in contrast with the results showed by Xiao-Yue Liu et al [3] where HB level significantly modified the effect of albumin and total protein on the 1-year survival.

There is no doubt that albumin and total protein are important indicators for nutritional status in cancer cachectic patients and also have significant effect on survival in those patients [3-8-9]. We observed significant improvement of albumin, PNI and the oral route of nutrition over time in cancer cachectic patients who received anticancer treatment and nutritional support.

There was a significant role of albumin level improvement on survival as increase in albumin level by 1 g/dl decreased the risk of death by 4.2% and this is consistent with Bland KA et al [6] in which increase in albumin level by 1 g/dl decreased the risk of death by 7%. Jouinot et al [10] documented that albumin level was an independent factor in survival of cancer lung cachectic patients and this is in line with our results.

BMI and age are also independent factors for patients survival and an increase of 1 year of age increased the risk of death by 2% while increase in BMI by 1 unit decreased the risk of death by 16%. Lihua Shang et al and Lisa Martin et al [11-12] agreed that BMI was an important prognostic factor in survival of cancer cachectic patients. Most of the included patients in our study were young age, Xiaodong chen et al [13] detected that young aged gastric cancer cachectic patients had shorter survival than elder ones associated with stage and tumor size all were independent prognostic factors for survival in those patients. Andrew E. Hendi et al [14] showed that the effect of cachexia on survival was modified by receiving chemotherapy as patients who received chemotherapy had improved survival with reduced effect of cachexia on survival and we also noticed that in our study patients showed improved parameters of cachexia and PNI over time. There was significant improvement in measurement of CC and skeletal muscle mass over time, but this was not translated to improvement in BMI with progression in time for patients who received treatment.

There are many other factors that affect survival but with collinearity and dependence on each other's as staging, BFR, skeletal muscle mass, TSF, MAC, CC, PLR, PNI, NLR and Ischii score as decreasing Ishii score and NLR were associated with improved survival and increasing BMI, BFR, SMM, TSF, MAC, CC, PLR and PNI were associated with better survival, while sex, PS, FFM, FFMI had no effect on survival. Several reports indicated that NLR values >3 and <0.7 were pathological and associated with worse outcomes and normalization of this inflammatory marker to set between 1-3 indicated a good prognosis, likewise PLR results of different literature indicated that the cutoff for

Table (5): Contributions of different clinicopathologic characteristics to cachexia parameters

Parameters	Skeletal mm	Body fat rate	MAC	TSF	CC
Age (r, p)	-0.06, 0.7	-0.1, 0.3	-0.09, 0.4	-0.2, 0.027	0.000, 0.99
Gender					
Male	22.6± 6.4	15.8± 8.1	21.3± 3.8	7.7± 2.5	28.3± 3.5
Female	20.1± 4.7	14.2± 7.9	19.2± 4.1	7.4± 2.8	26.7± 3.5
F	5.9	1.2	8.8	0.4	6.5
η^2	0.046	0.009	0.067	0.003	0.05
p-value	0.017	0.3	0.004	0.5	0.012
Stage					
1	28.8± 12.1	16.4± 2.2	18.2± 1.1	10.4± 0.5	26.0± 0.0
2	28.9± 8.7	19.6± 11.1	23.4± 4.1	9.0± 2.7	29.6± 2.8
3	21.9± 5.7	17.3± 9.8	21.7± 4.4	8.8± 3.1	29.0± 2.8
4	19.9± 3.7	13.6± 7.0	19.5± 3.8	6.9± 2.3	26.7± 3.8
F	11.2	2.5	4.2	7.3	4.5
η^2	0.22	0.06	0.096	0.16	0.102
p-value	<0.001	0.06	0.007	<0.001	0.005
PS					
0	23.6± 7.2	16.5± 8.3	20.8± 3.9	8.2± 2.4	28.2± 2.6
1	19.9± 4.04	15.4± 8.0	20.6± 3.8	8.02± 2.7	27.9± 3.4
2	19.9± 3.9	11.1± 5.2	18.8± 4.3	6.2± 2.4	25.7± 4.01
3	18.4± 1.1	13.0± 10.03	17.1± 4.5	4.6± 1.8	23.5± 5.5
F	5.2	2.4	3.03	7.4	6.5
η^2	0.115	0.06	0.07	0.154	0.14
p-value	0.002	0.07	0.03	<0.001	<0.001
Metastasis					
-Non-metastatic.	23.7± 7.5	17.4± 9.2	21.3± 4.3	8.8± 2.9	28.7± 2.8
-Single organ metastasis.	20.1± 3.8	13.4± 6.9	19.4± 3.4	6.7± 2.2	26.7± 3.9
-Multiple organs metastasis	17.0± 0.6	15.1± 9.1	21.0± 3.9	9.0± 2.4	26.8± 1.8
F	8.1	3.6	3.2	11.1	4.6
η^2	0.12	0.055	0.051	0.153	0.071
p-value	<0.001	0.031	0.042	<0.001	0.01
Comorbidity					
No	21.7± 6.02	14.4± 7.7	20.2± 4.2	7.5± 2.6	27.4± 3.6
Yes	19.2± 3.0	17.2± 9.1	20.1± 3.7	7.9± 3.0	27.3± 3.9
F	2.3	3.8	0.005	0.05	0.004
η^2	0.018	0.03	0.00	0.004	0.00
p-value	0.1	0.06	0.9	0.5	0.95

Data expressed as mean± SD, analyzed by Anova with partial eta squared (η^2)

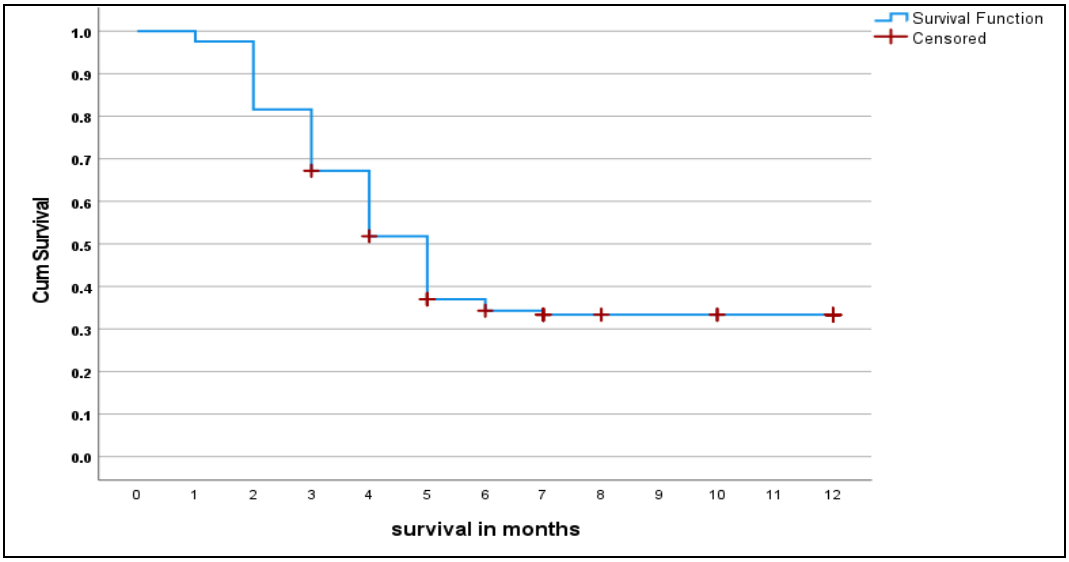

Figure (9): OS in months of 125 cachectic patients.

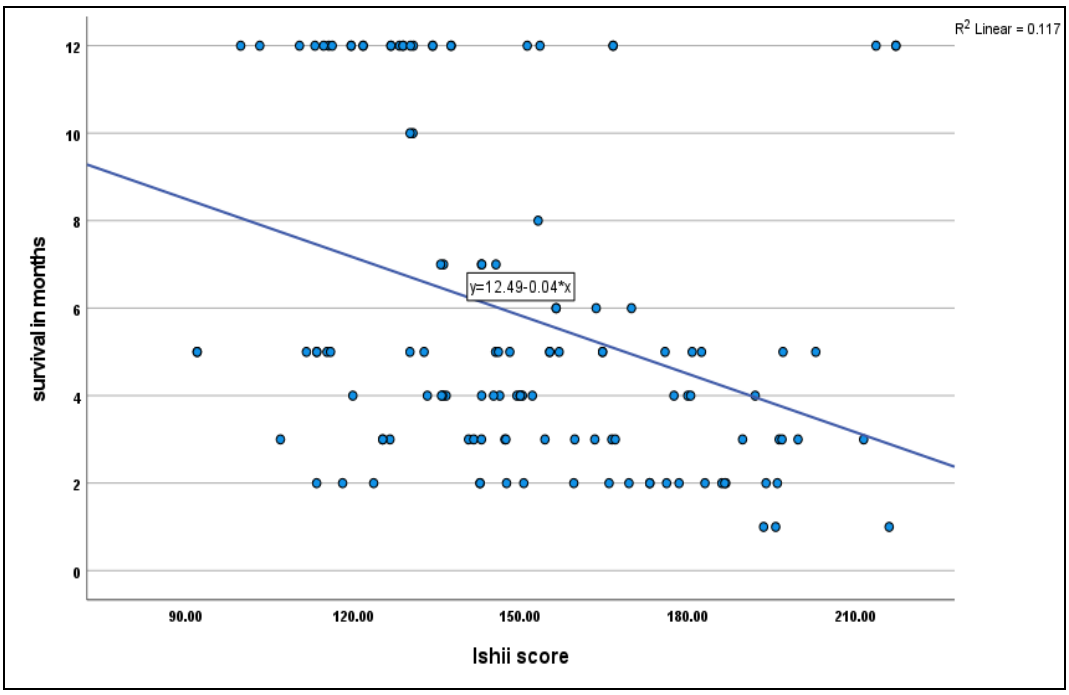

Figure (10): correlation between Ishii score and OS, Spearman rho=0.342, p<0.001

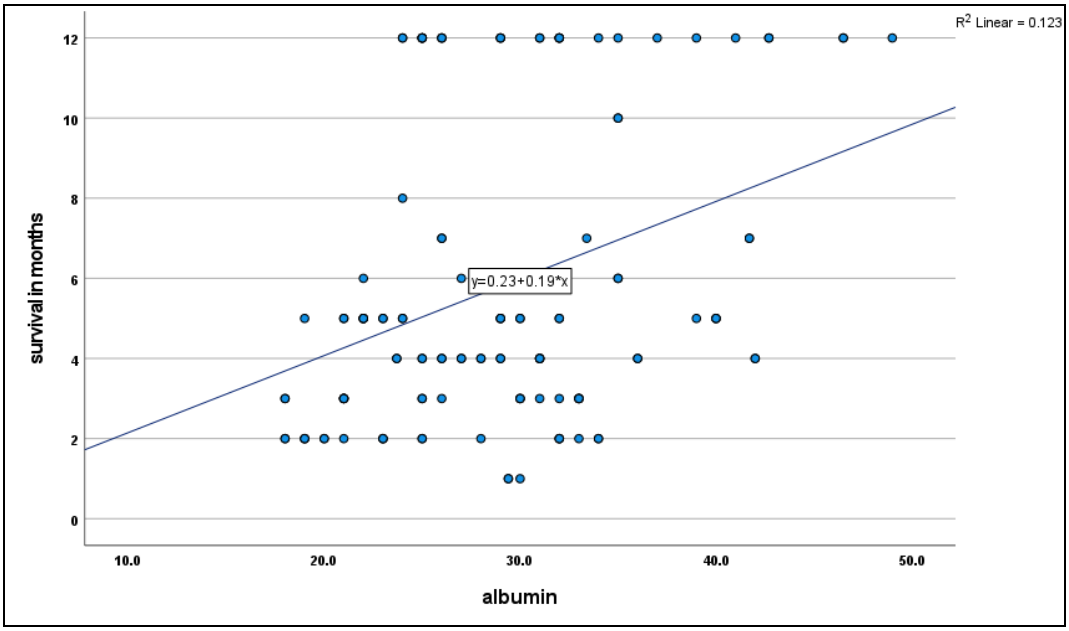

Figure (11): correlation between baseline albumin level and OS, p<0.001.

Table (6): Univariate and multivariate analysis of survival

Predictors of survival	**Univariate**		**Multivariate**	
	Coefficient	p-value	HR (95% CI)	p-value
Age (r, p)	-2.2	0.015	1.02 (1.0-1.03)	0.037
Sex (mean± SD)		0.4	0.6 (0.2-1.7)	0.3
Male	6.13± 4.1			
Female	5.5± 3.45			
Metastatic pattern (mean± SD)		0.007		
Non-metastatic	7.5± 4.0		1.1 (0.3-4.1)	0.8
Single site	3.21± 0.4		1.4 (0.4-5.1)	0.6
Multiple sites	4.3± 1.8		Reference	
PS (mean± SD)		0.2	1.3 (0.8-2.3)	0.4
≤2	6.02± 3.8			
>2	4.91± 3.7			
Albumin	0.35	<0.001	0.96 (0.92-0.99)	0.024
BMI	0.4	<0.001	0.84 (0.8-0.9)	0.002
FFM	-0.08	0.3	1.03 (0.98-1.1)	0.2
FFMI	-0.02	0.8	0.9 (0.7-1.2)	0.5
Body fat rate	0.21	0.02	1.02 (0.97-1.1)	0.3
Skeletal muscle mass	0.4	<0.001	0.98 (0.9-1.03)	0.4
Tissue skin fold	0.32	<0.001	1.04 (0.9-1.2)	0.7
Calf circumference	0.31	<0.001	1.03 (0.8-1.3)	0.8
Mid arm circumference	0.34	<0.001	0.95 (0.8-1.1)	0.5
Ishii score	-0.34	<0.001	0.9 (0.96-1.03)	0.2
Neutrophil-lymphocytic ratio	-0.20	0.02	1.1 (1.02-1.2)	0.011
Platelet lymphocyte ratio	0.22	0.015	0.99 (0.99-0.999)	0.024
Prognostic nutritional index	0.35	<0.001	0.97 (0.93-1.02)	0.2

Data analyzed by Spearman rho test, Mann Whitney test, Kruskal Wallis test, and cox regression.

this marker was 146.98 and correlated with prognosis, regarding prognostic nutritional index low values <45 was associated with poor survival.

Our study noticed an association between cachexia and clinic-pathological variables which showed the amount of contribution of each parameter to different cachexia parameters where male gender had significantly better skeletal muscle mass, middle arm circumference, and calf circumference than female gender. Sex difference was responsible for 4.6%, 6.7%, and 5% of changes in the pre mentioned cachexia parameters. Increasing the stages was responsible for 22%, 6%, 9.6%, 16%, and 10.2% of changes of cachexia parameters; skeletal muscle mass, body fat rate, MAC, TSF, and CC respectively with significant effect on all except body fat rate. Declining of performance status was associated with 11.5%, 6%, 7%, 15.4%, and 14% of changes in cachexia parameters with significant effect except in body fat rate, furthermore, getting more organ metastasis contributed to the changes of the prementioned cachexia parameters by 12%, 5.5%, 5.1%, 15.3%, and 7.1% with significant impact on all parameters. However, there is no significant contribution for age and comorbidities in the prementioned cachexia parameters.

Conclusion:

Improvement of albumin with progression of time in patients who received their anticancer treatment had significant positive effect on overall survival of cancer cachectic patients. The most independent predictors of OS were age, albumin level and BMI. Cachexia is multifactorial and in cancer patients many factors including staging and performance status affect its parameters significantly. We recommend more research to evaluate the effect of different clinic-pathologic parameters on cachexia parameters and to evaluate the changes of different parameters over time and their impact on cachexia parameters.

Authors' contributions

DA is the first author of the manuscript and made contributions to the protocol design. DA and NA Analyzed and interpreted the data, and all authors drafted the manuscript. DA, AM and NA provided support regarding the statistical analysis and discussion. SS, AM and DA performed all methodological procedure and was responsible for data analysis and manuscript revision. All authors have reviewed and approved the final version of the manuscript.

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Conflict of interest

No conflict of interest

Abbreviations

PS	Performance Status
FAS	fatigue assessment scale
BMI	body mass index
MAC	Mid arm circumference
TSF	Tissue skin fold
CC	Calf circumference
FFM	Fat free mass
FFMI	Fat free mass index
HB	hemoglobin
WBCs	white blood cells
RBCs	red blood cells
PLT	platelet
NLR	neutrophile lymphocytic ratio
PLR	platelet lymphocytic ratio
PNI	prognostic nutritional index
OS	overall survival

References:

1. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12:489-95. 2011 May;12(5):489-95.
2. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. Clin Nutr 2008 Dec;27(6):793-9.
3. Liu XY, Zhang X, Ruan GT, et al. One-Year Mortality in Patients with Cancer Cachexia: Association with Albumin and Total Protein. Cancer Manag Res. 2021 Aug 29;13:6775-6783.
4. da Rocha IMG, Marcadenti A, de Medeiros GOC, et al. Is cachexia associated with chemotherapy toxicities in gastrointestinal cancer patients? A prospective study. J Cachexia Sarcopenia Muscle. 2019 Apr;10(2):445-454.
5. Baracos VE, Martin L, Korc M, et al. Cancer-associated cachexia. Nat Rev Dis Primers. 2018 Jan 18;4:17105.
6. Bland KA, Zopf EM, Harrison M, et al. Prognostic Markers of Overall Survival in Cancer Patients Attending a Cachexia Support Service: An Evaluation of Clinically Assessed Physical Function, Malnutrition and Inflammatory Status. Nutr Cancer. 2021;73(8):1400-1410.
7. Brkic FF, Kadletz L, Jank B, et al. Impact of pretherapeutic neutrophil-to-lymphocyte ratio, serum albumin, body-mass index, and advanced lung cancer inflammation index on clinical outcome in sinonasal squamous cell carcinoma. J Craniomaxillofac Surg. 2020 Jan;48(1):33-37.
8. Naumann P, Eberlein J, Farnia B, et al. Cachectic Body Composition and Inflammatory Markers Portend a Poor Prognosis in Patients with Locally Advanced Pancreatic Cancer Treated with Chemoradiation. Cancers (Basel). 2019 Oct 26;11(11):1655.
9. Matsuzuka T, Kiyota N, Mizusawa J, et al. Japan Clinical Oncology Group (JCOG) Head and Neck Cancer Study Group Clinical impact of cachexia in unresectable locally advanced head and neck cancer: supplementary analysis of a phase II trial (JCOG0706-S2). Jpn J Clin Oncol. 2019 Jan 1;49(1):37-41.
10. Jouinot A, Ulmann G, Vazeille C, et al. Hypermetabolism is an independent prognostic

factor of survival in metastatic non-small cell lung cancer patients. Clin Nutr. 2020 Jun;39(6):1893-1899.

11. Shang L, Hattori M, Fleming G, et al. Impact of post-diagnosis weight change on survival outcomes in Black and White breast cancer patients. Breast Cancer Res. 2021 Feb 4;23(1):18.
12. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013 Apr 20;31(12):1539-47.
13. Chen X, Zeng Y, Huang Y, et al. Preoperative Cachexia predicts poor outcomes in young rather than elderly gastric cancer patients: a prospective study. Cancer Manag Res. 2019 Sep 2:11:8101-8110.
14. Hendifar AE, Chang JI, Huang BZ, et al. Cachexia and not obesity, prior to pancreatic cancer diagnosis worsens survival and is negated by chemotherapy. J Gastrointest Oncol. 2018 Feb;9(1):17-23.