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Relation between interleukin 6 level and Cachexia in patients with Hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) arises most frequently in the setting of chronic liver inflammation. In recent years evidence about the relation between inflammation and initiation, promotion and progression of tumors are accumulating. Chronic inflammation in cachectic patients is often a combination of both tumor and host derived factors. A multitude of cytokines including; TNF–α, IL-1β IL-6, glucocorticoids, and myostatin have been implicated in facilitating a cachectic state. The aim of this study is to evaluate associations between cachexia and serum levels of IL-6 in patients with HCV related hepatocellular carcinoma. This case control study was conducted on 113 naïve patients with confirmed diagnosis of HCV related liver disease with HCC; 40 patients were diagnosed with cachexia while 73 patients had no cachexia, there was A significant higher level of serum IL-6 level in HCC patients presented with cachexia syndrome (P value =0.0 HS) with mean level of 285 Pg/mL. Also a significant correlation between IL-6 level and AFP level BCLC stage significantly noticed in patients with cachexia These data suggest that IL-6 can be used as a marker for cachexia in patients with HCV related hepatocellular carcinoma.
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1. Introduction:

Hepatocellular carcinoma (HCC) arises most frequently in the setting of chronic liver inflammation. In recent years evidence about the relation between inflammation and initiation, promotion and progression of tumors are accumulating [(1)].

Cancer cachexia is a wasting syndrome that occurs in approximately 80% of cancer patients and is the primary cause of death for 22–30% of all cancer patients [(2)]. Significant complications and mortality related to cachexia may be attributed to the fact that cancer patients are usually diagnosed with cachexia very late [(3, 4)].

The prevalence of hepatocellular carcinoma (HCC) has progressively increased in Egypt due to the high prevalence of HCV infection, the last national results reports that the incidence of HCC is (23.8%) and is considered the second most common malignancy [(5)]

Chronic inflammation in cachectic patients is often a combination of both tumor and host derived factors. A multitude of cytokines including; TNF–α, IL-1β IL-6, glucocorticoids, and myostatin have been implicated in facilitating a cachectic state [(6)]. IL-6 has emerged as a major player in cancer cachexia progression with its levels correlating to survival time in patients [(7)].

Many reports noticed IL-6 correlation with cachexia in different cancers [(8)], However in HCC not well studied.

The aim of this study is to evaluate associations between cachexia and serum levels of IL-6 in patients with HCV related hepatocellular carcinoma.

2. Patients and Methods:

During period from April 2017 till November 2017 124 naïve patients with confirmed diagnosis HCV related liver disease with HCC (according to AASLD guidelines 2011) were included and assessed for presence of cachexia [(9)].

All studied patients were treatment naïve for HCV.

Cachexia syndrome was defined as weight loss of at least 5%in 12 months or less or BMI <20kg/m^2 plus 3 out of 5 of the following:

- Decreased muscle strength [(10)].
- Fatigue: Fatigue is defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance. [(11)].

- Anorexia: Anorexia is defined as Limited food intake (i.e. total caloric intake less than 20 kcal/kg body weight/d; <70% of usual food intake) or poor appetite. [12].
- Low fat free mass index: Lean tissue depletion (i.e. mid upper arm muscle circumference <10th percentile for age and gender; appendicle skeletal muscle index by DEXA (kg/m2) by DXA <5.45 in females and <7.25 in males [13].
- Abnormal biochemistry: C-reactive protein >10, hemoglobin<12gm/dl or serum albumin <3.2[14].

All patients were classified and managed according to recommendation of EASL clinical practice guidelines: management of hepatocellular carcinoma and according to BCLC staging [15]

All patients were subjected to full history taking and thorough clinical examination, Laboratory investigations including CBC, Liver profile tests (Albumin, Bilirubin (Total and Direct), ALP (Alkaline phosphatase), AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), INR (International Normalization Ratio)), kidney functions, fasting blood sugar, HbA1C, C-reactive protein, Alpha feto-protein, TSH and Interleukin-6 (IL-6).

Radiological investigations including Abdominal Doppler ultrasound and Triphasic computed tomography were done for diagnosis and staging of HCC.

None of the studied patients had any signs of infections at time of the study to elaborate other factors that might affect the level of cytokine and inflammatory markers.

11 patients were excluded from analysis due to uncontrolled diabetes HBA1C >7 (7), Hyperthyroidism (1), Malabsorption syndrome (1) and Renal failure (1)

Criteria of cachexia syndrome definition were fulfilled in 40 patients (group I) while 73 patients didn't meet cachexia syndrome definition (group II).

The study was approved and got acceptance through the ethical committee in Faculty of Medicine, Ain Shams University.

3. Results:

This case control study was conducted on 113 naïve patients with confirmed diagnosis of HCV related liver disease with HCC; 40 patients were diagnosed with cachexia while 73 patients had no cachexia.

Baseline data of included patients showed that blood urea nitrogen was significantly lower but AFP and CRP levels were significantly higher in patients with cachexia syndrome. However both groups were matched regarding age, gender, and child class, number of hepatic focal lesions and tumor size as shown in tables 1, 2.

In our results and as can be expected patients with cachexia syndrome had more advanced disease according to BCLC staging system (Table 2).

A quantitative analysis of serum IL-6 level among both groups showed a significant higher level in HCC patients presented with cachexia syndrome with mean level of 285 Pg/mL (Table 3).

A significant correlation between IL-6 level and AFP level was noticed in both groups. Also significant correlation between IL-6 level and BCLC stage was noticed in patients with cachexia but not in patients without cachexia. (Table 4).

Table (1): Demographics and Laboratory data for the study population:

Characteristic		**Group (I) Patients with cachexia n=40**	**Group (II) Patients without cachexia n=73**	**P value**
Gender	Females	10(25%)	11(15%)	**0.264**
	Males	30(75%)	62(85%)	
Age (yrs.)	Mean±SD	57.65 ±9.2724	57.3 ±8.087	**0.865**
BMI	Mean±SD	20. 3 ±1.7	25.9±3.4	**0.0(HS)**
Hemoglobin	Mean±SD	11.48 ±1.6851	13.6855 ±1.2027	**0.0(HS)**
Platelet	Range	27-270	42-322	**0.729**
	Median	95	80.5	
ALT	Range	10 - 109	21 – 161	**0.177**
	Median	70	53.5	
AST	Range	11 - 164	18 – 90	**0.064**
	Median	76	67.5	
Albumin	Mean± SD	3.13 ±0.7733	3.515 ±0.6878	**0.021(S)**
PT	Mean± SD	12.975	12.95	**0.914**

Characteristic		Group (I) Patients with cachexia n=40	Group (II) Patients without cachexia n=73	P value
		±1.0916	±0.9637	
INR	Mean± SD	1.285 ±0.29049	1.1835 ±0.14309	**0.052**
Bilirubin	Range	0.5 - 5	0.4 – 3.4	**0.076**
	Median	1.05	1.17	
Creatinine	Range	0.5 – 1.2	0.36 – 1.4	**0.768**
	Median	0.8	0.85	
Urea	Mean± SD	45.15 ±9.1723	45.2 ±10.3755	**0.982**
BUN	Mean± SD	15.05 ±3.1941	17.2 ±2.6136	**0.002**
CRP	Range	6-48	6-24	**0.002(HS)**
	Median	16	12	

Note: BMI, body mass index. Significant difference was seen in BMI, Hemoglobin level and serum CRP levels, and albumin between cachexia group and non-cachexia group.

Table (2): Tumor characteristics and Child score in the cachexia and non-cachexia groups:

Parameter		Group (I) Patients with cachexia	Group (II) Patients without cachexia	P value
AFP	Median (IQR)	159.35	116	**0.034(S)**
	Range	6-4000	1.9-1374	
Tumour size	Median (IQR)	6	5	**0.856**
	Range	2-10.5cm	2-8.5cm	
Number of Lesions	1	26 (65%)	44 (60.2%)	**0.862**
	2	10 (25%)	18 (24.6%)	
	3	2 (5%)	7 (9.6%)	
	>3	2 (5%)	4 (5.4%)	
Child class	Class A	18(45%)	48(65.7%)	**0.072**
	Class B	22(55%)	25(34.3%)	

AFP; alpha feto protein in ng/ml

Table (3): Comparison between the 2 studied groups regarding level of IL-6:

		Group (I) Patients with cachexia	Group (II) Patients without cachexia	p value
IL-6	Median (IQR)	285	150	0.0 (HS)
	Range	110-375	85-310	

Table (4): Correlation between level of IL-6 and AFP in cachectic and non-cachectic group:

IL-6		R	P value
AFP	**Group (I) Patients with cachexia**	0.311	0.046(S)
	Group (II) Patients without cachexia	0.364	0.023 (S)

4. Discussion:

Hepatocellular carcinoma (HCC) is the third leading cause of cancer related deaths worldwide [16]. The magnitude of the problem of HCC in Egypt is high as it represents (23.8%) among all malignancies [5]

Cancer cachexia is a disabling clinical condition that affects both survival and prognosis of many types of cancers [17]. Prevalence of cachexia reaches up to 40.3% in hepatocellular carcinoma patients. [18]

In the set of hepatocellular carcinoma on top of cirrhosisthe nutritional and metabolic consequences of cirrhosis because of malnutrition and hyper metabolic state add to the magnitude of the problem. [19]

Cachexia is a multifactorial syndrome characterized by an involuntary weight loss of>5% of

premorbid weight. [20]

IL-6 is a cytokine with complex biological functions including immune function either a pro or ant inflammatory action. [21] A potential role of IL- 6 has been verified in cancer patients with cachexia, it is assumed that increased circulating level of IL-6 increases tissue insulin resistance due to initiation of hyper metabolic state in the form of skeletal muscle metabolic dysfunction and adipose lipolysis [22]

This study focuses on the correlation between serum level of IL-6 and the development of cachexia in Hepatocellular carcinoma patients and we found that level of IL-6 was significantly higher in the cachectic group of patients compared to non-cachectic group with significant p value.

The evidence connecting between the level of IL-6 and the development of cachexia had been studied in many malignancies but the relation with hepatocellular carcinoma has not been studied on such number to our knowledge.

Martignoni and colleagues [23] reported that the serum IL-6 levels were significantly higher in pancreatic cancer patients with cachexia compared with the non-cachectic group.

Iwase S et al. measured the blood level of IL-6 in 28 patients with possible cachexia induced by various types of malignancy and reported that with a mean level of IL-6 concentration of 100 pg/mL there was an average period of 8 days before death and the concentration of IL-6 was seen to rise gradually during the early stages of cachexia group of patients followed by an intense increase in the days before death [24] This observation may point to the prognostic role of IL 6 in cancer patients with cachexia.

On the other hand Maltoniand and colleagues analyzed the relationship between the concentration of IL-6 and possible cachexia of various tumours found that no association can be detected between increase level of IL-6 and cachexia at least in its early stage yet this study was conducted on 61 patients with advanced malignancies that are no more suitable for treatment, most of the studied pool have lung and stomach cancer (21% & 18%) [25]

Positive correlation between level of IL-6 and serum level of AFP in the light of this observation we can support the role of IL-6 as a surrogate marker for screening or diagnosis of HCC suggested by **Porta** and his group [26] in comparing 3 groups of patients each with 30 patients (HCC, cirrhotic patients and healthy individuals) They found that significantly higher level of IL-6 in patients with HCC patients than in both cirrhotic and controls with a median of 22,5.4,0.89 respectively with even higher levels in more advanced disease (CLIP score >3, or with extra hepatic metastases versus CLIP score 1–3 (P = 0.003). [26]

Interestingly in our study patients with cachexia show significantly higher mean CRP serum level than those without cachexia, but the ranges were largely overlapped in both groups. These overlapping values may limit its role in cachexia detection.

Although CRP level was high lightened by Zhang D and his group as a marker for cachexia in patients with pancreatic malignancy [27] but more sensitivity and specify is addressed for IL-6 over CRP as a marker for cachexia.

Future consideration of serum Il-6 as a prognostic marker of cirrhosis related hepatocellular carcinoma and cachexia related syndrome targeting IL-6 receptor could be a revolution not only in treatment cancer related cachexia that affect patients survival but also as a treatment target for HCC by itself this may need further studies.

To summarize, the present study indicates that IL-6 as a marker is increased in cachexia in patients with HCV related hepatocellular carcinoma. Further studies on a large number of population and with different etiologies o cirrhosis are needed IL-6 to validate as a marker for cachexia and implication of it on the need for nutritional support.

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