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Original article

Serum visfatin level as a prognostic marker in colorectal cancer patients: A retrospective cohort study

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Abstract

Background: Colorectal cancer is the third common cancer in women and the fourth one among men, worldwide. Identifying prognostic factors are among the current challenges in cancer management. There are some evidence that visfatin, an adipocyte-secreted peptide, plays a significant role in cancer progression, proliferation, angiogenesis, metastasis, and drug resistance. In this study, we examined the serum concentration of visfatin and its impact on colorectal cancer prognosis.

Methods: Sixty-nine colorectal patients who had been followed up for two years at Razavi Hospital, Mashhad, Iran were evaluated. Information regarding the patients' cancer status, including primary tumor location, tumor size, histology, tumor differentiation, stage of TNM, metastasis or lymphatic invasion, treatment options over the past two years, as well as the disease status, including recurrences and survival, was collected. An ELISA kit was used to measure serum visfatin concentrations and the relationship between serum visfatin concentrations and the prognosis of colorectal cancer was examined using SPSS software.

Results: Visfatin played a small role in death, metastasis, and recurrence of colorectal cancer. Additionally, Cox regression analysis revealed no significant relationship between death, metastasis and recurrence rate and visfatin concentration ($p>0.05$). Additionally, no significant difference in visfatin concentration was found between two genders.

Conclusion: The results of this study showed that according to survival analysis and Cox regression, there was no significant association between serum concentration of visfatin and death, metastasis, or recurrence in colorectal cancer.So, visfatin does not seem a good biomarker for colorectal cancer prognosis prediction. Further studies are recommended.

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1. Introduction

With 945,000 new cases and 492,000 deaths annually, colorectal cancer is the third most common cancer diagnosed worldwide (1). It is estimated that there will be more than 2.2 million new cases of colorectal cancer and 1.1 million deaths by 2030 (2, 3). Cancer is the second most common chronic non-contagious disease in Iran and the third leading cause of death after ischemic heart disease and accidents (4). Cancer mortality rates in Iran are predicted to be 65 and 41.1 per 100,000 among men and women, respectively. Women have an age-specific incidence rate (ASIR) of 110 per 100,000, whereas men have an ASIR of 98.

There is some evidence that hyperinsulinemia and insulin resistance contribute to the pathogenesis of colon cancer. A number of studies have demonstrated that individuals who are obese or overweight are more likely to develop colorectal adenoma and colorectal cancer (5). Accordingly, diet-based weight loss in obese people reduces colorectal inflammation and effectively down-regulates proinflammatory and carcinogenic genes (6). The exact mechanism, however, remains unknown. The presence of visceral or central obesity is particularly associated with insulin resistance, hyperglycemia, hyperinsulinemia, dyslipidemia, hypertension, and prothrombotic and proinflammatory markers production (7). White adipose tissue is now considered an endocrine gland that triggers obesity (8).

Leptin, adiponectin, vascular endothelial growth factor (VEGF), and visfatin are adipokines that play an essential role in various biological processes including cell differentiation and proliferation, apoptosis, and angiogenesis. Local biological effects of adipokines are mediated by autocrine/paracrine or endocrinological mechanisms such as systemic blood flow and activation of receptors within target cells (9).

Several studies have shown that visceral fat levels are closely correlated with serum visfatin levels (9). According to various studies, elevated levels of visfatin have been associated with the progression of gastric cancer, colorectal carcinoma, and other types of cancer (10). There is a relationship between high levels of visfatin in breast cancer and tumor stage, lymph node involvement, and metastasis of the disease (11). Furthermore, serum visfatin levels are directly correlated with inflammation and lymph node metastasis in colorectal cancer (12). It is mainly secreted by adipocytes and inflammatory cells (such as activated macrophages) as well as hepatocytes (13, 14).

Initially, visfatin was identified as an insulin mimic that is released from visceral adipose tissue (15) and was considered as a stimulant of B cell colony precursor (16). It is believed that visfatin acts as a proinflammatory cytokine that can promote the production of other cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. Several metabolic disorders, including obesity, metabolic syndrome, and diabetes, have been linked to increased blood visfatin levels (6). Visfatin is known to bind to different binding sites on the insulin receptor, exerting insulin mimic effects, such as increasing glucose uptake and metabolism in myocytes and adipocytes, and inhibiting gluconeogenesis. These functions of visfatin lead to hypoglycemia (1).

Moreover, visfatin increases G1-S phase of the cell cycle (17). According to studies, visfatin also stimulates the expression of matrix metalloproteinase (MMP) 2, 9 and VEGF mRNA, which may contribute to cancer angiogenesis and metastasis (1).

The use of serum tumor markers can provide a non-invasive and simple method for diagnosis of cancer as well as for prognosis and patient outcome assessment. Based on the results of previous studies and the reported relationship between the expression of the aforementioned biomarkers and the prognosis of colorectal cancer, we aimed to evaluate serum visfatin level as a biomarker of colorectal cancer to predict the prognosis and survival of these patients.

2. Methods

2.1. Study population

A retrospective cohort study was conducted at Razavi Hospital in Mashhad, Iran between July 2018 and September 2019 on 69 patients with primary colorectal cancer. Inclusion criteria involved A) Early histopathological diagnosis of colorectal cancer B) age between 18 and 65 years C) completing the consent form for participating in the project. Exclusion criteria included A) metastatic disease at the time of diagnosis, B) history of malignancy or colorectal surgery, C) history of inflammatory bowel disease, D) history of collagen and vascular diseases, E) kidney or liver failure. These patients were followed up to four years. Baseline demographics (including gender, age, and family history of cancer), periodic lab tests (including a lipid profile and fasting blood sugar), blood pressure, and underlying disease were recorded for each patient. Additionally, data about the patient's cancer status, such as the primary tumor

location, tumor size, histopathology, tumor differentiation, TNM staging, as well as a treatment modality (surgery, chemotherapy) were also taken into account. During these 2 years patients' survival, tumor metastasis and recurrence rate were assessed.

2.2. Serum Visfatin measurement

Ten milliliters of patients' whole blood was collected from brachial vein, transferred to the Razavi hospital laboratory and centrifuged at 1000 rpm for 10 min. In order to determine visfatin concentration, the isolated serum was immediately transferred to the freezer at -80°C. An ELISA RAB 0377 kit was used to measure the serum concentration of visfatin.

2.3. Statistical analysis

Statistical analysis was carried out by SPSS 19, Results have been shown as mean ±standard deviation or median (interquartile range) for normally and non-normally distributed continuous variables respectively, and number (percentages) for nominal variables. A Kolmogorov-Smirnov test was used to evaluate the normality of the data distribution. Independent sample t-test and Mann–Whitney U-test were used respectively to compare normally and non-normally distributed variables between the two groups. For comparison of more than two groups in normally and non-normally distributed variable one way ANOVA and Kruskal–Wallis tests were used respectively. Besides, the Pearson correlation test (in the case of normal distribution) and Spearman's correlation test (in the case of non-normal distribution) were employed to examine the intensity and correlation between the two quantitative variables. A P-value of less than 0.05 was considered statistically significant in all cases.

3. Results

3.1. Patients' characteristics

This retrospective cohort study was performed on 69 patients with colorectal cancer who met the inclusion criteria. The average age of patients was 65 + 12.75 years old, and 42% of them being female. Twelve patients passed away during the study. After chemotherapy, 94% of patients were recurrence-free, but 11% developed metastases (**Table 1**).

3.2. Gender-based patient profile comparison

According to the data in **Table 2**, the mean age of females in the study was 65.07±11.8 and the mean age of males was 63.47±13.65 years. There was no significant difference in age between male and females (p =0.85). CEA concentration was 5.38. 4.28 in males and 0.99 3 3.67 in females. There was no significant difference between CEA concentration (pg / ml) (p =0.67). The visfatin concentration was 22.6 24 24.92 pg / ml in males and 24.88 33 33.8 pg / ml in females. There was no significant difference in the visfatin concentration (p= 0.13).

During the course of the study, two female patients and ten male patients died. The survival rate was not significantly different between males and females (p=0.054). Metastases developed in six female patients and two male patients. Results showed a significant difference between males and females (p=0.047).

Death, metastasis and recurrence relative risk association with serum visfatin concentration (**Table 3**)

The relative risks of death, metastasis, and recurrence based on serum visfatin concentrations are presented in **Table 6**. In the Wald test, visfatin=1.648 pg/ml was associated with death, 0.015 pg/ml with metastasis, and 0.489 pg/ml with recurrence. In this study, visfatin played an insignificant role in death, metastasis, and recurrence incidence. Additionally, Cox regression

Table 1. Demographic data of studied patients

Age (Year)		65.4±12.75
Gender (No., %)	Male	40 (58%)
	Female	29 (42%)
Survival		57 (82.6%)
Recurrence (No., %)		3 (5.7%)
Metastasis (No, %)		8 (11.3%)

Table 1. Comparison of patients' characteristics between genders

		Male	Female	P-Value
Age		63.65±13.47	65.07±11.88	0.85
CEA* (Mg/ml)		28/4 ±38/5	3.67±0.99	0.67
VISFATIN (Pg/ml)		24.92±22.6	33.8±24.88	0.13
Survival**	Survived	30 (75.0%)	26 (92.9%)	0.057
	Expired	10 (25.0%)	2 (7.1%)	
Metastasis**	Free	38 (95%)	22 (78.6%)	0.047
	Metastatic	2 (5%)	6 (21.4%)	

* T student analysis was performed
* * Chi-square analysis was performed

Table 3. Relative Risk of Death, Metastasis and Recurrence in association with Visfatin Serum Concentration in Patients with Colorectal Cancer during Four-Year Follow-up.

	OR (CI, 95%	Wald	p-value*
Death	0.979 (0.948-1.011)	1.648	0.199
Metastasis	0.996 (0.970-1.024)	0.015	0.799
Recurrence	1.014 (0.975-1.055)	0.489	0.484

* Cox-regression analysis was performed

analysis showed no significant relationship between visfatin concentration and death, metastasis, or recurrence (p>0.05).

Accordingly, the concentration of visfatin was divided into 33% and 66% percentiles, and the relative risk of death was calculated based on these percentiles. Moreover, there was no significant relationship between the incidence of death and the concentration of visfatin in the 33% and 66% percentiles (p> 0.05) (**Table 4**).

Table 4. Relative Risk of mortality in Patients with Colorectal Cancer during two-Year Follow-up.

	Tertile	Wald	p-value*
Visfatin	Reference (<13/15)		
13/15-84/30	641/2 (507/0-75/13)	33/1	24/0
>84/30	524/0 (043/0-78/5)	278/0	59/0

* Cox-regression analysis was performed

The Cox regression analysis revealed no significant relationship between metastasis incidence and visfatin concentration in the 33% and 66% percentiles (p> 0.05) (**Table 5**).

Table 5. Relative Risk of Metastasis in Patients with Colorectal Cancer during two-Year Follow-up

	Tertile	Wald	p-value*
Visfatin	Reference (<13/15)		
13/15-84/30	0	001/0	974/0
>84/30	847/0 (117/0-148/6)	203/2	138/0

* Cox-regression analysis was performed

Based on Cox regression analysis, the incidence of recurrence did not significantly correlate with visfatin concentration between the 33% and 66% percentiles (p>0.05) (**Table 6**).

Table 6. Relative Risk of Recurrence in Patients with Colon Cancer during Four-Year Follow-up

	Tertile	Wald	p-value*
Visfatin	Reference (<13/15)		
13/15-84/30	625/0 (147/0-248/2)	507/0	47/0
>84/30	327/0 065/0-63/1)	85/1	138/0

* Cox-regression analysis was performed

4. Discussion

The results of this study showed that according to survival analysis and Cox regression, there was no significant association between serum concentration of visfatin and death, metastasis, or recurrence in colorectal cancer. Visfatin plays a significant role in cancer progression, proliferation, angiogenesis, metastasis, and drug resistance, according to a review study in 2019 by Lin et. al (18). Researchers have found higher levels of serum visfatin in colorectal cancer patients in studies by Fazeli et al. and Nakajima et al. According to Nakajima, adipokines may play a role in carcinogenesis and the progression of colorectal cancer. Adiponectin, leptin, resistin, visfatin, and peptide C levels were measured in 115 patients with colorectal cancer. Multivariate analysis revealed that cancer patients had significantly higher levels of resistin and visfatin than controls. Disease progression is significantly associated with resistin and visfatin levels. Consequently, resistin and visfatin have been identified as potential biomarkers for the progression of malignant colorectal cancer (19, 20). However, Slomian et al. in their study, found lower levels of serum visfatin in patients with colorectal cancer who are receiving chemotherapy and developing relative responses. They pointed out that visfatin is considered as a biomarker of colorectal malignancies and tumor progression. Visfatin levels, however, remained constant in patients who experienced cancer progression (6), which is consistent with the results of our study. So, the findings of available studies on correlation of visfatin serum level and cancer progression, metastasis and recurrence are very controversial. Based on a 2010 study by Kim et al., visfatin regulates cell proliferation in the MCF-7 cell line and increases DNA replication and synthesis when administered exogenously. Moreover, visfatin increased the expression of MMP-2,9 and VEGF genes, which are

involved in angiogenesis and metastasis in breast cancer cells. It seems that visfatin contributes to the progression of breast cancer, according to this study (17).

Another study by Lee et al. in 2011 found that visfatin expression was significantly associated with tumor size, estrogen, and progesterone receptor negativity in breast cancer tissues. In patients with high levels of visfatin, hormone therapy has reduced the recurrence of the disease, but not radiotherapy. Overall survival and disease-free duration have been associated with higher levels of visfatin alone. Estrogen receptor, progesterone receptor negative patients with elevated visfatin expression also had a worse prognosis (21).

A 2013 study by Tian et al. found that serum visfatin levels were markedly higher among 234 patients with endometrial cancer. A positive correlation was observed between endometrial cancer and serum visfatin level, BMI, waist-to-pelvic ratio, diabetes, and hypertension in the logistic model of the univariate and multivariate regression. Endometrial cancer tissue expressed significantly more visfatin than healthy tissue. Endometrial cancer tissue with high expression of visfatin has been associated with myometrial invasion and advanced FIGO stages. Overall survival was significantly greater in the group with negative visfatin expression (22).

In another study, Ghaemmaghami et al. examined the expression of the visfatin and resistin genes in the HCT-16 Colorectal Cancer Cell Line in 2013. The aim of the study was to show whether colorectal cancer cells themselves are the source of secretion of these two adipokines. Visfatin expression was found to increase at both mRNA and HCT-116 protein levels. It appears that the visfatin gene is endogenously expressed and secreted by HCT-116 cells. Thus, visfatin acts as an endocrine hormone in colorectal cancer and as a carcinogen can increase cancer cell survival (23).

Neubauer et al. examined the correlation between visfatin gene expression and metastasis in colorectal tumors and blood as well as hypoxia and anemia. Compared to non-cancerous tissues, cancerous tissues express visfatin gene at higher levels, and with progression of cancer, the expression level increases (24). This is in accordance with the findings of the present study. Lv et al. examined the regulatory effects of visfatin on tumor progression and bioavailability of colorectal cancer cells in humans and concluded that visfatin has an important role in colorectal tumorogenesis and can be targeted for the treatment of colorectal cancer (25). A study conducted by Lu et al. examined the correlation between plasma visfatin levels and gastric cancer. A higher plasma visfatin level was associated with more tumor penetration, intraperitoneal metastases, and larger tumors, the researchers concluded (26).

Based on the aforementioned studies, the higher the level of visfatin is related to the greater the risk of metastasis and recurrence. According to Yang et al., recent studies have indicated that visfatin promotes the development of various cancers through proliferation, migration, invasion, and angiogenesis. As well, patients with colorectal cancer who have elevated serum levels of visfatin have a poor prognosis (27). The present study, however, found no significant correlation between serum visfatin levels and metastasis and recurrence likelihood. According to Nakajima et al., this discrepancy might be caused by a lack of sufficient information about patients' weight changes during the study (20).

There is a considerable concentration of visfatin in visceral adipose tissue. As a result, variations in body weight can affect serum visfatin levels. It was found that visfatin levels and BMI were positively correlated (19). In various studies high body mass index (BMI) and serum visfatin levels have been linked (28, 29). A meta-analysis by Yang and colleagues suggests that visfatin, a factor secreted by adipocytes, may play an important role in obesity and colorectal cancer (30).

According to our findings, visfatin concentrations did not differ significantly between genders. It is in accordance with a study carried out by Fazeli et al. on colorectal adenomas. In a study conducted in 2016, 34 patients with colorectal adenoma and 35 patients as a control group were included. According to the results, visfatin levels were not significantly different between two genders (20). So in conclusion, since visfatin, as a factor secreted from fat cells, is directly related to the weight of patients and their body mass index; It is recommended to check the weight of patients regularly during the study in order to minimize the bias caused by weight changes. Also, increasing the sample size and multicenter examination of patients can minimize the error caused by these variables.

5. Conclusion

As a result of the study, visfatin concentrations were not significantly different between the two genders.

Vifatin concentrations do not appear to be associated with death, metastasis, or recurrence of colorectal cancer. Studies with larger sample size and with considering all characteristics of patients that may be involved in the prognosis of cancer are recommended for better conclusion.

Conflict of Interests

There was no conflict of interest in this study.

Ethical Approval

This research was reviewed and approved by local Ethics Committee of Mashhad University of Medical Sciences (code: IR.MUMS.REC.1396.527).

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