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Elevated IL-37 Serum Levels in Patients With Transitional Cell Carcinoma of Bladder

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ABSTRACT

Background: Interleukin-37 (IL-37) is a recently described cytokine that emerges as a natural inhibitor of inflammatory and immune responses. However, IL-37 has not yet been investigated in bladder cancer, and its biological role is unknown.

Objective: The purpose of this study was to investigate IL-37 serum levels in patients with bladder cancer and determine whether they were linked to the patients' pathological characteristics.

Methods: IL-37 serum levels were measured using a commercial ELISA kit in 60 patients with transitional cell carcinoma (TCC) of the bladder (mean age: 64.55±12.93) and 50 healthy controls (mean age: 62.94±12.69). Non-parametric tests were used for statistical comparisons, and the Cohen's d effect size was calculated to evaluate the practical and clinical significance of the results.

Results: Our findings indicated an increasing trend in IL-37 serum levels in patients with TCC (42.77±3.36 pg/ml) in comparison with controls (40.51±7.32 pg/ml, P=0.09). However, IL-37 serum levels were found to be significantly higher in male patients (44.72±3.81 pg/ml) and patients aged ≥70 (46.92±6.77 pg/ml) in comparison with male controls (29.96±3.30 pg/ml, P=0.026) and controls aged ≥70 (23.62±4.43 pg/ml, P=0.009). In comparison to similar controls, Cohen's d effect size for patients aged ≥70 years was found to be 0.90.

Conclusion: The findings reveal a higher serum level of IL-37 in patients with TCC, which might be clinically associated with immunosuppression and tumor growth. However, this is a preliminary study, and more research on the biological role of IL-37 and its potential therapeutic effects in bladder cancer is required.

Keywords: Bladder cancer, Interleukin-37 (IL-37), Serum

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INTRODUCTION

Bladder cancer is a relatively prevalent and life-threatening neoplasm of the urinary system. Bladder cancer is a disease that primarily affects the elderly, and it is approximately 3-4 times more likely in men than women (1, 2). Urothelial carcinoma (also named transitional cell carcinoma (TCC)) is the most prevalent type of bladder cancer tumor, and its frequent recurrences, as well as challenges in early detection and efficient treatment, are the most complication for management of this malignancy (3). Despite significant advancements that have been made in understanding the biology of bladder cancer, there is still an interest to investigate immune system components and their therapeutic roles in this disease (4-6). Bladder cancer is known as an immunogenic cancer that benefits from immunotherapy (7). In this regard, application of Bacillus Calmette-Guérin (BCG) alone or in combination with cytokines, such as Interferon-gamma (IFNγ) recombinant or Interleukin-10 (IL-10) blockade, is one of the most successful methods of immunotherapy that improves clinical outcome of patients with bladder cancer (8). The bladder tumor microenvironment has been reported to be rich in inflammatory/anti-inflammatory cytokines that can affect tumor growth and recurrence in bladder cancer patients (5, 9). Cytokine dysregulation has been reported in many different types of human malignancies, and evidence of human research suggests that T helper type 1 (Th1) inhibitory cytokines, as well as immune cells with immunosuppressive phenotypes such as regulatory T cells (Tregs), are dominant in bladder cancer (6, 10, 11). Interleukin (IL)-37 is a newly described cytokine classified in the IL-1 family, which has recently received growing attention in the field of cancer research (12). IL-37 acts as an important inhibitor of innate and adaptive immunity and inflammatory responses. The anti-inflammatory activity of IL-37 is primarily mediated by the inhibition of an inflammatory cytokine called interleukin 18 (IL18), which is involved in innate and acquired immunity (13, 14). IL-37 is expressed in various tissues including synovial tissue macrophages cells, plasma cells, tonsillar B cells, as well as epithelial cells of the kidney, skin, and intestine (15). IL-37 is also expressed in tumor cells and affects not only the anti-inflammatory responses, but also could perform immunosuppressive or protective roles, as reported in melanoma, or was shown in hepatocellular carcinoma, renal cell carcinoma, and colon cancer (16-20). Accordingly, IL-37 can be an important candidate to be used as a novel therapeutic tool in patients with cancer (12). However, in experimental and clinical studies, determining the exact role of IL-37 in cancer protection and/or cancer development remains a major challenge. Due to the novelty of this cytokine, very few studies have investigated IL-37 serum levels in immune-related diseases, especially in cancer. IL-37 serum level was reported to be reduced in multiple myeloma (MM) and renal cell carcinoma (RCC), whereas it was higher in epithelial ovarian cancer (18, 21, 22). Interestingly, in ovarian cancer, this increase was found to be associated with tumor progression (21). However, the role of IL-37 in the TCC of the bladder has not yet been investigated. This study aimed to investigate the level of IL-37 in serum and determine its relationship with the pathological characteristic of the patients.

MATERIALS AND METHODS

Patients and Controls

This case-control study comprised 60 patients with newly diagnosed bladder cancer (51 males and 9 females, mean age 64.55±12.93, ranging from 34 to 91years) and 50 healthy individuals as the control group (32 males and 18 females, mean age 62.94±12.69, ranging from 34 to 91years). The patients' specimens were obtained prior to any medical treatment such as surgery, chemotherapy, or radiotherapy from Namazi and Ali Asghar Hospitals, both affiliated with Shiraz University of Medical Sciences, Shiraz,

Iran. The most important inclusion criteria for the patients was confirmation of the disease by both the clinician and the pathologist. Exclusion criteria for the patients included a history of another malignancy, autoimmunity, immune deficiencies, prior surgery as well as evidence of infectious diseases during the previous month. All of the patients had transitional cell carcinoma (TCC), as shown in Table 1, and the majority of them were men. Twelve (20%), 13 (21.67%), and 35 (58.33%) patients were in grades II, III, and IV, respectively. Perineural invasion (PNI) and Lymphovascular invasion (LVI) were seen in 16 (26.67) and 9 (15%) of the cases, respectively. The patients' pathological characterization are summarized in Table 1. The control group consisted of healthy volunteers with no family history of malignancy, autoimmune disease, recent infectious diseases (one-month interval). There was no statistically significant difference between the patients' age in both groups ($P>0.05$). After receiving written informed consent from all the subjects, 5ml fast blood venous was collected from them. The study was approved by the Ethics local committee at Shiraz University of Medical Sciences, Shiraz, Iran (IR.sums.med.rec.1397.539).

Cytokine Measurements

The blood samples were centrifuged at 2500 × g for 10 minutes at 4°C to separate serum, which was then aliquoted and stored at -80°C for further analysis. A commercial human IL-37 enzyme-linked immunosorbent assay (ELISA) kit (SHANGHAICRYSTAL DAY BIOTECH CO., LTD) was used to detect IL-37 in the serum. The ELISA kit had an assay range of 7 pg/mL to 400 pg/ml with a sensitivity of 4.5 pg/ml. Since the IL-37 levels in five patients with TCC of bladder and seven healthy controls were less than the kit's sensitivity, they were excluded from the statistical analysis.

Statistical Analysis

The SPSS software package was used for all statistical analyses (version 11.5; SPSS Inc, Chicago, IL, USA). The normality of data was checked using the Kolmogorov–Smirnov test in both the patient ($P=0.026$) and control ($P=0.001$) groups. Non-parametric tests, such as Kruskal–Wallis H and Mann–Whitney U, were used to make statistical comparisons. The Non-parametric Spearman rank correlation was also used to determine the relationship between IL-37 and age. Values in the text were expressed as mean±standard

Table 1. The pathological characterization of patients with bladder cancer

Parameters	Categories	Frequency	Percent
Gender	Male	51	85
	Female	9	15
Tumor type	Transitional cell carcinoma (TCC)	60	100
Grade	II	12	20
	III	13	21.67
	IV	35	58.33
Peri Neural Invasion	Seen	16	26.67
	Not Seen	44	73.33
Lympho Vascular Invasion	Seen	9	15
	Not Seen	51	85
Lamina Propria invasion	Seen	40	66.67
	Not Seen	20	33.33
Muscularis propria invasion	Seen	30	50
	Not Seen	30	50
Carcinoma Invasion'	Seen	4	6.67
	Not Seen	56	93.33
Tumor necrosis	Seen	10	16.67
	Not Seen	50	83.33

error of the mean (SEM), and P values less than 0.05 were considered statistically significant. Additionally, Cohen's d effect size was calculated to quantify the practical and clinical significance of the results.

RESULTS

Comparison of IL-37 Serum Levels Between Cancer Patients and Healthy Control Group

The sandwich ELISA method was used to determine the serum levels of IL-37. An increasing tendency in IL-37 serum levels were found in patients with TCC (42.77±3.36 pg/ml) in comparison to controls (40.51±7.32 pg/ml, P=0.09). Moreover, when compared to male control subjects (29.96±3.30 pg/ml), male patients with TCC indicated a significant increase in IL-37 serum level (44.72±3.81 pg/ml, P=0.026). The Cohen's d effect size for this comparison was observed to be 0.67. Although men had greater serum levels of IL-37 than women, the difference was not

Table 2. IL-37 serum levels in patients with transitional cell carcinoma (TCC) of bladder and control group and their association with patients' pathological characterization

		N	IL-37 serum levels (pg/ml)				P value
			Mean±SEM	Median	Min	Max	
Main groups	Total patients	55	42.77±3.36	37.65	9.94	121.98	0.09
	Total controls	43	40.51±7.32	27.76	5.73	297.80	
Sex	Male patients	47	44.72±3.81	41.94	9.94	121.98	0.18
	Female patients	8	31.27±2.42	31.15	21.61	41.47	
	Male patients	47	44.72±3.81	41.94	9.94	121.98	0.026
	Male controls	25	29.96±3.30	27.53	5.73	60.54	
	Female patients	8	31.27±2.42	31.15	21.61	41.47	0.76
	Female controls	18	55.16±16.54	29.05	15.01	297.80	
Age	Patients with≧70	20	46.92±6.77	31.03	13.21	121.98	0.009
	Controls with≧70	12	23.62±4.43	22.28	5.73	53.69	
	Male Patients with≧70	17	50.34±7.69	43.18	13.21	121.98	0.013
	Male controls with≧70	10	24.15±5.27	22.28	5.73	53.69	
	Male Patients with <70	30	41.54±4.09	41.86	9.94	105.78	0.44
	Male controls with <70	15	33.83±4.06	29.32	6.66	60.54	
	Patients with <70	35	40.39±3.56	39.91	9.94	105.78	0.65
	Controls with <70	31	47.04±9.81	30.33	6.66	297.80	
	Patients with≧70	20	46.92±6.77	31.03	13.21	121.98	0.68
	Patients with <70	35	40.39±3.56	39.91	9.94	105.78	
Histologically grade	Grade II	12	43.23±7.05	36.75	21.61	96.75	0.40
	Grade III	12	44.06±6.97	40.92	19.98	105.78	
	Grade IV	31	42.09±4.64	37.65	9.94	121.98	
Perineural invasion (PNI) status	Seen	14	49.50±6.59	42.67	24.42	103.53	0.09
	Not seen	41	40.47±3.84	31.27	9.94	121.98	
Lymphovascular invasion	Seen	8	45.35±6.87	42.83	22.63	83.36	0.39
	Not seen	47	42.33±3.74	36.12	9.94	121.98	
Lamina propria invasion	Seen	36	43.27±4.03	41.70	9.94	121.98	0.49
	Not seen	19	41.82±6.06	36.12	13.21	105.78	
Muscularis propria invasion	Seen	27	44.42±4.88	42.10	9.94	121.98	0.36
	Not seen	28	41.18±4.62	33.46	13.21	105.78	
Tumor necrosis	Seen	8	43.75±8.95	36.25	26.05	103.53	0.78
	Not seen	47	42.60±3.63	37.65	9.94	121.98	

P values less than 0.05 are considered as significant level. IL-37 levels in five patients with TCC of bladder and seven healthy controls were less than the sensitivity of the kit. So, they were excluded from the statistical analysis. Values are mean± SEM.

statistically significant (44.72±3.81 pg/ml vs. 31.27±2.42 pg/ml, P=0.18) (See Table 2 and Figure 1).

Association and Correlation of IL-37 Serum Levels with Age in Case and Control

To investigate the association of IL-37 level with patients' age, patients with TCC were divided into two different age groups (≥70 years and <70 years). 22 (36.7%) aged ≥70, and 38 (63.7%) aged <70 years. IL-37 serum levels showed a non-significant increase in patients ≥70 years old (46.92±6.77 pg/ml) in comparison to patients <70 years old (40.39±3.56 pg/ml, P=0.68). However, IL-37 serum levels were significantly higher in patients ≥70 years of age (46.92±6.77 pg/ml) than control subjects aged ≥70 (23.62±4.43 pg/ml, P=0.009). The Cohen's d effect size for this comparison was found to be 0.90. The data are summarized in Table 2 and Figure 1.

To further explore the correlation between these cytokines and the participants' age, spearman's rank correlation analysis was used. Regardless of age differences (≥70 and <70 years), the result revealed a reverse significant correlation between the IL-37 serum levels and the age of healthy participants in the control group (n=43, R=-0.336, P=0.028). However, no significant correlation was found between the IL-37 serum levels and the age of patients with the TCC (n=55, R=-0.009, P=0.68).

The Association between IL-37 serum Levels and Pathological Characterization of Patients

IL-37 serum levels in patients with grade II, grade III, and grade IV was 43.23±7.05 pg/ml, 44.06±6.97 pg/ml, and 42.09±4.64 pg/ml, respectively. However, the statistical analysis indicated no significant difference in IL-37 serum levels between different grades. As shown in Table 2 and Figure 1, patients with PNI had a non-significant trend of higher IL-37 serum levels (49.50±6.59 pg/ml) than those without it (40.47±3.84 pg/ml, P=0.09). Similarly, patients with PNI and aged ≥70, had a nearly significant higher level of IL-37 (67.75±10.76 pg/ml) than those without it (41.72±7.60 pg/ml, P=0.06, date not shown). Moreover, there was no significant difference in IL-37 serum levels between patients regarding lymphovascular invasion, lamina propria invasion, muscularis propria invasion, and tumor necrosis.

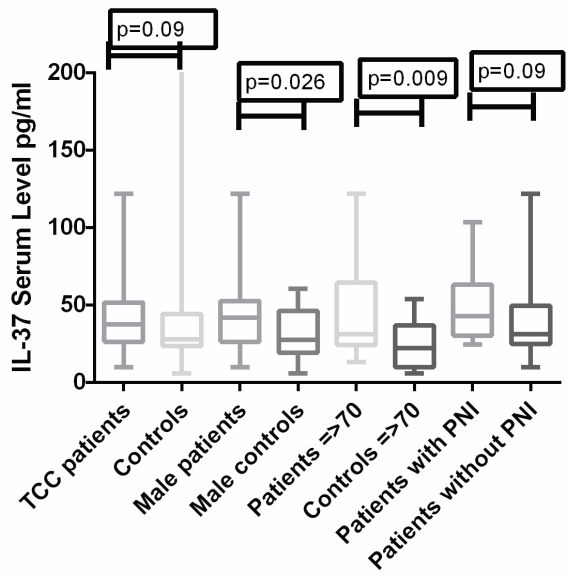

Figure 1. IL-37 serum levels in patients with transitional cell carcinoma (TCC) of the bladder. A trend toward a higher significant increase of IL-37 serum levels were found between TCC patients and healthy subjects, and between patients with PNI and those without PNI. IL-37 serum levels were observed to be significantly increased in male patients with TCC and patients ≥70 years in comparison to related controls. Values were expressed as the median interquartile range (IQR).

DISCUSSION

In our case-control study, we compared IL-37 serum levels between patients with TCC of bladder and healthy controls and then investigated their association with the patients' pathological characterization. Our revealed a trend toward higher significant increase of IL-37 serum levels in TCC patients compared to healthy subjects. As the males in the two groups were compared, the results showed a significant increase in IL-37 serum levels in the male patients compared to the male control subjects. In a recent study, IL-37

serum level was reported to be increased in epithelial ovarian cancer patients, and this was found to be associated with an unfavorable prognosis as well as tumor progression (21). Interestingly, in our study, patients with PNI had a non-significant trend of higher serum IL-37 levels than those without it. PNI is known as the neoplastic invasion of nerves, and broadly associated with a poor prognosis, as well as adverse pathological behaviors in many different types of malignancies (23). Immune system suppression is one of the most important hallmarks of cancer that is frequently reported in different types of malignancies, particularly bladder cancer, and leads to tumor escape and cancer development (7). It has been reported that human bladder cancer is a T regulatory type 1 (Tr1) dominant cancer with Tregs infiltration and inhibitory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) (10). IL-37, a newly described member of the Interleukin-1 (IL-1) family, has a significant suppressive effect on both innate and adaptive responses through the inhibition of IL-18 activity (24-26). Recently, some evidence has demonstrated that IL-37 can be expressed on human CD4+CD25+Tregs which contributes to the immunosuppressive properties of these cells (27). Increased expression of IL-37 in the blood of patients with melanoma and its association with enhanced suppressive activity of Tregs suggested that this cytokine may play an immunosuppressive role in cancer (20). Moreover, IL-37b can down-regulate the expression level of co-stimulatory molecules (CD80 and CD86) as well as the expression of pro-inflammatory cytokines (tumor necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6) in dendritic cells (DCs), which are related to immune response suppression (24). Our findings suggest that increased levels of IL-37 in serum of patients with TCC may exert a suppressive role in anti-tumor responses, and leads to tumor progression, probably through its positive effect on Tregs activation and DCs suppression. However, only a few studies have explored IL-37 in patients with cancer, and its biological role in bladder cancer is still unknown.

The results of our study appear to be in contrast to those reported in MM and RCC. In these cancers, the IL-37 serum levels were observed to be reduced. In RCC, a reduced levels of IL-37 was negatively associated with cancer progression (18, 22). It has been reported that IL-37b, at least in part, potentially inhibits hepatocellular carcinoma growth by interacting with the Smad3 signaling pathway (19). Consistent with these findings, IL-37 suppresses the tumor progression in RCC and colon cancer through inhibiting IL-6/STAT3 signaling and β-catenin, respectively (17, 18). Although contradictory results might be due to the different cancer types as well as the variety of tumor microenvironments, such controversies should be further investigated in various cancers to exactly define the pro-tumor or anti-tumor function of IL-37.

Furthermore, since the median age of patients with bladder cancer at the time of diagnosis is mostly 69 years for men and 71 years for women (28), the comparison was also made with respect to an age cut-off point of <70 years versus ≥70 years. Our findings showed a non-significant increase in the patients aged ≥70 years than patients aged <70 years. However, IL-37 serum levels were found to be significantly higher in serum of the patients aged ≥70 years in comparison with healthy individuals aged ≥70 years in the control group. Additionally, in TCC patients aged ≥70 years, an increasing trend of IL-37 levels in serum was observed in patients with PNI versus those without it. Bladder cancer is the best example of age-associated malignancy, whose prevalence is increasing in the elderly population. It has long been recognized that age is the greatest single risk factor for bladder cancer development and that the risk of the disease increases with age (2, 28, 29). Accordingly, the disease severity and clinical outcomes worsen in the elderly patients (2, 28, 29). An elevated levels of IL-37 in the serum of patients with TCC aged 70 years and older may be one of the age-related

physiological changes that occur in bladder cancer patients. Higher levels of this cytokine in patients aged ≥70 years may be associated with more severe illness conditions, which are more frequent in the elderly.

Then, regardless of sample size, we calculated the Cohen's d effect size to see whether the results were practical or clinically significant. Our result showed that the Cohen's d effect size for the comparison of patients and controls aged ≥70 years was 0.90. It has been shown that magnitude of Cohen's d effect size <0.2, 0.2-0.49, 0.5-0.79, and >0.8 are considered as negligible, small, moderate, and large, respectively (30). Our findings imply that IL-37 may be clinically important in bladder cancer outcomes, particularly in those aged ≥70, based on the large effect size (>0.8). Furthermore, according to our findings, there was no significant relationship between IL-37 serum levels and other pathological characterization such as histological grades, lymphovascular invasion, lamina propria invasion, muscularis propria invasion, and tumor necrosis. In RCC patients, IL-37 expression was found to be negatively correlated with tumor size and stage (18). In patients with epithelial ovarian cancer, an increased levels of IL-37 in serum was found to be significantly associated with disease stage, lymph node metastasis, positive recurrence, and residual tumor size (21). The discrepancies in the findings of various studies could be a consequence of different types of cancer and difference in sample size. More mechanistic molecular and cellular studies are required, however, to determine the exact role of IL-37 in bladder cancer outcomes.

CONCLUSION

Our findings reveal, for the first time, that patients with TCC have higher levels of IL-37 in their serum than healthy controls. IL-37 serum levels may be considered a candidate marker for immune system suppression and cancer progression in these patients. Thus, IL-37 targeting might be a novel and promising strategy for improving the clinical outcome of patients with bladder cancer, especially those over the age of 70. However, this is a preliminary study, and more research on the biological role of this cytokine and its potential therapeutic effects in bladder cancer is required.

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