JBUON 2019; 24(4): 1601-1609
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Serum IL-17 levels can be diagnostic for gastric cancer

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Summary

Purpose: *Gastric cancer (GC) is one of the most common malignancies worldwide. Although it has been strongly associated with immunopathology, IL-17 also has an important role in host defense so this makes it more important in GC, which is a microorganism-related cancer. The aim of this study was to determine the clinical significance of the serum levels of IL-17 in GC patients.*

Methods: *A total of 76 patients with GC and 30 healthy age- and sex-matched controls were enrolled in this study. Serum IL-17 levels were determined by the enzyme-linked immunosorbent assay method (ELISA) and these values were compared between groups.*

Results: *The median age at diagnosis was 60 years (21-84). Fifty-three (70%) patients were male and cardia was the most common tumor localization (n=40, 53%). Thirty-eight patients had metastasis (n=38, 50%) at presentation and liver was the most common organ with metastasis (n=17, 22%). Mean progression free survival (PFS) and overall survival (OS) of GC patients were 4.0 ± 0.9 months (95% CI: 2 - 6 months) and 14.6 ± 1.2 months (95% CI:12-17), respectively. 1-year OS rate was 52.8% (95% CI: 40.5-65.2). The median serum IL-17 levels of GC patients were significantly higher than of controls (9.04 vs. 8.07 pg/mL, p=0.01). There was no significant difference according to known disease-related clinicopathological and most of the laboratory parameters (p>0.05) but there was a positive relationship between CA-19.9 and IL-17 levels (p=0.04). Serum IL-17 levels had no significant impact on PFS, OS (p=0.51 and p=0.33) and also on response to chemotherapy (p>0.05).*

Conclusion: *While serum IL-17 levels were significantly higher in patients with GC compared to health subjects, it has no prognostic value on survival. Serum IL-17 levels may be a new candidate marker in the diagnosis of GC.*

Key words: *serum, interleukin-17, gastric cancer, diagnosis, marker*

Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide [1]. The global incidence of GC has declined rapidly over the recent few decades. Most patients with GC in the United States are symptomatic and already have advanced incurable disease at the time of presentation [2,3]. H.pylori-associated pre-neoplastic lesions are a feature of intestinal-type GC and not the diffuse-type. The diffuse type is more likely to have a primary genetic etiology, and the involvement of H.pylori is probably limited to a subset of sporadic cases [4]. The high mortality rate reflects the prevalence of advanced disease at presentation. In population-based series of Western populations, the 5-year survival rate for patients with completely resected stage I gastric cancer is approximately 70-75%, and it drops to 35% or less for stage IIB disease and beyond [5].

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Received: 29/12/2018; Accepted: 04/02/2019

The proinflammatory cytokine interleukin-17 (IL-17) plays a potent role in T-cell mediated angiogenesis, promotes carcinogenesis and it has effects on immune resistance, proliferation and metastasis. IL-17 is predominantly produced and secreted by activated CD4 T-cells [6] but data in humans have shown that CD8 T-cells can also produce IL-17 [7]. Moreover, recently, IL-17 emerged to have an outstanding performance against cancer and the role of Th17 cells in malignancy is still under discussion [8]. IL-17 expression is elevated in different human tumors, such as cervical cancer, hepatocellular carcinoma, ovarian cancer, esophageal cancer, breast cancer, gastric cancer and CRC [8,9]. It was shown that IL-17 can trigger some cancer pathways such as Src/PI3K/Akt/nuclear factor-κB (NFκB), MAPK, Stat3 and COX-2. These pathways have roles in tumorigenesis, angiogenesis and metastasis [9].

Increased understanding of the biology of IL-17 has revealed that this cytokine is a central player in immunity at the sites most exposed to microorganisms. Although it has been strongly associated with immunopathology, IL-17 also has an important role in host defense [10] so this makes it more important in gastric cancer, which is a microorganism-related cancer. IL-17 has a role as counterpart of interferon-γ (IFN-γ). Together IL-17 and IFN-γ provide a robust response against microorganisms, but they can equally contribute to immune pathology [10].

IL17A mRNA expression and intratumoral IL17A+ cells infiltration was correlated with antitumor immune contexture in gastric cancer patients [11] and the authors concluded that IL17A+ cells infiltration could be used as an independent prognostic biomarker for overall survival (OS) and predictive biomarker for superior response to adjuvant chemotherapy [11]. In new studies, there is data supporting the pivotal role of neutrophils in GC progression and reveal a novel immune escape mechanism in the distinct tumor microenvironment [12]. In the literature IL-17 gene polymorphisms are associated with GC development in Chinese population [13]. We aimed to investigate IL-17 levels in GC patients and its relationship with disease characteristics in Turkish people.

Methods

Characteristics of the patients and the disease

Serum samples of the 76 patients who were referred to Istanbul University Institute of Oncology and Bakirkoy Dr Sadi Konuk Training and Research Hospital from November 2012 to August 2014 were obtained. All patients had histologically confirmed GC diagnosis and had not received chemotherapy (CTx) or chemoradiation (CRT) within 6 months. The staging was determined according to the American Joint Committee on Cancer (AJCC) and International Union against Cancer (UICC) staging systems.

The pretreatment evaluation included assessment of detailed clinical history and physical examination with a series of biochemistry tests including lactate dehydrogenase (LDH), complete blood cell count (CBC) and serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels. Those with Eastern Cooperative Oncology Group (ECOG) performance status 2 or less and appropriate blood chemistry tests received CTx which included different combinations of fluorouracil, folinic acid, capecitabine, docetaxel, cisplatin and epirubicin, with/without radiotherapy depending on the stage of disease. Follow-up programs included clinical, laboratory, and radiological assessments performed at 12-week intervals during CTx and with no anticancer treatment. Response to treatment was determined according to the revised RECIST criteria version 1.1 by the investigators and classified as follows: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The tumour response after 3 months of CTx was used for statistical analysis. Follow-up programs of metastatic disease consisted of clinical, laboratory, and imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) depending on which imaging methods were used at baseline and performed at 12-week intervals. Patients with either PR or SD were classified as responders, and patients with PD were considered as non-responders.

Blood samples were obtained from patients with GC at first admission before any treatment. For comparison of serum levels of IL-17, 30 healthy controls (age- and sex-matched) were included into the analysis. Investigations were carried out following the rules of the Declaration of Helsinki of 1975, which was revised in 2013. Institutional review board approval of Istanbul University, Institute of Oncology in 2014 with the number 273 was obtained before the study.

Measurement of serum IL-17 levels

Fasting serum samples were obtained on first admission before any treatment was given to patients and the serum specimens were collected following centrifugation (10 min at 4000 rpm) at room temperature and frozen immediately at -80°C until analysis. Enzyme-linked immunosorbent assay (ELISA) (Diaclone SAS F-25020 Besançon Cedex, France) was used (a double-antibody sandwich ELISA) to determine the level of human IL-17 in samples. Serum samples were placed to the wells which were precoated with human IL-17 monoclonal antibody. Following incubation, IL-17 antibodies labeled with biotin and combined with streptavidin-HRP were added to form immune complex and allowed to incubate for 2 h. Unbound material was washed away, and then, chromogen solution was added for the conversion of the colorless solution to a blue solution (5-15 min), the intensity of which was proportional to the amount of IL-17 in the sample. Under the effect of the acidic stop

solution, the color became yellow. The colored reaction product was measured using an automated ELISA reader (ChroMate® 4300 Microplate Awareness Technology). The results were expressed as pg/mL.

Statistics

SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL., USA) was used for statistical analyses. Continuous variables were categorized using median values as cut-off point. Relationships and comparisons of several clinical/laboratory variables were evaluated via nonparametric tests. Mann-Whitney U test was used to assess the serum levels between the subgroups. OS was calculated from the date of cancer diagnosis to disease-related death, or date of last contact with the patient or any family member for patients known to be still alive. PFS was calculated from the date of admission to the date of first radiologic progression with or without elevated serum tumor marker. Kaplan-Meier method was used for the estimation of survival distribution and differences in PFS and OS were assessed by the log-rank test. All statistical tests were two-sided and a p value less than 0.05 was considered statistically significant.

Table 1. Patient and disease characteristics (n=76)

Characteristics	*n (%)*
Age (years), median (range)	60 (21- 84)
Gender	
Male	53 (70)
ECOG performance status[a]	
0	20 (26)
1	43 (57)
2	9 (12)
3	3 (4)
Smoking[a]	
Yes	41 (54)
No	31 (41)
Unknown	1 (1)
Alcohol intake[a]	
Yes	17 (22)
No	52 (68)
Comorbidity[a]	
Yes	21 (30)
No	52 (68)
Surgery type	
Total gastrectomy	23 (30)
Subtotal gastrectomy	12 (16)
Palliative surgery	19 (25)
Tumor localization	
Cardia	25 (33)
Antrum	31 (41)
Corpus	15 (20)
Small curvature	1 (1)
Pylorus	4 (5)
Response to chemotherapy	
Yes (PR + SD)	24 (31)
No (PD)	11 (14)
Metastasis	
Yes	38 (50)
No	38 (50)

[a]Patients with unknown data concerning the variables are not included in the analysis. ECOG: Eastern Cooperative Oncology Group, PR: partial response, SD: stable disease, PD: progressive disease

Results

Baseline demographic features and histopathological/laboratory characteristics of patients are shown in Tables 1 and 2. Median age at diagnosis was 60 years (21-84), and males constituted the majority of the group (n=53, 70%). The tumor localization was cardia in 33% (n=25) and antrum in 41% (n=31) of the patients. Liver (n=17, 22%) was the most frequent metastatic site in 38 patients with metastasis.

Table 2. Pathological/laboratory parameters in patients with gastric cancer (n=76)

Variables	*n*
Histology[a]	
Adenocarcinoma including signet ring cells	50/25
Pathologic tumor stage (T)[a,aa]	
1/2/3/4	4/3/3/12
Pathologic node stage (N)[a,aa]	
0/1/2/3	4/5/5/6
Grade[a]	
Good-intermediate/poor	12/43
Angiolymphatic invasion[aa]	
Yes/no	12/8
Perineural invasion[aa]	
Yes/no	13/7
White blood cell count[a] (UL)	
Normal (<10.000)/high (>10.000)	63/9
Hemoglobin[a] (g/dL)	
Normal (>12)/low (<12)	34/38
Platelet count[a] (UL)	
Normal (>400.000)/high (<400.000)	57/15
Lactate dehydrogenase[a] (IU/mL)	
Normal (<450)/high (>450)	63/5
Albumin[a] (g/dL)	
Normal (>4)/low (<4)	25/41
Carcinoembryonic antigen[a] (ng/mL)	
Normal (<5)/high (>5)	48/22
CA19.9[a] (U/mL)	
Normal (<38)/high (>38)	35/21

[a]Patients with unknown data concerning the variables are not included in the analysis, [aa]In 38 patients with nonmetastatic, CA19.9: carbohydrate antigen 19.9

Table 3. The values of serum marker levels in gastric cancer patients and healthy controls

Variables	*Patients (n=76)*		*Controls (n=30)*		*p*
	Median	*Range*	*Median*	*Range*	
IL-17 (pg/mL)	9.04	5.80-63.63	8.07	5.23-11.82	0.01

Table 4. Results (median and range) of comparisons between the IL-17 levels and various clinical/laboratory parameters in gastric patients

Variables	*N*	*IL-17A (pg/mL) Median (range)*	*p*
Age (years)			0.17
<60	41	9.54 (5.80-20.45)	
>60	35	8.86 (5.80-63.63)	
Sex			0.34
Male	53	8.75 (5.80-63.63)	
Female	23	9.20 (6.36-26.59)	
ECOG performance status			0.76
0	20	9.15 (6.02-18.64)	
1-3	55	8.86 (5.80-63.63)	
Smoking			0.66
Yes	41	9.09 (6.02-63.63)	
No	31	8.98 (5.80-26.59)	
Alcohol intake			0.59
Yes	17	9.77 (6.59-20.45)	
No	52	8.98 (5.80-63.63)	
Comorbidity			0.32
Yes	21	8.64 (5.80-63.63)	
No	52	9.15 (5.80-20.45)	
Surgery			0.43
Yes	54	9.15 (5.80-63.63)	
No	22	8.81 (5.80-16.36)	
Localization			0.32
Cardia	40	9.15 (5.80-63.63)	
Antrum	36	8.75 (5.80-19.20)	
Histology			0.26
Adenocarcinoma	50	8.64 (5.80-63.63)	
Signet ring	25	9.54 (6.02-20.45)	
Grade			0.60
Good-intermediate	12	8.24 (6.25-14.77)	
Poor	43	9.20 (5.80-26.59)	
Angiolymphatic invasion			0.62
Yes	12	8.24 (6.02-13.29)	
No	8	9.77 (5.80-12.84)	
Perineural invasion			0.70
Yes	13	8.07 (6.02-13.29)	
No	7	9.20 (5.80-12.84)	
Tumor			0.41
Small (1-2)	7	9.20 (5.80-12.84)	
Large (3-4)	15	8.07 (6.02-15.11)	

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Variables	*N*	*IL-17A (pg/mL) Median (range)*	*p*
Nodal stage			0.64
Low (1-2)	10	7.90 (6.02-13.29)	
High (3)	6	8.58 (6.93-11.14)	
Response to CT			0.41
Yes (PR+SD)	16	9.04 (5.80-20.45)	
No (PD)	11	9.66 (5.80-15.11)	
Metastasis			0.86
Yes	38	8.92 (5.80-63.63)	
No	38	9.20 (5.80-20.45)	
Liver metastasis			0.60
Yes	17	8.86 (5.80-63.63)	
No	21	8.98 (6.25-26.59)	
Hemoglobin			0.66
Normal	34	8.92 (6.02-20.45)	
Low	38	8.98 (5.80-63.63)	
White blood cell count			0.58
Normal	63	8.98 (5.80-63.63)	
High	9	8.75 (5.80-10.79)	
Platelet count			0.12
Normal	57	8.18 (5.80-63.63)	
High	15	10.23 (6.59-15.11)	
Albumin			0.20
Normal	25	9.20 (6.02-26.59)	
Low	41	8.75 (5.80-63.63)	
Lactate dehydrogenase			0.70
Normal	63	8.98 (5.80-63.63)	
High	5	9.09 (7.05-20.45)	
Carcinoembryonic antigen			0.90
Normal	48	8.92 (6.02-63.63)	
High	22	9.15 (5.80-15.34)	
CA19.9			0.04
Normal	35	7.95 (5.80-15.34)	
High	21	8.98 (6.02-63.63)	

The levels of serum IL-17 in GC patients and healthy controls are shown in Table 3. The baseline serum IL-17 levels were significantly lower in the control group (8.07;5.23-11.82); 5.80-63.63 vs 9.04 (pg/mL, p=0.01] (Figure 1). Table 4 shows the correlation between the serum levels IL-17 and clinical/laboratory parameters. Higher CA 19.9 levels were found to be significantly correlated with high serum IL-17 concentrations (p=0.04).

During a median follow-up of 8.0 months (1-24), disease progression developed in 11 (15%) patients, the mean PFS and OS of the GC patients group were 4.0 ± 0.9 (95%CI: 2-6) months and 14.6 ± 1.2 (95% CI=12-17) months, and 1-year OS rate was 52.8% (95%CI: 40.5-65.2) (Tables 5,6 and Figures 2,3).

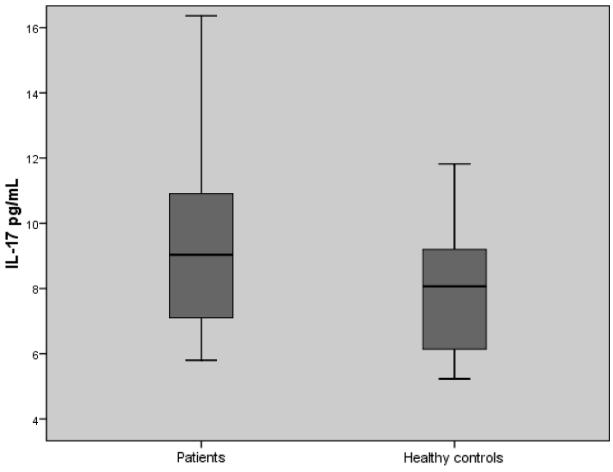

Figure 1. The values of serum IL-17A assays in cancer patients and controls (p=0.01).

Table 5. Univariate analyses of serum IL-17 for progression-free survival

Parameters	*N of events/Total N*	*Survival (months) (Mean±SD)*	*p*
All patients	20/76	4.0 (0.9)	N/A
IL-17			0.51
<Median level	10/60	4.0 (1.6)	
>Median level	10/46	3.0 (1.6)	

IL-17: interleukin-17

Table 6. Univariate analyses of overall survival for patients with GC

Parameters	*Number of events/ Total N*	*Survival n (%)*	*1-year-survival n (%)*	*p*
All patients	33/76	14.6 (1.2)	52.8 (6.3)	N/A
Age of patients, years				0.82
Young (<60)	17/41	13.4 (1.4)	52.1 (8.7)	
Older (>60)	16/35	14.3 (1.8)	53.6 (9.0)	
Sex				0.67
Male	22/53	14.5 (1.4)	56.6 (7.3)	
Female	11/23	13.8 (2.2)	45.3 (11.5)	
ECOG performance status				0.008*
0	4/20	17.5 (1.5)	73.1 (11.7)	
1-3	29/55	12.7 (1.4)	44.9 (7.2)	
Surgery				<0.001*
Yes	15/54	18.0 (1.3)	69.7 (6.9)	
No	18/22	6.4 (1.5)	20.2 (8.9)	
Tumor localization				0.40
Cardia	16/40	14.9 (1.5)	58.2 (8.5)	
Antrum	17/36	13.7 (1.8)	46.3 (9.3)	
Histopathological grade				0.006*
Good-intermediate	1/12	21.3 (1.5)	100	
Poor	24/43	12.4 (1.6)	40.4 (7.9)	
Angiolymphatic invasion				0.88
Yes	2/12	20.0 (1.9)	88.9 (10.5)	
No	1/8	14.9 (2.0)	87.5 (11.7)	
Perineural invasion				0.23
Yes	1/13	21.5 (1.4)	90.0 (9.5)	
No	2/7	13.4 (2.3)	85.7 (13.2)	
Clinical tumor stage				0.22
Small (1-2)	2/7	12.9 (2.3)	85.7 (13.2)	
Large (3-4)	2/15	20.9 (1.4)	85.7 (9.4)	
Nodal stage				0.70
Low (1-2)	2/10	18.5 (1.6)	88.9 (10.5)	
High (3)	1/6	19.2 (3.5)	83.3 (15.2)	
Metastasis				0.001*
Yes	23/38	10.6 (1.6)	34.2 (8.8)	
No	10/38	17.8 (1.4)	70.3 (8.0)	
Liver metastasis				0.02*
Yes	15/17	6.3 (1.4)	32.3 (11.6)	
No	8/21	14.6 (2.4)	55.6 (12.7)	

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Parameters	*Number of events/ Total N*	*Survival n (%)*	*1-year-survival n (%)*	*p*
Hemoglobin level				0.80
Normal	14/34	14.8 (1.8)	50.5 (9.9)	
Low	17/38	14.0 (1.6)	55.1 (8.5)	
White blood cell count				0.02*
Normal	26/63	14.2 (1.1)	54.7 (6.9)	
High	5/9	11.0 (3.9)	44.4 (16.6)	
Platelet count				0.71
Normal	24/57	14.9 (1.4)	51.2 (7.4)	
High	7/15	13.2 (2.7)	59.3 (12.9)	
Albumin				0.71
Normal	6/25	18.6 (1.9)	51.2 (7.4)	
Low	21/41	13.0 (1.5)	59.3 (12.9)	
Lactate dehydrogenase				0.30
Normal	27/63	14.3 (1.2)	53.2 (6.9)	
High	1/5	19.4 (4.1)	80.0 (17.9)	
Carcinoembryonic antigen				0.01*
Normal	17/48	16.1 (1.5)	60.9 (7.9)	
High	15/22	7.0 (1.0)	30.3 (10.2)	
CA19.9				0.09
Normal	15/35	14.1 (1.5)	56.1 (9.0)	
High	13/21	10.7 (2.2)	31.3 (11.2)	
Response to chemotherapy				<0.001*
Yes (PR+SD)	5/16	19.7 (1.7)	79.6 (9.3)	
No (PD)	11/11	4.8 (0.8)	NR	
IL-17				0.33
<Median	19/60	12.8 (1.6)	44.5 (9.1)	
>Median	14/46	16.2 (1.7)	61.4 (8.2)	

*p<0.05, NR: Not reached; CA19.9: carbonhydrate antigen 19.9, PR: partial response, SD: stable disease, PD: progressive disease, IL-17: interleukin-17, ECOG: Eastern Cooperative Oncology Group

There was no significant relationship between other clinicopathologic variables including age, sex, localization, angiolymphatic invasion, perineural invasion, tumor diameter, lymph node status, and also levels of hemoglobin, platelets, albumin, LDH, CA19.9, IL-17 levels with OS (Table 6) but there was a significant relationship with performance status, histologic subtype, having surgery, grade, metastatic status, liver metastasis, leucocyte count, and CEA levels, response to CTx and OS (p=0.08, p=0.001, p=0.001, p=0.006, p=0.001, p=0.02, p=0.02, p=0.01 and p=0.001, respectively). However, serum IL-17 levels showed no significant adverse effect on PFS and OS (p=0.51 and p=0.33, respectively) (Tables 5, 6 and Figures 2, 3, respectively).

Discussion

GC is the fourth most common cause of cancer-related death in the world and it remains difficult to cure in western countries, primarily because most patients present with advanced disease. This indicates a need for new diagnostic and prognostic markers. There are numerous biomarkers which have been investigated in advanced GC [14]. IL-4, IL-6, IL-10, IL-11, IL-17, IL-21, IL-32 and IL-33 are investigated in pathogenesis, progression and metastasis of GC [14-20].

One of the most widely used histological classification of GC is based on Lauren's criteria, in which gastric adenocarcinoma is a heterogeneous disease histologically divided into intestinal, diffuse, mixed, and indeterminate subtypes [20]. Inflammation and cancer are related to each other and GC in which H. pylori has a role, is one of the most related cancers with infections and inflammatory markers. Among numerous cytokines one of the most investigated that has role in both hallmarks of cancer is the recently described IL-17 [11]. In a new study, IL-17 was found to be positively correlated with the transformation of quiescent GC stem cells into invasive GC stem cells and the investiga-

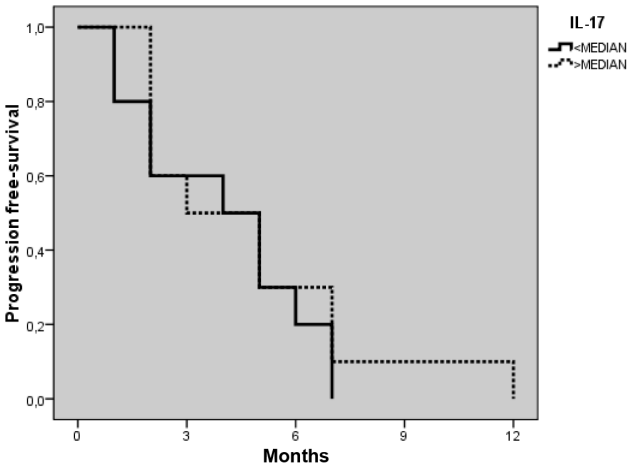

Figure 2. Progression-free survival curves in gastric cancer patients according to serum IL-17A levels (p=0.51).

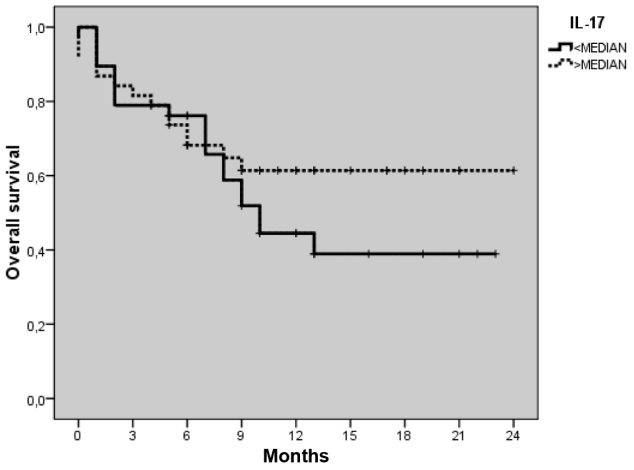

Figure 3. Overall survival curves in gastric cancer patients according to serum IL-17 levels (p=0.33).

tors concluded that targeting IL-17 may emerge as a possible novel therapeutic strategy for GC [21]. Various genetic variants of IL-17 are likely to be associated with risk of GC in Chinese population [22]. Signaling by IL-17A activates the NFκB, AP1, and C/EBP pathways leading to cancer progression [23]. Analyses of IL-17 expression have shown that patients with diffuse GC had significantly lower expression of IL-17 in comparison to patients with intestinal type [23]. In all these new published studies, it is seen that IL-17 has an emerging role in GC. In our study, we found that GC patients had significantly higher levels of IL-17 than the control group. There was a positive relationship between CA 19.9 and IL-17 levels; however, it had no effect on survival.

In H.pylori infected individuals, the frequencies of IFNγ and IL-17A cells were found to be increased in the antrum, particularly in patients with H.pylori-induced gastric ulcers [24]. IL-17 was found to be an important marker for genetic alterations in GC associated with H.pylori [25]. Moreover, Iida et al. have shown that patients whose infiltrates in GCs had increased number of Th17 cells with increased expression of IL-17 and IL-23 mRNA had more invasive form of tumors [26]. IL-17 has an important role as a proangiogenic factor in GC pathogenesis [27]. Meng et al found similar findings in their study with us which showed that patients with GC had higher levels of IL-17 in serum and cancer tissues, while no statistically significant correlation between the serum IL-17 and the clinicopathological features was found in their study [28]. The limitation of this study was that the authors didn't look for the laboratory parameters, such as CA 19.9 [28].

In conclusion, although we were not able to demonstrate the effect of IL-17 on survival and clinical course, the significant elevation of IL-17 in GC compared to healthy individuals suggests that IL-17 may be a candidate as diagnostic marker for GC. Future studies will provide a better understanding of this molecule.

Author contributions

Conceptualization: S.K. and C.U.A; Methodology: C.U.A; Software: M.K.; Validation: M.K.; Formal Analysis: M.S.; Investigation: S.K.; Resources: M.K.; Data Curation: M.K and M.S.; Writing-Original Draft Preparation: C.U.A.; Writing; Review & Editing: C.U.A. and S.K.; Visualization: M.S.; Supervision: M.K.; Project Administration: S.K.; Funding Acquisition: M.K.

Conflict of interests

The authors declare no conflict of interests.

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