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Elevated serum levels of interleukin-37 correlate with poor prognosis in gastric cancer

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ABSTRACT

Background: interleukin-37 (IL-37) is as a natural suppressor of the innate inflammatory and immune responses. It has also been reported to be involved in carcinogenesis and metastasis. The present case-control study was designed to investigate the role of serum levels of IL-37 in patients with gastric cancer.

Methods: serum IL-37 levels were determined using the enzyme-linked immunosorbent assay in 180 patients diagnosed with gastric cancer and 100 healthy controls. The association between IL-37 levels and clinical factors was assessed. Univariate and multivariate analyses were performed to investigate the prognostic significance of these parameters in gastric cancer.

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Results: serum IL-37 levels in gastric cancer patients (5.606 ± 0.837 pg/ml) were significantly higher than those in healthy controls (2.364 ± 0.210 pg/ml, p < 0.001). High serum IL-37 levels were related to a poorly differentiated histologic type (p = 0.046) and advanced T stage (p = 0.003). The Kaplan-Meier survival analysis indicated that the high-IL-37 group had a poorer overall survival and progression-free survival (overall survival [OS]: 39.0 months *vs* 13.0 months, p < 0.001, progression-free survival [PFS]: 25.0 months *vs* 10.0 months, p < 0.001). Multivariate analyses showed serum IL-37 to be an independent prognostic factor for gastric cancer patients (OS: hazard ratios [HR] = 1.842, 95% CI: 1.190-2.854, p = 0.006; PFS: HR = 1.547, 95% CI: 1.014-2.359, p = 0.043).

Conclusions: in conclusion, serum IL-37 levels were associated with poor overall survival and progression-free survival in gastric cancer patients. IL-37 may be a potential predictor of prognosis in gastric cancer.

Key words: Gastric cancer. Serum IL-37. Prognosis. Inflammation. Immune.

INTRODUCTION

Gastric cancer (GC) is the most prevalent cancer in Eastern Asia, as well as the second leading cause of cancer-related deaths worldwide (1). Despite great improvements in diagnosis and treatment, the majority of GC patients suffer from recurrences and metastasis and the survival of GC patients remains unsatisfactory (2). Identifying more predictive markers for cancer progression and prognosis is important to distinguish high-risk patients, help guide treatment strategies and improve clinical outcome.

It is well-documented that interleukin-37 (IL-37) is the seventh interleukin factor of interleukin 1 family (IL-1F7). It acts as a natural inhibitor of innate immunity and suppresses systemic and local inflammatory response (3,4). Previous studies demonstrated that IL-37 inhibited TLR-induced pro-inflammatory cytokines such as IL-1α, IL-1β, IL-8 and TNF-α (5). *In vivo,* IL-37 was reported to reduce the production of cytokines in several autoimmune and inflammatory diseases, such as obesity-induced inflammation (6), psoriasis (7), Graves' disease (GD) (8) and ankylosing

spondylitis (AS) (9). Up-regulated expression of IL-37 in serum have also been reported in several types of cancer (10). Huo et al. found that serum IL-37 levels in patients with epithelial ovarian cancer (EOC) were significantly higher than that in healthy controls and high serum IL-37 levels were associated with an unfavorable prognosis of EOC patients (11). On the other hand, one study reported a reduced expression of IL-37 in renal cell carcinoma (RCC) patients that negatively correlated with tumor progression (12). However, there is no study that has investigated the clinical significance of IL-37 in GC.

The aim of this retrospective study was to evaluate the association between serum IL-37 and prognosis of GC patients.

MATERIALS AND METHODS

Patients and blood sampling

This retrospective study firstly selected 204 gastric adenocarcinoma cases diagnosed between January 2011 and January 2014 in the Affiliated Kunshan Hospital of Jiangsu University. After screening, 180 cases with available clinical records and follow-up information were finally enrolled. The inclusion criteria were as follows: a) patients with available serum samples obtained before the primary treatment and stored at -80 °C; b) histologically confirmed GC by gastroscopy or surgery; c) not treated previously; d) no second primary tumor; and e) no active concurrent infection. Moreover, 100 healthy volunteers were also included in the study and blood samples were collected. The controls were sex and age-matched with the cases in order to address any potential bias. Written informed consent was obtained from all patients and healthy subjects. The study was performed in agreement with the guidelines of the Declaration of Helsinki.

Data collection

The detailed clinical characteristics for most of the patients, including age, gender, surgery, chemotherapy, tumor location, clinical TNM stage, pathologic type and survival time were obtained from clinical records. Given that some cases lacked survival data, we also contacted their families by phone. The tumors were staged

according to the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC 8th ed., 2018). Overall survival (OS) was defined as the time from diagnosis to the date of death or the last visit. Progression-free survival (PFS) was calculated from the time of diagnosis to the time of progression, relapse, death or the last follow-up. This observational study was reviewed by our Institutional Review Board.

Measurement of serum IL-37 levels

IL-37 serum levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human IL-37 ELISA kit; Mlbio, Shanghai, China, detection range: 0.1-32 ng/ml), according to the manufacturer's instructions. Briefly, standards at different concentrations, a blank control and blood samples were added to 96-well plates that were pre-coated with biotinylated antibodies specific for IL-37. The 96-well plates were washed after incubation at 37 °C for one hour. A substrate solution was added to the wells and color development was finally terminated using a Stop Solution. Enzymatic reactions were developed and the absorbance was measured at 450 nm (A450) using a microplate photometer (Multiskan™ FC; Thermo Scientific, Yokohama, Japan) within 15 minutes after stopping color development. IL-37 levels were calculated according to standard curves and all samples were assayed in triplicate. The results average was calculated for each sample.

Statistical analysis

Statistical analyses were performed using the SPSS 16.0 software (SPSS, Chicago, IL, USA). Serum IL-37 concentration was expressed as the median (min, max). Comparisons between various clinicopathologic factors and IL-37 concentration were analyzed using the Mann-Whitney U test or the Kruskal-Wallis test. A receiver operating characteristic (ROC) curve was constructed to estimate the optimal cutoff value of serum IL-37. Survival curves were constructed according to the Kaplan-Meier method and comparisons between survival curves were performed using the log-rank test. Furthermore, multivariate analyses were performed to identify

significant independent prognostic factors. Hazard ratios (HR) and 95% confidence intervals (CI) were generated. Statistical significance was defined as p values (two sides) < 0.05.

RESULTS

Clinicopathologic characteristics of the patients

One hundred and eighty patients were included in the further analyses. The clinical/pathological characteristics of the 180 patients (120 males and 60 females with a median age 65 years) are presented in table 1. In total, 55 (30.56%) patients had gastric cardia adenocarcinoma and 47 (26.11%) were diagnosed with **gastric antrum cancer**. One hundred and thirty-three (73.89%) patients underwent a surgical resection of the tumor and 149 (82.78%) patients received at least one cycle of chemotherapy. More than half (66.11%) were classified as poorly differentiated GC. The stages of III-IV accounted for 71.11% of the patients.

Association of serum IL-37 with clinicopathological variables

The mean concentration of serum IL-37 for all patients was 5.606 ± 0.837 pg/ml with a median of 3.960 pg/ml (range 0.960-31.265 pg/ml). Concurrently, we also detected serum IL-37 level for 100 sex and age-matched healthy volunteers. The mean concentration was 2.364 ± 0.210 pg/ml with a median of 2.457 pg/ml (range 0.237-6.187 pg/ml), which was significantly lower than that of GC patients ($p < 0.001$) (Fig. 1). According to the results of the ROC analysis, the optimal cutoff concentration of serum IL-37 was 4.72 pg/ml with an area under the curve (AUC) of 0.617 (sensitivity: 38.7%; specificity: 85.1%, $p < 0.001$) (Fig. 2). Serum IL-37 levels were elevated in 52 (28.89%) patients and these individuals were categorized in the high-IL-37 group. The remaining (71.11%) were classified as the low-IL-37 group. The clinicopathologic variables of the patients were compared between the low and high-IL-37 groups. As shown in table 1, the serum IL-37 level was significantly higher in patients with a poorly differentiated histologic type ($p = 0.046$) and advanced T stage ($p = 0.003$).

Prognostic factors for OS and PFS

In this study, the median OS and PFS for all patients were 28.5 months and 19.5 months, respectively. Furthermore, the low-IL-37 group had a significantly better outcome compared with those in the high-IL-37 group (OS: 39.0 months *vs* 13.0 months, $p < 0.001$, PFS: 25.0 months *vs* 10.0 months, $p < 0.001$), which was shown in figure 3A and B.

Tables 2 and 3 show the prognostic effect of clinicopathologic variables. Univariate Cox regression analysis showed that patients who did not undergo surgery ($p < 0.001$), a poorly differentiated histologic type ($p < 0.001$), advanced T ($p < 0.001$), N ($p < 0.001$) and clinical stage ($p < 0.001$) and higher IL-37 levels ($p < 0.001$ for OS and $p = 0.021$ for PFS) were negative prognostic factors associated with OS and PFS. After multivariate analysis with these selected parameters using the Cox regression model, only IL-37 level was identified as an independent prognostic factor associated with OS (HR = 1.842, 95% CI: 1.190-2.854, $p = 0.006$) and PFS (HR = 1.547, 95% CI: 1.014-2.359, $p = 0.043$).

DISCUSSION

The major findings of this study were that serum level of IL-37 was higher in patients with GC than healthy controls and elevated baseline IL-37 was associated with a poor outcome. IL-37 level was identified as an independent prognostic factor for OS and PFS. These results confirmed the important role of IL-37 in disease development and progression of GC.

IL-37 was previously considered as an inhibitor of innate inflammatory and immunity (4,13) and is commonly associated with disease activities (8,14,15). In addition, the effects of IL-37 in cancer have the attention of clinicians and scientist but the results are still controversial. Zhao et al. showed that patients with high expression levels of IL-37 in HCC tumor tissue had a better overall survival and disease-free survival. Furthermore, low expression of IL-37 in tumor tissue was an independent risk factor for poor prognosis (16). Other studies in non-small cell lung cancer and (NSCLC) and RCC also supported the antitumor effect of IL-37 (12,17). However, Huo et al. reported that high serum IL-37 levels are associated with an unfavorable prognosis of EOC patients (11). We believe that the pathogenesis of different tumors varies

and IL-37 may be a double-edged sword that plays different roles in different cancer types.

The exact role of IL-37 in GC is still unknown. The present study measured serum IL-37 levels in healthy volunteers and GC patients and found that serum IL-37 was low in the healthy controls. Furthermore, IL-37 levels were significantly differentiated between patients with poorly differentiated adenocarcinoma and well-differentiated types. Kaplan-Meier survival analysis showed that high serum IL-37 levels were correlated with an unfavorable OS and PFS in GC. Taken together, our results suggest that IL-37, as a new anti-inflammatory cytokine, may play a suppressive role in the antitumor immune response. A number of studies have explored the precise mechanism of how IL-37 negatively regulates antitumor activity. Xu et al. showed *in vitro* that IL-37 expression in human CD4+CD25+Treg can promote the suppressive effect on T lymphocyte activation (18). In addition, Wu et al. previously reported that IL-37 could suppress T cell priming by modulating dendritic cell maturation and cytokine production via down-regulating ERK/NF-κB/S6K signaling (19). It is generally accepted that Treg cells can significantly suppress T cell responses and the cytotoxic lymphocyte effect, which weaken antitumor responses (20). Considering these findings, IL-37 may play a key role in dampening antitumor immune responses, which in turn promote tumor growth. However, further studies are needed to elucidate the cellular mechanisms of IL-37-mediated signaling in GC.

The present study did have some potential limitations. First, it is a retrospective study performed in a single institution and the sample size is relatively small. Second, some potential co-factors related to GC development and systematic inflammation such as the infection status of *Helicobacter pylori* (HP) and the EB virus as well as the level of CEA and C-reactive protein have not been considered in all analyses due to missing data. The next step would be to collect more data that may directly affect gastric cancer development and explore the association between these factors and IL-37. More evidence should be collected to support our results.

CONCLUSION

In conclusion, our data demonstrated for the first time that serum IL-37 level was

associated with poor OS and PFS in GC patients. IL-37 was identified as a potential prognostic indicator for GC. These results suggest a role for IL-37 in the pathogenesis of GC and offer new insights into potential therapeutic strategies.

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280 **Table 1. Correlation of serum IL-37 level with clinical characteristics in gastric**
281 **cancer patients**

Characteristics	All n = 180 (%)	Median concentration of IL-37, pg/ml (range)	p value	Low IL-37 group (< 4.720 pg/ml) n (%)	High IL-37 group (≥ 4.720 pg/ml) n (%)	p value
Age (years)			0.629			0.672
< 65	89 (49.44)	4.125 (0.960-29.061)		62 (48.44)	27 (51.92)	
≥ 65	91 (50.56)	3.672 (1.032-31.265)		66 (51.56)	25 (48.08)	
Sex			0.224			*0.048*
Male	120 (66.67)	3.784 (0.960-31.265)		91 (71.09)	29 (55.77)	
Female	60 (33.33)	4.252 (1.032-31.179)		37 (28.91)	23 (44.23)	
Tumor location			0.150			0.458
Cardia	55 (30.56)	4.223 (1.403-28.582)		36 (28.125)	19 (36.54)	
Gastric body	78 (43.33)	3.756 (0.960-31.265)		56 (43.75)	22 (42.31)	
Antrum	47 (26.11)	3.519 (1.032-28.814)		36 (28.125)	11 (21.15)	
Surgery			0.974			0.594
No	47 (26.11)	3.968 (0.960-25.748)		32 (25.0)	15 (28.85)	
Yes	133 (73.89)	3.950 (1.032-31.265)		96 (75.0)	37 (71.15)	
Chemotherapy			0.409			0.394
No	31 (17.22)	3.925 (1.863-13.539)		24 (18.75)	7 (13.46)	
Yes	149 (82.78)	3.968 (0.960-31.265)		104 (81.25)	45 (86.54)	
Histologic type			*0.046*			*0.031*
Poorly differentiated	119 (66.11)	4.223 (1.032-31.265)		79 (61.72)	40 (76.92)	
Moderately differentiated	57 (31.67)	3.756 (2.202-29.061)		45 (35.15)	12 (23.08)	
Well differentiated	4 (2.22)	4.149 (0.960-4.709)		4 (3.13)	0 (0)	
Depth of invasion			*0.003*			*0.001*
T1-T2	29 (16.11)	3.756 (0.960-12.519)		25 (19.53)	4 (7.69)	
T3-T4	151 (83.89)	4.525 (1.032-31.265)		103 (80.47)	48 (92.31)	

Node status			0.986		0.515
N0-N1	76 (42.22)	4.008 (0.960-28.582)		56 (43.75)	20 (38.46)
N2-N3	104 (57.78)	3.845 (1.032-31.265)		72 (56.25)	32 (61.54)
Stage			0.850		0.711
I-II	52 (28.89)	4.132 (1.436-28.582)		38 (29.69)	14 (26.92)
III-IV	128 (71.11)	3.896 (0.960-31.265)		90 (70.31)	38 (73.08)

283 **Table 2. Univariate and multivariate analyses of factors for the prediction of OS**

284

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)				
< 65	1.000		1.000	
≥ 65	1.197 (0.831-1.724)	0.334	1.108 (0.675-1.537)	0.932
Sex				
Male	1.000		1.000	
Female	1.207 (0.823-1.771)	0.336	1.109 (0.729-1.688)	0.628
Tumor location				
Cardia	1.000		1.000	
Gastric body	0.911 (0.593-1.399)	0.670	0.834 (0.500-1.134)	0.451
Antrum	1.000 (0.620-1.611)	0.998	1.129 (0.519-1.338)	0.462
Surgery				
Yes	1.000		1.000	
No	2.373 (1.614-3.490)	*< 0.001*	1.476 (0.929-2.345)	0.099
Chemotherapy				
Yes	1.000		1.000	
No	0.985 (0.602-1.612)	0.953	1.246 (0.730-2.125)	0.421
Histologic type				
Poorly differentiated	1.324 (0.887-1.977)	0.170	1.113 (0.691-1.792)	0.661
Moderately differentiated	1.000		1.000	
Well differentiated	0.366 (0.050-2.674)	0.322	0.998 (0.113-8.797)	0.999
Depth of invasion				
T1/T2	1.000		1.000	
T3/T4	4.277 (2.072-8.831)	*< 0.001*	2.199 (0.893-5.419)	0.087
Node status				
N0/N1	1.000		1.000	
N2/N3	3.019 (1.996-4.566)	*< 0.001*	1.397 (0.798-2.445)	0.241
Stage				

I-II	1.000		1.000	
III/IV	3.961 (2.352-6.671)	*< 0.001*	1.995 （0.925-4.306）	0.078
IL-37				
Low IL-37	1.000		1.000	
High IL-37	1.759 (1.192-2.596)	*0.004*	1.842 (1.190-2.854)	*0.006*

285

286 CI: confidence interval; HR: Hazard ratios; OS: overall survival.

287 **Table 3. Univariate and multivariate analyses of factors for the prediction of PFS**

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Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)				
< 65	1.000		1.000	
≥ 65	1.146 (0.804-1.633)	0.450	0.957 (0.637-1.438)	0.832
Sex				
Male	1.000		1.000	
Female	1.155 (0.795-1.677)	0.449	1.080 (0.719-1.622)	0.711
Tumor location				
Cardia	1.000		1.000	
Gastric body	0.916 (0.604-1.390)	0.681	0.861 (0.543-1.364)	0.523
Antrum	1.077 (0.677-1.712)	0.754	1.197 (0.724-1.981)	0.483
Surgery				
Yes	1.000		1.000	
No	2.085 (1.430-3.041)	*< 0.001*	1.373 (0.882-2.137)	0.161
Chemotherapy				
Yes	1.000		1.000	
No	0.840 (0.515-1.371)	0.486	1.006 (0.596-1.699)	0.982
Histologic type				
Poorly differentiated	1.247 (0.848-1.836)	0.262	1.030 (0.643-1.650)	0.902
Moderately differentiated	1.000		1.000	
Well differentiated	0.311 (0.043-2.272)	0.250	0.780 (0.091-6.686)	0.820
Depth of invasion				
T1/T2	1.000		1.000	
T3/T4	3.623 (1.891-6.939)	*< 0.001*	2.041 (0.912-4.568)	0.082
Node status				
N0/N1	1.000		1.000	
N2/N3	2.717 (1.838-4.016)	*< 0.001*	1.526 (0.882-2.639)	0.131
Stage				

I-II	1.000		1.000	
III-IV	3.099 (1.945-4.937)	*< 0.001*	1.517 (0.739-3.113)	0.256
IL-37				
Low IL-37	1.000		1.000	
High IL-37	1.567 (1.071-2.293)	*0.021*	1.547 (1.014-2.359)	*0.043*

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290 CI: confidence interval; HR: hazard ratios; PFS: progression-free survival.

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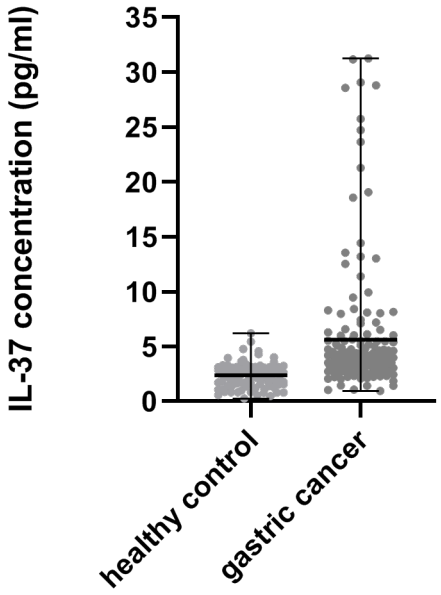

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294 Fig. 1. Serum IL-37 levels in patients with gastric cancer (n = 180) and healthy
295 controls (n = 100) ($p < 0.001$).

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298 Fig. 2. The ROC curve analysis for the optimal cutoff point of serum IL-37. The cutoff

299 value was 4.72. Sensitivity: 38.7%; specificity: 85.1%; AUC = 0.617; $p < 0.001$.

300

Fig. 3. A. Kaplan-Meier survival curves of overall survival according to serum IL-37 level. B. Kaplan-Meier survival curves of progression-free survival according to serum IL-37 level.