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Assessment of Serum Interleukin-38 Levels in Iranian Patients with Benign and Malignant Salivary Gland Cancers: A Case-Control Study

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Abstract

Background: Similar to other cancers, the development of salivary gland cancers (SGCs) is influenced by the tumor microenvironment and controlled by the host's immune system. Interleukin-38 (IL-38) is highly expressed in inflammatory conditions to prevent excessive inflammatory responses and tissue injury; however, its role in SGCs remains unclear. This study aimed to evaluate IL-38 serum levels in Iranian patients with benign and malignant SGCs and in healthy individuals to explore its potential as a diagnostic biomarker for SGCs.

Methods: In this retrospective cross-sectional study, IL-38 levels were measured in serum samples from 120 patients with SGCs (64 benign and 56 malignant cases) and 60 age- and sex-matched healthy control participants using a sandwich enzyme-linked immunosorbent assay (ELISA) kit.

Results: There was a significant difference in IL-38 serum levels between patients and the control group (49.1 ± 6.2 ng/L vs. 38.6 ± 6.8 ng/L, $P<0.0001$), but not between benign and malignant cases (48.2 ± 7.1 ng/L vs. 50.2 ± 4.8 ng/L, $P=0.085$). A significant negative correlation was observed between SGC size and IL-38 serum levels ($R=-0.195$, $P=0.042$). However, IL-38 was not associated with other clinicopathologic factors, including gender, age, tumor type, lesion location, and tumor stage ($P>0.05$).

Conclusion: This study, for the first time, supports the clinical value of IL-38 serum levels as a valuable biomarker for diagnosing patients with SGCs. Focusing on IL-38 production or its release mechanism could offer therapeutic benefits for these patients. However, further research with a larger sample is required.

Keywords: Salivary gland neoplasms, Interleukin-38, Prognosis

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Introduction

Salivary glands are a group of exocrine glands that originate from an epithelial placode during embryonic development. They are divided into two main types: major and minor glands. These glands synthesize, modify, and secrete a multifunctional watery content called "saliva" into the oral cavity. Saliva plays an important role in mucosal lubrication, teeth protection, speech, mastication, food digestion, tissue repair, and more. The proper function of salivary glands is critical for maintaining oral health and overall well-being. Defects in salivary gland function can cause significant disruptions to our daily lives and diminish quality of life (1-3).

Salivary gland cancers (SGCs) are a relatively rare and aggressive group of lesions, accounting for 3–6% of all tumors in the head and neck region. They are characterized by complex clinicopathological characteristics and distinct biological behaviors, presenting in various benign and malignant forms. The rarity and heterogeneity of SGCs cause significant challenges in patient management. The incidence of SGCs within the Iranian population is estimated to reach as high as 4.9% (4-6). However, reports from different parts of the world have shown considerable variation in the epidemiology of SGCs, with an estimated

annual incidence of 0.4–13.5 new cases per 100,000 individuals. The highest incidence of SGCs is seen in European and North American populations, particularly affecting those over 65 years of age (7-10). The exact origin of the disease remains largely unknown. However, several predisposing factors may contribute to the development of SGCs, including exposure to radiation or radioactive materials, tobacco use, heavy alcohol consumption, and environmental, geographic, immunological, and genetic factors (11).

The importance of inflammation as the seventh hallmark of cancer is now well established. Properly controlled inflammation is essential for maintaining tissue and organ homeostasis. However, excessive, uncontrolled inflammation contributes to the overproduction of cytokines and chemokines, autoimmunity, persistent tissue damage, and malignant transformation. Increased expression of pro-inflammatory cytokines plays fundamental roles in regulating tumor-related processes, including growth, metastasis, apoptosis, and angiogenesis (12, 13). The interleukin-1 family 10 (IL-1F10) comprises 11 members, each exhibiting distinct pro-inflammatory or anti-inflammatory properties. Interleukin-38 (IL-38) is the 10th member of the IL-1F10 family, acting as an anti-inflammatory cytokine highly expressed in inflammatory conditions. Its primary function is to prevent agonist ligands from binding to the IL-36 receptor (IL-36R), which is specific for IL-38. Therefore, it inhibits excessive inflammation and tissue damage. Although a growing number of studies have shown that IL-38 plays an important role in the pathogenesis of various inflammatory and autoimmune diseases, its role in cancer remains incompletely elucidated (14-16). Recent studies indicate that IL-38 can directly inhibit tumor progression by regulating host immunity, potentially contributing to its antitumor properties (14, 17, 18). Overexpression of IL-38 has been found to suppress tumor development in a murine model of inflammatory colorectal cancer (19). Nevertheless, IL-38 can modulate both the inflammatory state and antitumor immune responses within the tumor microenvironment through its immunosuppressive properties. It may act as an antagonist and bind to the IL-36R similarly to the IL-36 receptor antagonist (IL-36Ra). Therefore, IL-38 overexpression inhibits IL-36 signaling, thereby downregulating T helper 1 (Th1) differentiation and resulting in poor survival. The homology of IL-38 to IL-1Ra (41%) and IL-36Ra (43%) has raised expectations for its potential therapeutic utility; however, currently available data indicate that this cytokine has type-specific effects on different cancers (14, 18, 20-22).

Like other tumors, the development of SGCs is influenced by the tumor microenvironment and controlled by the host's immune system (23, 24), suggesting that IL-38 may play a role in SGC development and progression. To the best of our knowledge, IL-38 has not been assessed in individuals diagnosed with SGCs. Therefore, this study aimed, for the first time, to assess IL-38 serum levels in Iranian individuals diagnosed with both benign and malignant SGCs, compared with healthy individuals, to explore its potential as a diagnostic biomarker. Additionally, to address the role of IL-38 in SGCs, the correlation between this cytokine and patients' clinicopathological characteristics was also assessed.

Methods

Ethics

Patients participated in the study in accordance with the guidelines established by the local Ethics Committee of Shiraz University of Medical Sciences (approval ID: IR.SUMS.DENTAL.REC.1401.028). Written informed consent was obtained from all participants in the study.

Study Design

This retrospective cross-sectional study included 120 Iranian patients with SGCs who were referred to the Ear, Nose, and Throat (ENT) department at Khalili Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. The sample size was determined based on previous studies. Eligible patients were pathologically confirmed cases of benign ($n=64$) and malignant ($n=56$) SGCs, aged over 18 years at diagnosis, who had not received any treatment prior to inclusion. Patients were excluded from the research if they had genetic or systemic inflammatory diseases, received any medication for SGCs, or had any tumors other than SGCs. The international staging system (www.cancer.org) was used to determine the tumor-node-metastasis staging for SGCs. Medical records were retrieved from the patient database. The control group for this study consisted of 60 healthy blood donors who met the inclusion and exclusion criteria. They were matched to each case based on their age and gender.

Evaluation of IL-38 Serum Levels

Approximately 5 mL of whole blood was collected from each participant and centrifuged at 3000 RPM for 5 minutes. A commercially available ELISA kit (Cat. No. E4686Hu, Bioassay Technology Laboratory, China) was used to measure IL-38 levels in serum. Briefly, all samples, reagents, and standard solutions were prepared and added to their respective wells according to the manufacturer's guidelines. The working solution of Streptavidin-HRP was subsequently added to all wells, except the blank control well. The plate was then incubated at 37 ºC for 60 minutes. After several washes to remove excess enzyme conjugate, each well received the substrate solution, and the plate was incubated for 10 minutes at 37 ºC. Finally, the stop solution was added to terminate the enzymatic reaction. Immediately afterward, the optical density (absorbance) of each well was measured at 450 nm using a microplate reader (Biochrom Anthos 2020, Cambridge, UK).

Statistical Analysis

IBM SPSS software version 22.0 (IBM, Armonk, NY, USA) was used for all statistical analyses. To assess data normality, the Kolmogorov–Smirnov test was used. When comparing categorical variables, Fisher's exact test or the Pearson chi-square test ($\chi 2$) was used, depending on the situation. The independent-samples *t*-test was used to compare continuous variables between groups. To test for significant differences among the means of three or more independent groups, a one-way analysis of variance (ANOVA) was conducted, followed by Tukey's post hoc test. All reported probabilities (*p*-values) were considered statistically significant if less than 0.05.

Results

The patient group ($n=120$) had a mean age of 43.7 ± 17.3 years, ranging from 19 to 79 years, with 56 (46.7%) males and 64 (53.3%) females. The control group consisted of 30 (50%) males and 30 (50%) females, with a mean age of 47.5 ± 13.8 years, ranging from 20 to 78 years. The distribution of age ($P=0.111$) and gender ($P=0.752$) among the study groups did not differ significantly.

IL-38 Serum Levels in Patients and Control Groups

Compared to the control group, patients with SGCs had significantly higher serum levels of IL-38 (38.6 ± 6.8 ng/L vs. 49.1 ± 6.2 ng/L, $P<0.0001$). The mean IL-38 serum levels did not differ significantly between participants aged below or over 50 years, neither in patients (48.5 ± 6.7 ng/L vs. 50.1 ± 5.3 ng/L, $P=0.172$) nor in controls (37.7 ± 7.5 ng/L vs. 39.8 ± 5.8 ng/L, $P=0.332$). Additionally, IL-38 serum levels were similar between males and females in patients (48.5 ± 6.5 ng/L vs. 49.6 ± 6.1 ng/L, $P=0.369$) and in the control group (38.1 ± 8.5 ng/L vs. 39.1 ± 5.7 ng/L, $P=0.672$).

To assess the diagnostic value of IL-38, a receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated. As shown in Figure 1, IL-38 serum levels demonstrated strong diagnostic potential for SGCs (AUC = 0.870, 95% CI: 0.815– 0.924, $P<0.0001$).

IL-38 Serum Levels in Patients with Benign and Malignant Salivary Gland Cancers

The patient group was further divided into two subgroups of benign ($n=64$) and malignant ($n=56$) SGCs. While mucoepidermoid carcinoma (35.7%), adenoid cystic carcinoma (35.7%), and acinic cell carcinoma (10.7%) were the most common malignant SGCs, pleomorphic adenoma was the most common benign tumor, accounting for 100% of cases. Table 1 provides an overview of the clinical and demographic traits of patients with SGCs.

Compared to the benign group, patients with malignant SGCs had significantly higher serum levels of IL-38 (48.2 ± 7.1 ng/L vs. 50.2 ± 4.8 ng/L), but the difference was not statistically significant ($P=0.085$). However, the mean IL-38 serum levels in both benign and malignant SGC groups were significantly ($P<0.0001$) higher than those in the control group (Figure 2).

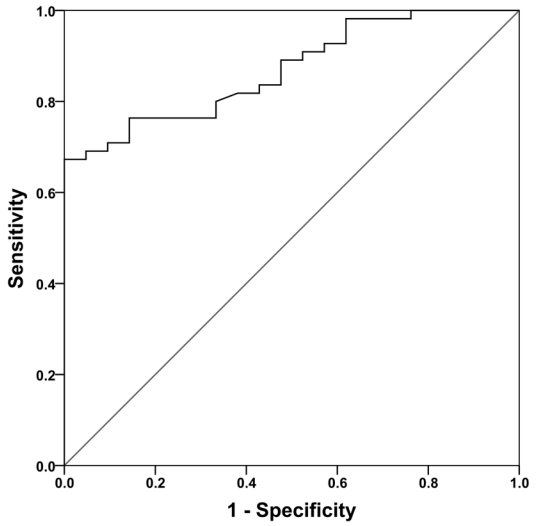

Figure 1. ROC curve analysis for the diagnostic value of IL-38 serum levels

Correlation of IL-38 Serum Levels with Clinicopathological Characteristics of Patients with Salivary Gland Cancers

There was a significant negative correlation between IL-38 serum levels and SGC size ($R=-0.195$, $p=0.042$). However, no significant correlation was found between serum IL-38 levels and other clinicopathologic features of patients, including SGC stage ($P=0.649$), tumor type ($P=0.198$), and lesion location ($P=0.136$), neither in all patients nor in the benign and malignant subgroups.

Discussion

Dysregulation of immune responses is often linked to the development of multiple chronic diseases, including cancer. Inflammation is a biological response of the immune system to harmful stimuli that involves the upregulation of pro-inflammatory signals (12, 13). IL-38 is a unique cytokine that exerts broad anti-inflammatory properties by inhibiting downstream signaling pathways, especially the secretion of pro-inflammatory cytokines. Therefore, it plays a crucial role in a wide array of immune-mediated disorders. Currently, the signaling pathways activated by pro-inflammatory cytokines represent the most innovative strategies for antitumor therapies (22, 25, 26). However, the exact mechanism by which IL-38 expression contributes to carcinogenesis, cancer growth, and poor prognoses is still unknown.

In the current study, we first examined serum IL-38 levels in patients with SGC and found that IL-38 levels were significantly higher in SGC patients than in control subjects. The serum levels of this enigmatic cytokine

Table 1. Demographic and clinical characteristics of patients diagnosed with SGCs

Variables			Benign $n=64$	Malignant $n=56$	P value
Sex	Male, *n* (%)		32 (50%)	24 (42.9%)	$P=0.467$
	Female, *n* (%)		32 (50%)	32 (57.1%)	
Age	Mean ± SD		36.8 ± 12.9	51.1 ± 18.4	$P<0.0001$
	< 50 years, *n* (%)		52 (81.2%)	22 (39.3%)	$P<0.0001$
	≥ 50 years, *n* (%)		12 (18.8%)	34 (60.7%)	
Tumor characteristics	Size	Main tumor Mean ± SD	3.44 ± 1.51	2.75 ± 0.91	$P=0.003$
	Location	Major glands	56 (87.5%)	42 (75%)	$P=0.099$
		Minor glands	8 (12.5%)	14 (25%)	
	Type	Acinic cell adenocarcinoma	N/F	6 (10.7%)	$P<0.0001$
		Adenoid cystic carcinoma	N/F	20 (35.7%)	
		Mucoepidermoid carcinoma	N/F	20 (35.7%)	
		Squamous cell carcinoma	N/F	4 (7.1%)	
		Pleomorphic adenoma	64 (100%)	N/F	
		Others	N/F	6 (10.7%)	
	Stage	I	----	6 (10.7%)	----
		II	----	15 (26.8%)	
		III	----	21 (37.5%)	
		IV	----	14 (25%)	

N/F: not found

Categorical and continuous variables were compared using Pearson's chi-square test and independent samples *t*-test, respectively. All reported *P*-values were considered statistically significant if less than 0.05.

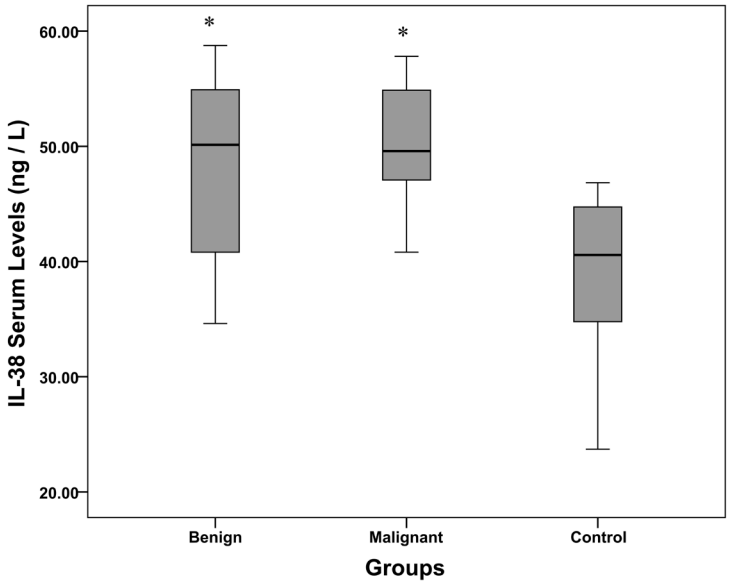

Figure 2. IL-38 serum levels in the study groups. An asterisk (*) indicates a statistically significant difference ($P<0.0001$) between patient subgroups and the control group

also showed strong potential to differentiate patients from the control group. To the best of our knowledge, there is no existing data on IL-38 serum levels in SGCs, making this the first report on the subject. However, IL-38 is constitutively expressed across multiple tissues to maintain homeostasis, including the thymus, tonsils, placenta, heart, lungs, spleen, fetal liver, urogenital system, and intestine. The highest levels of expression were detected in skin and salivary gland tissues (14-16). Although the origin of circulating IL-38 in patients with SGCs remains unknown, its expression is elevated in immune cells and other cell types during inflammatory conditions (14). This upregulation may lead to the release of IL-38 protein into patients' bloodstreams.

According to this study's findings, mean IL-38 serum levels did not differ significantly between patients with

benign and malignant SGCs; however, circulating IL-38 levels in both groups were significantly elevated compared to the control group. The absence of substantial differences in IL-38 serum levels between patients with benign and malignant tumors may be due to several factors. IL-38 is an anti-inflammatory cytokine that may modulate general immune responses in a non-specific manner rather than directly impacting tumor progression or malignancy. Therefore, its role in malignancy may not be as pronounced as that of other cytokines, such as IL-10 or TGF-β, which promote tumor growth and metastasis (14, 27-29). Both benign and malignant tumors have highly complex and heterogeneous microenvironments that include a variety of immune cells, cytokines, and signaling pathways. This complexity can make it difficult to pinpoint the specific effects of cytokines, such as IL-38, within the system (18, 30-32). Another reason could be that IL-38 may not exhibit sufficient sensitivity or specificity to differentiate between benign and malignant conditions effectively. The inflammatory response in benign tumors is usually less aggressive and may involve distinct cytokine profiles compared to that in malignant tumors (18, 33). Research on ovarian tumors has demonstrated that although specific cytokines such as IL-6 and IL-8 show intermediate levels between benign and malignant cases, they do not provide definitive differentiation (34). A study on thymus tumors also utilized Mendelian randomization and proteomics to identify potential causal cytokines, highlighting the intricate relationship between cytokines and tumor pathology (35). Additionally, serum cytokine levels may not fully reflect the local inflammatory processes in the tumor microenvironment. Thus, cytokine activity may be more localized to tumor tissue itself, and the absence of significant differences in systemic circulation does not necessarily reflect local biological activity (36, 37). These findings suggest that relying solely on circulating IL-38 levels may not reveal significant differences between benign and malignant tumors.

In SGCs, the clinical course of the disease is closely related to the time of diagnosis; therefore, identifying diagnostic/prognostic biomarkers and novel therapeutic targets could improve clinical outcomes (38, 39). The current gold standard for cancer diagnosis is based on histopathological examination of tumor tissues; however, this is considered an invasive and expensive approach. As a result, research interests have shifted toward other tools, such as blood-based screening tests, to improve not only tumor diagnosis but also patient clinical management (40-42). In comparison to the control group, our Iranian patients with SGCs, both benign and malignant, had higher levels of IL-38. This suggests that IL-38 could serve as a non-invasive biomarker to support the early diagnosis of SGCs. However, further studies with larger sample sizes are highly warranted.

Several studies in the literature have evaluated IL-38 expression by immunohistochemistry and its prognostic value in other human cancers, yielding contradictory results. Takada et al (20) conducted a study on tumor tissue sections that revealed elevated expression of IL-38 in several cancer types, including lung, breast, liver, gastric, and colon cancers. However, the value of this research is limited by a small sample size (10 cases per cancer type). IL-38 expression was elevated in approximately 56% of samples in other studies involving a larger number of patients with primary lung adenocarcinoma (18, 20). In contrast, lower levels of IL-38 mRNA and protein were detected in patients with non-small cell lung cancer (NSCLC) compared to paired adjacent non-cancerous tissues. This was confirmed by Western blot analysis (17). A notable decrease in IL-38 expression (up to 95%) was also observed in the gut epithelium of patients with colorectal cancer (19, 43). Higher levels of IL-38 expression were associated with more prolonged survival in patients with colorectal cancer (43), while intense staining of IL-38 in lung adenocarcinoma correlated with shorter survival and higher tumor grade (20). The reasons for the divergent and opposite effects of IL-38 in different tumors are unknown. However, they may be attributed to differences in study design, patient population, tumor micro-environment, and mechanisms by which IL-1 family cytokines are produced.

Generally, IL-1 family cytokines are considered central mediators of interactions between non-immune and immune cell types in the tumor microenvironment. These cytokines are produced by tumor cells themselves and/or by infiltrating immune cells. The production of these cytokines is also influenced by the specific tissues or organs involved, the level of inflammation, and the progression of the tumor. The distinct processing of the precursor form of IL-38 by various tumor types, along with the functional differences between full-length IL-38 and its truncated form, may also be additional factors influencing outcomes. However, distinguishing these conditions in clinical samples was unfeasible with the existing tools. Opposing roles in cancer have been described for several members of the IL-1 family, including IL-1α, IL-1β, IL-18, IL-33, and IL-37 (14, 44). Due to the limited number of studies and conflicting findings, understanding the role of IL-38 in human cancers requires much more research.

We also found a significant negative correlation between IL-38 serum levels and SGC size, but not with other clinicopathologic characteristics, including type, location, and stage. Chen et al (43) found that IL-38 was correlated with tumor differentiation, left-sided lesion location, and smaller tumor size in patients with colorectal cancer. Takada et al (20) also found a significant association between IL-38 expression and clinicopathological characteristics of patients with primary lung adenocarcinoma, including tumor grade, stage, pleural invasion, and vascular invasion. Non-small

cell lung cancer patients with strong, weak, or negative IL-38 expression also showed significant differences in some clinicopathological factors, including tumor-node-metastasis stage and differentiation (17). Typically, IL-38 expression can be influenced by factors such as tumor size, histologic type, clinical stage, lymph node involvement, and distant metastasis. Therefore, variations in IL-38 levels may be related to the specific conditions of each cancer type and to different molecular pathways that contribute to cancer development.

This study is the first to investigate serum levels of IL-38 in patients with benign and malignant SGCs. It is important to note that the study has several limitations due to methodological flaws and possible unmeasured confounding factors. Firstly, the limited sample size of patients across tumor stages precluded a correlation between IL-38 and tumor grade. Secondly, this study was a single-institutional retrospective study. Thirdly, a disparity in the number of patients with SGCs compared to control participants may result in residual confounding. Therefore, further studies with larger sample sizes, more cases per tumor grade, and extended follow-up periods are highly warranted.

Conclusion

This research demonstrates that IL-38 serum levels are markedly elevated in patients with SGCs compared to control participants, implying that IL-38 could be a reliable biomarker for distinguishing between the two groups. Additionally, IL-38 may be a valuable tool for non-invasive diagnostic tests to identify individuals at high risk. Furthermore, IL-38 seems to be involved in the development and progression of SGCs by affecting both host immunity and the tumor microenvironment. Therefore, targeting cell types that produce IL-38 or its release pathway could hold promise as a therapeutic approach for patients with SGCs. While this initial study underscores the clinical relevance of IL-38 serum levels, further research is needed to fully understand its impact on SGCs and other cancer types.

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Authors' Contribution

Conceptualization: Ali Tadayon, Mohammad Javad Fattahi, Maryam Mardani.
Data curation: Behnaz Nazari, Javad Moayedi.
Formal analysis: Javad Moayedi.
Funding acquisition: Maryam Mardani.
Investigation: Mohammad Javad Fattahi, Behnaz Nazari, Maryam Mardani.
Methodology: Ali Tadayon, Behnaz Nazari, Mohammad Javad Fattahi.
Software: Javad Moayedi.
Supervision: Maryam Mardani.
Writing–original draft: Javad Moayedi.

Competing Interests

The authors declare that they have no conflicts of interest.

Data Availability

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The research protocol was approved by the local Ethics Committee of Shiraz University of Medical Sciences (approval ID: IR.SUMS.DENTAL.REC.1401.028).

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