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Study of Gene Expression Variation of Heat Shock Factor 1 and Estimates of the Concentration of Epithelial- Derived Neutrophil-Activating Protein-78, and Ability for Bacterial Biofilm Formation in Patients with Tonsillitis

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Abstract

Background: Tonsillitis is an inflammation of the tonsils, often spreading to the adenoids and lingual tonsils. It is influenced by immune and genetic factors. This study aimed to evaluate the gene expression of *Heat Shock Factor 1(HSF1),* a protein that regulates cellular responses to stress, especially heat stress, and to measure the concentration of epithelial-derived neutrophil-activating protein-78, a chemokine involved in neutrophil activation and recruitment during inflammation. The study also sought to explore the relationship between these molecules and their roles in inflammation and stress responses. Additionally, it aimed to isolate bacterial species responsible for tonsillitis and assess their ability to form biofilms.

Patients and Methods: Sixty blood samples from tonsillitis patients and 30 from healthy individuals were collected, along with 200 throat swabs from patients, between December 2023 and March 2024. Blood samples were processed for ELISA to quantify ENA-78 and for RNA extraction to analyze *HSF1* gene expression. Bacterial cultures were grown on Congo Red Agar to detect biofilm production.

Results: Out of 120 positive cultures, 70% were Gram positive, 23% were Gram negative, and 7% mixed. ENA-78 levels were significantly higher in patients (619.2±123.4) than in controls (490.1±145.8) pg/mL ($P \leq 0.0001$) *HSF1* gene expression was also significantly elevated in patients (9.913) ($P = 0.0001$).

Conclusion: Gram positive bacteria, particularly *Staphylococcus aureus*, were the predominant biofilm producers, while *Escherichia coli* was common among Gram-negative isolates. Significant differences in ENA-78 levels and *HSF1* expression suggest their potential as diagnostic markers and targets for immune - based therapies.

Keywords: Tonsillitis, ENA-78, *HSF1,* Biofilm formation.

Introduction

Tonsillitis is the inflammation of the tonsils, which typically spreads to the adenoid and lingual tonsils. The tonsils are part of Waldeyer's ring, which consists of lymphatic tissue (1). The tonsil is an autonomous organ composed of Mucosal-Associated Lymphoid Tissue (MALT), As the initial line

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of defense against invading infections, the tonsil has the ability to selectively modulate immunological responses throughout the body (2).

The palatine tonsil, situated near the pharyngeal opening, is a suitable location for exposure to foreign substances, including bacteria and viruses, and their subsequent transfer to lymphoid cells. The immune system depends on the creation of lymphoid cells, such as T and B cells, which is continuously stimulated by healthy palatine tonsils (3). Although it affects people of all ages and genders, school–aged children are especially more likely to experience this, particularly during the fall and winter months. A tonsillar infection may be hypertrophic, recurring, chronic, or acute (4).

The inflammation of the palatine tonsils, known as tonsillitis, is brought on by bacteria, viruses and other immunologic causes (5). Although tonsillitis is typically treated symptomatically with good clinical outcomes, complications such as, rheumatic fever, abscesses, acute glomerulonephritis, and scarlet fever, can arise due to the fact that many organisms inhabit the oropharynx, including *Streptococcus pyogenes*, *Staphylococcus aureus*, *Hemophilus influenza*, and *Streptococcus pneumoniae* (6). Tonsillitis refers to a variety of infectious and inflammatory disorders that can be bacterial or viral. Since most viral tonsillitis episodes resolve on their own, it is crucial to distinguish between the two etiologies for treatment purposes. Nonetheless, bacterial tonsillitis patients can benefit from treatment by experiencing a shorter illness duration and fewer sequelae (7). In healthy tissue, epithelial cells are the crucial source of the CXC chemokine, well-known as epithelial cell-derived neutrophil-activating peptide 78 (ENA-78). In inflammatory tissue, however, inflammatory cells that penetrate the submucosa are the most significant cellular source of this chemokine. The body's initial line of defense, neutrophils, respond swiftly to invading microorganisms and tissue injury (8). This chemokine is composed of 78 amino acids and comprises four cysteines; it seems to be a homologue of IL-8 (9).

Most tissue and cell types express *Heat Shock Factor 1*, a key transcription factor that is activated by heat. It is dormant when no stimuli are present (10) .An increase in temperature is necessary for *HSF1* activation because heat separates the *HSF1* inhibitory complex in the cytosolic compartment and creates a DNA-binding competent homotrimer complex (11).

The current study aimed to study gene expression variation of *Heat Shock Factor1*, to estimate the concentration of epithelial-derived neutrophil- activating protein- 78 in patients compared to healthy individuals, and to isolate bacterial species causing bacterial tonsillitis and producing biofilm.

Patients and Methods

Study design: This study is a cross-sectional study at Tikrit Teaching Hospital. Swab samples were obtained from patients admitted to the ear, nose, and throat unit at Tikrit Teaching Hospital, in Salah AL Din Governorate between December 2022 to March 2023. Patients were divided into two groups: acute infection into 32 and chronic infection 88.

Swabs were removed from the tonsil surface without touching any neighboring surfaces, and all samples were collected in a way that prevented contamination. The swabs were then closed immediately until transferred to the microbiology laboratory of Tikrit Teaching Hospital and cultured on various media for 24 hours at 37 °C, followed by Gram staining and biochemical tests for bacterial identification. Transport media were utilized for delayed cases (12).

Detection of biofilm-producing bacteria: Congo red agar plates were prepared, inoculated with the bacterial isolates, and then incubated in an incubator at 37°C for 24-48 hours. After incubation, the color of the growing bacterial colonies was observed, with black colonies

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indicating that they were biofilm producers. Red colonies did not produce biofilms (13).

Immunological and genetic evaluation: For immunological and molecular detection, five milliliters of venous blood were obtained from each patient and control individual's, transferred into a gel tube, centrifuged at 4500 rpm for 8 minutes, and the serum was collected in sterile Eppendorf tubes in two copies and kept frozen at -20 ℃ for ELISA testing to limit the level of ENA-78, using the ENA-78 ELISA kit made by Sun Long (China). Additionally, 250 ml of whole blood was added to Eppindr of tube containing 750 µl of TransZol and mixed well to use for gene expression variation, The primers were designed specifically for this study (F: ATCTTCCGTGGACACCCTCT, R: GCTACG CTGA GGCACTTTTC)

Gene expression analysis: After collecting the blood sample, 250 microliters were combined with 750 microliters of Trizol. RNA was extracted from Trizol-preserved whole blood samples from 30 control subjects and 60 tonsillitis patients. The mRNA was extracted using the Transzol up Plus RNA kit from TRANS Company(china). To measure gene expression using the two-step qPCR technique, during the two-step thermal cycling, single strands of RNA were converted into complementary strands of cDNA using the Easyscript First-Strand cDNA Synthesis Diagnostic Kit prepared by TRANS Company. At Tikrit University, College of science, Department of Biology-Molecular Laboratory, the RT-qPCR reaction was performed. the reaction mixture was prepared using Biolab's Luna® Universal qPCR Master Mix extraction kit.

Statistical analysis

Microsoft Excel 2010 and the statistical program for social science (SPSS) version 23 and ROC curve were used to gather, compile, analyze, and present the data. When means and standard deviation data were analyzed using the t-test, a P-value of 0.05 was deemed significant. The Δct value and the ΔΔct value were utilized to perform statistical evaluations during qPCR, and to determine the relative fold change in gene expression of the sample.

Results

Distribution patterns of tonsillitis based on infection type: A total of 120 swab specimens were obtained for the current investigation from patients with tonsillitis of both genders in various age groups between December 2023 and March 2024. Additionally, blood samples were taken from both healthy individuals and those who were sick.

Acute and chronic tonsillitis were separated into two categories based on the specialist doctor's assessment, with varying numbers and percentages. As seen in Figure 1, the majority of tonsillitis patients with chronic infection, 88(73.3%), emerged first, followed by acute infection 32(26.6%).

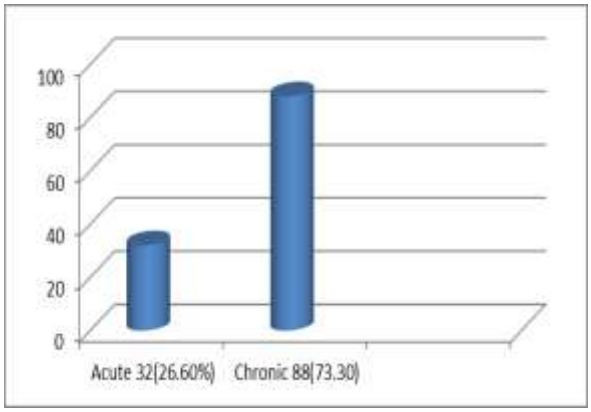

Figure 1. Distribution of Tonsillitis cases according to type of infection.

Gender differences in tonsillitis incidence: The distribution of patients in this study, according to their gender, was as follows: male (115) and female (85). These sample size represent the number of people from each gender who were tested or diagnosed with tonsillitis in our study and showed that males were more likely than females to have tonsillitis, as shown in Figure 2.

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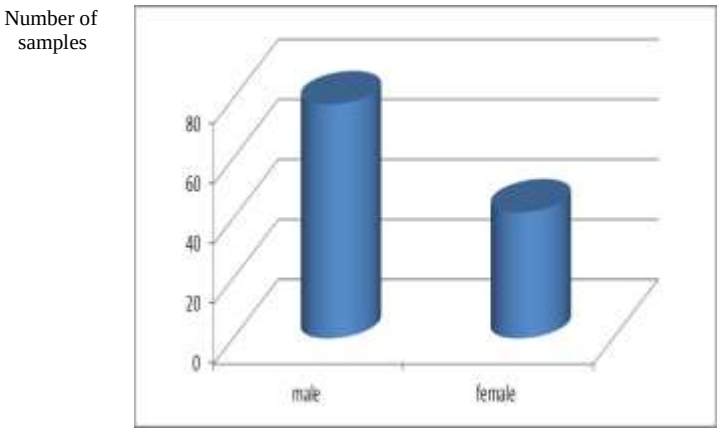

Figure 2. Distribution of tonsillitis cases according to gender.

Distribution of tonsillitis cases according to age: Patients were divided into four age categories: The group from 1 to 10 years had the highest infection rate at 48%. This indicates that nearly half of the patients in this group were affected by the infection. The infection rate for the 11–20-year-old group was 33%, which is lower than that of the 1–10-year-old age group but still represents a significant proportion of patients. The 21-30 years group had an infection rate of 13%, which is much lower than both of the younger groups, indicating that fewer patients in this age range were infected. The infection rate of group 31- 40 years was 7%, which is lower than all groups, as shown in Figure 3.

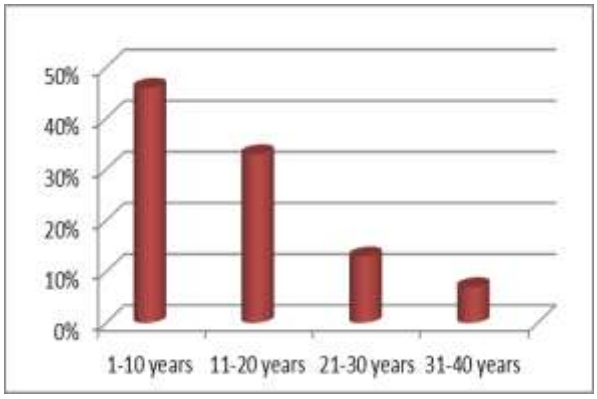

Figure 3. Distribution of Tonsillitis cases according to the Age.

Bacterial isolation and identification: Biochemical tests and culture characteristics were used to diagnose the bacterial isolates. The Vitek 2 technique was also used to diagnose several isolates at the species level. Culture was the major method used to characterize the bacterial isolates. All of the isolated bacteria were then subjected to morphological, microscopic, and biochemical testing using blood agar, Mannitol salt agar, MacConkey, Eosin Methylene Blue agar, and Gram stain (14).

According to the bacteriological study, numerous bacteria were found in the tonsil swabs of patients who were examined; of these, 70% were found to be Gram positive, 28% to be Gram negative, and 7% to be mixed growth. The Gram-positive bacteria were *Staphylococcus aureus and Streptococcus pyogenes*, while the Gram negative were *Esherichia coli*, *Klepsiella Pneumoniae*, and *Seratia fonticola.* The results revealed a predominance of Gram-positive bacteria, with the most common isolates being *S.aureus* and *S.pyogenes*, there was also a significant presences of Gram-negative bacteria, with *E.coli* and *K.pneumoniae* being the most notable pathogens, as shown in Figure 4.

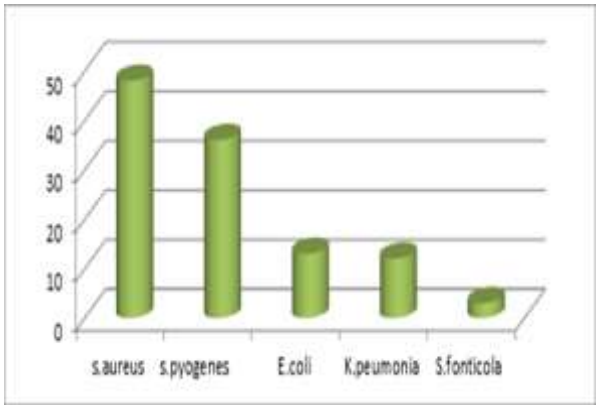

Figure 4. Bacterial species isolated from tonsil swabs.

Biofilm Formation of Bacterial Isolates: As shown in Figure 5, the study demonstrated that

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S. aureus isolates were biofilm producers at a percentage of 38 (79%), *S. pyogens* at 25 (70%), *E. coli* at 8 (62), *K. pnemoniae* at 7 (58%), while *S. fonticola* was at 0 (0%). The ability of 114 isolates to produce biofilm was examined, as shown in Table 1. The results indicate that *S. aureus*, *S. pyogenes*, *E. coli*, and *K. pneumoniae* all exhibit varying abilities to produce biofilms, with *S. aureus* and *S. pyogenes* being the most prominent biofilm producers. Conversely, *S. fonticola* does not produce biofilms under the tested conditions, which might have implications for its role in infections. These findings highlight the potential importance of biofilm formation in the pathogenicity and persistence of certain bacterial species.

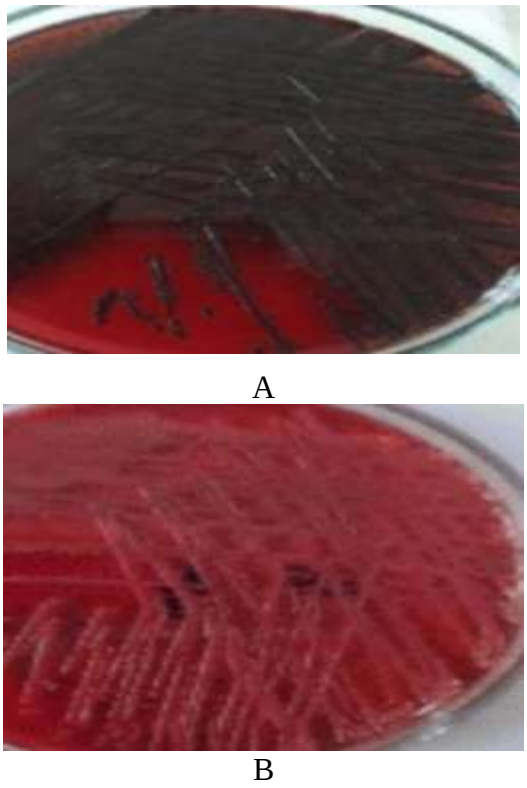

Figure 5. Biofilm production on Congo red agar: A: Positive result, B: Negative result.

Table 1. Comparative Analysis of *H. pylori* Infection in Benign and Malignant Lesions. N.S.: not significant (p > 0.05).

Bacteria	Positive to biofilm production	Negative to biofilm production	Characteristic of the participants
S.aureus	12(25%)	38(75%)	88 chronic and 26 acute
S.pyogenes	11(30%)	25(70%)	
E.coli	5(38%)	8(62%)	
K.pnemoniae	5(41%)	7(58%)	
S.fonticola	3(100%)	0(0%)	

ENA-78 levels for tracking inflammatory signals from epithelial cells: The findings demonstrated a notable difference in ENA-78 levels between patients and control individuals. The Mean ±SD were (619.2 ± 123.4) and (490.1 ± 145.8) pg/mL respectively, as shown in Figure 6, which visually presents this difference in the form of a box plot, where the patients group has a higher average ENA-78 level than the control group, with variation shown by the error bars.

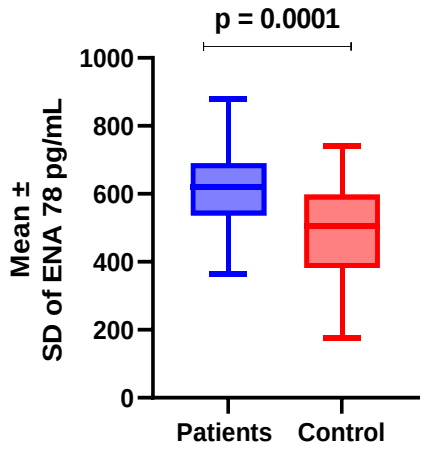

Figure 6. The level of ENA-78 in patients and in healthy people.

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The expression of HSF1: Figure 7, Table 2, and ROC curve (Figure 8) demonstrate that the variation reaches a significant value when comparing the gene expression data between the patient and healthy groups (9.913). The values of ΔCT (mean ± SD) were (-0.7615±0.452) (7.975±4.342), respectively. These were the Roc curve readings (AUC = 0.9607) (sensitivity% = 93.33) (specificity%=85.56), (P=0.0001).

The variation reaching a significant value refers to a notable difference in the gene expression data when comparing the patient group to the healthy group, the P value indicates statistically significant results, meaning the observed differences are highly unlikely to have occurred by chance. ΔCT refers to the difference in the threshold cycle between the target gene and a reference gene (GAPDH) in the PCR analysis. This indicates that the patients show a lower CT value compared to the healthy group, suggesting a higher expression of the gene in patients compared to healthy individuals, a lower CT value typically corresponds to higher gene expression.

Table 2. Expression of *HSF1* in patients and control.

Gene	ΔCT of patients (mean ± SD)	ΔCT of control (mean± SD)	P value	Expression fold ($2^{-\Delta\Delta ct}$)
HSF1	-0.7615± 0.452	7.975± 4.342	0.001	9.913

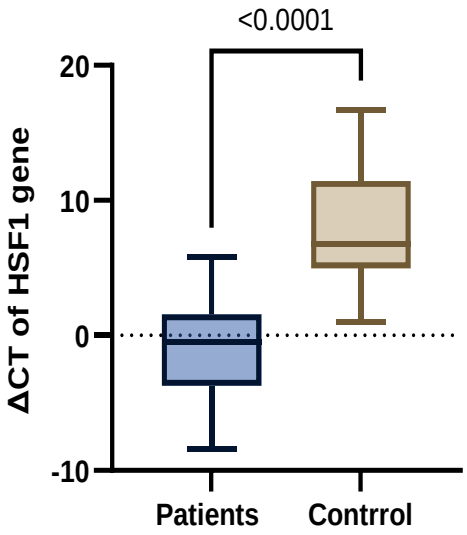

Figure 7. Relative expression levels of *HSF1* in patients compared with controls, ΔCT = Delta cycle threshold.

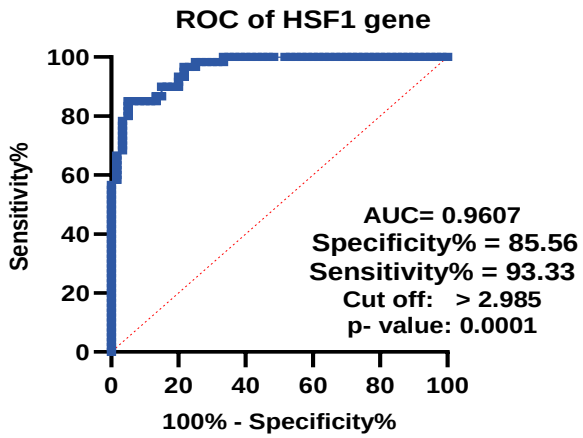

Figure 8. ROC curve of *HSF1*.

Discussion

This study separated patients into two types of infection. The high percentage of tonsillitis appeared with chronic tonsillitis. This study differed from a study by (14), which revealed that the proportion of acute infections was higher than that of chronic infections. The synthesis of β-lactamase and resistance in numerous organisms resulted in failed medical therapy and chronic or recurrent forms of tonsillitis. The influence of various types of food kinds is one of the risk factors for chronic tonsillitis since children often eat artificial sweeteners with a lot of preservatives and neglect their dental hygiene

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(15).

This study showed that males had a higher prevalence of infection compared to females. This finding is consistent with previous studies by (16, 17). Theoretically, gender differences in disease have been linked to genetic, biochemical, environmental, or psychosocial factors [19], Males are more likely to be exposed to infectious microorganisms and come into contact with ill individuals due to their environmental interactions (18), Woman have higher immune response to self and foreign antigens than men, resulting in gender disparities in autoimmunity and infectious disease. Males are more prone to bacterial infections than females, both in animals and humans (19).

This study separated patients into four age groups. The highest percentage of infection appeared in 1-10 age group. These findings were similar to other research, which has found that the majority of tonsillitis patients were children (5). Children increased activity at this age may enhance their susceptibility to infection compared to other age groups. In addition, this is the school age when children mingle and speak in the classroom (20). In children, the immune system is still developing to recognize and protect against germ. However, in adolescents and adults, the immune system quickly recognizes and attacks germs (21).

The bacteriological study revealed the presence of various bacteria in the tonsil swabs of the examined patients, illustrating that Gram-positive bacteria are the most common cause of bacterial tonsillitis. *S. aureus* was frequently found, followed by *S. pyogenes*. This result is similar to a study done by (22); gram-positive bacteria are the most common and most virulent cause of tonsillitis. They can also live as normal colonies on the skin and in other oral cavities, so that they may be more numerous than the Gram-negative bacteria (23).

Biofilm production by bacteria is highly relevant to tonsillitis, a condition characterized by inflammation of the tonsils, as it significantly impacts both the pathogenesis and treatment of the disease. The biofilm matrix, which is made up of extracellular polymeric substances (EPS), is essential for shielding bacteria from environmental stresses. It functions as an effective diffusion barrier, preventing dangerous substances from entering the biofilm (24). The host's immune system, antibiotics resistance, and other environmental factors have made bacterial biofilms a significant contributor to global health issues; the persistence of bacteria in biofilms can complicate the effectiveness of standard antibiotics. Antibiotics often struggle to penetrate the biofilm, and bacteria within it may have a slower growth rate, reducing the antibiotics' efficacy. In some cases, the biofilm can even cause bacteria to become more tolerant to the antibiotic treatment, leading to treatment failure or relapse of the infection (25, 26). A research (27) pointed out that a *S.aureus* is one of the most gram-positive bacteria forming biofilms, while another study (28) mentioned that *E.coli* is the most gram-negative bacteria forming biofilms, which agrees with our current study. Researchers' (29) showed that *S.aureus* and *E.coli* bacteria have the ability to form biofilms in tonsillitis patients, and this result similar to our current study, This is because of the crypt tissue structure and direct, repetitive exposure to respiratory bacterial pathogens, such as *S.aureus*, which cause chronic infections in the upper respiratory tract, including chronic tonsillitis, the tonsillar tissue and adenoids are prone to biofilm formation. Therefore, understanding biofilm production is crucial for improving the treatment of tonsillitis. Strategies to disrupt biofilms or develop drugs that can penetrate biofilm layers are areas of active research and could significantly enhance treatment outcomes, reducing the chances of chronic or recurrent infections and minimizing the need for frequent or prolonged antibiotic use.

Inflammation-activating peptide-78, a CXC chemokine, is produced by epithelial cells and attracts neutrophils (30).

The CXCL5 gene encodes, the inflammatory CXC chemokine ENA-78, and many inflammatory disease have elevated amounts of this chemokine (8). ENA-78 is involved in leukocyte recruitment and activation in autoimmune illnesses and inflammatory diseases. It can speed up the exodus of monocytes and macrophages and granulocyte from the

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bloodstream through the endothelium, this can lead to a significant increase in chronic inflammation (31). An elevated ENA-78 gradient in the blood leads to increased accumulation of neutrophils surrounding the lesions, and generating severe clinical symptoms (32).

There was a substantial difference in the relative expression of *HSF1* between patients and healthy individuals (-0.7615±0.452) (7.975±4.342), respectively, ($p=0.0001$), as shown in Figure 7 and ROC curve (Figure 8). Numerous studies have shown that changes in *HSF1* function impact protein homeostasis and are strongly linked to disease. *HSF1* is a member of the heat shock factor (*HSF*) family, which is activated under a variety of stressors and subsequently causes the upregulation of heat shock genes such as Hsp27 (33). The majority of tissues and cell types constitutively express *HSF1*, which has been shown to support the immune system's proper function (34). A basic and well- preserved cellular mechanism, the stress response, is also referred to as heat shock gene expression, shielding organisms from a variety of physical and chemical stresses, such as high temperatures, heavy metals, oxidants, and toxins, as well as bacterial and viral infections, is crucial. Anti-inflammatory prostaglandins and the high temperatures found in fever and inflammatory tissues can both cause *HSF1* (35).

One important metabolic mechanism that influences the resolution of inflammation, particularly in situations involving proteotoxic stress, is the heat shock response. Heat shock transcription factor 1, which is necessary for the expression of heat shock proteins and other chaperones, mediates this potent anti-inflammatory mechanism (36). Similar effects are seen in microbes, where *HSF1* activation causes an increase in HSPs in response to stress or injury. The association between ENA 78 and *HSF1* in tonsillitis may indicate that elevated ENA- 78 levels may lead to an increased inflammatory response in immune cells, which may stimulate increased expression of *HSF1*, furthermore, *HSF1* may play a role in regulating the immune response against pathogens such as bacteria or viruses during inflammation, and thus may influence inter-individual variation in the extent of immune cell response to inflammation (30, 37). This study is an extension of research focused on understanding the body's responses to chronic or acute infections; it aligns with current literature investigating the role of genetics and immune factors in the development of tonsillitis. Previous research focuses on the association of chemokines and genetic factors with disease progression, which may contribute to the development of more personalized treatment strategies. These finding are expected to help open up a deeper understanding of how chemokines, such as ENA-78, influence the immune system response in the tonsils. Studying *HSF1* gene expression may also provide insights into how to improve treatment response or predict treatment responses in patients. For example, this research may contribute to improved immunotherapies or gene modification strategies that target specific pathways in immune cells.

Conclusions

The results indicated that percentage of Gram-positive isolates was higher than Gram-negative isolates, in patients with tonsillitis, *S.aureus* was the most abundant biofilm-forming gram-positive bacteria, while *E.coli* was the most abundant biofilms- forming gram-negative bacteria. Males had a higher prevalence infection compared to females. The highest percentage of infection appeared in 1-10 age group, and there was a notable variation in ENA-78 levels between patients tonsillitis and healthy individuals. There was also a significant variation in the relative expression of *HSF1* between patients and controls. This study reveals potential links between increased ENA-78 concentrations and elevated *HSF1* gene expression and the severity of tonsillitis, offering a new path to understanding the immune dynamics of the disease, this could significantly impact improving immunotherapy for tonsillitis

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patients, as well as contributing to the development of targeted therapeutic strategies based on identifying the genetic factors involved. It can be used as a diagnostic marker. It was recommended to do more genetic studies to identify host factors required for successful bacterial tonsillitis infection.

Source of funding: No source of funding.

Ethical clearance: The Ethics Committee for this investigation at Tikrit Teaching Hospital, Salah Al Din, Iraq, approved the study with No. 2157 on 26 December 2022.

Conflict of interest: None.

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دراسة تباين التعبير الجيني لعامل الصدمة الحرارية ١ وتقدير تركيز البروتين المنشط للعدلات المشتق من الخلايا الظهارية والقدرة على تكوين الأغشية الحيوية البكتيرية لدى مرضى التهاب اللوزتين

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الملخص

الخلفية: التهاب اللوزتين هو التهاب يصيب اللوزتين يتأثر بعوامل مناعية ووراثية.

الأهداف: هدفت الدراسة الحالية الى تقييم التعبير الجيني لعامل الصدمة الحرارية ١,وهو بروتين ينظم الاستجابات الخلوية للإجهاد, وخاصة الاجهاد الحراري, وقياس تركيز البروتين المنشط للعدلات المشتق من الخلايا الظهارية -٧٨,وهو كيموين يشارك في تنشيط العدلات , كما سعت الدراسة الى استكشاف العلاقة بين هذين الجزيئين ودورهما في الاستجابة الالتهابية الضغوط الخلوية, بالإضافة الى ذلك, هدفت الى عزل الانواع البكتيرية المسببة لالتهاب اللوزتين وتقييم قدرتها على تكوين الاغشية الحيوية.

المرضى والطرق: تم جمع ٦٠ عينة دم من المرضى و٣٠ عينة من اشخاص اصحاء, بالإضافة الى ٢٠٠ مسحة من حلق المرضى خلال الفترة من كانون الاول ٢٠٢٣ الى اذار٢٠٢٤,تم معالجة عينات الدم باستخدام تقنية الاليزا للاختبار المناعي وتم استخلاص الحامض النووي الرايبي من عينات الدم كما تم زرع العزلات على وسط الكونغو الاحمر للكشف عن قدرتها على تكوين الاغشية الحيوية.

النتائج: من بين ١٢٠ مزرعة ايجابية , كانت ٧٠٪ ايجابية لكرام , و٢٣٪ سلبية لكرام, و٧٪ مختلطة, وكانت مستويات البروتين المنشط المشتق من العدلات أعلى بشكل ملحوظ لدى المرضى (١٢٣,٤±٦١٩,٢) مقارنة بالأصحاء (١٤٥,٨ ±٤٩٠,١) بيكوغرام/مل قيمة (P =(0.0001 كما كان تعبير الجين النسبي لعامل الصدمة الحرارية ١ مرتفعا لدى المرضى (٩,٩١٣) قيمةP=0.0001.

الاستنتاج: كانت نسبة البكتريا الايجابية لجرام اعلى من نسبة السلبية والمختلطة , ووجد تباين ملحوظ في مستويات البروتين المنشط للعدلات المشتق من الظهارية, و تباين كبير في التعبير الجيني النسبي لعامل الصدمة الحرارية بين المرضى والاصحاء, يمكن ان يكون لهذا تأثير كبير على تحسين العلاج المناعي لمرضى التهاب اللوزتين فضلا عن المساهمة في تطوير استراتيجيات علاجية مستهدفة تعتمد على تحديد العوامل الوراثية المعنية ويمكن استخدامها كعلامات تشخيصية للمرض.

الكلمات المفتاحية: التهاب اللوزتين, البروتين المنشط للعدلات المشتق من الخلايا الظهارية – ,٧٨ عامل الصدمة الحرارية ١ , تكوين الاغشية الحيوية.

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