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Correlation analysis of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α in refractory chronic rhinosinusitis: A retrospective study

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KEYWORDS
correlation analysis; interleukin; matrix metalloprotein 9; refractory chronic rhinosinusitis; tissue inhibitor of metalloproteinases 1; transforming growth factor-β

Abstract
Objective: To investigate the potential correlation of transforming growth factor-β (TGF-β), matrix metalloprotein 9 (MMP-9), tissue inhibitor of metalloproteinases 1 (TIMP-1), Interleukin 1 (IL-1), IL-4, IL-6, IL-17, and tumor necrosis factor alpha (TNF-α) in refractory chronic rhinosinusitis.
Methods: A total of 150 participants were retrospectively included in this study from August 2018 to February 2020. The people enrolled were equally allocated into refractory group (patients with refractory chronic rhinosinusitis), chronic group (patients with chronic rhinosinusitis), and control group (normal people). The level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α were recorded. The unconditional multivariate binary logistic regression was used to analyze the factors affecting refractory chronic rhinosinusitis.
Results: The Davos score, T&T olfactometer threshold test, and Lund-Mackay CT scores in refractory group were significantly higher than the chronic group ($P<0.05$). The level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α in the refractory group were significantly higher than the chronic group and the control group (all $P<0.05$). Similarly, the level of the above mentioned indexes in the chronic group were significantly higher than the control group ($P<0.05$). The Davos score, T&T olfactometer threshold test score, Lund-Mackay CT score, and the level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α positively correlated with refractory chronic rhinosinusitis. Moreover, the unconditional multivariate binary logistic regression showed that the influencing factors of refractory chronic rhinosinusitis included TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α.
Conclusion: The findings of the present study provide evidence for TGF-β1, MMP-9, TIMP-1, IL-4, IL-6, IL-17, and TNF-α as the influencing factors of refractory chronic rhinosinusitis.
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Introduction

Chronic rhinosinusitis (CR) is one of the most common diseases in otolaryngology-head and neck surgery, known as the heterogeneous inflammatory disease caused by multiple factors that occur in the mucosa of nasal cavity and paranasal sinus.[1] The incidence of this disease has experienced an increased trend through time, approximately 4.8% to 9.7% in China and 6.9% to 27.1% in Europe.[2,3] Currently, the glucocorticoid combined with surgery is often used to treat chronic sinusitis. However, many patients still developed a variety of symptoms such as head and face tightness, heavy feeling, nasal congestion, and mucopurulent rhinitis after receiving treatment.[4] Besides, the recurrence rate has been reported to be 4% to 6%, and the reoperation rate varies from 3% to 42% in different studies.[5]

Refractory chronic rhinosinusitis (RCR) is acknowledged as intractable CR among patients harboring simple chronic sinusitis and chronic sinusitis with nasal polyps, characterized by refractory to therapy and a high potential for recurrence.[6] Previous studies have shown that refractory to RCR can be summarized into two types: systemic and local. Systemic manifestations are mainly systemic inflammatory reactions, especially systemic lesions reflected in the local areas of the nasal cavity and sinus mucosa; local manifestations include perioperative operation errors and improper treatment, resulting in sinus mucosa, nasal wall and mucoperiosteum injury or excessive resection of intranasal tissues; in addition to local nasal bacterial infection, osteitis, and antigen variation, in some patients, it can also lead to increased difficulty in the treatment of refractory rhinosinusitis.[7] RCR is chronically prolonged and recurrent under the action of immune deposition, environmental substances, bacterial toxins and metabolites, which can have a substantial negative impact on the patient's mood, sleep, and memory, often resulting in impaired quality of life.[8] Many studies have been performed by researchers to explore the etiology, pathogenesis, diagnosis, and treatment of RCR. Genetic factors, immune deficiency, abnormal anatomy, and adverse environmental factors, including allergen stimulation, air pollution, and bacterial and fungal infection, have been considered to be the potential risk factors.[7] However, no final conclusion could be drawn with regard to the disease occurrence, development, clinical efficacy and prognosis of RCR. At present, the complex basis of RCR mainly lies in the involvement of multiple inflammatory mediators in the progression of the disease.[8] Studies have showed that TGF-β1 plays a potential role in the CR occurrence.[9] However, whether TGF-β1 and other inflammatory mediators, including MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α, are involved in the occurrence of RCR remained to be investigated.

Therefore, this study sought to investigate the correlation of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α in RCR by collecting and analyzing the Davos score, Toyota and Takagi (T&T) olfactometer threshold test score, and Lund-Mackay CT score.

Methods

Participants

Patients with RCR and CR who consulted the department of ENT from August 2018 to February 2020, were retrospectively included in this study. The inclusion criteria of the RCR group (refractory group) were as follows:

1. Refractory chronic rhinosinusitis diagnosed based on *the Chinese Guidelines for the Diagnosis and Treatment of Chronic Sinusitis (2018)*.[10]
2. Patients undergoing endoscopic sinus surgery.
3. Patients receiving standard perioperative treatment and nasal care.
4. Patients with persisting symptoms, more than six months even after receiving over three months of systematic post-operative medications, including oral or nasal glucocorticoids, antibiotics and nasal irrigation, with inflammatory changes of nasal sinus mucosa in CT images.

The inclusion criteria of CR group (chronic group) were as follows:

1. Chronic rhinosinusitis diagnosed according to *the Chinese Guidelines for the Diagnosis and Treatment of Chronic Sinusitis (2018)*. The diagnosis could be made if patients met one of the following primary symptoms with a combination of secondary symptoms and examination results. The primary symptom includes nasal obstruction and mucinous or mucopurulent nasal discharge. The secondary symptoms include head and face pain, anosmia, or loss of smell. The positive examination results indicate inflammatory lesions of sinus ostiomeatal complex and/or nasal sinus mucosa showed in paranasal sinus scan.
2. Patient had good compliance and healthy psychology.
3. There was no systemic application of antibiotics and glucocorticoid in the first half months of the study.

The exclusion criteria of both groups were as follows:

1. Patients with severe systemic diseases.
2. Patients with non-chronic inflammation or nasal polyps in pathological diagnosis.
3. Patients with acute paroxysmal sinusitis.
4. Patients receiving antibody treatment within 15 days.
5. Patients with acute paroxysmal sinusitis with pathogenic, other inflammatory, immune deficiency diseases and tumor diseases.
6. The refractory sinusitis is secondary to trauma.
7. The pathological diagnosis does not support chronic inflammation or nasal polyps.
8. Patients with lost follow-ups.

Another set of 50 healthy people were included in the control group for health examination.

This study was approved by the ethics committee of The First People's Hospital of Yinchuan (No. 2019-21-3). All participants provided written informed consent for participating in the study.

Scale evaluation

The information of patients, including age, sex, aspirin allergy, and asthma condition were collected and recorded. Besides, the Davos score, T&T olfactometer threshold test score, and Lund-Mackay CT score were also collected. The Davos score was used to evaluate the degree of polyp presentation. The Davos score was divided into three values for unilateral nasal cavity, where value 0 indicated that no polyps were found under endoscopy, value 1 indicated that polyps were seen in the middle nasal tract, and value 2 indicated that polyps were seen in the nasal cavity, but the nasal cavity was not blocked, and value 3 indicated polyps filled the nasal cavity. The total score ranged from 0 to 6. The T&T olfactometer threshold test was used to assess the olfactory function.[11] The olfactory function was divided into five values. Values 1 to 5 respectively represented normal, mild, moderate, severe hyposmia, and anosmia respectively. The Lund-Mackay CT score was used to evaluate the patency of each sinus, and had a total score range from 0 to 24 (higher scores indicate worse status).[12]

Evaluation of blood biochemical indexes

Around 8 ml fasting venous blood was collected from every patient and all the blood samples were divided into three parts. One sample was used for skin prick test to evaluate whether there was an allergic reaction. The other two samples were used for centrifugation. After centrifugation at 2500 r/min for 15 min, the supernatant was collected to detect the level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α by enzyme-linked immunosorbent assay (Boster Biological Technology, Wuhan, China).

Statistical analysis

The statistical analysis was performed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). For the measurement the data conforming to normal distribution, the data were expressed as mean ± SD. Univariate ANOVA test was used to compare the measurement data among the three groups, and Fisher's least significant difference test for pairwise comparison of inter group and intra group data. For the measurement data not conforming to normal distribution, the data were expressed as M (P25, P75), and Rank sum test was applied for comparison between the two groups. The counting data was expressed as percentage, and compared by Chi-square test. Unconditional multivariate binary logistic regression analysis was performed to analyze the relationship between biochemical indixes and RCR. $P<0.05$ was considered statistically significant.

Results

General information

The general information, including sex, age, aspirin allergy, asthma condition, Davos score, T&T olfactometer threshold test score, and Lund-Mackay CT score, were represented in the Table 1. There was no significant difference in sex ($P=0.778$), age ($P>0.999$), aspirin allergy ($P=0.169$), and asthma condition ($P=0.065$) among the three groups. In comparison with the chronic group, the refractory group was significantly associated with higher scores in the Davos score ($P<0.001$), T&T olfactometer threshold test score ($P<0.001$), and Lund-Mackay CT scores ($P<0.001$).

Comparison of the level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α among different groups

The level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α in refractory group were significantly higher than the chronic group ($P<0.05$) and the control group

Table 1 Patients' general information.

	Refractory group (n=50)	Chronic group (n=50)	Control group (n=50)	Z/F	P
Sex (male/female)@	39/11	38/12	36/14	0.502	0.778
Age (year)@	41.76±8.36	41.69±8.43	41.72±8.39	0.001	0.999
Aspirin allergy# (n)@	4	1	-	1.895	0.169
Asthma# (n)	9	3	-	3.049	0.065
Davos score#	2.31±0.15	2.08±0.16	-	7.415	<0.001*
T&T olfactometer threshold test score#	5.18±0.32	2.89±0.29	-	37.496	<0.001*
Lund-Mackay CT score#	18.79±0.42	13.29±0.37	-	69.481	<0.001*

@Comparison among three groups; #comparison between refractory group and chronic group; *P<0.05

Table 2 Comparison the level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α among different groups.

	Refractory group (n=50)	Chronic group (n=50)	Control group (n=50)	Z/F	P
TGF-β1 (pg/ml)@	402.31±75.29	629.98±79.14	1003.87±83.45	732.315	<0.001*
MMP-9 (μg/l)@	739.87±38.92	612.98±33.98	501.29±48.91	422.279	<0.001*
TIMP-1 (μg/l)@	16.92±2.12	12.01±2.09	7.28±2.03	268.440	<0.001*
IL-1 (pg/ml)@	336.87±8.98	212.98±9.07	38.87±34.87	2438.078	<0.001*
IL-4 (pg/ml)@	389.98±49.78	302.87±45.31	63.98±5.98	935.734	<0.001*
IL-6 (pg/ml)@	179.86±9.75	134.86±9.98	45.92±8.96	2534.625	<0.001*
IL-17 (pg/ml)@	78.98±5.19	45.45±5.02	17.98±5.13	1784.455	<0.001*
TNF-α (pg/ml)@	33.24±3.24	24.98±3.01	13.29±3.11	515.643	<0.001*

TGF-β: transforming growth factor-β; MMP-9: matrix metalloprotein 9; TIMP-1: tissue inhibitor of metalloproteinases 1; IL: Interleukin; TNF-α: tumor necrosis factor alpha; @Comparison among three groups; *P<0.05

(P<0.05), with the chronic group being significantly higher than the control group (P<0.05). (Table 2)

Correlation analysis between the RCR and level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, TNF-α and different scores.

The Spearman rank correlation analysis showed that the following parameters and indexes were positively correlated with refractory chronic rhinosinusitis, including Davos score (r=0.455, P=0.014), T&T olfactometer threshold test score (r=0.671, P=0.011), Lund-Mackay CT score (r=0.371, P=0.024), and the level of TGF-β1 (r=0.287, P=0.027), MMP-9 (r=0.897, P=0.009), TIMP-1 (r=0.431, P=0.015), IL-1 (r=0.172, P=0.043), IL-4 (r=0.109, P=0.047), IL-6 (r=0.298, P=0.011), IL-17 (r=0.766, P=0.011), and TNF-α (r=0.932, P=0.011).

Analysis of influencing factors of RCR by unconditional multivariate binary logistic regression

After setting the Davos score, T&T olfactometer threshold test score, Lund-Mackay CT scores as independent variables, and CS=Yes and RCR=No as dependent variable, the unconditional multivariate binary logistic regression was performed. The results showed that the influencing factors of refractory chronic rhinosinusitis were TGF-β1 (OR=0.879, CI%=0.749-0.912, P=0.007), MMP-9 (OR=0.208, CI%=1.675-2.421, P=0.003), TIMP-1 (OR=0.311, CI%=1.981-4.762, P=0.013), IL-1 (OR=0.211, CI%=0.031-0.612, P=0.007), IL-4 (OR=0.039, CI%=1.022-1.632, P=0.037), IL-6 (OR=2.803, CI%=1.517-4.387, P=0.003), IL-17 (OR=1.439, CI%=1.129-2.723, P=0.018), and TNF-α (OR=1.587, CI%=1.087-2.209, P=0.029). (Table 3)

Table 3 Logistic regression analysis of influencing factors of refractory chronic rhinosinusitis.

Variable	OR value (95%CI)	P
Davos score@	0.741 (0.511, 0.981)	0.083
T&T olfactometer threshold test score@	0.898 (0.509, 1.913)	0.099
Lund-Mackay CT score@	1.328 (0.802, 1.887)	0.104
TGF-β1@	0.879 (0.749, 0.912)	0.007*
MMP-9@	0.208 (1.675, 2.421)	0.003*
TIMP-1@	0.311 (1.981, 4.762)	0.013*
IL-1@	0.211 (0.031, 0.612)	0.007*
IL-4@	0.039 (1.022, 1.632)	0.037*
IL-6@	2.803 (1.517, 4.387)	0.003*
IL-17@	1.439 (1.129, 2.723)	0.018*
TNF-α@	1.587 (1.087, 2.209)	0.029*

TGF-β: transforming growth factor-β; MMP-9: matrix metalloprotein 9; TIMP-1: tissue inhibitor of metalloproteinases 1; IL: Interleukin; TNF-α: tumor necrosis factor alpha; @Comparison among three groups; *P<0.05

Discussion

Given that the Davos score, T&T olfactometer threshold test score, and Lund-Mackay CT scores have advantages of good operability and repeatability, they have been widely used for RCR study. Several studies have reported similar results.[13,14] According to Li et al.,[15] RCR had significant correlation with the Lund-Mackay nasal endoscopy score and Lund-Mackay CT score. The results of the present study are compatible with previous findings that the refractory group had significantly higher score in the Davos score, T&T olfactometer threshold test score, and Lund-Mackay CT scores than the chronic group.

Studies show that chronic sinusitis is not only a chronic inflammatory process, but also the abnormal remodeling of tissue repair. The remodeling process and chronic inflammation are parallel to each other. Tissue remodeling could occur in the early period of the disease, and might be necessary for the persistence of inflammation.[16] There are many causes of tissue remodeling, including chronic inflammation, mechanical trauma and so on.[17] However, the potential mechanism of bone tissue remodeling in RCR is largely unknown. Although no related pathogens were found in the pathological bone, the presence of a large number of inflammatory mediators in the bone tissue suggested that it may be aseptic inflammation. Ito et al.[18] and Ghisi et al.[19] reported the release of inflammatory mediators in rat otitis media model and rabbit sinusitis model, respectively, which suggested that some mediators of arachidonic acid pathway were the stimulating factors of bone remodeling. The regulation of bone remodeling depends

on a series of cytokines on the differentiation and activation of osteoclasts, including TNF, IL-1, IL-6, IL-11, IL-15, and IL-17.[20] TNF-α is a common multi-effector cytokine, and plays an important role in the pathogenesis of chronic sinusitis. It is able to mediate the adhesion and aggregation of leukocytes, lymphocytes, and vascular endothelial cells at the inflammatory site, thus inducing granulocytes to secrete cytokines such as IL-1, and promoting fibroblasts and vascular endothelial cells to secrete colony stimulating factors. This process may lead to the aggregation of neutrophils and eosinophils, and enable inflammatory cells to secrete inflammatory mediators such as leukotrienes and chemokines and injure nasal mucosa.[21] In addition, some studies have pointed out that TNF-α could activate the NF-kappaB and stimulate the expression of mRNA, and therefore likely to prompt the amplification effect between cells and factors, and aggravate the inflammatory response.[22] IL-1, mainly produced by macrophages, plays an essential role in transmitting information, activating and regulating immune cells, proliferation and differentiation.[23] IL-4 is an important inflammatory index. It could activate vascular endothelial cells and inflammatory cells, and promote lymphocyte proliferation and induce adhesion molecules. Additionally, it is able to promote the release of allergic mediators, and aggravate the symptoms of rhinitis.[24] IL-6 is mainly produced by T lymphocytes, which can coordinate with TNF-α, forming an inflammatory mediator network, causing cell damage. The dynamic detection of its level could effectively reflect the degree of inflammation. Besides, it directly or indirectly promotes the aggregation and activation of inflammatory cells, promote the vicious cycle of cytokines and inflammatory cells, and aggravate the inflammatory response of nasal mucosa.[25] IL-17 had been reported to be highly expressed in patients with chronic sinusitis. It could mediate growth-related oncogene α and IL-8 to stimulate nasal mucosa, accelerate fibroblast growth and induce tissue remodeling.[26] TIMP-1 and MMP-9 are regarded as the main enzymes regulating the degradation and synthesis of extracellular matrix. TIMP-1 is a physiological inhibitor of MMP-9, which protects the tracheal matrix protein from degradation by inhibiting the activity of MMP-9.[27] As an important factor of respiratory tract remodeling, TIMP-1 and MMP-9 participate in the remodeling process of RCR.[28] TGF-β1 is a cytokine with extensive biological effects. It plays an important role in regulating the cell growth, differentiation, and immune function, especially in inflammation and tissue repair.[29] Nevertheless, no final conclusion could be drawn due to the limited data on the relationship of RCR and indexes including TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α. In the present study, the level of the above indexes in refractory group were significantly higher than the chronic group and the control group, with the chronic group being significantly higher than the control group. It indicated that these indexes may play a potential role in the diagnosis and treatment of diseases.

The analysis of this study also highlighted that the Davos score, T&T olfactometer threshold test score, Lund-Mackay CT score, and the level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α were positively correlated with RCR. Besides, the statistical analysis showed that TGF-β1, MMP-9, TIMP-1, IL-4, IL-6, IL-17, and TNF-α were the influencing factors of RCR. Hence, these indicators could be used clinically as evaluation with regard to the severity of the disease.

There were a few limitations in the study. Firstly, the sample size was limited, which may result in the sample bias. Secondly, the limitation of retrospective study was recognized. Further work is needed in a multi-central, large sample-size and prospective study, aimed at clarifying the potential mechanism of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17 and TNF-α in RCR

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Conclusion

Taken together, the present study revealed that the Davos score, T&T olfactometer threshold test score, Lund-Mackay CT score, and the level of TGF-β1, MMP-9, TIMP-1, IL-1, IL-4, IL-6, IL-17, and TNF-α were positively correlated with RCR. Besides, TGF-β1, MMP-9, TIMP-1, IL-4, IL-6, IL-17, and TNF-α were considered as the influencing factors of the disease. These indexes may play a potential role in the clinical evaluation and guidance of the diagnosis and treatment of RCR.

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