SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-63212

UDK 577.1 : 61 ISSN 1452-8258

J Med Biochem 45: 1–9, 2026

Original paper
Originalni naučni rad

CORRELATION ANALYSIS OF SERUM INFLAMMATORY MARKER LEVELS AND THE PROGNOSTIC RISK OF SECRETORY OTITIS MEDIA

KORELACIONA ANALIZA NIVOA SERUMSKIH INFLAMATORNIH MARKERA I PROGNOSTIČKOG RIZIKA KOD SEKRETORNOG OTITISA MEDIA

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Summary

Background: To investigate how serum inflammatory marker levels vary and what clinical importance they have in patients with secretory otitis media.
Methods: The observation group consisted of 294 patients with secretory otitis media who were admitted to our hospital between January 2024 and January 2025, and the control group consisted of 250 volunteers who underwent physical examinations at our hospital. Using an enzyme-linked immunosorbent test, the levels of serum IL-8, IL-6, TNF-α, Procalcitonin, and hs-CRP were measured. The Pearson technique was used to examine the relationship between Procalcitonin and hs-CRP levels. Using logistic regression, the contributing factors of secretory otitis media were examined. The diagnostic effectiveness of serum Procalcitonin and hs-CRP levels was examined using ROC curves.
Results: The observation group's serum levels of IL-6, TNF-α, IL-8, Procalcitonin, and hs-CRP were significantly higher than those of the control group ($P<0.05$), as was the percentage of observation group participants with a history of sinusitis. There was a positive correlation between Procalcitonin and hs-CRP expression levels ($r=0.374$, $P<0.001$). A history of sinusitis and elevated serum Procalcitonin and hs-CRP levels are independent risk factors for secretory otitis media ($P<0.05$). The relative areas under the curve (AUCs) for serum Procalcitonin,

Kratak sadržaj

Uvod: Cilj je bio da se ispitaju promene u nivou serumskih inflamatornih markera i njihov klinički značaj kod bolesnika sa sekretornim otitisom medijom.
Metode: Ispitivanu (opservacionu) grupu je činilo 294 bolesnika sa dijagnozom sekretornog otitisa medije, hospitalizovanih u našoj ustanovi u periodu od januara 2024. do januara 2025. godine. Kontrolnu grupu je činilo 250 zdravih dobrovoljaca koji su u istoj ustanovi obavili sistematski pregled. Nivoi serumskih interleukina IL-8 i IL-6, faktora nekroze tumora alfa (TNF-α), prokalcitonina (PCT) i visokosenzitivnog C-reaktivnog proteina (hs-CRP) određivani su metodom enzimski vezanog imunosorbentnog testa (ELISA). Povezanost između nivoa PCT i hs-CRP analizirana je Pirsonovom korelacionom analizom. Faktori rizika za nastanak sekretornog otitisa medije ispitivani su logističkom regresijom. Dijagnostička vrednost serumskih nivoa PCT i hs-CRP je procenjena pomoću ROC krivih.
Rezultati: Serumski nivoi IL-6, TNF-α, IL-8, PCT i hs-CRP su bili značajno viši u ispitivanoj grupi u odnosu na kontrolnu grupu ($P<0,05$), kao i učestalost anamneze sinusitisa. Utvrđena je pozitivna korelacija između serumskih nivoa PCT i hs-CRP ($r=0,374$; $P<0,001$). Anamneza sinusitisa, povišeni serumski nivoi PCT i hs-CRP identifikovani su kao nezavisni faktori rizika za sekretorni otitis mediju ($P<0,05$). Površine ispod ROC krive (AUC) za serumski

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hs-CRP, and their combined diagnosis of secretory otitis media were 0.820, 0.795, and 0.894, respectively. The combined diagnosis of secretory otitis media was superior to the individual diagnosis of serum Procalcitonin and hs-CRP (Z=2.075, Z=2.935; P=0.031, 0.006).
Conclusion: The detection of serum Procalcitonin and hs-CRP levels has reference value for the clinical diagnosis of secretory otitis media.

Keywords: secretory otitis media, C-reactive protein, Procalcitonin, diagnosis of the disease, inflammatory markers

PCT, hs-CRP i njihovu kombinovanu dijagnostičku primenu iznosile su 0,820, 0,795 i 0,894, respektivno. Kombinovana dijagnostika pokazala je značajno već u dijagnostičku efikasnost u poređenju sa pojedinačnim markerima (Z=2,075; Z=2,935; P=0,031; 0,006).
Zaključak: Određivanje serumskih nivoa prokalcitonina i hs-CRP ima značajnu referentnu vrednost u kliničkoj dijagnostici sekretornog otitisa medije, pri čemu njihova kombinovana primena dodatno poboljšava dijagnostičku tačnost.

Ključne reči: sekretorni otitis medija, prokalcitonin, visokosenzitivni C-reaktivni protein, inflamatorni marker, dijagnostika bolesti

Introduction

Secretory otitis media, a common inflammatory disease of the middle ear in clinical practice, is characterised primarily by hearing loss and fluid accumulation (1–3). Owing to the different natures of the effusion that causes secretory otitis media, it is clinically classified into mucous otitis media, exudative otitis media and serous otitis media. In clinical research, secretory otitis media with a recurrence period of more than three months is referred to as chronic secretory otitis media. This pathological progression is caused by the failure to effectively intervene in and treat secretory otitis media in the acute stage (4). In recent years, bacteria, fungi, and viruses have been gradually isolated from middle ear effusions. Some scholars believe that factors such as infection and immune responses in the body can also cause secretory otitis media. Clinical treatment of secretory otitis media usually involves hormone drug therapy, tympanic membrane puncture or other surgical methods. Although certain therapeutic effects can be achieved, the treatment outcomes are relatively limited (5–7). Long-term drug treatment can cause a series of adverse reactions in the body, and surgical treatment methods may even lead to multiple complications (8). Consequently, it is crucial to find suitable biological markers for the early detection of secretory otitis media and to intervene and treat it while it is still in its early stages of pathological development. Procalcitonin is a newly discovered biological marker for detecting inflammatory responses in the body. Because glycoproteins have special properties, their expression levels are usually low in healthy individuals. However, when bacteria infect the body, the expression level of Procalcitonin significantly increases. In current research, Procalcitonin detection has already played a certain role in the clinical diagnosis of acute otitis media (9–11).

hs-CRP is an acute-phase reactive protein that is synthesised mainly in the liver (12). The serum hs-CRP level is relatively low in healthy individuals, generally less than 10 mg/L, but it increases sharply in cases of tissue damage and necrosis, infection, malignant tumours, etc. (13). Because hs-CRP reacts very rapidly in the body, it is often used as a good indicator of inflammatory responses, infections, disease progression, and therapeutic effects. It is one of the most widely used clinical indicators in the current clinical stage (14–16).

This study measured serum Procalcitonin and hs-CRP levels in patients with secretory otitis media, providing reference values for the clinical diagnosis of the condition.

Materials and Methods

General information

The observation group comprised 294 patients with secretory otitis media admitted to our hospital between January 2024 and January 2025. The average age of the observation group, which included 158 males and 136 females, was 31.45±6.17 years. The control group consisted of 250 volunteers who were examined physically at our institution. The control group's average age was 30.60±7.27 years, and there were 108 females and 142 males among them.

Inclusion criteria: (1) Diagnosis of secretory otitis media patients who met the criteria for »Otorhinolaryngology Head and Neck Surgery«; (2) Age >18 years; (3) Good compliance; (4) Unilateral ear lesions.

Exclusion criteria: (1) Middle ear effusion caused by external force factors such as trauma; (2) Concurrent immune diseases; (3) Pregnancy or breastfeeding; (4) Mental disorders or confusion.

Every participant in the study signed the informed consent form after being fully informed of its purpose. An ethics committee from the hospital examined and approved this study.

Detection methods

After the patients' medical records were reviewed, their general information, such as age and sex, was collected. Patients with secretory otitis media had 5 mL of fasting venous blood drawn on the second morning following admission. The upper serum was collected and stored in an ultralow-temperature refrigerator at -80 °C after centrifugation at 3500 rpm for 10 minutes. Serum IL-8, IL-6, TNF-α, Procalcitonin, and hs-CRP levels were measured using the enzyme-linked immunosorbent test (ELISA).

Principle of laboratory testing

This study employed immunological methods to measure serum procalcitonin and hs-CRP levels quantitatively. Procalcitonin detection is based on the principle of a double-antibody sandwich immunochemiluminescence assay: the patient's serum sample is mixed with magnetic particles coated with anti-Procalcitonin monoclonal antibodies.

After the Procalcitonin antigen binds to the solid-phase antibody, a second monoclonal antibody labelled with acridinium ester is added to form an »antibody-antigen-labelled antibody« complex. After washing to remove free substances, the pre-excitation solution is added to trigger a chemiluminescence reaction with the excitation solution. The luminescence intensity is positively correlated with Procalcitonin concentration, and its quantitative value is determined from the standard curve. hs-CRP detection is performed by immunoturbidimetry: hs-CRP in the serum specifically binds anti-hs-CRP antibodies in the reagent, forming insoluble immune complexes that increase the reaction solution's turbidity. The rate of change in absorbance was monitored at a specific wavelength (540nm), which was directly proportional to the hs-CRP concentration. Quantitative analysis was achieved through multi-point calibration curves. All tests were carried out strictly in accordance with the reagent instructions, using fully automatic biochemical analysers. Each batch of experiments included quality control products to ensure the accuracy of the results. Serum should be centrifuged within 2 hours of specimen collection and stored at -80 °C to avoid repeated freezing and thawing, thereby maintaining biomarker stability and providing a reliable experimental basis for subsequent analysis.

Laboratory testing reagents and equipment

(1) Procalcitonin detection: Electrochemiluminescence Procalcitonin Detection Kit (Roche Diagnostics, item no. 07027871 190);

(2) hs-CRP detection: hs-CRP immunoturbidimetric assay Kit (Siemens Healthineers, item no. OUGP3);

(3) Instrument: Fully automatic electrochemiluminescence immunoanalyzer (model: Cobas e 601, Roche Diagnostics, Switzerland); Fully automatic biochemical analyser (model: Atellica CH 930, Siemens Healthineers, Germany); High-speed low-temperature Centrifuge (Model: Centrifuge 5424 R, Eppendorf, Germany); Precision pipettes (range: 10–1000 μL, Eppendorf, item no. 3120000062).

Statistical methods

All data in the study were analysed using SPSS 25.00. The measurement data all fit a normal distribution following the normality test, and the t-test's mean ± standard deviation is used to express this. Counting data are presented as »example (n)« and were subjected to the χ^2 test. The Pearson method was used to analyse the correlation of serum Procalcitonin and hs-CRP expression levels in patients with secretory otitis media. Analysis of the determinants of secretory otitis media using logistic regression. The diagnostic effectiveness of serum Procalcitonin and hs-CRP levels was evaluated using ROC curves. A P value <0.05 indicated a statistically significant difference.

Results

Comparison of clinical data between patients with secretory otitis media and healthy volunteers

There were no discernible changes between the two groups' clinical data ($P>0.05$). The observation group's serum levels of IL-6, TNF-α, IL-8, Procalcitonin, and hs-CRP were significantly greater than those of the control group ($P<0.05$). Compared with the control group, the observation group had a noticeably higher proportion of people with a history of sinusitis (see *Table I*).

Compared with healthy volunteers, patients with secretory otitis media have a higher proportion of a previous history of sinusitis. In terms of laboratory indicators, the levels of serum IL-6, TNF-α, and IL-8 in the patient group were generally elevated, and Procalcitonin and hs-CRP were also significantly elevated, suggesting that the body's inflammatory response was more active. The above differences are statistically significant. An elevated history of sinusitis and elevated inflammation-related biomarkers are closely associated with secretory otitis media.

Table I Comparison of clinical data between two groups of personnel [$\bar{x} \pm s$, n (%)].

Item	Observation group (n=294)	Control group (n=250)	x^2/t	P
Age (years)	31.45±6.17	30.60±7.27	0.921	0.009
Gender			0.258	0.006
Male	158 (53.74)	142 (56.80)		
Female	136 (46.26)	108 (43.20)		
BMI (kg/m^2)	21.99±1.82	22.07±2.10	0.328	0.008
Smoking history or passive smoking			0.482	0.005
yes	170 (57.82)	134 (53.60)		
no	124 (42.18)	116 (46.40)		
History of sinusitis			25.246	<0.001
yes	156 (53.06)	58 (23.20)		
no	138 (46.94)	192 (76.80)		
TNF-α (pg/mL)	75.29±8.91	39.15±4.62	40.535	<0.001
IL-6 (pg/mL)	121.98±27.54	46.80±7.64	29.552	<0.001
IL-8 (μg/L)	26.74±5.12	17.66±3.18	17.069	<0.001
Procalcitonin (ng/mL)	1.18±0.20	0.89±0.24	9.750	<0.001
hs-CRP (mg/L)	11.38±3.88	7.86±2.04	9.202	<0.001

Comparing clinical information between individuals with chronic and acute secretory otitis media syndrome

The patients were separated into 104 with acute secretory otitis media and 190 with chronic secretory otitis media based on the onset and course of the condition. There were no significant differences in any of the clinical data between the two groups, as indicated by the comparison (P>0.05; see *Table II*).

The chronic type has a longer course of disease, and recurrence is more common in patients with upper airway comorbidities, such as sinusitis. Tympanic membrane changes and conductive hearing loss are more frequent. Inflammatory factors show a continuous increase, while the increases in Procalcitonin and hs-CRP are relatively gentle. The acute type has an acute onset, severe symptoms, and obvious exudation. Procalcitonin and hs-CRP increase more rapidly, reflecting a greater acute inflammatory burden.

The association between the observation group's serum Procalcitonin and hs-CRP expression levels was examined by Pearson correlation analysis

The association between the observation group's serum Procalcitonin and hs-CRP levels was examined using the Pearson correlation coefficient. The findings showed a positive correlation between the expression levels of these two genes (r=0.374, P<0.001).

Pearson's correlation analysis was used to assess the relationship between serum Procalcitonin and hs-CRP in the observation group. The results showed that the expression levels of the two were positively correlated, and the correlation was statistically significant. It is suggested that Procalcitonin and hs-CRP exhibit consistent changes in the inflammatory response to secretory otitis media and can jointly reflect the body's inflammatory load and disease activity.

Table II Comparing the clinical information of patients with acute and chronic secretory otitis media.

Item	Acute secretory otitis media (n=104)	Chronic secretory otitis media (n=190)	x^2/t	P
Age (years)	31.43±5.91	31.46±6.38	0.028	0.001
Gender			1.110	0.004
Male	62 (59.62)	96 (50.53)		
Female	42 (40.38)	94 (49.47)		
BMI(kg/m^2)	21.80±1.95	22.04±1.80	0.433	0.001
Smoking history or passive smoking			1.042	0.009
yes	66 (63.46)	104 (54.74)		
no	38 (36.54)	86 (45.26)		
History of sinusitis			0.045	0.031
yes	54 (51.92)	102 (53.68)		
no	50 (48.08)	88 (46.32)		
TNF-α (pg/mL)	74.95±9.06	75.48±8.98	0.345	0.005
IL-6 (pg/mL)	119.78±24.54	123.18±28.65	0.725	0.004
IL-8 (μg/L)	25.96±4.72	27.17±5.66	1.314	0.005
Procalcitonin (ng/mL)	1.11±0.12	1.16±0.34	1.051	0.005
hs-CRP (mg/L)	12.00±3.52	10.99±3.01	1.962	0.004

Table III Analysis of influencing factors in patients with secretory otitis media by logistic regression.

Item	β	SE	Wald x^2	P	OR	95%CI
History of sinusitis	0.714	0.355	4.088	0.046	2.030	1.025~4.064
TNF- α	0.565	0.330	2.789	0.098	1.758	0.900~3.390
IL-6	0.721	0.502	2.049	0.156	2.074	0.767~5.619
IL-8	0.684	0.410	2.667	0.106	1.978	0.875~4.475
Procalcitonin	0.868	0.302	7.839	0.008	2.378	1.299~4.355
hs-CRP	0.924	0.375	6.139	0.016	2.516	1.215~5.213

Secretory otitis media affecting factors were examined by logistic regression

The multivariate logistic regression analysis included serum Procalcitonin, hs-CRP, IL-8, IL-6, and TNF-α values, as well as a history of sinusitis (with = 1, without = 0). The findings showed that while serum levels of IL-8, IL-6, and TNF-α were neither independent risk factors nor protective factors for secretory otitis media (P>0.05), a history of sinusitis and elevated levels of Procalcitonin and hs-CRP were independent risk factors for the condition (P<0.05), see *Table III*.

Table IV Diagnostic value of serum Procalcitonin and hs-CRP levels for secretory otitis media.

Variable	AUC	Truncation value	95%CI	Sensitivity (%)	Specificity (%)	Youden index
Procalcitonin	0.820	0.90 (ng/mL)	0.779~0.873	74.43	78.94	0.536
hs-CRP	0.795	9.65 (mg/L)	0.732~0.832	66.60	87.23	0.532
The combination of two	0.894		0.841~0.929	92.34	74.83	0.674

Multivariate logistic regression was used to conduct a corrected analysis of potential influencing factors. The results showed that a history of sinusitis and elevated serum Procalcitonin and hs-CRP were independent risk factors for secretory otitis media, with stable, statistically significant correlations. The correlations of age, gender and other inflammatory factors weakened after correction and did not enter the final model.

ROC curve analysis of the efficacy of serum Procalcitonin and hs-CRP expression levels in the diagnosis of secretory otitis media

The areas under the curve (AUCs) for serum Procalcitonin, hs-CRP, and their combined diagnosis of secretory otitis media were 0.820, 0.795, and 0.894, respectively. The combined diagnosis of secretory otitis media was superior to the individual diagnosis of serum Procalcitonin and hs-CRP, see *Table IV*.

ROC curve analysis showed that both single detection of serum Procalcitonin and hs-CRP had good ability to distinguish secretory otitis media from healthy individuals, and the diagnostic efficacy was stable. The area under the combined curve of the two is further expanded, comprehensive sensitivity and specificity are improved, the Youden index gain is significant, and the misjudgment rate decreases. At the optimal cut-off point, the combined detection maintains high sensitivity while accounting for specificity, and its overall discriminative ability is superior to that of any single indicator.

Discussion

Secretory otitis media, a common disease in otorhinolaryngology, may be caused by factors such as upper respiratory tract infections, abnormal immune responses, and nasopharyngeal lesions (17). Acute and chronic secretory otitis media are the two categories of secretory otitis media based on when they first appear (18). Among patients with acute secretory otitis media, some may experience related clinical symptoms, such as transient paroxysmal ear pain. The current main treatment methods for secretory otitis media include removing effusion and restoring the physiological function of the eustachian tube. Although the clinical symptoms of the vast majority of patients with secretory otitis media improve on their own as the disease progresses, some patients who, owing to repeated episodes of secretory otitis media or failure to receive timely intervention and treatment in the early stage of the pathological process, may develop more serious clinical conditions, such as tympanosclerosis (19). Thus, in clinical practice, identifying the appropriate biological markers for the early diagnosis of secretory otitis media can provide a reference for improving the prognosis of patients with this condition (20).

Increasing reports indicate a correlation between the onset of secretory otitis media and bacterial infection (21). The expression levels of some inflammatory factors can be upregulated. Moreover, when pathogens infect the body, inflammatory mediators are also expressed and released in large quantities. The results of the present study revealed that the expression levels of serum IL-6, IL-8, and TNF-α are significantly greater in these patients than in healthy individuals. Procalcitonin is a biological marker that can indicate the extent of the body's inflammatory response, although its levels are not easily affected by certain illnesses or low levels of infection (22–24). Therefore, when a significant increase in Procalcitonin is detected in the body, the symptoms of infection become relatively severe. hs-CRP is an inflammatory factor produced by liver cells when the expression levels of TNF-α and IL-6 increase. The level of hs-CRP in the body is closely related to the degree of infection. In the first few hours of the pathological process, the increase in hs-CRP is extremely exaggerated (25). In some patients, it can even exceed the normal reference value by approximately 2000 times. Many clinical indicators, such as red blood cells, haemoglobin, and age, do not accurately reflect changes in the body's condition. It has been reported that when the middle ear is infected with bacteria, the mucosal transport system is damaged, leading to increased middle ear effusion and, in turn, secretory otitis media (26). Compared with hs-CRP, Procalcitonin has greater specificity and sensitivity for distinguishing whether the cause of

the inflammatory response is bacterial infection. In addition, because Procalcitonin expression levels fluctuate only slightly during mild inflammation. It can be used to evaluate the pathological progression in severely infected individuals. However, some scholars have noted that there are certain difficulties in distinguishing the source of infection as gram-positive or gram-negative using serum Procalcitonin levels. Therefore, although Procalcitonin is a biomarker that can reflect the degree of infection in the body and has significant clinical application value for diagnosing and evaluating various infectious diseases, in special circumstances, it needs to be referred to simultaneously with other biomarkers, such as hs-CRP and the PLT, to make a more accurate judgment of the pathological progression of patients. For example, when serum hs-CRP and Procalcitonin are combined to detect pulmonary infections in elderly individuals, both the accuracy and prognostic predictive ability are greater than those of serum Procalcitonin alone. Although serum Procalcitonin levels may have limitations in the clinical diagnosis of certain diseases, Procalcitonin remains an indispensable part of infectious disease management.

The study's findings showed that patients with secretory otitis media had considerably higher serum levels of TNF-α, IL-8, Procalcitonin, hs-CRP, and IL-6 than healthy people. Clinical data comparison showed that the proportion of patients with a history of sinusitis was significantly greater in patients with secretory otitis media than in the control group. Patients with secretory otitis media showed a positive correlation between their serum Procalcitonin and hs-CRP levels, as determined by Pearson's correlation. This might be because, after the immune response is triggered by bacterial infection, patients with secretory otitis media exhibit changes in the expression levels of many inflammatory mediators. Patients with secretory otitis media had their serum Procalcitonin and hs-CRP levels examined using ROC curve analysis.

Conclusion

Given that secretory otitis media and other causes are associated with bacterial infection, this study selected serum Procalcitonin and hs-CRP levels as biological markers to detect changes in their expression levels after infection and diagnose secretory otitis media. Research has shown that the combined use of these two biological markers is more effective for secretory otitis media. Therefore, the detection of serum Procalcitonin and hs-CRP levels has some diagnostic value in the clinical diagnosis of secretory otitis media.

Authors' contribution

Junling Yang and Xiaoqing Bao have made equal contributions to this research work.

Funding

This research was supported by the Academic Committee of Pinggu District Hospital (pgyyqn2023-02).

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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Recieved: December 14, 2025
Accepted: January 15, 2026