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Correlations of soluble TRAILR4, white blood cell count, and 25-hydroxyvitamin D with acute upper respiratory infection in children

Korelacije solubilnog TRAILR4, broja belih krvnih zrnaca i 25-hidroksivitamina D i akutne respiratorne infekcije gornjih disajnih puteva kod dece

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Abstract

Background/Aim. Rapid diagnosis and treatment guidance for acute upper respiratory infection (AURI) are challenging due to difficulties in specimen collection and the need for advanced laboratory conditions. The aim of this study was to investigate the correlations between soluble tumor necrosis factor-related apoptosis-inducing ligand receptor 4 (sTRAILR4), white blood cell (WBC) count, and 25-hydroxyvitamin D [25(OH)D] with AURI in children. **Methods.** A total of 80 children with AURI treated from January 2022 to January 2023 were enrolled in the study group. Another 80 healthy children undergoing physical examinations during the same period were enrolled in the control group. The levels of serum sTRAILR4 and 25(OH)D, and WBC count were measured. Receiver operating characteristic (ROC) curves were plotted to analyze the predictive values of serum sTRAILR4 and 25(OH)D levels and WBC count for AURI. Unconditional logistic stepwise regression analysis was employed for multivariate analysis. **Results.** Compared with the control group, the study group had a significantly elevated level of sTRAILR4 and WBC count and a reduced level of 25(OH)D ($p < 0.05$). The areas under the ROC curves of sTRAILR4 and 25(OH)D levels, and WBC count were 0.893, 0.765, and 0.937, respectively, suggesting that they were predictors of AURI. An elevated level of sTRAILR4 (≥ 88.751 pg/mL), elevated WBC count (≥ 10.223×10^9/L), along with a reduced level of 25(OH)D (≤ 48.943 nmol/L), were identified as significant influencing factors for AURI ($p < 0.05$). The level of sTRAILR4 and WBC count were positively correlated with AURI, while the 25(OH)D level had a negative correlation ($p < 0.05$). **Conclusion.** The children with AURI have a significantly higher level of sTRAILR4 and WBC count and a lower level of 25(OH)D than healthy children. In addition to WBC, sTRAILR4 and 25(OH)D may have a role in the assessment of pediatric upper respiratory infection.

Key words:
child; leukocytes; respiratory tract infections; tumor necrosis factor – alpha; vitamin d.

Apstrakt

Uvod/Cilj. Brza dijagnoza i smernice za lečenje akutne infekcije gornjih disajnih puteva (*acute upper respiratory infection* – AURI) predstavljaju izazov zbog teškoća u prikupljanju uzoraka i potrebe za visokospecijalizovanim laboratorijama. Cilj rada bio je da se ispitaju korelacije između solubilnog receptora 4 apoptoza-indukujućeg liganda povezanog sa faktorom nekroze tumora (*soluble tumor necrosis factor-related apoptosis-inducing ligand receptor 4* – sTRAILR4), broja belih krvnih zrnaca (*white blood cell* – WBC) i 25-hidroksivitamina D –[25(OH)D] i AURI kod obolele dece. **Metode.** Ukupno 80 dece obolele od AURI lečene od januara 2022. do januara 2023. godine, uključeno je u ispitivanu grupu. Još 80 zdrave dece koja su u istom periodu bila podvrgnuta fizičkim pregledima uključeno je u kontrolnu grupu. Izmereni su nivoi sTRAILR4 i 25(OH)D u serumu i broj WBC. Konstruisane su *receiver operating characteristic* – ROC krive kako bi se analizirale prediktivne vrednosti nivoa sTRAILR4 i 25(OH)D u serumu i broja WBC za AURI. Za multivarijantnu analizu korišćena je bezuslovna logistička regresija *stepwise* metodom. **Rezultati.** U poređenju sa kontrolnom grupom, ispitivana grupa je imala značajno povišen nivo sTRAILR4 i broj WBC i smanjen nivo 25(OH)D ($p < 0,05$). Površine ispod ROC kriva nivoa sTRAILR4 i 25(OH)D i broja WBC bile su 0,893, 0,765, 0,937, redom, što ukazuje na to da su prediktori AURI. Povišeni nivo sTRAILR4 (≥ 88,751 pg/mL), broj WBC (≥ $10,223 \times 10^9$/L), zajedno sa smanjenim nivoom 25(OH)D

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(≤ 48,943 nmol/L) identifikovani su kao značajni faktori koji utiču na AURI ($p < 0,05$). Nivo sTRAILR4 i broj WBC bili su u pozitivnoj korelacji sa AURI, dok je nivo 25(OH)D imao negativnu korelaciju ($p < 0,05$). **Zaključak.** Deca obolela od AURI imaju značajno viši nivo sTRAILR4 i broj WBC i niži nivo 25(OH)D, u odnosu na zdravu decu. Pored WBC, sTRAILR4 i 25(OH)D mogu imati ulogu u proceni infekcije gornjih disajnih puteva u pedijatrijskoj populaciji.

Ključne reči:
deca; leukociti; respiratorni trakt, infekcije; faktor nekroze tumora – alfa; vitamin d.

Introduction

Infectious diseases (IDs) of the upper respiratory tract include rhinitis, sinusitis, nasopharyngitis, the common cold, and laryngitis [1]. These conditions typically present as acute self-limited defensive responses occurring within 1–3 days after exposure to viruses, characterized by inflammatory symptoms such as coughing, sneezing, runny nose, nasal obstruction, and sore throat. IDs of the upper respiratory tract are the most frequent reason for hospitalization in children under 5 years of age, if not treated in time [2]. The diseases can be exacerbated through pathogen invasion into the sinuses, trachea, lungs, and other adjacent organs, thereby increasing the difficulty of treatment [3]. Acute upper respiratory infection (URI) – AURI is mainly diagnosed based on clinical findings; however, rapid diagnosis and treatment guidance are challenging due to difficulties in specimen collection and the high demands of laboratory testing [4]. Hence, it would be useful to have alternative approaches to confirm AURI.

White blood cell (WBC) count is a commonly used indicator in the diagnosis of IDs [5]. Although an elevated WBC count may signal an ongoing immune response, its low specificity restricts its ability to distinguish between different types of pathogens or the severity of the infection [6]. Soluble tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor 4 – sTRAILR4, an inflammatory factor receptor in the TNF family, participates in the progression of inflammation in IDs [7]. Although most studies of sTRAILR4 have focused on chronic inflammatory conditions [8], its potential role in the immune response during acute infections needs further investigation. An important indicator of vitamin D nutritional status, 25-hydroxyvitamin D [25(OH)D], has immune-modulating and immune response functions and plays a role in systemic inflammatory responses [9]. It has been demonstrated that sufficient levels of 25(OH)D, or supplementation in deficient individuals, are associated with lower risk and reduced severity of acute respiratory tract infections [10]. Until now, however, reports on WBC count and levels of sTRAILR4 and 25(OH)D in children with AURI, as well as their correlations with the disease, have been limited.

The aim of this study was to investigate the correlations between levels of sTRAILR4 and 25(OH)D and WBC count with AURI in children, in order to provide valuable evidence for future treatment.

Methods

A total of 80 children with AURI treated from January 2022 to January 2023 were enrolled in the study group. According to the diagnostic criteria for AURI [8], 22 cases were mild, 41 were moderate, and 17 were severe. Another 80 healthy children undergoing physical examinations during the same period were enrolled in the control group. The study was approved by the Ethics Committee of the Ningbo Yinzhou No. 2 Hospital, China (approval No. NYN2H202201003), and informed consent was obtained from all participating family members.

The inclusion criteria were as follows: children who met the diagnostic criteria for URI [11] and were in the acute stage, those with bacterial infections, and those aged ≤ 12 years.

The exclusion criteria involved children with the following: allergic diseases; malignancies; those with contraindications to pulmonary function tests; those with cardiovascular, central nervous system, connective tissue, metabolic, or endocrine diseases; those with infections at other sites; those receiving medications affecting the level of serum 25(OH)D; those who took hormones, immunotherapy, or vitamins two weeks before examination.

Fasting venous blood (6 mL) was drawn from each child in both groups from 8:00 am to 10:00 am and collected into Eppendorf Tubes® (Germany). Then, half of that dose, i.e., 3 mL of blood, was used for WBC detection using an automated hematology analyzer (Sysmex Shanghai Ltd., China). The remaining 3 mL of blood was centrifuged at 3,000 rpm for 15 min, and the serum was separated and stored at -80 °C for analysis.

Serum sTRAILR4 level was measured by UniCel DxI 800 immunoassay analyzer (Beckman Coulter, USA) using an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (Shanghai Xinyu Biotechnology Co., Ltd., USA). Serum 25(OH)D level was measured using the iBright electrochemiluminescence immunoassay system (Thermo Fisher Scientific, USA) with a commercial kit, following the manufacturer's instructions (DiaSorin Inc., USA). Quality control and calibration products were bought from Randox (UK). Quality control indicators such as intra-batch variability and inter-batch variability met the requirements.

Statistical analysis

All data were processed using SPSS 22.0 software. The measurement data were subjected to the Kolmogorov-Smirnov test, and the normally distributed data were expressed as mean ± standard deviation and compared by the independent samples *t*-test between the two groups. The count data were expressed as percentages and compared using the χ^2 test between groups. Receiver operating character-

istic (ROC) curves were plotted to analyze the predictive values of serum sTRAILR4 and 25(OH)D levels and WBC count for AURI. Multivariate analysis was conducted by unconditional logistic stepwise regression analysis. The correlations of sTRAILR4, WBC count, and 25(OH)D with AURI were detected through Spearman's rank analysis. The value of $p < 0.05$ suggested a statistically significant difference.

Results

A total of 80 children with AURI were selected as a study group, including 45 boys and 35 girls. Their age was 2–12 years (mean: 7.72 ± 2.86 years). The course of disease was 3–15 days (average: 6.24 ± 2.12 days). The body mass index (BMI) was 11.31–17.75 kg/m^2, with a mean of 14.25 ± 2.17 kg/m^2. Another 80 healthy children receiving physical examinations in the same period were enrolled as a control group, including 49 boys and 31 girls. They were aged 2–12 years (mean: 7.16 ± 3.13 years). BMI was 11.28–17.68 kg/m^2 (average: 14.16 ± 2.25 kg/m^2). The baseline data, such as gender, age, and BMI, showed no statistically significant differences between the two groups ($p > 0.05$).

Levels of sTRAILR4 and 25(OH)D and WBC count

The baseline data, such as gender, age, and BMI, showed no statistically significant differences between the two groups ($p > 0.05$). Compared with the control group, the study group had a significantly higher sTRAILR4 level and WBC count and a significantly lower 25(OH)D level ($p < 0.05$) (Table 1).

Results of ROC curve analysis of sTRAILR4 and 25(OH)D levels and WBC count for predicting AURI

The results of the ROC curve analysis revealed that the areas under the curves (AUCs) of sTRAILR4 and 25(OH)D levels and WBC count, were 0.893, 0.765 and 0.937 (Table 2), indicating that sTRAILR4 and 25(OH)D levels and WBC count can act as predictors of AURI. The ROC curves of sTRAILR4 and 25(OH)D levels and WBC count for predicting AURI are shown in Figure 1.

Table 1

Comparison of sTRAILR4 and 25(OH)D levels and WBC count between the two groups of patients

Parameters	sTRAILR4 (pg/mL)	WBC (×10^9/L)	25(OH)D (nmol/L)
Study group (n = 80)	114.28 ± 40.25	16.35 ± 5.82	41.58 ± 15.65
Control group (n = 80)	59.62 ± 18.94	7.24 ± 2.19	57.34 ± 16.37
t	10.974	13.103	6.224
p	< 0.001	< 0.001	< 0.001

sTRAILR4 – soluble tumor necrosis factor-related apoptosis-inducing ligand receptor 4; WBC – white blood cell; 25 (OH)D – 25-hydroxyvitamin D; n – number.
All values are given as mean ± standard deviation.

Table 2

Results of the ROC curve analysis of sTRAILR4 and 25(OH)D levels and WBC count for predicting acute upper respiratory infection

Variables	AUC	SE	*p*	95%CI	Cut-off	Sensitivity	Specificity
sTRAILR4	0.893	0.027	< 0.001	0.835~0.936	88.751 pg/mL	0.962	0.737
WBC	0.937	0.022	< 0.001	0.887~0.969	10.223 × 10^9/L	0.937	0.675
25(OH)D	0.765	0.038	< 0.001	0.691~0.828	48.943 nmol/L	0.787	0.712

ROC – receiver operating characteristic; AUC – area under the curve; SE – standard error; CI – confidence interval. For other abbreviations, see Table 1.

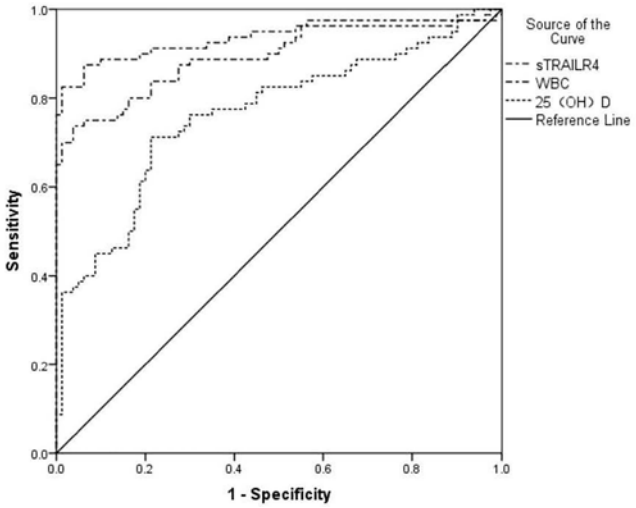

Fig. 1 – ROC curves of sTRAILR4 and 25(OH)D levels and WBC count for predicting acute upper respiratory infections. For abbreviations, see Tables 1 and 2.

Results of multivariate logistic regression analysis of AURI

The significantly different data from the univariate analysis were incorporated as the independent variables in the multivariate logistic regression analysis, with AURI as the dependent variable, followed by variable assignment for subsequent multivariate logistic regression analysis (Table 3). The results showed that sTRAILR4 (≥ 88.751 pg/mL), WBC count (≥ 10.223 × 10^9/L), and 25(OH)D (≤ 48.943 nmol/L) were influencing factors for AURI ($p < 0.05$) (Table 4 and Figure 2).

Correlations of sTRAILR4 and 25(OH)D levels and WBC count with AURI

The level of sTRAILR4 and WBC count were positively correlated with AURI, whereas the 25(OH)D level had a negative correlation with AURI ($p < 0.05$) (Table 5).

Table 3

Quantitative assignments for multivariate logistic regression analysis

Parameters	Assignment	
	1	0
sTRAILR4	≥ 88.751 pg/mL	< 88.751 pg/mL
WBC	≥ 10.223 × 10^9/L	< 10.223 × 10^9/L
25(OH)D	≤ 48.943 nmol/L	> 48.943 nmol/L

For abbreviations, see Table 1.

Table 4

Results of multivariate logistic regression analysis of acute upper respiratory infection

Factor	β	SE	Wald χ^2	*p*	OR	95%CI
sTRAILR4	1.211	0.303	15.918	< 0.001	3.358	1.852~6.088
WBC	1.301	0.442	8.630	0.003	3.674	1.542~8.753
25(OH)D	1.322	0.475	7.739	0.005	3.752	1.478~9.524

For abbreviations, see Tables 1 and 2, and Fig. 2.

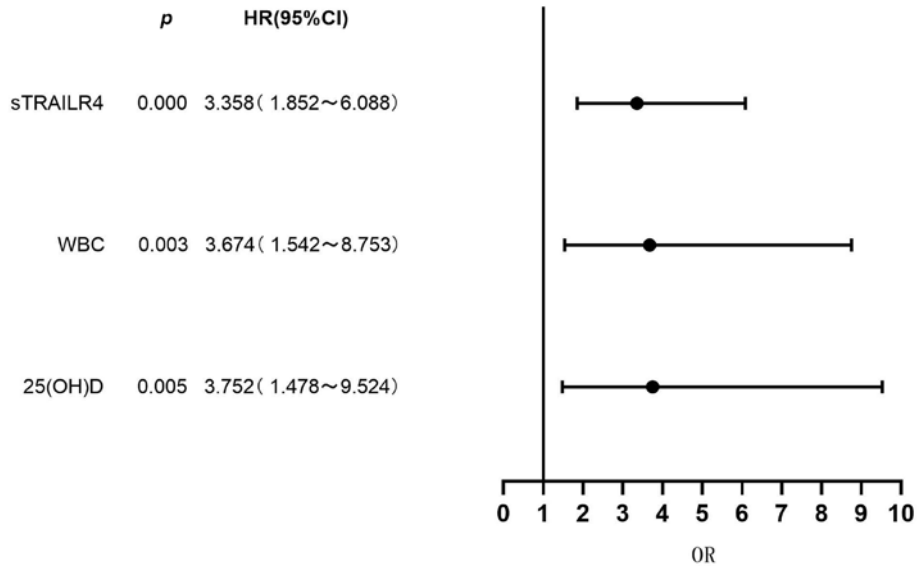

Fig. 2 – Forest plot of clinical characteristics based on multivariate logistic regression analysis. HR – hazard ratio; CI – confidence interval; OR – odds ratio. For other abbreviations, see Table 1.

Table 5

Correlations of sTRAILR4 and 25(OH)D levels and WBC count with acute upper respiratory infection

Parameters	Acute upper respiratory tract infection	
	r	*p*
sTRAILR4	0.643	< 0.05
WBC	0.582	< 0.05
25(OH)D	-0.517	< 0.05

For abbreviations, see Table 1.

Discussion

Pediatric AURI has a high incidence rate among children aged ≤ 10 years due to tonsillitis, laryngitis, and sinusitis. AURI caused by viruses has no routinely available diagnostic tests [12]. Bacterial culture of throat swabs is mainly employed for the diagnosis of acute bacterial URI, which, however, is time-consuming and not conducive to early diagnosis and treatment [13]. In addition, pediatric diseases often progress rapidly, making it difficult for pediatricians to assess the potential severity of an infectious disease based on initial symptoms alone. This greatly impacts the clinical decision-making process and can affect patient outcomes [14]. Therefore, it is necessary to explore the correlations of potential indicators with pediatric AURI in order to provide evidence for determining the onset and progression.

Blood indicators have been widely applied in the diagnosis of pediatric IDs in recent years, as laboratory equipment and testing techniques constantly improve [15]. The levels of sTRAILR4 and 25(OH)D and WBC count, in human peripheral blood, can be quickly and accurately detected. WBC count is one of the oldest laboratory markers of URI in use, as an important functional parameter of the immune system. It can reflect the inflammatory status and play a key role in the early diagnosis of IDs and medication guidance. However, WBC detection has low accuracy due to the influence of various external factors and is therefore often used in combination with other serum indicators for disease diagnosis in clinical practice [16]. In this study, WBC count showed a significant correlation with AURI, suggesting that elevated WBC values were associated with the onset and progression of the infection. In the case of bacterial URI, the WBC count is high, but its detection is not specific. For instance, it is also high in mycoplasma-induced URI, but there is no statistically significant difference between patients with viral URI and healthy populations. Thus, WBC count has high sensitivity but poor specificity in the assessment of IDs of the upper respiratory tract [6, 17].

As a receptor of TRAIL, sTRAILR4 is also an apoptosis-inducing ligand, which belongs to the TNF superfamily together with TNF-α. It is involved in the inflammatory processes of IDs, enhancing the immune response and anti-infective ability of the human body. Moreover, it can competitively suppress TRAIL-induced apoptosis through its extracellular structural domain and promote the activation of anti-apoptotic transcription factors [18]. In this study, the sTRAILR4 level was significantly higher in children with AURI than in healthy children. In a previous study [19], a higher expression of sTRAILR4 meant higher risk and faster progression of upper respiratory tract infection, similar to the results of the present study.

Through macrophages and T lymphocytes, 25(OH)D is capable of regulating the division and proliferation of WBC, thus potentially affecting the efficiency of an immune response [20]. Besides, 25(OH)D can also enhance the resistance of the human body to infection by promoting the expression of antimicrobial dopamine and Toll-like receptors and strengthening the innate defense of the immune system against viruses and bacteria [21]. Moreover, 25(OH)D has been closely related to autoimmune diseases, IDs, cardiovascular diseases, neuropsychiatric diseases, and even tumors, in addition to its traditional effects on the skeletal system [22]. In this study, the 25(OH)D level was significantly lower in the study group than in the control group. Additionally, there was a significant correlation between URI and 25(OH)D level, suggesting that the level was valuable for predicting URI. Jolliffe et al. [23] reported that 25(OH)D was of great significance to the diagnosis of respiratory tract infection, and the level rose significantly after treatment, which is in agreement with the results of the present study.

Nevertheless, this study had several limitations. First, the sample size was relatively small. In addition, subgroup analyses were not performed for specific diagnoses such as pharyngitis, rhinitis, and others. Moreover, the analysis focused exclusively on acute bacterial URI, without including cases caused by viral or mycoplasma infections. In future studies, the sample size will be expanded, and a comprehensive analysis will be conducted to examine the correlations between AURIs caused by various agents and the levels of sTRAILR4 and 25(OH)D and WBC count.

Conclusion

Children with acute upper respiratory infection tend to have relatively high levels of sTRAILR4 and white blood cell count and low 25(OH)D levels. Markers such as sTRAILR4, WBC, and 25(OH)D may be useful in assessing upper respiratory infection in children.

Conflict of interest

The authors declare no conflict of interest.

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