European Journal of Prosthodontics and Restorative Dentistry (2026) 34(4s), 623–629

Keywords
Recurrent aphthous stomatitis, IL-19, IL-21, salivary biomarkers, Roc analysis

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Received: 10.04.2026
Revised-01.06.2026
Accepted: 13.06.2026
Doi: 10.1922/ejprd.v34i4s.1522

Salivary Interleukins-19 and Interleukins-21 as Diagnostic Biomarkers in Recurrent Aphthous Stomatitis: A Case-Control Study

ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is a prevalent oral mucosa disorder characterized by recurrent ulceration and immune dysregulation with C interleukins implicated in its pathogenesis.
Objective: To evaluate salivary interleukin-19 (IL-19) and interleukin-21 (IL-21) as diagnostic biomarkers in patients with RAS.
Methods: This case-control study enrolled 90 participants (45 RAS patients and 45 healthy controls). Unstimulated salivary IL-19 and IL-21 levels were quantified by ELISA. Data were analyzed using independent t-test, ANOVA, and ROC curve analysis (SPSS v. 22)
Results: Salivary Il-19 and IL-21 were significantly elevated in RAS patients versus controls (P=0.001). No significant differences were observed across ulcer subtypes; however, IL-19 was significantly higher in buccal mucosal lesions (P=0.042). ROC analysis demonstrated excellent diagnostic performance: Il-19 achieved an AUC of 0.928 (95% CI: 0.854-0972; p< 0.001), sensitivity 88.89%, specificity 88.89% (cut-off> 88.90 pg/mL); IL-21 achieved an AUC 0.930, (95% CI: 0.856-0.973; p< 0.001), (95% CI: 0.856-0.973; p< 0.001), sensitivity 86.67%, specificity of 95.56% (cut-off > 56.50 pg/mL)
Conclusions: salivary IL-19 and IL-21 are significantly elevated in RAS and exhibited high diagnostic accuracy, supporting their values as non-invasive biomarkers and implicating cytokine dysregulation in RAS immunopathogenesis.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most common ulcerative conditions affecting the oral mucosa, characterized by recurrent episodes of painful, self-limiting ulcers in otherwise healthy individuals. Epidemiological data indicate that RAS affects approximately 5–25% of the global population, with higher prevalence in adolescents and young adults (1, 2). Clinically, lesions present as shallow, round or oval ulcers with a yellow-white fibrinous base surrounded by an erythematous halo3. Ulcers typically occur on non-keratinized mucosal surfaces such as the buccal and labial mucosa, floor of the mouth, and ventral tongue (3). Although individual episodes usually resolve spontaneously within 7–14 days, recurrence can cause substantial pain and functional limitation, impairing eating, speaking, swallowing, and quality of life (4).

RAS is traditionally classified into minor, major, and herpetiform subtypes. Minor RAS accounts for about 75–90% of cases and involves small ulcers (<10 mm) that heal without scarring. Major aphthae are larger and deeper, may persist for weeks, and often heal with scarring (2, 5).

Herpetiform ulcers are least common and present as multiple small ulcers that can coalesce into larger irregular lesions (2,5). Despite its characteristic clinical presentation, the etiology and pathogenesis of RAS remain incompletely understood.

Current evidence supports a multifactorial basis involving genetic susceptibility, environmental triggers, nutritional deficiencies, and immune dysregulation (6,7). Reported precipitating factors include local trauma, psychological stress, food hypersensitivity, microbial agents, and hematinic deficiencies (iron, folate, and vitamin B12) (8). Associations with systemic inflammatory and autoimmune diseases (e.g., Behçet's disease, inflammatory bowel disease, and celiac disease) further implicate immune-mediated mechanisms (6, 9).

Cytokine imbalance, particularly altered interleukin signaling, has been repeatedly linked to RAS, with increased pro-inflammatory mediators such as IL-2, IL-12, IFN-γ, and TNF-α suggesting a T-cell–driven response (10, 11) . Elevated salivary cytokines (including IL-2 and IL-22) have also been reported in RAS, supporting saliva as a source of non-invasive inflammatory biomarkers (12).

Interleukin-21 (IL-21), mainly produced by T follicular helper and Th17 cells, promotes B-cell differentiation, antibody production, and cytotoxic T-cell activity, amplifying inflammatory pathways implicated in autoimmunity and chronic inflammation (13,14). Its involvement in Th17-driven responses suggests relevance to mucosal immune dysregulation (15). Interleukin-19 (IL-19), an IL-10 family cytokine produced by monocytes and epithelial cells, participates in immune modulation and epithelial signaling and has been implicated in chronic inflammatory disorders (16). However, the roles of IL-19 and IL-21 in RAS-associated local inflammation remain insufficiently characterized.

Therefore, this study evaluated salivary IL-19 and IL-21 levels in patients with RAS versus healthy controls, hypothesizing that both are elevated in RAS and may serve as non-invasive diagnostic biomarkers reflecting underlying immune dysregulation.

MATERIALS AND METHODS

Study Design and Setting

This case–control study was conducted at a specialized dental clinic from March 15 to June 20, 2026.

Study Population

A total of 90 participants were enrolled in this study, including 45 patients with clinically diagnosed recurrent aphthous stomatitis (RAS) (females 26 and 19 males; age range 23-84 years) and 45 apparently healthy individuals (females 30 and 15 males; age range 23–79 years) serving as the control group. Patients in the RAS group presented with active aphthous ulcers at the time of clinical examination. Control participants were recruited from the same clinic during routine dental examinations or cosmetic consultations and had no history of recurrent oral ulceration or active oral mucosal lesions. None of the participants were first- degree relatives.

Inclusion Criteria

Participants in the RAS group were including if they had a clinical diagnosis of recurrent aphthous stomatitis with active lesions at the time of examination and were within the specified age range. Controls subjects were included if they had no history or recurrent oral ulceration, no active oral mucosal lesions, and no systemic inflammatory or autoimmune diseases. Written informed consent was obtained from all participants prior to enrolment.

Exclusion Criteria

Participants from both groups were excluded if they had systemic diseases associated with oral ulceration (e.g., systemic lupus erythematosus, Oral lichen planus, Behçet's disease, diabetic mellitus and autoimmune blistering disorders), were pregnant, smokers, or used orthodontic appliance or removable dental prostheses, periodontal disease or active oral infections, recent use of antibiotics, corticosteroids or anti-inflammatory medications. And any systemic condition known to influence salivary cytokine levels.

Ethical Approval and Informed Consent

The protocol was approved by an institutional research ethics committee of the College of Dentistry, Diyala University, Iraq (approval No. 2026FKA5; March 12, 2026). Written informed consent was obtained from all participants. The study followed the Declaration of Helsinki.

Saliva Collection and Processing

Unstimulated whole saliva was collected using the standardized protocol described by Navazesh17. Participants abstained from eating, drinking, chewing gum, smoking, and oral hygiene procedures for ≥2 hours before sampling. Participants rinsed with distilled water immediately before collection.

Sampling was performed between 9:00 and 11:00 AM. Participants expectorated saliva into sterile 5 mL polypropylene tubes over ~5 minutes (minimum 3 mL). Samples were placed on ice, centrifuged at 3000 rpm for 10 minutes, aliquoted, and stored at −20°C until analysis.

Measurement of Salivary IL-19 and IL-21

Salivary IL-19 and IL-21 concentrations were determined using sandwich ELISA kits (Human IL-19 ELISA Kit, Abcam, ab231922, UK; Human IL-21 ELISA Kit, Abcam, ab119542, UK) according to manufacturer instructions. Samples were measured in duplicate by personnel blinded to participant group. Absorbance was read at 450 nm and concentrations were calculated from standard curves.

Clinical Assessment of Recurrent Aphthous Stomatitis

RAS diagnosis was based on history and clinical examination. Lesions were recorded as recurrent, painful, round/oval ulcers with a yellowish-Gray pseudo membrane and erythematous halo, typically on non-keratinized mucosa. Patients were categorized into minor, major, or herpetiform subtypes based on lesion number and size. Anatomical site (e.g., buccal mucosa, tongue) was recorded.

Statistical Analysis

Data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Independent samples t-test compared cytokine levels between RAS and controls; chi-square test compared sex distribution. One-way ANOVA evaluated cytokine differences among RAS subtypes. ROC curve analysis (MedCalc version 23.1.5) assessed diagnostic performance via area under the curve (AUC), optimal cut-off values, sensitivity, and specificity. Statistical significance was set at $p<0.05$.

RESULTS

Demographic and clinical Characterises

A total of 90 participants were enrolled in this study, compromising 45 patients with clinically confirmed recurrent aphthous stomatitis (RAS) and 45 apparently healthy controls. As shown in Table 1, the mean age of RAS patients was (52.40 ± 17.63 years), which was statistically significant greater than that of the control group (45.58± 15.58 years; < 0.01). With respect to sex distribution, females predominated in both groups, accounting for 57.8% of RAS patients (n=26) and 66.7% of controls (n=30), with a statistically significant difference in sex distribution between groups (< 0.01).

Table 1. Comparison of demographic characteristics between patients with recurrent aphthous stomatitis (RAS) and healthy controls.

Variables	RAS (n=45)	Controls (n=45)	P. value
Age (Years) Mean ± SD	52.40 ± 17.63	45.58± 15.58	< 0.01
Sex, n (%)			< 0.01
Female	26 (57.8%)	30 (66.7%)	
Male	19 (42.2%)	15(33.3%)	

P-value: t-test for age and chi-square test for sex distribution.

The clinical characteristics of RAS patients are summarized in Table 2. The minor ulcer subtype was the most prevalent, representing 68.9% of cases (n=31), followed by the major subtype (n=9; 20.0%) and herpetiform subtype (n=5; 11.1%). Regarding anatomical distribution, the buccal mucosa was the most commonly affected site, involved in 31 patients (68.9%), while the tongue was affected in 14 patients (31.1%), consistent with the well-established predilection of RAS for non-keratinized oral mucosal surfaces.

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Table 2. Clinical characteristics of recurrent aphthous stomatitis (RAS) patients (n=45), including ulcer type and anatomical site.

Clinical Parameters	Subgroups	N (%)
Ulcer type	Minor	31 (68.9%)
	Major	9 (20.0%)
	Herpetiform	5 (11.1%)
Anatomical site	Buccal Mucosa	31 (68.9%)
	Tongue	14 (31.1%)

Salivary concentrations of both IL-19 and IL-21 were significantly elevated in RAS patients compared with healthy controls (Table3). The mean salivary IL-19 concentration in the RAS patients was (114.26 ± 28.63 pg/mL), compared with (76.63 ± 13.85 pg/mL) in controls, yielding a mean difference of 37.63 pg/mL (95% CI: 27.60 to 47.67 pg/mL; p=0.001). Similarly, mean salivary IL-21 were significantly higher in RAS patients (65.56 ± 13.20pg/mL) than in controls (40.50 ± 11.43pg/mL), with a mean difference of 25.05 pg/mL (95% CI: 19.22 to 39.89pg/mL; p=0.001).

Table 3. Comparison of salivary IL-19 and IL-21 concentrations between RAS patients and healthy controls

Biomarkers	RAS (n=45) (Mean ± SD)	Controls (n=45) (Mean ± SD)	Mean Difference (95% CI)	p-value*
IL-19 (pg/mL)	114.26 ± 28.63	76.63 ± 13.85	37.63 (27.60 to 47.67)	0.001
IL-21(pg/mL)	65.56 ± 13.20	40.50 ± 11.43	25.05 (19.22 to 39.89)	0.001

*Independent Sample t-test.

One-way analysis of variance (ANOVA) was performed to examine whether salivary IL-19 and IL-21 concentrations differed across the three clinical subtypes of RAS. As presented in Table 4, mean salivary IL-19 concentrations were (117.14 ± 32.29 pg/mL) in patients with minor ulcers, (104.24± 16.66 pg/mL) in those with

major ulcers, and (114.44 ± 18.84 pg/mL) in patients with herpetiform ulcers, with no statistically significant intergroup difference (p=0.503). Likewise, mean IL-21 levels did not differ significantly among the minor (66.70 ± 13.21 pg/mL), major (60.51 ± 12.62 Pg/mL), and herpetifrom (67.54 ± 14.71 pg/mL0 subtypes (p=0.446).

Table 4. Association between salivary IL-19 and IL-21 concentrations and ulcer type in patients with recurrent aphthous stomatitis (RAS).

Biomarker (pg/mL)	Minor ulcer (n=31) (Mean ± SD)	Major ulcer (n=9) (Mean ± SD)	Herpetiform ulcer (n=5) (Mean ± SD)	p-value
IL-19	117.14 ± 32.29	104.24± 16.66	114.44 ± 18.84	0.503
IL-21	66.70 ± 13.21	60.51 ± 12.62	67.54 ± 14.71	0.446

The relationship between salivary cytokine concentrations and the anatomical location of ulcerative lesions was assessed using the independent sample t-test (Table 5). A statistically significant difference in salivary IL-19 concentrations was observed between patients with buccal mucosa lesions (115.47 ± 32.86 pg/mL) (p=0.042), suggesting a modest but significant site-specific modulation of IL-19 expression. In contrast, mean salivary IL-21 concentration did not differ significantly between patients with buccal mucosa lesions (66.08 ± 12.33 pg/mL) and those with tongue lesions (64.41 ± 15.39 pg/mL) (p=0.089).

Table 5. Association between salivary IL-19 and IL-21 concentrations and anatomical site of lesions in patients with recurrent aphthous stomatitis (RAS).

Biomarker (pg/mL)	Buccal mucosa (n=31) (Mean ± SD)	Tongue (n=14) (Mean ± SD)	p-value
IL-19	115.47 ± 32.86	111.58 ± 16.49	0.042
IL-21	66.08 ± 12.33	64.41 ± 15.39	0.089

The diagnostic accuracy of salivary IL-19 and Il-21 in discriminating patients with RAS from healthy controls was assessed using ROC curve analysis. The results confirmed that both cytokines exhibited high and statistically significant diagnostic accuracy (AUC >0.092; $p < 0.001$ for both. IL-19 achieved an AUC0.928 (95% CI: 0.854-0972; $p< 0.001$), with sensitivity of 88.89% and specificity of 88.89% at an optimal cut-off value of > 88.90 pg/mL. IL-21 yielded an AUC 0.930, (95% CI: 0.856-0.973; $p< 0.001$), with sensitivity of 86.67% and specificity of 95.56% at an optimal cut-off value of > 56.50 pg/mL. Comparative evaluation revealed that IL-21 demonstrated a marginally superior AUC and specificity, whereas IL-19 exhibited a comparably higher sensitivity, suggesting complementary diagnostic profiles for both cytokines. These findings suggest that elevated salivary levels of both IL-19 and IL-21 may serve as valuable non-invasive potential diagnostic biomarkers in the clinical and immunological assessment for RAS. A summary of all Roc curve parameters is presented in Table 6 and Figures 1 and 2.

Table 6. Diagnostic performance of salivary IL-19 and IL-21using Receirver Operating Characteristic (ROC) Curve Analysis in Patients with RAS.

Parameters	AUC	95%CI	Cut-off value	P-value	Sensitivity (%)	Specificity (%)
IL-19	0.928	0.854-0.972	> 88.90 pg/mL	<0.001	88.89	88.89
IL-21	0.930	0.856-0.973	>56.50 pg/mL	<0.001	86.67	95.56

Diagnostic performance metrics including Area Under Curve (AUC), Optimal cut-off values, sensitivity, specificity- are presented with 95% Confident intervals (CI). All analyse were conducted using MedCalc statistical software. A p- value < 0.05 was statistically significant

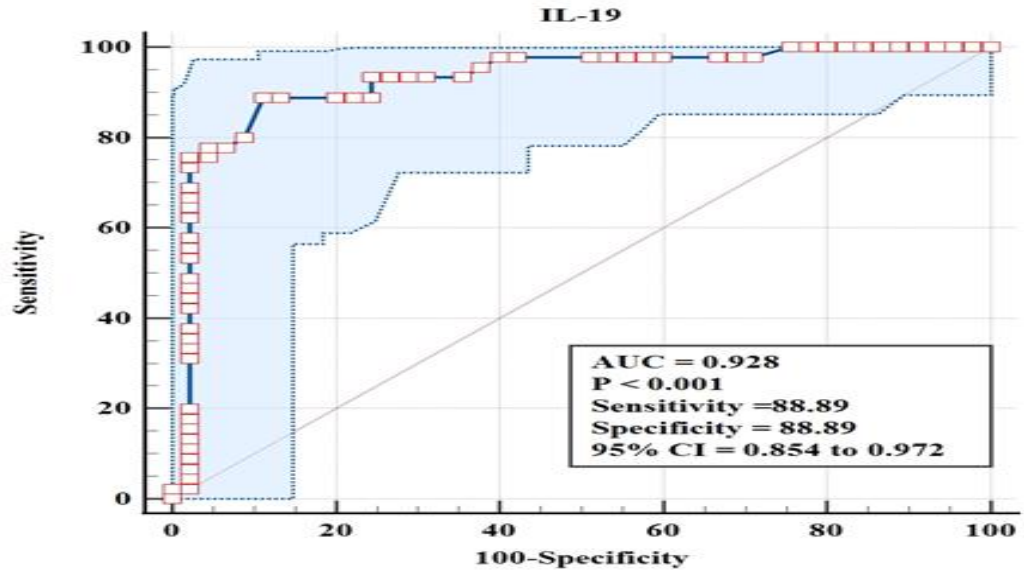

Figure 1. Diagnostic performance of IL-19 assessed by ROC curve analysis

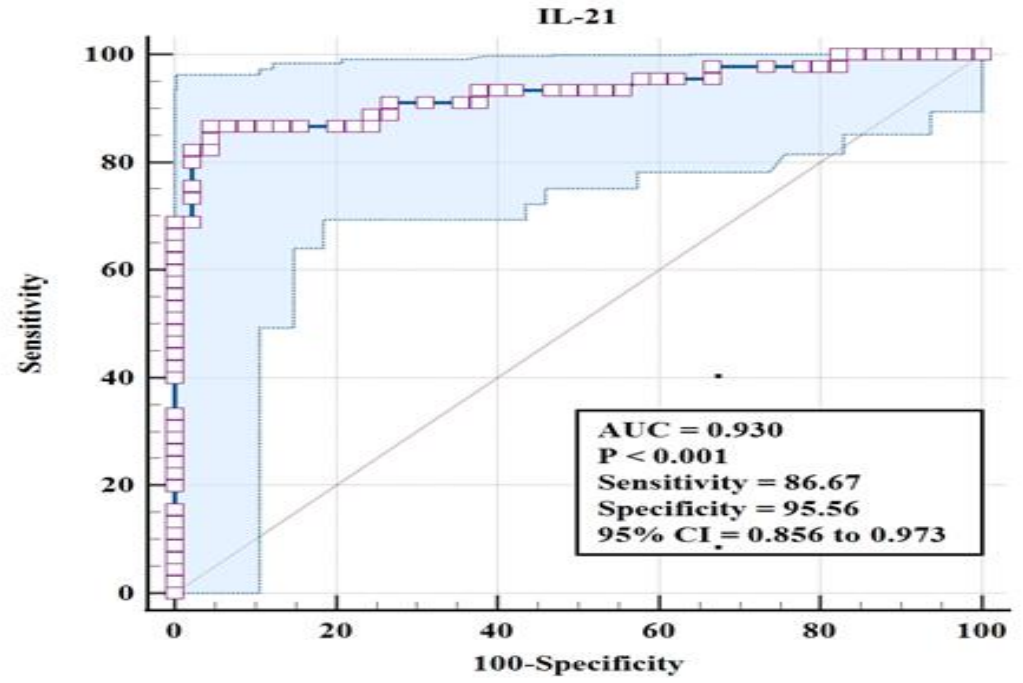

Figure 2. Diagnostic performance of IL-21 assessed by ROC curve analysis.

DISCUSSION

Recurrent aphthous stomatitis (RAS) is widely regarded as an immune-mediated disorder of the oral mucosa, and our findings support a dysregulated local cytokine milieu during active ulceration. In this case–control study, salivary IL-19 and IL-21 levels were significantly higher in patients with RAS than in healthy controls, suggesting enhanced inflammatory signaling and altered epithelial–immune interactions that may contribute to mucosal injury (3, 7).

Our results align with prior evidence showing increased interleukin activity in RAS. Bhosale et al. reported elevated salivary interleukin levels in RAS compared with controls, consistent with the cytokine upregulation observed in the present study (15). Similarly, Albanidou-Farmaki et al. documented increased interleukins in RAS, supporting the concept that cytokine imbalance contributes to disease onset and persistence (16). In addition, the systematic review and meta-analysis by Teng and Jin found significantly increased cytokine expression across multiple interleukins in saliva and serum of RAS patients, which corroborates our observation of elevated salivary IL-19 and IL-21 (18).

The diagnostic relevance of these findings is notable because saliva reflects local mucosal immune activity and can be collected non-invasively (19). IL-19 (an IL-10 family member) is often linked to regulatory pathways, yet its upregulation in inflammatory disorders suggests context-dependent pro-inflammatory or compensatory behavior; thus, increased IL-19 in RAS may represent an

insufficient counter-regulatory response to ongoing inflammation (16). Conversely, IL-21, produced largely by activated CD4+ T cells, particularly Th17 cells, enhances B-cell activation and sustains T-cell responses, thereby amplifying inflammatory networks (20, 21). The concurrent elevation of IL-21 in our cohort is consistent with Th17-skewed immunity and supports models implicating Th17/Treg imbalance in RAS pathogenesis (19).

Demographically, the female predominance and higher mean age among RAS cases were consistent with established epidemiologic patterns; hormonal influences and age-related immune regulatory changes have been proposed as contributors to susceptibility (22, 23). Clinically, minor aphthae were the most common subtype, in agreement with Began et al. and Keenan and Spivakovsky (24, 25). In contrast, Krause et al. reported a higher prevalence of major ulcers, suggesting that population differences and study design may influence observed subtype distributions (26). Importantly, IL-19 and IL-21 did not differ significantly among RAS subtypes in our study, implying a shared inflammatory pathway across clinical phenotypes (19, 25).

Site analysis showed the buccal mucosa as the most frequently affected location, consistent with the predilection of RAS for non-keratinized mucosa exposed to mechanical stress (20). IL-19 was higher in buccal lesions, potentially indicating stronger local epithelial cytokine signalling at mechanically stressed sites, whereas IL-21 showed no clear site variation, consistent with broader Th17-associated activity (20, 21).

ROC analysis indicated that salivary IL-19 and IL-21 discriminate RAS from controls with acceptable-to-excellent performance, supporting their potential as adjunctive diagnostic biomarkers (19). Future multicenter studies should validate cut-offs, assess longitudinal changes with treatment, and clarify whether targeting IL-21 (e.g., cytokine- or JAK-pathway inhibition) or modulating IL-19–related regulation can improve outcomes (19, 25).

Limitation and future Direction

This study is limited by its modest sample size, single-center design, and unequal distribution of clinical subtypes, which may affect generalizability and ststistical power. The cross-sectional nature precludes causal inference, and the lack of serum cytokine assessment limits comparison between local and systematic immune responses. Additionally, potential confounding factors such as stress and hormonal influence were not quantitatively evaluated. Future multicenter and longitudinal studies are needed to validate these findings, establish standardized diagnostic cut-off values, and further explore the immunopathogenic and therapeutic implications of IL-19 and IL-21 in RAS.

CONCLUSION

Salivary IL-19 and IL-21 concentrations are significantly elevated in patients with active recurrent aphthous stomatitis compared with healthy controls. Both cytokines showed excellent diagnostic accuracy by ROC analysis, supporting their potential as reliable, non-invasive adjunctive biomarkers for RAS assessment. Further studies are required to validate diagnostic cut-off values and determine clinical utility in routine practice.

Acknowledgments

The authors thank all participants and the clinic staff for assistance with sample collection and logistics.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Author Contributions

Haween T. Nanakaly designed the study, interpreted the data, and critically revised the manuscript. Mustafa Ghani Taher and Fighan Jalal Hussein performed clinical examinations and collected clinical data. Fatimah Kadhim Ibrahim Al-Mahdawi performed saliva collection, sample processing, and laboratory analyses. All authors contributed to manuscript preparation and approved the final version.

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