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Clinical and Nasal Mucosal Functional Phenotype of PCR-Positive Epstein-Barr Virus- Associated Acute Rhinosinusitis: A Prospective Comparative Study

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ABSTRACT: Acute rhinosinusitis (ARS) is usually viral and self-limited, but marked heterogeneity exists in symptom burden and mucosal recovery. Epstein-Barr virus (EBV) can persist in nasopharyngeal epithelium, yet the clinical significance of EBV DNA detection during ARS remains uncertain. Objective: To compare clinical severity and nasal mucosal function in EBV PCR-positive and EBV-negative ARS. Methods: A prospective comparative study enrolled 120 adults aged 18-65 years between 2024 and 2026. Sixty had EBV-negative ARS and 60 had PCR-positive EBV-associated ARS. Standardized clinical assessment, nasal endoscopy, computed tomography for study phenotyping, saccharin-based mucociliary clearance testing, nasal secretory and absorptive function tests, and nasal secretion pH assessment were performed. Effect estimates were reconstructed from aggregate study data as risk ratios (RRs) or mean differences (MDs) with 95% confidence intervals (CIs). Results: EBV-positive patients more frequently had persistent nasal obstruction (88.3% vs 71.7%; RR 1.23, 95% CI 1.03-1.48), mucopurulent discharge (48.3% vs 23.3%; RR 2.07, 95% CI 1.22-3.51), olfactory dysfunction (68.3% vs 46.7%; RR 1.46, 95% CI 1.06-2.02), and fatigue/sleep disturbance (78.3% vs 51.7%; RR 1.52, 95% CI 1.15-2.00). Mucociliary clearance was prolonged by 6.5 minutes (28.9 ± 4.2 vs 22.4 ± 3.8 min; MD 6.50, 95% CI 5.07-7.93), nasal secretion pH was lower by 0.44 units (5.98 ± 0.27 vs 6.42 ± 0.24), and secretory volume was reduced by 0.40 mL. Within the EBV-positive group, clearance time correlated with obstruction severity ($r=0.69$, $p<0.001$), while pH correlated inversely with clearance time ($r=-0.68$, $p<0.001$). Conclusion: PCR-positive EBV-associated ARS showed a more severe clinical and mucosal-functional phenotype than EBV-negative ARS. These findings support EBV positivity as a potential marker of a subgroup with delayed mucosal recovery, while not establishing viral causality.

1. INTRODUCTION

Acute rhinosinusitis is an inflammatory syndrome of the nasal cavity and paranasal sinuses characterized by nasal obstruction and/or discharge, often accompanied by facial pressure and olfactory disturbance. Contemporary EPOS and ICAR-RS frameworks emphasize that most acute episodes are viral and that imaging is not routinely required for uncomplicated disease [1-4]. Nevertheless, clinical trajectories vary substantially, and a subset of patients develops prolonged symptoms, marked mucosal edema, or delayed functional recovery.

Increasing attention has shifted from a purely anatomic model of sinonasal disease toward a mucosal model in which epithelial barrier integrity, ciliary function, local secretory activity, and immune-epithelial signaling determine disease expression and recovery [5-8]. Viral infections can impair mucociliary clearance and epithelial barrier function and may amplify downstream inflammatory responses [5-8]. These mechanisms are especially relevant when symptoms persist despite otherwise standard management.

EBV is a ubiquitous herpesvirus with lifelong persistence and epithelial as well as B-cell tropism [9-12]. Experimental work in pseudostratified nasopharyngeal epithelium has shown that EBV can infect ciliated, goblet, and basal-cell compartments and disrupt epithelial integrity [9]. These data provide biologic plausibility for an association between EBV activity and altered nasal mucosal function, although detection of EBV DNA in respiratory samples does not by itself establish that EBV is the primary cause of an acute inflammatory episode.

The present study therefore focused on a clinically pragmatic question: whether ARS patients with PCR-detectable EBV exhibit a reproducibly different clinical and functional mucosal phenotype from patients with EBV-negative ARS. We hypothesized that EBV positivity would be associated with greater symptom burden, slower mucociliary clearance, altered nasal secretion pH, and impaired secretory and absorptive function.

MATERIALS AND METHODS

Study design and setting

This prospective comparative clinical study was conducted from 2024 to 2026 at the Otorhinolaryngology Department of the multidisciplinary clinic of Tashkent State Medical University and in collaboration with the virology department of the Research Institute of Epidemiology, Microbiology and Infectious Diseases. The analytic cohort comprised 120 adults with clinically confirmed ARS: 60 with negative EBV PCR and 60 with PCR-confirmed EBV-associated ARS. The manuscript was prepared according to STROBE reporting principles.

Eligibility criteria

Adults aged 18-65 years were eligible when they met contemporary clinical criteria for ARS and had characteristic symptoms such as nasal obstruction, rhinorrhea, facial pain/pressure, headache, or olfactory dysfunction. Endoscopic and computed-tomographic evaluation was performed as part of the research phenotyping protocol. Exclusion criteria documented in the dissertation were age outside 18-65 years, chronic rhinosinusitis with nasal polyps, severe decompensated systemic disease, immunodeficiency or autoimmune disease, malignancy, acute suppurative complications requiring emergency surgery, pregnancy or breastfeeding, active fungal infection or another active viral infection likely to influence the study results, sinus surgery within the previous 6 months, refusal to participate, or protocol non-adherence.

EBV classification

EBV classification was based on real-time PCR performed before antiviral or antibacterial therapy. Nasopharyngeal mucosal swabs and peripheral venous blood were collected under standardized conditions. Viral DNA was extracted using certified test systems according to the manufacturer protocol. Patients with diagnostically significant EBV DNA detection were assigned to the EBV-associated group; patients with negative EBV PCR were assigned to the comparison group. Because EBV can persist and intermittently shed, the term “EBV-associated” is used descriptively and does not imply proven causation.

Clinical, endoscopic, and functional assessment

Symptoms and history were recorded systematically. Nasal videoendoscopy used rigid 2.7- and 4.0-mm, 0° and 30° endoscopes to assess edema, hyperemia, middle-meatal patency, and secretion character. Multislice CT with 0.5-1.0-mm slices and multiplanar reconstruction was used for study characterization; this research use should not be interpreted as a recommendation for routine CT in uncomplicated ARS [1-4].

Mucociliary clearance was assessed with the saccharin test. A small saccharin particle was placed on the anterior inferior turbinate after nasal toilet, and the interval to perception of a sweet taste was recorded. Secretory function was evaluated by quantitative collection of nasal secretion under standardized conditions; the dissertation reports mean secretion volume in milliliters. Absorptive function was evaluated with a standardized water-soluble indicator test, with longer absorption time

indicating greater dysfunction. Nasal secretion pH was measured according to the standardized study protocol. All functional tests were performed under controlled conditions and before treatment.

Outcomes and statistical analysis

For this manuscript, mucociliary clearance time was designated the principal functional outcome. Secondary outcomes included persistent obstruction, mucopurulent discharge, olfactory dysfunction, systemic symptoms, secretory volume, absorptive dysfunction, and nasal pH. The parent study assessed distribution using Shapiro-Wilk and Kolmogorov-Smirnov tests; Student t, Mann-Whitney, paired t, Wilcoxon, chi-square, Fisher exact, Pearson, or Spearman methods were used as appropriate, with $p < 0.05$ considered significant. To strengthen clinical interpretability, this manuscript additionally reconstructed RRs and 95% CIs from aggregate categorical counts and MDs with 95% CIs from reported means and SDs. These derived estimates are secondary calculations and were not based on individual-level reanalysis.

Ethics

All participants provided voluntary informed consent for clinical, laboratory, virologic, and immunologic testing. The institutional ethics committee name, approval number, and approval date must be inserted from the original study record before journal submission.

RESULTS

Participant characteristics

The two groups were demographically comparable. Each group included 34 women (56.7%) and 26 men (43.3%). Mean age was 39.8 ± 2.7 years in the EBV-negative group and 41.2 ± 2.5 years in the EBV-associated group, with no statistically significant age difference reported in the parent study.

Table 1. Baseline demographic characteristics. Dispersion for age is reproduced as reported in the dissertation.

Characteristic	EBV-negative ARS (n=60)	EBV-associated ARS (n=60)
Women, n (%)	34 (56.7)	34 (56.7)
Men, n (%)	26 (43.3)	26 (43.3)
Age range, years	18-65	18-65
Mean age, years	39.8 ± 2.7	41.2 ± 2.5

Clinical phenotype

Several clinically relevant features were more frequent in the EBV-associated group. The largest relative difference was observed for mucopurulent discharge (48.3% vs 23.3%; RR 2.07, 95% CI 1.22-3.51). Persistent obstruction, olfactory dysfunction, fever/intoxication features, and weakness/fatigue/sleep disturbance were also significantly more frequent. Headache/facial pressure showed a directionally higher frequency but the aggregate Fisher exact comparison did not reach $p < 0.05$.

Table 2. Key clinical outcomes. *Fisher exact p values and RRs were calculated from the aggregate counts for this manuscript.

Clinical feature	EBV-negative n (%)	EBV-associated n (%)	RR (95% CI)	P*
Persistent obstruction	43 (71.7)	53 (88.3)	1.23 (1.03-1.48)	0.039
Mucopurulent discharge	14 (23.3)	29 (48.3)	2.07 (1.22-3.51)	0.007
Facial pressure/headache	39 (65.0)	48 (80.0)	1.23 (0.98-1.54)	0.101
Olfactory dysfunction	28 (46.7)	41 (68.3)	1.46 (1.06-2.02)	0.026
Fever/intoxication	21 (35.0)	34 (56.7)	1.62 (1.07-2.44)	0.027
Fatigue/sleep disturbance	31 (51.7)	47 (78.3)	1.52 (1.15-2.00)	0.004

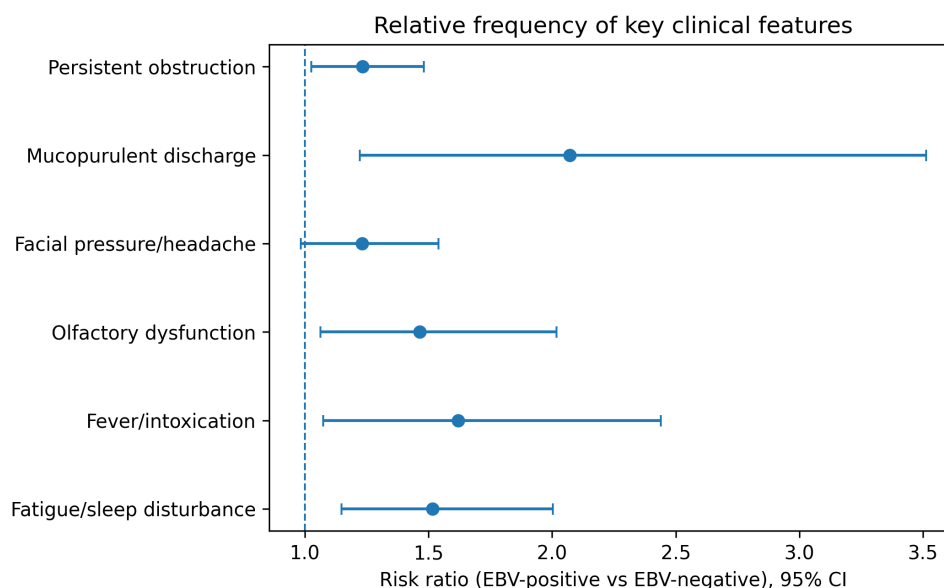


Figure 1. Risk ratios for selected clinical features in EBV-associated versus EBV-negative ARS. Points represent RRs and horizontal bars represent 95% CIs.

Nasal mucosal functional phenotype

Functional abnormalities were consistently more pronounced in EBV-associated ARS. Mean mucociliary clearance time was 28.9 ± 4.2 minutes versus 22.4 ± 3.8 minutes, corresponding to an MD of 6.50 minutes (95% CI 5.07-7.93; standardized effect size $d \approx 1.62$). Mean absorption time was 20.3 ± 3.6 versus 15.8 ± 2.9 minutes. Mean nasal secretion volume was lower by 0.40 mL, and nasal secretion pH was lower by 0.44 units. Marked clearance delay >25 minutes occurred in 58.3% versus 26.7%.

Table 3. Continuous functional outcomes. Effect estimates were reconstructed from reported group means, SDs, and $n=60$ per group; signs reflect EBV-associated minus EBV-negative.

Functional measure	EBV-negative	EBV-associated	Mean difference (95% CI)	Cohen d
Mucociliary clearance time, min	22.40 ± 3.80	28.90 ± 4.20	6.50 (5.07 to 7.93)	1.62
Absorption time, min	15.80 ± 2.90	20.30 ± 3.60	4.50 (3.33 to 5.67)	1.38
Nasal secretion volume, mL	2.10 ± 0.40	1.70 ± 0.50	-0.40 (-0.56 to -0.24)	-0.88
Nasal secretion pH	6.42 ± 0.24	5.98 ± 0.27	-0.44 (-0.53 to -0.35)	-1.72

Table 4. Categorical functional abnormalities as reported in the dissertation.

Functional abnormality	EBV-negative n (%)	EBV-associated n (%)
Any mucociliary impairment	47 (78.3)	54 (90.0)
Marked delay >25 min	16 (26.7)	35 (58.3)
Absorptive dysfunction	41 (68.3)	52 (86.7)
Secretory dysfunction	46 (76.7)	54 (90.0)
Nasal pH <6.5	34 (56.7)	49 (81.7)
Nasal pH <6.0	9 (15.0)	26 (43.3)

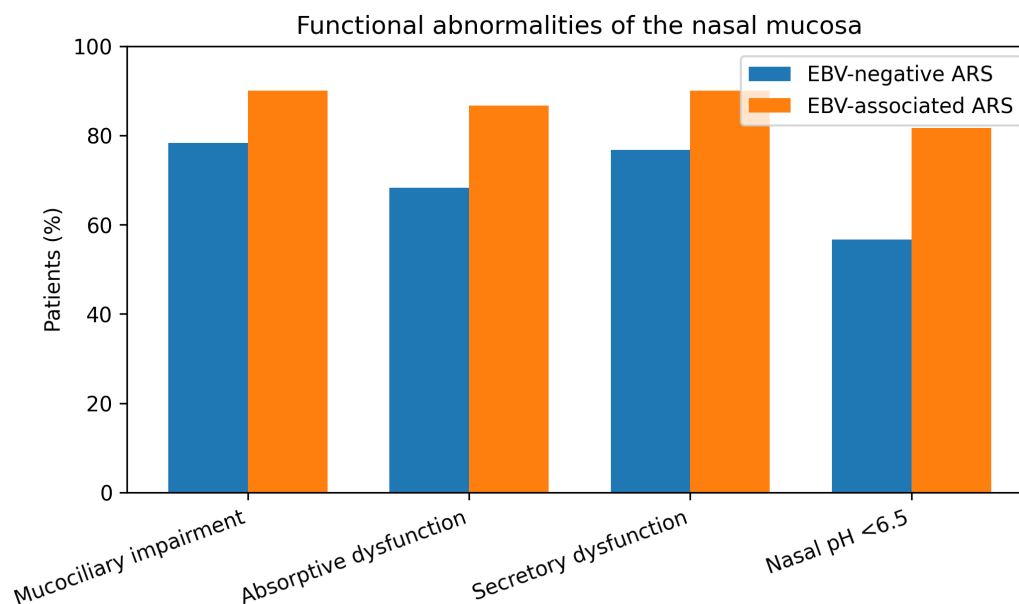


Figure 2. Prevalence of major nasal mucosal functional abnormalities by EBV status.

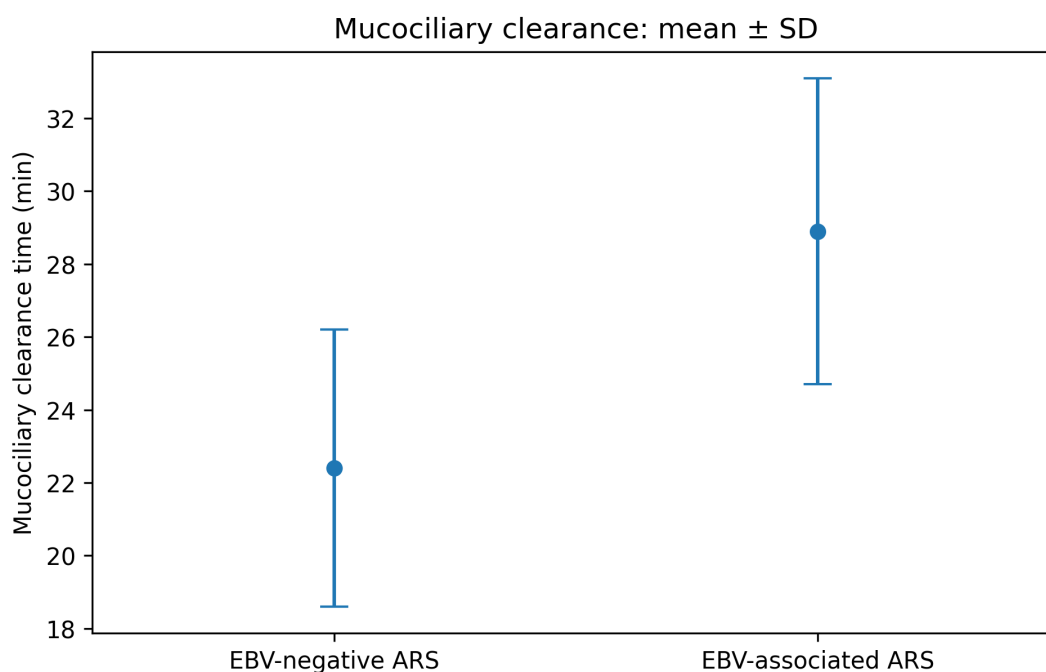


Figure 3. Mean $\pm$ SD mucociliary clearance time in EBV-negative and EBV-associated ARS.

Correlation analysis

In EBV-associated ARS, mucociliary clearance time correlated positively with nasal obstruction severity ($r=0.69$, $p<0.001$), and nasal secretion pH correlated inversely with clearance time ($r=-0.68$, $p<0.001$). The parent dataset also showed an inverse relationship between nasal secretion volume and disease duration ($r=-0.58$, $p<0.01$), supporting progressive impairment of secretory function in more prolonged EBV-associated disease.

DISCUSSION

This study identifies a coherent clinical-functional phenotype associated with EBV PCR positivity in adults with ARS. The signal was not restricted to symptom reporting: EBV-positive patients had more frequent mucopurulent discharge and olfactory dysfunction together with longer mucociliary clearance, slower absorptive function, lower secretion volume, and greater acidification of nasal secretion. The concordance of symptom, endoscopic, and functional findings strengthens the interpretation that EBV positivity marked a subgroup with more pronounced mucosal dysfunction.

The most clinically interpretable differences were a roughly twofold higher frequency of mucopurulent discharge and a 6.5-minute prolongation of mean mucociliary clearance. The magnitude of the latter difference was large relative to within-group variability. Current mucosal models of rhinosinusitis place impaired ciliary transport and epithelial barrier dysfunction at the center of persistent inflammation [5-8]. Viral infection may slow ciliary activity, impair barrier integrity, and alter innate signaling, thereby prolonging secretion retention and mucosal edema [5-8].

The biologic plausibility of an EBV-related epithelial effect is supported by evidence that EBV has epithelial tropism and can infect differentiated nasopharyngeal epithelial cultures [9-12]. Yu et al. demonstrated EBV infection in ciliated, goblet, and basal-cell compartments of pseudostratified nasopharyngeal epithelium and showed disruption of epithelial integrity [9]. These mechanistic observations align with the present pattern of prolonged clearance and impaired secretory/absorptive function, although the present clinical data cannot demonstrate that EBV directly produced those changes.

The pH finding may also be relevant. Airway surface liquid composition contributes to ciliary function, mucus rheology, and antimicrobial defense. In this cohort, lower pH tracked with slower clearance, particularly in the EBV-positive group. Because pH may be influenced by inflammation, secretion composition, medication exposure, and sampling technique, it should currently be interpreted as a physiologic correlate rather than an established diagnostic biomarker.

Olfactory dysfunction was 46% more frequent in EBV-associated disease. Contemporary work on sinonasal epithelial dysfunction emphasizes that inflammatory remodeling, mucus stasis, barrier disruption, and local cytokine signaling can collectively impair olfactory function [6-8]. The present data do not distinguish conductive from sensorineural olfactory mechanisms, but the association with more extensive mucosal edema provides a plausible pathway.

These findings should not be interpreted as an argument for routine EBV PCR testing in all ARS. EPOS, ICAR-RS, and newer consensus documents recommend primarily clinical diagnosis for uncomplicated ARS and caution against indiscriminate imaging and testing [1-4]. Instead, the results generate a testable hypothesis that targeted EBV assessment could be informative in selected patients with unusually prolonged, recurrent, or functionally severe disease, particularly in research or specialist settings.

Strengths and limitations

Strengths include prospective recruitment, balanced group size, identical sex distribution, objective functional testing, and concordant clinical-functional outcomes. Several limitations are important. First, EBV is highly prevalent and PCR positivity may represent reactivation or shedding rather than direct causation. Second, viral PCR was used for group assignment, creating an etiologic classification that may still include heterogeneous non-EBV inflammatory drivers. Third, treatment differed between groups according to virologic and immunologic status, limiting causal interpretation of post-treatment comparisons; this article therefore focuses primarily on pretreatment phenotype. Fourth, the analysis was single-center/two-site, and smoking, allergy, environmental exposure, and other confounders were not available for multivariable reanalysis in the aggregate dataset. Fifth, several effect estimates in this manuscript were reconstructed from summary data rather than patient-level data. Finally, CT and endoscopy were used for research phenotyping and should not be generalized to routine uncomplicated ARS care.

CONCLUSION

Adults with PCR-positive EBV-associated ARS had a more severe clinical phenotype and greater nasal mucosal dysfunction than EBV-negative ARS, including prolonged mucociliary clearance, impaired absorption and secretion, and lower nasal pH. EBV positivity may therefore identify a subgroup with delayed mucosal recovery. Confirmation in multicenter cohorts with standardized quantitative EBV assays, patient-level confounder adjustment, and longitudinal viral and functional measurements is required before EBV testing can be incorporated into routine ARS algorithms.

DECLARATIONS

Ethics approval and consent to participate: The study was approved by the Ethics Committee of Tashkent State Medical Academy (Approval No. 10, dated april 10,2026). **Consent for publication:** Not applicable to aggregate, non-identifiable study data.

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Data availability: The availability of the underlying study data is subject to institutional policy and participant confidentiality requirements. Requests for access should be addressed to the corresponding author.

Author Contributions

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