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# Nasal Mucociliary Clearance and Its Relationship With Disease Severity in Patients With Multiple Sclerosis

Authors' Contribution:

Study Design A

Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

Literature Search F

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**Background:** Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease associated with increased susceptibility to infections. Nasal mucociliary clearance (NMC) is a primary defense mechanism of the respiratory system; however, its status in patients with MS remains insufficiently explored.

**Material/Methods:** This prospective, matched case-control study included 60 patients with MS and 60 age- and sex-matched healthy controls. NMC time was measured using the saccharin test under standardized conditions. Clinical data, including disease duration, Expanded Disability Status Scale (EDSS) scores, MS subtype, and treatment regimens, were recorded. Between-group comparisons and correlation analyses were performed to evaluate the relationship between NMC and clinical parameters.

**Results:** Mean NMC time was significantly longer in patients with MS compared with healthy controls ( $11.68 \pm 5.10$  vs  $7.47 \pm 1.83$  minutes,  $P < 0.001$ ). NMC time showed a significant positive correlation with EDSS scores ( $r = 0.378$ ,  $P = 0.003$ ). Patients with progressive MS exhibited significantly prolonged NMC times compared with those with relapsing-remitting MS ( $P = 0.004$ ). In addition, subgroup analyses demonstrated differences according to MS subtype and treatment groups, supporting the association between NMC and disease characteristics.

**Conclusions:** NMC was impaired in patients with MS and was associated with disease severity. These findings suggest that NMC assessment may serve as a potential noninvasive marker of disease-related physiological dysfunction and may help identify patients at increased risk for respiratory complications. Further studies are required to confirm these findings and to clarify their clinical implications.

**Keywords:** **Disability Evaluation • Multiple Sclerosis • Nasal Mucociliary Clearance • Neurology • Respiratory Tract Infections**

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## Introduction

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune disease of the central nervous system [1]. Recent epidemiological data indicate that the global prevalence of MS has increased over time, affecting approximately 2.9 to 3 million individuals worldwide [1]. Although many factors are involved in the etiology of MS, the exact cause of the disease remains unknown. Patients with MS are more prone to infections due to immune dysregulation and immunosuppressive treatments [2] and have higher rates of infection-related healthcare utilization compared with the general population [3]. Upper and lower respiratory tract infections constitute a significant proportion of these cases. Therefore, early diagnosis and infection prevention strategies are of great importance.

The mucociliary clearance system contains mucus secreted from epithelial cilia and goblet cells. This system is one of the most important protective mechanisms of the nasal and respiratory system, functioning in the body's defense against certain pathogens and harmful particles in the inhaled air [4]. Attempting to measure mucociliary clearance from the trachea and lower respiratory tract is a costly and time-consuming procedure. Therefore, the saccharin clearance test may be a simple and cost-effective test for nasal mucociliary clearance (NMC) measurement [5].

In this study, NMC values of patients with MS and healthy controls were compared. We aimed to determine whether there is a significant relationship between the degree of disability due to MS and NMC. In addition, as disability increases in patients with MS, the risk for additional disease burden and other system diseases may increase [6]. Therefore, we designed this study with aim of evaluating NMC as a potential early indicator of infection risk and as a tool to help identify the causes of infections that are frequently observed, especially in patients with progressive MS.

## Material and Methods

This study was designed as a prospective, matched case–control study conducted at a single center. After obtaining approval from the local ethics committee of our university (decision No. 02, dated April 5, 2023), patients with MS who presented to our hospital's neurology and MS outpatient clinics between April 15, 2023, and April 15, 2024, were included.

For the study, the recommendations of the Declaration of Helsinki were followed, and written informed consent was obtained from the patients. A total of 60 patients in subgroups divided by MS type—relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS),

and primary progressive multiple sclerosis (PPMS)—between the ages of 18 and 60 who were diagnosed with definite MS according to the McDonald 2017 revised diagnostic criteria were prospectively evaluated [7]. In addition to demographic data, such as age and sex, disease years were recorded from the time of the first diagnosis of MS until study enrollment. The immunomodulatory and immunosuppressive treatments used were noted. Patients were assessed for disability using the Expanded Disability Status Scale (EDSS) score [8]. Detailed history was taken from the patients, and detailed neurologic and physical examinations were performed. The exclusion criteria included additional neurologic disease, history of systemic disease, pregnancy, and use of another drug affecting the nervous system. In addition, patients who had an MS relapse in the last 1 month or who had received steroid treatment in the last 1 month were excluded from the study. Sixty volunteers of similar age and sex were included as the control group. Selected patients and control group healthy volunteers underwent detailed endoscopic examinations in our ear nose and throat (ENT) polyclinic, and NMC measurements were performed by an ENT specialist. Patients were also excluded on the basis of secondary pathologies that may cause nasal obstruction, including severe septal deviation, turbinate hypertrophy, and nasal polyposis; upper respiratory tract infection; active infection at the time of examination; history of nasal surgery; diabetes mellitus; hypertension; history of allergy; and active or passive smoking.

NMC measurements were evaluated with the sodium saccharin test by the same ENT specialist. Measurements were performed using an accepted standardized technique [9]. Before the NMC measurement, the participants were instructed to rest for at least 30 to 45 minutes, not to eat or drink, and to clean their noses thoroughly. In the sitting position, the saccharin particle was placed without the participant leaning forward, and then the participant was made to lie down. A 1-mm sodium saccharin particle was placed on the medial side of the inferior nasal concha with a distance of 10 mm with the help of a forceps. During the test, participants were asked not to make sniffing reflexes and not to blow and wipe their noses. The time between the perception of the sweet taste in the oropharyngeal region and the placement of the particle was measured with a stopwatch and recorded as NMC time.

## Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM Corp, Armonk, NY, USA). Categorical variables are expressed as numbers and percentages, while continuous variables are presented as mean±standard deviation. Normality of continuous variables was assessed using skewness and kurtosis values [10]. Independent samples *t* test was used for comparisons between 2 groups, and 1-way ANOVA was applied

**Table 1.** Demographic and clinical characteristics of the multiple sclerosis (MS) and control groups.

Variable	MS (n=60)	Control (n=60)	P
Age (years)	31.10±11.27	34.66±9.23	0.541
Sex (male/female)	20/40	20/40	–
Disease duration (years)	5.25±3.82	–	–
EDSS (mean±SD)	1.72±1.30	–	–
EDSS (median [IQR])	1.5 (1.0-2.5)	–	–

Values are presented as mean±standard deviation unless otherwise indicated. Expanded Disability Status Scale (EDSS) values are additionally presented as median and interquartile range (IQR) due to the ordinal nature of the scale.

**Table 2.** Comparison of nasal mucociliary clearance among healthy controls, multiple sclerosis subtypes, and disease-modifying treatment groups.

Group	n	Mean±SD (min)	P
Control	60	7.47±1.83	<0.001
MS	60	11.68±5.10	
<b>MS subtype</b>			
RRMS	46	10.65±5.05	0.004
SPMS+PPMS	14	15.07±3.64	
<b>Treatment groups</b>			
Teriflunomide	16	9.40±2.40	0.036
Ocrelizumab	5	15.70±4.18	
Fingolimod	12	12.64±6.51	
Dimethyl fumarate	15	10.83±6.48	
Other	12	13.16±3.16	

Values are presented as mean±standard deviation in minutes. Abbreviations: RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis.

for comparisons among multiple groups. Pearson correlation analysis was used to evaluate associations between NMC values and clinical parameters. As EDSS is an ordinal scale, its analysis as a continuous variable may represent a limitation; therefore, results were interpreted with caution, and non-parametric approaches were considered where appropriate. In addition, EDSS values were summarized using median and interquartile range (IQR) to better reflect the ordinal nature of the scale. A *P* value <0.05 was considered statistically significant.

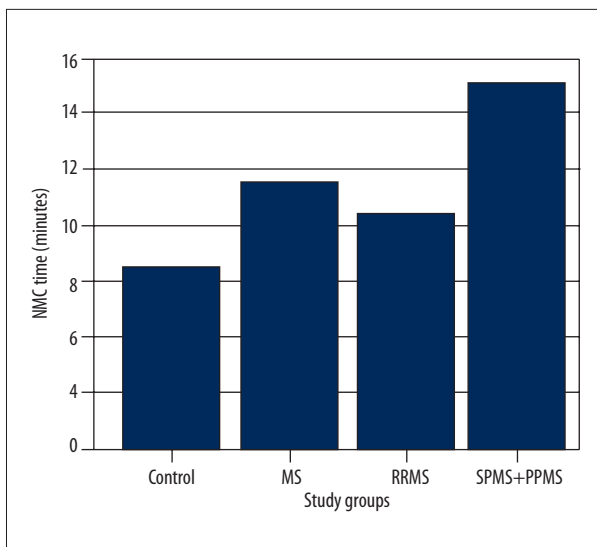
## Results

A total of 60 patients with multiple sclerosis (MS) and 60 age- and sex-matched healthy controls were included in the study. There were no significant differences between the groups in terms of age or sex distribution (*P*>0.05) (Table 1). Median EDSS values with interquartile ranges were 1.5 (1.0-2.5), reflecting the ordinal nature of the scale.

NMC times were significantly longer in patients with MS compared with healthy controls (11.68±5.10 vs 7.47±1.83 minutes, *P*<0.001) (Table 2). In addition, patients with progressive MS (SPMS and PPMS) demonstrated longer NMC times than did those with RRMS. These differences are illustrated in Table 2 and Figure 1 (15.07±3.64 vs 10.65±5.05 minutes, *P*=0.004).

In treatment subgroup analyses, NMC times differed significantly among treatment groups (*P*=0.036). Patients receiving ocrelizumab had the longest NMC times (15.7±4.18 minutes), followed by those receiving fingolimod (12.64±6.51 minutes) and other treatments, whereas patients treated with teriflunomide had comparatively shorter NMC durations (9.4±2.4 minutes) (Table 2, Figure 2).

Pearson correlation analysis demonstrated a significant positive correlation between NMC time and EDSS scores (*r*=0.378, *P*=0.003), indicating that higher disability levels were associated with prolonged mucociliary clearance. No significant correlations



**Figure 1.** Comparison of nasal mucociliary clearance (NMC) times between healthy controls and patients with multiple sclerosis (MS), including subgroup analysis of relapsing-remitting MS (RRMS) and secondary progressive and primary progressive MS (SPMS and PPMS).

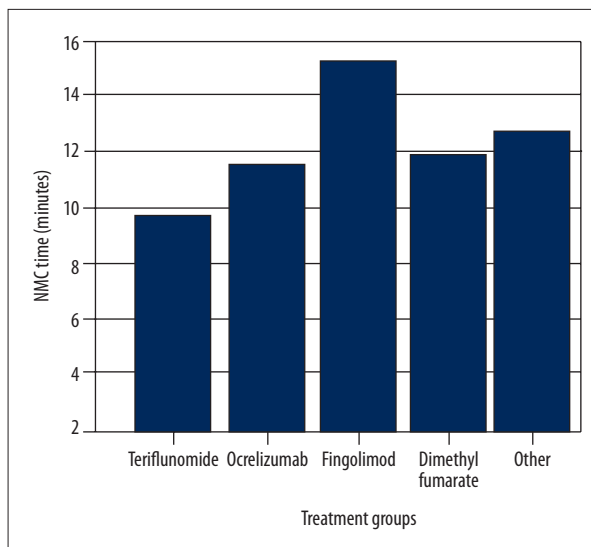
were observed between NMC time and age ( $r=0.183, P=0.162$ ) or disease duration ( $r=0.145, P=0.269$ ) (Table 3).

### Discussion

MS is one of the leading causes of non-traumatic disability in young adults and is associated with an increased susceptibility to infections. Infectious complications, particularly involving the respiratory tract, contribute substantially to morbidity and healthcare utilization in patients with MS. Previous studies investigating infection risk in MS have primarily focused on hospitalized populations, reporting higher rates of respiratory tract infections compared with the general population [11,12].

Upper and lower respiratory tract infections have also been implicated as potential triggers for disease exacerbations in RRMS. Viral and bacterial infections may contribute to inflammatory activation, and relapses have been reported in up to 30% to 40% of patients following upper respiratory tract infections [13-15]. In the present study, NMC was significantly prolonged in patients with MS, particularly in those with progressive disease, suggesting impaired airway defense mechanisms in this subgroup.

The observed association between prolonged NMC and higher disability scores supports the concept that systemic involvement may accompany disease progression in MS. Although the exact mechanisms underlying impaired mucociliary function



**Figure 2.** Comparison of nasal mucociliary clearance (NMC) times across different treatment groups in patients with multiple sclerosis.

**Table 3.** Correlation between nasal mucociliary clearance (NMC) and clinical parameters.

Variable	r	P
Age	0.183	0.162
Disease duration	0.145	0.269
EDSS	0.378	<b>0.003</b>

Pearson correlation analysis was used. Abbreviation: EDSS, Expanded Disability Status Scale. Note, the EDSS was analyzed with caution due to its ordinal nature.

in MS remain unclear, chronic inflammation, reduced mobility, and autonomic dysfunction may contribute to alterations in nasal clearance dynamics. Autonomic dysfunction, which is present in up to 45% to 85% of patients with MS, may contribute to impaired mucociliary clearance through altered regulation of nasal gland secretion and ciliary activity. This is consistent with previous studies demonstrating that autonomic nervous system dysfunction can influence sinonasal physiology and mucociliary transport [16,17].

Disease-modifying therapies used in MS have been associated with varying degrees of infection risk, particularly involving the upper respiratory tract [18,19]. In our cohort, patients receiving ocrelizumab exhibited longer NMC durations than did other treatment groups. However, this finding should be interpreted with caution, as patients receiving ocrelizumab generally had higher disability scores and more advanced disease. Given the cross-sectional design of the study, a causal relationship between specific disease-modifying therapies and prolonged NMC cannot be established [20,21].

From a clinical perspective, NMC measurement may be considered as a simple and noninvasive screening tool in patients with higher disability scores to help identify those at increased risk for respiratory complications. However, further studies are needed to validate its routine clinical use [11].

Impaired NMC may lead to increased bacterial colonization and heightened susceptibility to respiratory infections, as previously reported in patients with MS [4,22-24].

### Study Limitations

This study has several limitations. First, it was conducted at a single center with a relatively limited sample size, which may restrict the generalizability of the findings. In particular, some treatment subgroups, such as the ocrelizumab group, included a small number of patients, which limits the robustness of subgroup analyses and the interpretation of treatment-related differences.

Second, although significant associations between NMC and clinical parameters were observed, multivariable analyses were not performed. Therefore, potential confounding effects of factors such as disability severity (EDSS), disease duration, and treatment characteristics cannot be fully excluded.

Third, EDSS is an ordinal scale, and although it was analyzed as a continuous variable in this study, this approach may represent a methodological limitation.

Fourth, magnetic resonance imaging parameters were not included; therefore, the relationship between mucociliary clearance and radiological disease burden could not be evaluated.

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Finally, the cross-sectional design precludes causal inferences regarding the relationship between nasal mucociliary clearance and disease progression. Future multicenter studies with larger cohorts and longitudinal designs, including multivariable analyses and radiological data, are needed to further validate these findings.

### Conclusions

NMC was prolonged in patients with MS and was associated with disability severity, particularly in progressive disease. These findings suggest that NMC assessment may provide supportive clinical information regarding respiratory vulnerability in selected patients with MS. Further multicenter studies with larger cohorts are required to validate these observations.

### Ethics Committee Approval

This study was approved by the Van Yuzuncu Yıl University Hospital Clinical Research Ethics Committee (decision No. 02, dated April 5, 2023). All procedures were conducted in accordance with the Declaration of Helsinki.

### Patient Consent

Patient consent was obtained after detailed information was provided in accordance with the Declaration of Helsinki.

### Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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