



RESEARCH

The impact of the COVID-19 pandemic on the incidence and clinical disease activity of multiple sclerosis

COVID-19 pandemisinin multipl skleroz'un insidansı ve klinik hastalık aktivitesi üzerindeki etkisi

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Abstract

Purpose: The aim of this study was to describe temporal trends in multiple sclerosis (MS) incidence and relapse frequency in Türkiye across pre-pandemic, pandemic, and post-pandemic periods, and to assess whether the pandemic was associated with population-level changes.

Materials and Methods: This retrospective, nationwide population-based study used the Turkish national healthcare database. Newly diagnosed MS cases recorded between January 2018 and December 2023 were analyzed to assess incidence trends. Relapses were identified using prescription and procedure records, including high-dose intravenous methylprednisolone (≥ 3 consecutive days, ≥ 1500 mg cumulative dose, ≥ 30 -day interval) and plasmapheresis as a marker of severe relapse. Annualized relapse rates (ARRs) with 95% confidence intervals were calculated for 2018–2023.

Results: MS incidence declined sharply in early 2020, coinciding with nationwide lockdowns, but returned to pre-pandemic levels thereafter. Relapse activity showed a transient decrease in 2020, followed by a temporary increase in 2021 (ARR 0.057), and stabilization in 2022–2023. Overlapping confidence intervals across years indicated no sustained change.

Conclusion: The COVID-19 pandemic was not associated with a lasting change in MS incidence in Türkiye but was accompanied by temporary fluctuations in relapse frequency. These findings highlight the resilience of MS epidemiology and emphasize the importance of maintaining continuity of care during public health crises.

Keywords: Multiple sclerosis, COVID-19, incidence, relapse

Öz

Amaç: Bu çalışmanın amacı Türkiye'de pandemi öncesi, pandemi dönemi ve pandemi sonrası süreçlerde multipl skleroz (MS) insidansı ve atak sıklığındaki zamansal örüntüleri tanımlamak ve pandemi döneminin toplum düzeyinde ölçülebilir değişikliklerle ilişkili olup olmadığını değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif, ulusal, toplum temelli çalışmada Türkiye ulusal sağlık veri tabanı kullanıldı. Ocak 2018–Aralık 2023 arasında kaydedilen yeni MS tanılarını insidans eğilimlerini değerlendirmek amacıyla analiz edildi. Ataklar; yüksek doz intravenöz metilprednizolon kullanımı (≥ 3 ardışık gün, ≥ 1500 mg kümülatif doz, kürler arasında ≥ 30 gün) ve ağır atak göstergesi olarak plazmaferez işlemleri temel alınarak tanımlandı. Yıllık atak oranları (ARR), %95 güven aralıkları ile birlikte, 2018–2023 yılları arasında hesaplanarak dönemler arası değişimler incelendi.

Bulgular: MS insidansı, ülke çapındaki kapanmalarla eş zamanlı olarak 2020'nin başlarında belirgin şekilde azalmış, sonraki dönemde pandemi öncesi düzeylere geri dönmüştür. Atak aktivitesi 2020 yılında geçici bir düşüş göstermiş, 2021'de kısa süreli bir artış (ARR 0,057) izlenmiş ve 2022–2023 döneminde güven aralıkları örtüşecek şekilde stabil hale gelmiştir.

Sonuç: COVID-19 pandemisi, Türkiye'de MS insidansında kalıcı bir değişiklik ile ilişkili bulunmamış, ancak toplum düzeyinde atak sıklığında geçici dalgalanmalar gözlemlenmiştir. Bu bulgular, MS epidemiyolojisinin dayanıklılığını ortaya koyarken, halk sağlığı krizleri sırasında bakım sürekliliğinin ve atak izleminin önemini vurgulamaktadır.

Anahtar kelimeler: Multipl skleroz, COVID-19, insidans, relaps

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INTRODUCTION

Multiple Sclerosis (MS) is a chronic, demyelinating autoimmune disease of the central nervous system, characterized by relapsing or progressive neurological dysfunction. Notably, MS pathogenesis is multifactorial, with both genetic predispositions and environmental exposures contributing to the disease course. Understanding these interactions is critical for anticipating periods of increased relapse risk. Environmental and immunological triggers, including viral infections, are implicated in both disease onset and relapse activity¹.

In late December 2019, clusters of pneumonia cases of unknown etiology were first reported in Wuhan, China, with rapid escalation in incidence. Subsequent virological investigations identified a novel beta coronavirus, later designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the causative pathogen². The World Health Organization (WHO) subsequently named the associated disease coronavirus disease 2019 (COVID-19)³. Characterized predominantly by acute respiratory illness, COVID-19 soon revealed systemic involvement, ranging from cardiovascular and thromboembolic complications to neurological and immunological sequelae, establishing itself as a life-threatening condition in susceptible individuals⁴.

The global spread of SARS-CoV-2 placed unprecedented strain on healthcare infrastructures worldwide⁵. Parallel to these efforts, multiple vaccine platforms including mRNA, adenoviral vector, inactivated, and protein subunit vaccines were rapidly developed and deployed under emergency use authorizations. Despite their demonstrated efficacy in reducing severe disease and mortality, disparities in access, waning immunity, and variable vaccine acceptance limited the achievement of global uniform protection⁶⁻⁸. These factors not only influenced the epidemiology of COVID-19 but also indirectly affected patients with chronic neurological conditions, potentially modifying relapse rates, treatment adherence, and overall outcomes.

MS as mentioned before is immune-related disease and characterized by recurrent inflammatory demyelinating episodes (relapses) and progressive neurodegeneration⁹⁻¹¹. Viral infections have long been recognized as potential modulators of MS disease activity, acting through mechanisms such as molecular mimicry, immune activation, or bystander

inflammation¹²⁻¹⁵. Emerging evidence from case reports, cohort studies, and mechanistic hypotheses suggests that SARS-CoV-2 infection may precipitate demyelinating events or exacerbate relapse activity in patients with established MS^{16,17}. While pseudo-exacerbations are well documented in the context of systemic infections, data on whether COVID-19 serves as a genuine trigger for new disease activity remain inconclusive¹⁸. Nevertheless, some studies have indicated higher relapse rates, new radiological activity, or worsened long-term outcomes in MS patients following SARS-CoV-2 infection¹⁹. For instance, longitudinal cohorts have demonstrated that individuals recovering from COVID-19 may experience increased frequency of relapses, accumulation of new T2 or gadolinium-enhancing lesions on magnetic resonance imaging (MRI), and delayed recovery of neurological function. These findings, though preliminary, suggest that SARS-CoV-2 may act as both a trigger of disease activity and a modifier of the long-term disease course in a subset of patients²⁰.

Given the chronic nature of multiple sclerosis and its long preclinical phase, short-term societal disruptions are unlikely to alter the true biological incidence of the disease. However, relapse activity -representing acute inflammatory events - may be more sensitive to systemic stressors and changes in healthcare delivery.

Therefore, the primary aim of this nationwide, population-based study was to describe temporal patterns in MS incidence and relapse frequency in Türkiye across the pre-pandemic, pandemic, and post-pandemic periods, and to determine whether the pandemic era was associated with measurable changes at the population level.

We hypothesized that while MS incidence would remain largely stable, relapse frequency operationally defined using nationwide corticosteroid and plasmapheresis treatment records might exhibit transient fluctuations during the pandemic period. Importantly, this study was designed as a descriptive, hypothesis-generating analysis rather than a causal investigation.

MATERIALS AND METHODS

Sample and population

This retrospective, population-based study was conducted using the Turkish national healthcare database, which comprehensively records diagnostic

codes, therapeutic interventions, and prescription data for the entire population. The database provides nationwide coverage and allows longitudinal tracking of healthcare utilization, enabling objective evaluation of disease incidence and relapse-related healthcare use across Türkiye. The nationwide scope of this database ensures that findings are not limited to a specific region or healthcare provider and reflect real-world clinical practice at the population level.

For the incidence analysis, newly diagnosed MS cases recorded between January 2018, and December 2023 were identified. These data were used to examine potential changes in MS incidence patterns before and during the COVID-19 pandemic.

For the relapse analysis, all individuals with an established diagnosis of MS who were registered in the national database between January 2018, and December 2023 were included. This approach enabled the evaluation of relapse activity over an extended period encompassing the pre-pandemic, pandemic, and post-pandemic phases.

Outcome definition

The primary outcomes of the study were (i) the annual number of newly diagnosed MS cases (incidence) and (ii) relapse frequency, expressed as annualized relapse rates (ARRs). Incidence was assessed using annual and monthly counts of new MS diagnoses between 2018 and 2023. Relapse activity was evaluated from 2018 through 2023 to capture long-term temporal trends.

To facilitate temporal comparisons, the study timeline was divided into three predefined periods: pre-pandemic (2018–2019), pandemic (2020–2021), and post-pandemic (2022–2023).

Relapse definition

Relapses were identified using a stringent, prescription- and procedure-based algorithm designed to minimize subjective bias. A relapse was defined as the administration of intravenous methylprednisolone (IVMP) for at least three consecutive days with a cumulative dose of ≥ 1500 mg, provided that at least 30 days had elapsed since any prior IVMP course. This washout period was applied to distinguish discrete treatment episodes¹⁸.

In addition, plasmapheresis procedures were included as indicators of severe relapses, reflecting clinical scenarios in which conventional

corticosteroid therapy was insufficient. This objective definition was applied uniformly across the nationwide dataset to ensure consistency in relapse identification.

Statistical analysis

Descriptive statistical methods were used to summarize nationwide trends in MS incidence and relapse activity. Annual and monthly numbers of newly diagnosed MS cases were calculated for each calendar year between 2018 and 2023 to evaluate temporal changes in incidence.

Relapse frequency was assessed using annualized relapse rates (ARRs), defined as the total number of relapses divided by the total number of registered MS patients for each calendar year. For period-based analyses, the total number of relapses and the total number of MS patients were obtained for each two-year interval (pre-pandemic, pandemic, and post-pandemic). ARR values were calculated by dividing the number of relapses by the number of patients within each period and standardizing per year and were expressed as the mean number of relapses per patient-year.

Assuming a Poisson distribution for relapse counts, 95% confidence intervals were estimated for all ARR values. Temporal changes were primarily evaluated descriptively by comparing annual and period-based ARR values, percentage changes, and graphical trends coinciding with major pandemic-related events, including nationwide lockdowns and the national COVID-19 vaccination campaign.

All analyses were performed on aggregated, de-identified data, and the statistical evaluation focused on identifying population-level temporal patterns rather than individual-level causal associations.

RESULTS

This nationwide analysis examined temporal trends in MS incidence and relapse frequency between 2018 and 2023. Relapse frequency was operationally defined based on the use of high-dose intravenous methylprednisolone and plasmapheresis, as detailed in the Methods section. Annual and monthly incidence counts, and annualized relapse rates were evaluated across the pre-pandemic, pandemic, and post-pandemic periods to characterize population-level patterns.

Incidence of MS

Between 2018 and 2023, the annual number of newly diagnosed MS cases demonstrated an average of $6,102 \pm 926$. The highest incidence was observed in 2018 with 7,191 cases, while the lowest occurred in 2020 with 4,984 cases. When examined on a monthly basis, the mean number of new diagnoses was $517 \pm$

88, ranging from a peak of 691 in March 2018 to a nadir of 194 in April 2020 (Figure 1). The marked reduction in early 2020 coincided with the onset of nationwide lockdowns and limitations in hospital access, strongly suggesting that healthcare service disruptions rather than true epidemiological changes accounted for this decline.

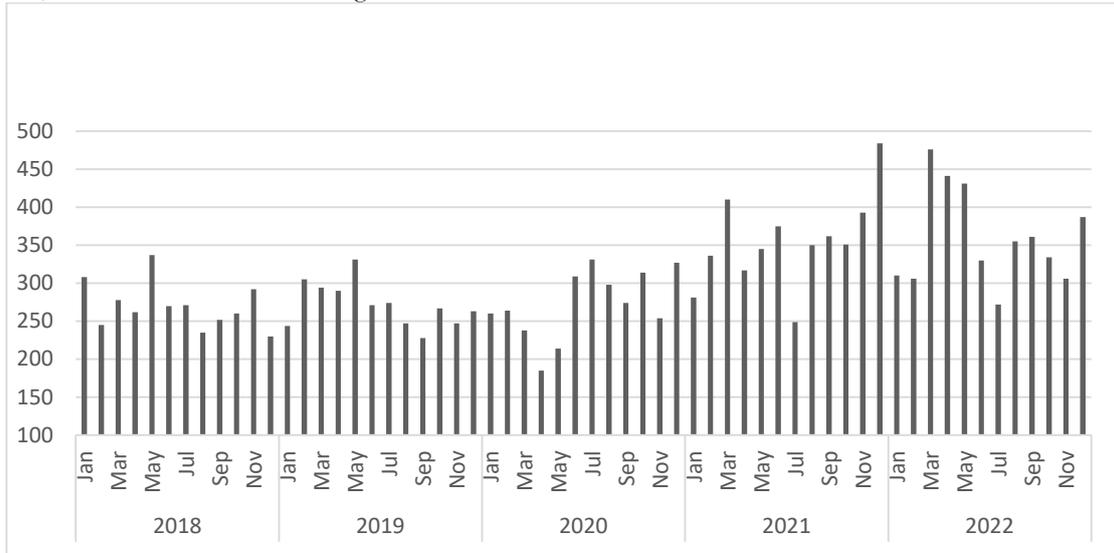


Figure 1. Monthly new MS patient diagnosis

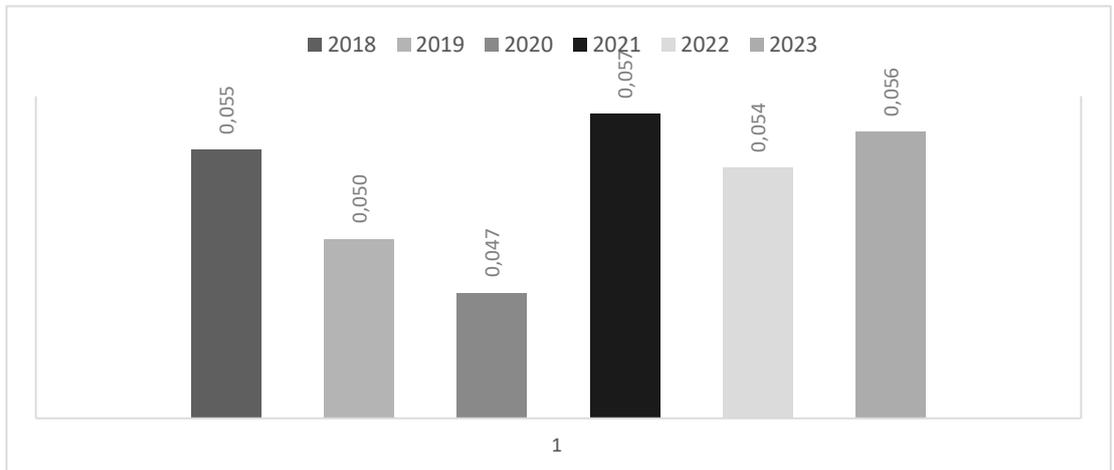


Figure 2. Annual relapse rate

Relapse frequency and annualized relapse rates

Between 2018 and 2023, the total number of registered MS patients increased steadily from 58,672

to 83,409, while the annual number of relapses ranged from 3,240 to 4,687. Annualized relapse rates (ARRs) were calculated by dividing the total number of relapses by the total number of MS patients for

each calendar year. Assuming a Poisson distribution for relapse counts, 95% confidence intervals (CIs) were estimated for all ARR values.

In the pre-pandemic period, ARR was 0.055 (95% CI: 0.053–0.057) in 2018 and 0.050 (95% CI: 0.049–0.052) in 2019, corresponding to a mean ARR of approximately 0.052. During the pandemic period, ARR declined to 0.047 in 2020 (95% CI: 0.046–0.049), followed by a marked increase to 0.057 in 2021 (95% CI: 0.055–0.059), representing an approximate 21% rise compared with the previous year. When considered together, the mean ARR for the pandemic period (2020–2021) was 0.052, indicating a transient fluctuation rather than a sustained elevation in relapse activity (Figure 2).

In the post-pandemic period, ARR values remained comparable to pre-pandemic levels, measuring 0.054 in 2022 (95% CI: 0.053–0.056) and 0.056 in 2023

(95% CI: 0.055–0.058), with a mean ARR of 0.055. Overall, relapse activity demonstrated a temporary decline during the first pandemic year, followed by a rebound in 2021 and subsequent stabilization, with overlapping confidence intervals across years suggesting the absence of a persistent increase in relapse frequency (Figure 3). These findings indicate that while short-term variations in relapse frequency occurred during the pandemic, no persistent increase in relapse activity was observed across the study period.

Overall, these results indicate that the COVID-19 pandemic did not lead to a sustained increase in MS incidence in Türkiye, but transient changes in relapse activity were observed, most notably a short-lived increase during 2021 that subsequently returned to baseline.

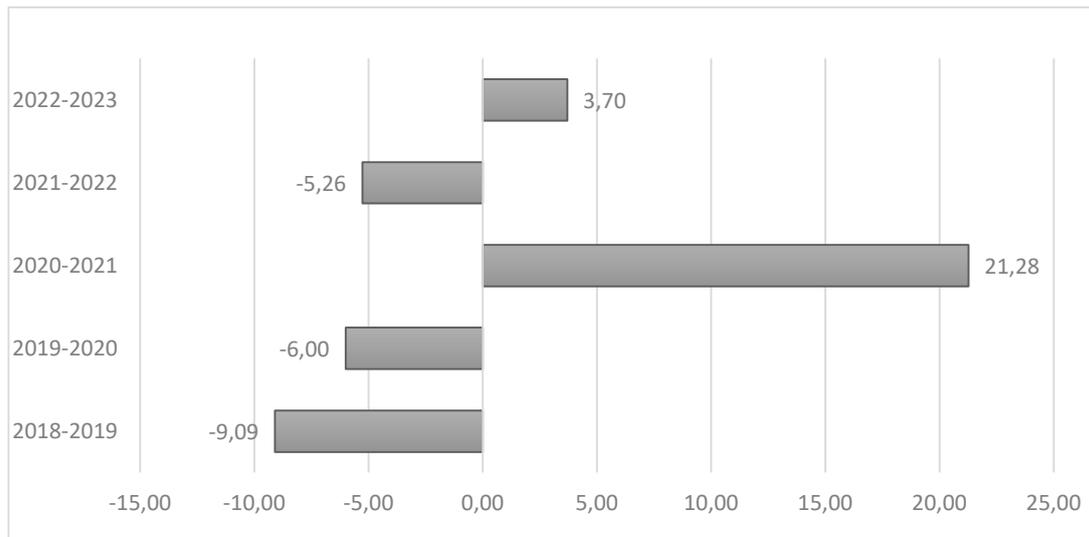


Figure 3. Rate of change in the number of attacks

DISCUSSION

This nationwide study demonstrated that the COVID-19 pandemic did not substantially alter the incidence of MS in Türkiye, though transient fluctuations were observed in relapse frequency. Specifically, incidence declined sharply during the initial lockdown period in early 2020, while relapse activity decreased in 2020 but temporarily increased

in 2021 before returning to baseline. These temporal trends suggest that external factors related to healthcare accessibility and patient behavior may have played a key role in observed variations.

These findings are consistent with the hypothesis that healthcare access restrictions, rather than biological changes in disease risk, account for the transient decline in incidence. Similarly, changes in relapse frequency may reflect the interplay between

healthcare access, patient behavior, vaccination campaigns, and psychosocial stressors. Taken together, these observations emphasize the need to consider both systemic and behavioral factors when interpreting epidemiological data during global crises.

International studies have yielded heterogeneous results. A Saudi Arabian retrospective cohort found decreased reported MS activity during the pandemic, likely reflecting underreporting due to reduced healthcare access²¹. A multi-centre registry-based analysis demonstrated major shifts in prescribing practices, with increased use of natalizumab and cladribine, and decreased use of anti-CD20 therapies and fingolimod²². Real-world evidence from Germany showed largely stable prescription patterns overall, despite initial fluctuations during lockdowns²³.

Some studies report that in people with epilepsy or migraine who become infected with COVID-19, seizure or headache frequency may increase. For instance, in a cohort of 107 epilepsy patients, seizure frequency rose in the two months following SARS-CoV-2 infection compared to before infection, while some migraine patients reported increased headache episodes. At the same time, several reports emphasize that indirect consequences of the pandemic -such as disruptions in medical care, stress, anxiety, and sleep disturbances - may play a significant role in worsening both seizure control and migraine frequency^{24,25}.

Our results parallel those of Babbain et al., who found reduced disease activity during the pandemic in Saudi Arabia, though attributed this to underreporting rather than biological suppression of disease. Both studies underscore the importance of distinguishing true epidemiological changes from healthcare access artifacts²¹.

Lal et al. reported global shifts in disease-modifying therapy (DMT) prescribing, with decreased use of therapies associated with immunosuppression (anti-CD20 antibodies, fingolimod) and increased reliance on natalizumab and cladribine. These shifts were likely motivated by clinicians' concerns regarding infection severity in patients receiving lymphocyte-depleting agents²². While our dataset did not directly capture prescribing patterns, the transient increase in ARR in 2021 may reflect treatment modifications or interruptions during the peak of the pandemic. Orschi et al. observed stable prescription rates in Germany despite lockdowns, highlighting the resilience of healthcare infrastructure²³.

The pandemic imposed widespread psychosocial stressors - social isolation, economic instability, uncertainty - that may have contributed to transient immune dysregulation and increased relapse susceptibility in 2021.

The rise in ARR in 2021 temporally overlapped with mass vaccination campaigns. While vaccines are critical for preventing severe infection, transient immune activation may have triggered relapses in a subset of susceptible patients. However, the return to baseline ARR in 2022 argues against any sustained detrimental impact. Disruptions in DMT administration, reduced infusion center access, or clinician-driven delays in initiating high-efficacy therapies could have contributed to the transient relapse increase.

Our findings have several implications. The findings of this study carry several important clinical implications. First, the stability of MS incidence during the pandemic and the subsequent normalization of relapse rates provide reassurance that the COVID-19 pandemic and associated vaccination programs did not exert a sustained negative impact on the disease course. This evidence supports the safety of COVID-19 vaccination in the MS population and can be used to address vaccine hesitancy among patients who remain concerned about potential disease exacerbation. Second, the transient fluctuations in relapse activity emphasize the importance of uninterrupted access to healthcare services. Safeguarding continuity of MS care, particularly during public health crises, is essential to avoid underdiagnosis, delayed treatment initiation, and suboptimal management of relapses. Third, the study highlights the value of relapse monitoring during periods of systemic stress, such as pandemics, when psychosocial, immunological, and logistical factors may converge to increase disease activity in vulnerable individuals. Finally, the results underline the need for robust healthcare preparedness strategies, ensuring that infusion centers, diagnostic facilities, and routine follow-up pathways remain accessible during emergencies.

This study has several notable strengths. By leveraging the nationwide healthcare database of Türkiye, it provided comprehensive population-level coverage and enabled an evaluation of both incidence and relapse activity on an unprecedented scale. The nationwide scope ensured that findings were not limited to a single region or healthcare center, thereby enhancing their generalizability. Furthermore, the use

of a strict, prescription-based relapse definition improved methodological rigor by minimizing subjective variability in relapse reporting. The incorporation of plasmapheresis as an indicator of severe relapses added further robustness, allowing for the detection of clinically significant disease activity beyond corticosteroid use. Together, these methodological advantages strengthen the validity and reliability of the results.

Several important limitations should be acknowledged. First, relapse frequency was operationally defined using prescription-based treatment records rather than clinically adjudicated relapses supported by neurological examination or MRI findings. Consequently, milder relapses not requiring corticosteroid therapy may have been missed, while some treatments may have been administered for pseudo-relapses or non-MS-related indications. ARRs were calculated at the population level using aggregated data rather than individual longitudinal follow-up; therefore, these estimates reflect average relapse burden across periods rather than true patient-level annualized relapse rates. Second, the 30-day interval applied to distinguish relapse episodes was based on commonly used administrative data algorithms but cannot fully exclude the possibility of prolonged treatment courses or misclassification. Third, the database did not provide individual-level information on COVID-19 infection status, vaccination type, dose number, timing, disease-modifying therapies, disability level, or MRI activity. Therefore, this study cannot address the biological or treatment-related causes of relapse fluctuations. Finally, as a nationwide ecological analysis, our findings describe population-level temporal associations and should not be interpreted as evidence of causality.

In this nationwide population-based study, the COVID-19 pandemic period was not associated with a sustained change in MS incidence in Türkiye but was accompanied by transient fluctuations in relapse frequency at the population level. Incidence and relapse rates declined during the early pandemic, rebounded modestly in 2021, and subsequently returned to pre-pandemic levels.

These findings suggest that, despite major societal and healthcare disruptions, the overall epidemiology of MS remained stable, while short-term variations in relapse frequency may reflect changes in healthcare utilization and systemic stress during the pandemic era. Future studies integrating clinical, imaging,

treatment, and vaccination data are needed to clarify the mechanisms underlying these temporal patterns.

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