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Original article

# Treatment discontinuation in older patients with multiple sclerosis

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ABSTRACT

*Objective:* To examine disease activity in older people with multiple sclerosis (pwMS) following discontinuation of disease-modifying treatments (DMTs).
*Methods:* PwMS aged 60 years or older who discontinued DMTs were included. Data on clinical and demographic factors, as well as new or gadolinium-enhancing lesions on magnetic resonance imaging (MRI) during the final year on DMT and after discontinuation, were analysed. McNemar's test was used to assess intra-patient MRI activity differences before and after discontinuation. Cox regression evaluated factors influencing MRI activity post-discontinuation.
*Results:* We included 114 pwMS (78.1 % female) from 3 Italian MS centres who discontinued a DMT. The mean age at disease onset was 42.4 years (SD: 11.74), and at DMT discontinuation, 65.7 years (SD: 3.84). Median EDSS was 5.5 (IQR: 2.5–6.0). First-line DMTs were discontinued in 105 participants. No significant changes in MRI activity before and after discontinuation were observed ($p = 0.5$). Pre-discontinuation MRI activity was the only factor associated with post-discontinuation activity ($p = 0.021$).
*Conclusions:* In pwMS aged over 60 years, discontinuing DMTs does not increase the risk of MRI-detected disease activity. Discontinuation may be a viable option for this population.

## 1. Introduction

Multiple Sclerosis (MS) is a demyelinating disease that typically begins in young adults. However, an increased prevalence in older individuals has been observed in recent decades. This rise is attributed to improved global life expectancy, a higher incidence of late-onset cases (over 50 years), and very late-onset cases (over 60 years). Additionally, advancements in the management of people with MS (pwMS) resulted in better prognosis and prolonged life expectancy. (Naseri et al., 2021; Portaccio et al., 2024) Many factors contribute to the prolonged life expectancy of pwMS, including the early use of disease-modifying treatments (DMTs), particularly high-efficacy therapies (HETs), improved symptom management, a multidisciplinary care approach, and a growing emphasis on lifestyle interventions. (Fernández et al., 2024)

Currently, the peak prevalence of MS in Europe occurs in the 6th decade of life. (Portaccio et al., 2024) An Italian study found that 18 % of people with MS (pwMS) are over 65 years old. (Solaro et al., 2015)

The management of older pwMS presents unique challenges compared to younger individuals. Aging affects the immune system, as well as the pharmacokinetics and pharmacodynamics of medications. Older pwMS carry a higher risk of comorbidities, including psychiatric and cardiovascular diseases, cognitive impairment, and diabetes. Polypharmacy is more common in this population and is associated with poorer physical and cognitive performance. Additionally, a progressive course of MS is more frequent than a relapsing one, with compartmentalized inflammation and degeneration being more prevalent than focal inflammation. (Fernández et al., 2024; Ostolaza et al., 2021)

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The greater impact of neurodegeneration in older pwMS is closely associated with accelerated disease progression and increased disability accumulation. (Jakimovski et al., 2022)

The gradual accumulation of disability, combined with a reduced frequency of relapses in older pwMS, is closely linked to immunosenescence and the prevalence of low-grade chronic inflammation, known as "inflammaging". (DiMauro et al., 2024) In addition, the failure of compensatory mechanisms such as neural plasticity and remyelination contributes to the predominantly neurodegenerative course observed in this population. (Kuhlmann et al., 2023) Moreover, chronic active lesions, which are linked to disability progression, increase with age and disease duration. However, data on the efficacy of DMTs in resolving these lesions are conflicting. Numerous retrospective studies, registry studies, and meta-analyses have shown a reduced efficacy of DMTs in elderly pwMS. (Gelibter et al., 2024)

The analysis of randomized clinical trials (RCTs) has shown that the impact of DMTs on disability is reduced after the age of 53, and the superiority of HET over moderate-efficacy treatments (MET) is not significant in people over 40.5 years. (Weideman et al., 2017) This result was also replicated in a real-world study involving 1246 pwMS, where no advantage of HET was observed after the age of 45. (Vollmer et al., 2022)

A meta-analysis pooling data from RCTs emphasized that age was the most relevant baseline factor related to DMT efficacy, with both relapse rates and disability progression being lower in older pwMS. (Signori et al., 2015)

Notably, in clinical trials of DMTs, the upper age limit for randomized patients was typically 55 years or lower, making it difficult to generalize their results to older populations. (Vaughn et al., 2019)

Indeed, there is evidence not only of a gradual decline in efficacy, but also of a reduction in safety with age for all DMTs. (Buscarinu et al., 2022)

A meta-regression performed on 45 RCTs highlighted that immune-depleting agents are associated with a higher risk of malignancies in older individuals, and this effect is evident even in those over 45 years of age. (Prosperini et al., 2021)

Considering all these factors, one of the challenges in older pwMS is the management of DMTs, particularly in evaluating the risks and benefits of continuing or interrupting therapy. The aim of this study is to investigate neurological outcomes following DMTs discontinuation in older pwMS, to enhance the understanding of this issue and to potentially offer guidance for clinical practice.

## 2. Methods

All subjects with a confirmed diagnosis of MS according to the McDonald criteria, (Thompson et al., 2018) aged 60 years and older, who discontinued DMTs after at least 6 months of treatment, were included in the study conducted at three Italian MS centres: Binaghi Hospital in Cagliari, the Tor Vergata university hospital in Rome, and IRCCS San Martino Hospital in Genoa.

The subjects were selected from the clinical practice databases at each centre. As per standard clinical practice in Italy, patients were asked to sign an informed consent form at the start of DMT therapy, authorizing the anonymous use of their clinical data for research purposes. The consent forms, specific to each therapy, were created by a group of Italian neurologists specialized in MS and were endorsed by the Italian Society of Neurology.

A neurologist at each centre anonymized the data before sharing the dataset.

The study was conducted retrospectively between January and November 2024.

The enrolled subjects discontinued their DMT between September 2006 and March 2024, and for each participant the follow-up period started one year before DMT suspension and ended at the last visit recorded in 2024

Clinical and demographic data were collected from paper or electronic medical records by neurologists specialized in MS, including sex, age at onset, age at discontinuation, reason for discontinuation, the DMT discontinued, the Expanded Disability Status Scale (EDSS) score at discontinuation and at the last follow-up, and the presence of new or gadolinium-enhancing (Gd+) lesions on magnetic resonance imaging (MRI) during the last year on DMT and after discontinuation until the last follow-up.

MRI scans were performed for each subject according to clinical practice, using different scanners at various time points. An MRI was considered active if at least one new lesion and/or a Gd+ lesion was detected.

The clinical course was not recorded at either the time of discontinuation or at the last follow-up, as we focused on the presence of "active disease" rather than on the simple classification of relapsing or secondary progressive course.

Due to the retrospective design of the study and the high risk of misinterpreting simple fluctuations in neurological symptoms—common in older patients and not necessarily linked to inflammation—as relapses, we decided to use MRI activity data rather than clinical relapses as primary outcome.

Among METs, the following were included: interferon, glatiramer acetate, teriflunomide, dimethyl fumarate, azathioprine, and methotrexate. HETs included anti-CD20 antibodies, cyclophosphamide, and fingolimod.

The reasons for discontinuation were classified as follows: adverse events, shared decision-making, and autonomous decision by the patient.

### 2.1. Statistical analysis

Continuous variables were presented as means with standard deviations (SD) for normally distributed data, or as medians with 25th-75th percentiles for non-normally distributed data. Categorical variables were summarized as absolute frequencies (n) and percentages ( %).

McNemar's test was used to assess whether there was a significant difference in intra-patient MRI activity between the year before and the period after DMT discontinuation, up to the last follow-up.

Univariate and multivariate Cox proportional hazards regression analyses were performed to evaluate factors associated with the time to MRI activity after treatment discontinuation. Hazard ratios (HRs) and 95 % confidence intervals (CIs) were reported, along with p-values.

All variables, including sex, age at onset, MRI activity during the year prior to discontinuation, disease duration, specific DMT interrupted, age and EDSS at discontinuation, and reason for discontinuation, were included in the univariate analysis to ensure all clinically relevant variables were considered.

All analyses were performed with a significance threshold set at 0.05.

## 3. Results

A total of 114 pwMS were recruited from the three centres, of which 89 (78.1 %) were females. The mean age at MS onset was 42.4 years (SD: 11.74), while the mean age at discontinuation was 65.7 years (SD: 3.84). The mean disease duration at the time of DMT interruption was 23 years (SD: 10.85). The demographic and clinical characteristics of the cohort, along with the treatments discontinued, are summarized in Table 1. DMTs were classified as METs in 105 subjects (92.1 %) and HETs in the remaining 9 (7.9 %).

The reasons for discontinuation were as follows: shared decision-making in 57 individuals (50 %), primarily due to ongoing disability progression without clinical or radiological signs of inflammation, or disease stability after prolonged treatment; adverse events in 36 individuals (31.6 %); and autonomous patient decision in 21 individuals (18.4 %), secondary to chronic treatment burden, perceived lack of

**Table 1**
– Baseline characteristics.

| Characteristic | Value |
|---|---|
| **Sex** | |
| Female | 89 (78.1 %) |
| Male | 25 (21.9 %) |
| **Onset Age** | 42.4 ± 11.74 years |
| **Disease duration at the discontinuation time** | 23 ± 10.85 years |
| **Therapy discontinued** | |
| Interferon | 42 (36.8 %) |
| Glatiramer acetate | 29 (25.4 %) |
| Teriflunomide | 14 (12.3 %) |
| Dimethyl fumarate | 10 (8.8 %) |
| Azathioprine/Methotrexate | 10 (8.8 %) |
| Anti-CD20 (e.g., Ocrelizumab) | 7 (6.1 %) |
| Cyclophosphamide | 1 (0.9 %) |
| Fingolimod | 1 (0.9 %) |
| **Therapy Line** | |
| First line | 105 (92.1 %) |
| Second line | 9 (7.9 %) |
| **MRI Activity in the Previous Year** | |
| No | 102 (89.5 %) |
| Yes | 12 (10.5 %) |
| **EDSS in the Previous Year** | 5.5 (2.5 – 6.0) |

benefit, or treatment dissatisfaction.

After discontinuation, pwMS were monitored for a median follow-up of 52 months (range: 5.0–189.0 months).

DMT was restarted in 7 individuals: 5 due to MRI activity and 2 due to new symptoms unrelated to new or Gd+ lesions.

The median EDSS score was 5.5 (25th-75th percentiles: 2.5–6.0) at both the time of discontinuation and at the last follow-up.

During the year before DMT discontinuation, 12 subjects had new or Gd+ lesions, while 16 had such lesions during the follow-up period after discontinuation. Overall, 94 patients showed no change in lesion status, with MRI being either active or inactive both before and after discontinuation; 12 patients experienced worsening, with active MRI only after discontinuation; and 8 patients showed improvement, with active MRI only before discontinuation. The distribution of these individual changes was not statistically significant ($p = 0.5$)

MRI activity before discontinuation was the only significant predictor of MRI activity after discontinuation (HR=5.55, 95 % CI: 1.29–23.91, $p = 0.021$). Details are provided in Table 2 and in Fig. 1.

**Table 2**
– Factors associated with time to MRI activity after treatment interruption.

| Factor | Univariate HR (95 % CI) | p-value | Multivariate HR (95 % CI) | p-value |
|---|---|---|---|---|
| **Sex** | 1.46 (0.51 – 4.20) | 0.49 | 1.10 (0.34 – 3.58) | 0.88 |
| **Onset Age** | 1.02 (0.98 – 1.06) | 0.41 | 1.01 (0.96 – 1.06) | 0.67 |
| **MRI Activity in the Previous Year** | 3.60 (1.14 – 11.36) | 0.029 | 5.55 (1.29 – 23.91) | 0.021 |
| **Therapy** | | | | |
| Medium-efficacy treatments | Ref. | – | Ref. | – |
| High efficacy treatments | 1.49 (0.19 – 11.50) | 0.70 | 0.45 (0.04 – 5.54) | 0.54 |
| **Age at Interruption** | 1.09 (0.94 – 1.25) | 0.26 | 1.12 (0.95 – 1.31) | 0.19 |
| **Reason for Interruption** | | | | |
| Adverse events | Ref. | – | Ref. | – |
| Shared decision-making | 1.50 (0.46 – 4.88) | 0.50 | 1.29 (0.37 – 4.55) | 0.69 |
| Patient decision | 1.41 (0.32 – 6.32) | 0.65 | 1.72 (0.34 – 8.59) | 0.51 |
| **Δ EDSS Interruption-Previous Year** | 1.24 (0.24 – 6.49) | 0.80 | 0.73 (0.08 – 6.69) | 0.78 |

## 4. Discussion

Managing older pwMS presents distinct challenges compared to younger individuals. First, neurologists must consider a changing risk/benefit profile, as both the efficacy and safety of DMTs gradually decline with age. (Buscarinu et al., 2022; Prosperini et al., 2021) Moreover, certain DMTs—such as injectable therapies—may cause side effects that are poorly tolerated, thereby reducing quality of life. (Tallantyre et al., 2024) Finally, a non-active progressive course characterized by prevalent neurodegeneration is more common in older pwMS, and none of the available DMTs effectively address this condition. (Kuhlmann et al., 2023)

The first randomized study evaluating the non-inferiority of DMT discontinuation after 55 years of age was the DISCOMS study, in which the null hypothesis—that DMT discontinuation is inferior to continuation—could not be rejected (Corboy et al., 2023). In the extension phase of the study, the time to new MS activity was shorter in the discontinuation group (Corboy et al., 2025). However, the number of events related to disease activity was very low in both the primary study and its extension (Corboy et al., 2023; Corboy et al., 2025). During the extension phase no relapses were observed, and new brain lesions occurred in only three subjects: 1 out of 30 continuers and 2 out of 44 discontinuers.

A study conducted in the USA, which analysed the impact of treatment discontinuation on healthcare utilization, showed an increase in visits and hospitalizations among midlife patients aged 45–54 years, but not in those over 54. This suggests that discontinuation may be considered safe only in older individuals. (Qian et al., 2024)

The vast majority of available data comes from real-life studies, and a recent meta-analysis concludes that the risk of relapses decreases with age at discontinuation, becoming very low after 60 years. (Prosperini et al., 2023) When MRI activity was considered, the results were consistent with another registry-based study showing a lower risk of MRI activity after discontinuation at 45 years, and an even lower risk after 60 years. (Gisela et al., 2023)

Based on this evidence, our study adopted a more cautious approach than many previous studies, evaluating DMT discontinuation only in individuals over the age of 60. No increase in inflammatory activity was observed during the follow-up. Notably, the vast majority of the subjects included in the study stopped a MET, with only one patient discontinuing an anti-cell trafficking therapy (fingolimod).

Among the previous studies, two others used the same age threshold as we did, and their results were very similar in terms of disease activity. (Hua et al., 2019; Salavisa et al., 2023) In the first study, the authors found no increase in MRI activity after discontinuation, along with a very low risk of clinical relapses. It is worth noting that the follow-up period was shorter than ours (two years). (Hua et al., 2019) On the other hand, Salavisa et al. analyzed only 35 patients—13 discontinuers and 23 continuers—over a mean follow-up of 77 months. Despite the small sample size, they found no difference in disease activity between the two groups. (Salavisa et al., 2023)

Concerns about the discontinuation of some second-line DMTs also arise from some studies. In a French study, the discontinuation of second-line treatments was associated with higher disease activity compared to the discontinuation of first-line treatments, even in individuals older than 55 years. (Chappuis et al., 2023) Notably, the second-line DMTs associated with reactivation were natalizumab and fingolimod.

Unified data from MSBase and the French MS observatory, which evaluated clinical data from over 14,000 subjects, highlighted that discontinuing natalizumab or fingolimod increases the risk of disease reactivation, particularly in patients with a higher relapse rate during the year prior to cessation. On the other hand, protective factors included older age, lower EDSS, and male gender. (Roos et al., 2022)

None of the patients in our cohort discontinued natalizumab, and the only patient who stopped fingolimod at age 65 for personal, not shared,

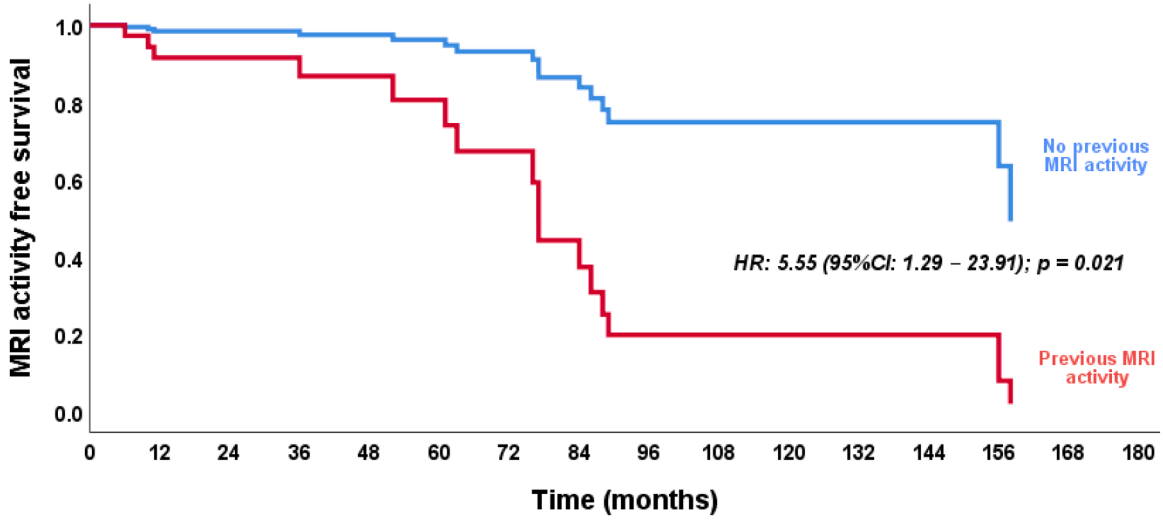


**Fig. 1.** Impact of previous MRI activity on MRI activity following treatment discontinuation.

reasons did not experience any relapses during the following three years of follow-up.

Our cohort, aside from the inflammatory activity, also showed stability in terms of disability, as assessed by comparing the EDSS score at discontinuation and at the last follow-up.

Previous studies, however, have shown conflicting results on this point. It is important to note that, when using the EDSS scale in healthy individuals aged 55 and older, some degree of disability may be found, suggesting that EDSS scores can be influenced by factors other than MS. (Lynch et al., 2021) Moreover, the perceived lack of DMT efficacy due to insidious progression, or the transition to a non-active secondary progressive MS course, could lead to treatment discontinuation. This shift in clinical course might itself contribute to higher EDSS scores. A study found disability progression in discontinuers with a mean age of 50 years, but the reasons for discontinuation were not collected, and only 37.5 % of participants were over 55 years. (Jakimovski et al., 2022)

Some studies have noted a trend toward higher EDSS scores in discontinuers compared to continuers at the last follow-up, even though no difference in relapses or chronic disability progression was found. (Salavisa et al., 2023) However, in the randomized DISCOMS study, no difference in disability progression was observed between continuers and discontinuers. (Corboy et al., 2023)

Data from a meta-analysis remain inconclusive about the role of DMT discontinuation in disability progression, as the studies evaluated did not differentiate between relapse-related progression and progression independent of relapses. (Prosperini et al., 2023)

An important factor that neurologists must consider is the quality of life of pwMS. Often, due to side effects—especially if the treatment is long-term and the patient has not experienced relapses for an extended period—the patient may choose to discontinue therapy. Both a French survey and a North American study identified the perceived lack of efficacy and the presence of side effects or adverse events as the primary reasons for DMT discontinuation. (Donzé et al., 2015; Fox et al., 2013)

In our study, about 20 % of individuals chose to discontinue therapy autonomously, while in half of the cohort, the decision was shared and approved by the neurologist. The remaining cohort discontinued therapy due to adverse events, and this data highlights the safety concerns in this patient population. In a retrospective study involving individuals over 60 years of age, those who discontinued treatment reported a better quality of life compared to the group who continued therapy. (Hua et al., 2019)

A more cautious approach to the decision of discontinuing DMTs is essential for pwMS who have a late onset of the disease. Both disease duration and age must be considered when evaluating the risk of relapses, as DMTs may still offer more benefits than risks, even in some older individuals. (Tremlett et al., 2008; Androdias et al., 2024)

However, data from the Italian registry indicate that pwMS with late onset and a relapsing course experience more frequent spinal symptom onset and a worse long-term prognosis compared to those with early-onset MS. (Lorefice et al., 2024) Moreover, the use of DMTs appears to be less effective in this population when compared to individuals with young-onset MS in terms of disease progression. (Amato et al., 2020)

A very important aspect after discontinuation is the continuation of both clinical and MRI follow-up, with the goal of detecting any potential inflammatory reactivation early and restarting a DMT if necessary. Indeed, in a subset of older patients, active inflammation may resume in the absence of a DMT. In our cohort, very few patients required another therapy after discontinuation, mainly due to MRI reactivation. In the near future, when serum biomarkers are more widely available, they could be integrated into the follow-up process. Notably, increases in serum neurofilaments and glial fibrillary acidic protein have been found to predict MRI activity after DMT discontinuation. (Bose et al., 2023)

Furthermore, the management of pwMS should place particular emphasis on lifestyle factors, which is even more critical in older individuals who often have comorbidities and are on polypharmacy. Among these interventions, regular physical exercise plays a crucial role, as it helps reduce depression and fatigue, improves quality of life, and enhances neuroplasticity. Other important interventions include attention to diet, prevention and treatment of cardiovascular diseases, physical therapy, cognitive rehabilitation, psychological and social support, and mindfulness-based interventions. (Fernández et al., 2024)

Our study has several limitations. First, only a few patients discontinued HETs, which means the results may not be generalized to other treatments beyond METs. It is important to note that data on the discontinuation of natalizumab and fingolimod in elderly patients are fairly clear and do not suggest their direct suspension. This knowledge likely influenced the decisions about discontinuing these specific DMTs at the three MS centres involved in the study. On the other hand, ofatumumab and ocrelizumab have only been used in Italy for a few years, and the relatively short duration of treatment could explain why few pwMS in the study discontinued these therapies.

Additionally, the study was not randomized, and we did not include a control group of patients who continued treatment. However, we believe these two factors are also strengths of the study. Real-world data are a key source of knowledge about the routine use of treatments in actual clinical settings. Moreover, using each subject as their own control offers several advantages. In particular, it reduces the impact of inter-individual differences (such as genetic factors, environmental

influences, and prior MS history), stabilizes confounding factors within the same person, and allows for a more thorough evaluation of the direct effects of discontinuation.

Another strength is the use of MRI data to detect disease activity. Interpreting symptoms as relapses can be challenging, especially in older individuals with a medium-high EDSS score (the median EDSS in our study was 5.5), who often report temporary worsening of symptoms that do not correspond to inflammatory activity. MRI activity is certainly a more objective tool for detecting disease activity, particularly in this patient population.

Finally, the median follow-up duration was more than four years, which is considered sufficiently long, especially given the age at the time of treatment discontinuation. In fact, the majority of studies have either shorter follow-up periods or lower age limits. The study by Salavisa et al. is the most similar to ours in terms of age limit and follow-up duration, although it included only 35 patients. (Salavisa et al., 2023)

In order to better manage the pharmacological treatment of elderly individuals with MS, real-world data are essential. However, the results of ongoing clinical studies on discontinuation—after 3 years of stable disease in people over 50 years (STOP-I-SEP) and after 5 years of stable disease in individuals over 55 years (EUCT 2024–513,475–41–00)—are even more crucial. (Androdias et al., 2024) Notably, none of the completed or ongoing RCTs consider the more cautious age cut-off of 60 years, which could be crucial given all the evidence reported, including our own.

## 5. Conclusion

Our study suggests that in individuals over 60 years of age without inflammatory activity of the disease, it is recommended to carefully evaluate whether to continue or interrupt the current DMT, following a thorough discussion with the patient. Both MS-related factors, such as the type of DMT, disease stability, and disability, as well as person-related factors, such as comorbidities and the patient's preferences, must be considered.

Thus, the decision should be personalized and shared, in order to make the best choice and maintain a strong alliance between patient and physician.

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## CRediT authorship contribution statement

**Frau Jessica:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Schiavetti Irene:** Writing – original draft, Methodology, Formal analysis, Data curation. **Landi Doriana:** Writing – review & editing, Investigation, Data curation. **Lapucci Caterina:** Writing – review & editing, Investigation, Data curation. **Saporito Valentino:** Investigation, Data curation. **Di Gianvito Valentina:** Investigation, Data curation. **Cavalli Nicola:** Investigation. **Atzei Letizia:** Investigation. **Signori Alessio:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Girolama Marfia:** Writing – review & editing, Supervision. **Cocco Eleonora:** Supervision.

## Declaration of competing interest

The authors have nothing to disclose about this work.

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