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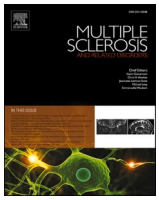

Original article

Sexual dysfunction in multiple sclerosis: The impact of different MSISQ-19 cut-offs on prevalence and associated risk factors

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ABSTRACT

Background: Although multiple sclerosis (MS) Intimacy and Sexuality Questionnaire-19 (MSISQ-19) is a widely applied tool, no unique definition of sexual dysfunction (SD) based on its score exists.
Objective: To explore the impact of different MSISQ-19 cut-offs on SD prevalence and associated risk factors, providing relevant information for its application in research and clinical settings.
Methods: After defining SD according to two different MSISQ-19 cut-offs in 1155 people with MS (pwMS), we evaluated SD prevalence and association with sociodemographic and clinical features, mood status and disability *via* logistic regression.
Results: Depending on the chosen cut-off, 45% to 54% of pwMS reported SD. SD defined as MSISQ-19 score >30 was predicted by age (OR=1.01, p=0.047), cognition (OR=0.96, p=0.004) and anxiety (OR=1.03, p=0.019). SD defined as a score >3 on any MSISQ-19 item was predicted by motor disability (OR=1.12, p=0.003) and cognition (OR= 0.96, p=0.002).
Conclusion: Applying different MSISQ-19 cut-offs influences both the estimated prevalence and the identification of risk factors for SD, a finding that should be considered during study planning and data interpretation. Preserved cognition exerts a protective effect towards SD regardless from the specific study setting, representing a key point for the implementation of preventive and therapeutic strategies.

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1. Introduction

Sexual dysfunction (SD) is a common issue in Multiple Sclerosis (MS). Indeed, SD frequency is higher in MS than in other neurological diseases, and almost five times higher than in the general population (Lewis et al., 2010; Rees et al., 2007). However, estimates of SD prevalence in MS are highly variable, depending on definitions and instruments applied for its evaluation (Lew-Starowicz and Rola, 2013; Tepavcevic et al., 2008; Zorzon et al., 1999). From a theoretical perspective, SD can be classified in three classes: (i) primary SD, resulting from demyelinating lesions and neuroaxonal loss affecting the neural pathways that regulate sexual function (i.e. limbic and paralimbic regions, spinal cord); (ii) secondary SD, resulting from MS-related neurological symptoms and physical disabilities that can affect sexual functions (i.e. fatigue, spasticity, tremor, poor coordination, pain, urogenital paraesthesia, dysaesthesia, allodynia, bladder and bowel incontinence, pelvic floor muscle weakness, cognitive impairment, visual impairment); (iii) tertiary SD, resulting from psychosocial and emotional burden associated with living with MS (i.e. depression, anxiety, anger, altered self-image) (Li et al., 2020). Among instruments developed for SD evaluation, the MS Intimacy and Sexuality Questionnaire-19 (MSISQ-19) is a self-administered tool which captures different contributors pertaining to the three classes and interfering with sexual activity or satisfaction in both sexes (Sanders et al., 2000). Despite these advantages, MSISQ-19 suffers from the same pitfalls of many patient reported outcome measures. According to the original publication of the instrument, "the higher the score (of MSISQ-19), the greater the impact of SD on patients' lives" (Sanders et al., 2000). However, a cut-off to determine the clinical meaningfulness of the reported symptoms, and therefore the presence of SD, has never been defined, hampering the comparison and interpretation of results across studies. Here, we addressed this issue exploring the impact of two widely used MSISQ-19 cut-offs on the prevalence of SD and concomitant risk factors in a large population of people with MS (pwMS).

2. Methods

2.1. Study design

Participants' recruitment was web-based. An on-line survey, developed through the European Commission's official survey management tool (https://ec.europa.eu/eusurvey), was shared *via* SMsocialnetwork.com, a social Facebook-like network dedicated to people with MS, and *via* the web-pages of the participating MS centers, selected in order to be representative of the Italian territory (North, Center and South). To obtain informative data on SD prevalence from a large population, the study enrollment target was fixed at 1000 participants. Inclusion criteria were age equal or higher than 18 years and diagnosis of MS. The enrollment period was set to 6 months (from February to July 2021), with a backup strategy to extend the enrollment period in case the enrollment target could not be reached. The following information was self-reported: (1) referring center, (2) sociodemographic features (age, sex, sexual orientation, marital status, height, weight); (3) comorbidities (smoking habit, comorbid conditions); (4) sexual activity in the prior six months; (5) past experiences and interest in discussing sexuality and sexual dysfunction with the treating neurologist; (6) ongoing treatments; (7) cognitive status, depression and anxiety investigated using the relative Short Forms from the Neuro-QoL (Cella et al., 2012); (8) physical disability, assessed *via* the Patient-Determined Disease Steps (PDDS) scale (Lavorgna et al., 2018); (9) sexual dysfunction evaluated *via* the Multiple Sclerosis Intimacy and Sexuality Questionnaire-MSISQ-19 (Sanders et al., 2000). As the survey was not anonymized, disease onset and phenotype were provided by the MS Centers at the end of the enrollment period.

2.2. Standard protocol approvals, registrations, and participants consents

The study was approved by the Carlo Romano ethics committee of the University of Naples Federico II (n.171/19), and was performed in accordance to the Declaration of Helsinki, EU regulations 2016/679 (general data protection regulation - GDPR) and 2018/1725 (data protection obligations for the EU institutions and bodies). All participant gave their informed consent before completing the online survey.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 25.0, with a significance level set at $\alpha = 0.05$. Frequency of global, primary, secondary and tertiary SD was reported for the entire sample as well as subgroups of sexually active and inactive pwMS (over the last 6 months). Between-group comparisons were performed with Chi-Square, Mann-Whitney test or independent sample T-test, as appropriate. The linear relationship between MSISQ-19 scores and predictors was tested with Pearson bivariate correlation. We considered: demographic features (age and sex), MS unrelated risk factors (smoking habit, body mass index-BMI, presence of pulmonary, cardiovascular, endocrine and metabolic comorbidities), MS related risk factors (disease duration, phenotype, PDDS, cognition), and emotional factors (depression and anxiety). Factors surviving this preliminary screening ($p<0.004$, Bonferroni corrected for multiple comparisons) were entered in a logistic regression with SD as dependent variable. Two different definition of SD were explored: MSISQ-19 score >30 (da Silva et al., 2015; Carotenuto et al., 2021a) and a score above 3 (which equals the presence of semi-constant or constant symptoms) on any MSISQ-19 item (da Silva et al., 2015; Domingo et al., 2018).

3. Results

3.1. Study population

From February to September 2021, 1229 people completed the online survey. Among these, twelve who had diagnoses different from MS, forty duplicate answers and twenty-two who did not complete the MSISQ-19 were excluded from the analysis. The final study population included 1155 people with MS. Clinico-demographic features of the study population are summarized in Table 1.

3.2. Sexuality and sexual dysfunction

Using as cut-off MSISQ-19 score >30, 54% of pwMS reported SD (54% of sexually active pwMS and 53% of sexually inactive pwMS; 51% of males and 55% of females).

Defining SD as the presence of semi-constant or constant symptoms reported for any MSISQ-19 item, 45% of pwMS reported SD (both in sexually active and sexually inactive pwMS; 43% of males and 46% of females). Among these, primary, secondary and tertiary SD were reported in 67%, 63% and 53% of cases, respectively, either alone or in association (Fig. 1). Association of SD classes was more frequent in sexually inactive pwMS than sexually active pwMS (66% vs 52%, $p=0.016$).

Among respondents, 18% declared to have discussed sexuality and sexual dysfunction with their treating neurologist in the past, while 45% declared their interest in discussing the topic.

Among items contributing to primary SD, the main complaint (item more frequently scored above 3) was the prolonged time needed to reach orgasm or climax (item 18) in females and difficulty getting or keeping a satisfactory erection (item 19) in males. Among items contributing to secondary SD, the main complaint was the presence of mobility issues during sexual activity (item 8) in both sexes. Among items contributing to tertiary SD, the main complaint was feeling less attractive (item 7) in females and feeling less masculine due to MS (item 9) in males (Fig. 2).

Table 1
Clinico-demographic features of the study population. Unless otherwise indicated, values are expressed as mean ± standard deviation.

	Study population (n=1155)	Sexually active (n=949)	Sexually inactive (n=206)	P
Age	40.39 ± 10.58	39.62 ±10.23	43.94 ±11.44	**<0.001**
Sex (female/male), %	67/33	66/34	71/29	0.166
Sexual orientation (heterosexual/ homosexual/bisexual/ other/no answer), %	79/1/1/0/ 19	80/1/1/0/ 18	75/2/0/ 0/23	0.213
Marital status (married/ cohabiting/single/ divorced), %	50/17/27/ 6	53/18/ 24/5	39/9/40/ 12	**<0.001**
Disease duration	11.62 ± 8.09	11.12 ±7.70	13.86 ± 9.33	**<0.001**
Phenotype (RR/PMS), %	88/12	90/10	77/23	**<0.001**
Smokers (yes/no), %	36/64	34/66	43/57	0.02
BMI	23.99 ± 3.99	24.00 ± 3.96	24.40 ± 4.19	0.953
Presence of comorbidities (yes/no), %	33/67	31/69	42/58	**0.002**
Presence of comorbidities affecting sexuality (yes/ no), %	26/74	24/76	35/65	**0.002**
DMT (injectables, oral, infusion, transplant, none), %	17/39/39/ 0/5	17.5/ 38.5/39/ 0/4	13/44/ 35/0/8	0.054
PDDS, median and range	1 (0–8)	0 (0–7)	2 (0–8)	**<0.001**
Cognitive function	33.01 ± 6.53	33.37 ± 6.31	31.37 ± 7.87	**0.001**
Depression	13.67 ± 6.77	13.21 ± 6.46	15.78 ± 7.34	**<0.001**
Anxiety	19.39 ± 6.91	19.13 ± 6.77	20.60 ± 7.42	0.006
MSISQ-19	36.04 ± 14.89	35.89 ± 14.48	36.74 ± 16.70	0.500
Primary SD subscore	10.53 ± 4.95	10.50 ± 4.83	10.67 ± 5.46	0.674
Secondary SD subscore	16.12 ± 7.25	16.06 ± 7.10	16.40 ± 7.94	0.566
Tertiary SD subscore	9.39 ± 4.71	9.33 ± 4.61	9.66 ± 5.19	0.399

P refer to between-group comparison performed with Chi-Square, Mann–Whitney test or independent sample T-test, as appropriate. Statistically significant differences after Bonferroni correction (0.05/19=0.003) are highlighted in bold.

3.3. Relationship between clinico-demographic variables and MSISQ-19 scores

Significant correlations were identified between MSISQ-19 score and age, PDDS, cognitive function, depression and anxiety (r ranging from −0.23 to 0.20, p≤0.001).

3.4. Relationship between clinico-demographic variables and SD

3.4.1. SD defined as MSISQ-19 score >30

The logistic model including factors that survived the preliminary screening significantly predicted SD (Nagelkerke R Square = 0.065, p<0.001), with a significant role identified for age (OR = 1.01, 95% CI: 1—1.02, p = 0.047), cognition (OR = 0.96, 95% CI: 0.94—0.99, p=0.004) and anxiety (OR = 1.03, 95% CI: 1—1.06, p = 0.019). No significant role was identified for PDDS (OR = 1.05, 95% CI: 0.97—1.13, p = 0.245), or depression (OR = 0.99, 95% CI: 0.97—1.02, p = 0.670).

3.4.2. SD defined as a score above 3 on any MSISQ-19 item

The logistic model including factors that survived the preliminary screening significantly predicted SD (Nagelkerke R Square = 0.073, p<0.001), with a significant role identified for PDDS (OR = 1.12, 95% CI: 1.04—1.21 p=0.003) and cognition (OR = 0.96, 95% CI: 0.94—0.98, p=0.002). No significant role was identified for age (OR = 1, 95% CI: 0.99—1.02, p = 0.342), anxiety (OR = 1, 95% CI: 0.98—1.04, p = 0.536), or depression (OR = 1.01, 95% CI: 0.99—1.04, p = 0.363).

4. Discussion

Applying different cut-offs of a validated tool for SD assessment in MS (Carotenuto et al., 2021a) we identified a variable prevalence of SD in a large population of Italian pwMS.

In Italy, the prevalence of SD in MS has been estimated between 42% and 74% (Zorzon et al., 1999; Carotenuto et al., 2021a; Gava et al., 2019; Balsamo et al., 2017). Such variability could be explained by the rather small samples examined by few monocentric studies, which might be not fully representative of the entire spectrum of the disease. Additionally, previous works conducted in the Italian MS population mostly focused on specific aspect of SD (i.e. erectile dysfunction in males or abnormalities of the sexual response cycle in females) and evaluated only the role of depression as contributing factor to SD development (Gava et al., 2019; Balsamo et al., 2017). The one study that explored more widely the effect of cognitive deficit, anxiety and depression, applied a structured interview rather than a validated tool for SD evaluation (Zorzon et al., 1999).

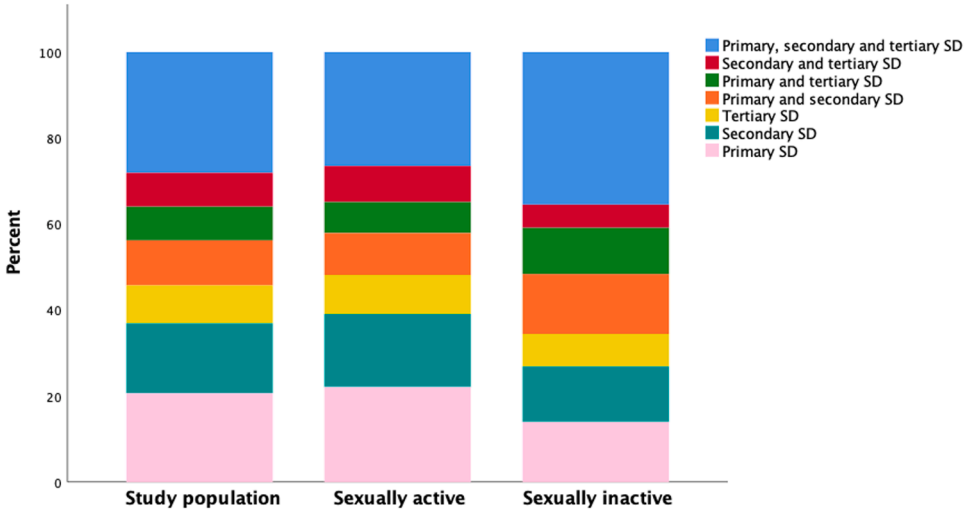

Fig. 1. *Distribution of sexual dysfunction (SD) categories across study groups.* Stacked bar chart showing the relative frequency of primary, secondary and tertiary SD, either alone or in association, among patients reporting SD in the entire study population and in the two subgroups of sexually active/inactive patients. In order to offer an immediate visualization of the relative distributions of each SD category across patients' groups, each primary bar (study population/sexually active/sexually inactive) was scaled to have the same height, so that each sub-bar (color coded category of SD) expresses a percentage contribution to the total of each group.

More broadly, previous works applying MSISQ-19 reported a SD prevalence between 41% and 71%, likely reflecting not only population intrinsic features but also differences in the criteria chosen to define SD (da Silva et al., 2015; Carotenuto et al., 2021a; Domingo et al., 2018; Altmann et al., 2021). Indeed, applying two different MSISQ-19 cut-offs to the same population we obtained a 10% difference in SD prevalence. Beyond this quantitative difference, the application of different criteria for SD definition likely captures different aspects of this complex issue. When looking at predictors, SD defined by MSISQ-19 score above 30 was related to age, cognition and anxiety, while SD defined by the presence of semi-constant or constant symptoms in at least one MSISQ-19 item was related to motor disability and cognition. This finding is of great relevance, as it underlines how the role of putative risk factors might substantially change redefining the outcome of interest in the context of the same instrument. The latter should be therefore carefully selected according to the study question. Of note, looking at the two cut-offs we explored, the definition of SD as the presence of semi-constant or constant symptoms is closer to the definition of SD according to the 5th Edition of the American Psychiatric Association's Diagnostic and Statistical Manual (American Psychiatric Association, 2013), which defines SD as sexual behaviors and experiences characterized by insufficient quality, duration or frequency affecting 75–100% of sexual behaviors and experiences (Gabriel Tobia, 2013). On the other hand, MSISQ-19 scores above 30 might derive from a combination of mild symptoms, rather than from a severe complaint in one specific domain, thus explaining the differences observed in our population in terms of risk factors. From a therapeutic perspective, it follows that, when SD is driven by the mild involvement of different domains, anxiety management could be beneficial. When dealing with more severe involvement of a specific domain, than motor rehabilitation could play a more significant role. As motor disability seems to affect SD both directly and indirectly by enhancing negative illness perception, favoring adaptive coping strategies might represent an additional approach for SD mitigation (Scandurra et al., 2023). As highlighted by our results, in all cases of SD strategies for cognitive preservation and rehabilitation should be implemented. Apart from its beneficial effect on SD, such approach could also result in broader symptomatic improvements. Indeed, cognition is known to also affect bowel and bladder function in MS (Carotenuto et al., 2021b), and, since SD often coexists with neurogenic urinary dysfunction (Bientinesi et al., 2022a, 2022b), addressing patients' cognitive issues might result in beneficial effects on related symptoms and their consequences. In this study we considered a wide variety of predictors, including demographic features, lifestyle habits and comorbidities potentially affecting sexuality as well as different aspects of disability and emotional distress. In particular, pwMS suffering from comorbidities potentially affecting sexuality have been excluded from validation studies (Sanders et al., 2000; Carotenuto et al., 2021a), while we aimed to render a complete picture of real life conditions. Surprisingly, lifestyle habits and comorbidities did not play any role in SD prediction, possibly given their low prevalence in the enrolled population. Interestingly, higher score in self-reported cognitive performance was the only factor consistently associated with a decreased SD risk, mirroring previous works reporting on associations between cognitive disability, perceived cognitive impairment and SD (Zivadinov et al., 1999; Wu et al., 2020).

Regardless from the chosen cut-off, SD prevalence did not vary when classifying pwMS according to the presence of sexual activity over the last six months. Indeed, although MSISQ-19 interrogates respondents about symptoms occurred over the last six months, symptoms leading to sexual dissatisfaction likely interfere with sexual activity per se, thus explaining our finding. Sexually inactive pwMS were older, with longer disease duration, more likely showing progressive phenotype and comorbidities than sexually active pwMS, and presented with higher motor and cognitive disability and emotional distress, reflected by the higher frequency of association between SD classes in this subgroup.

Likewise, within each cut-off, no differences where identified in terms of SD prevalence between men and women. Data about sex difference in SD prevalence are contradictory, but a recent scoping review summarized prevalence estimates from 13,259 cases of MS, indicating mostly overlapping ranges, with a slight prevalence in men (SD prevalence between 50% and 90% in men, and between 40% and 80% in women) (Pöttgen et al., 2018). Of note, no study so far has investigated the issue of SD in non-binary pwMS, and future works should focus on this aspect.

Notwithstanding the high prevalence and the impact of SD in MS, SD is often under-reported and undertreated (Zorzon et al., 1999; Altmann et al., 2021). In our population, only 18% of enrolled pwMS declared to have discussed sexuality with their treating neurologist, and less than 50% declared their interest in discussing the topic. This likely reflects cultural aspects as well as time constraints during routine visits, and it is

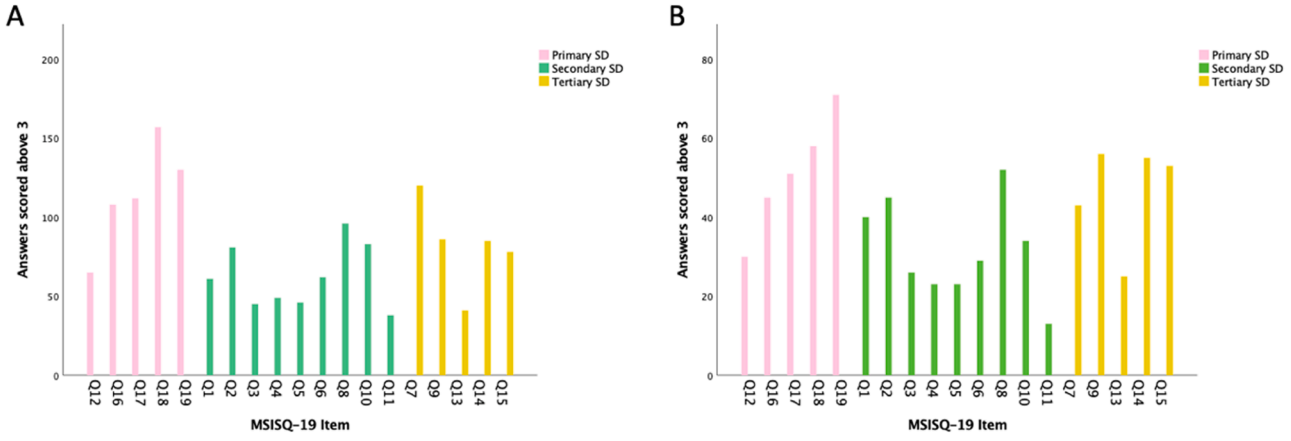

Fig. 2. *Frequency of semi-constant or constant symptoms across MSISQ-19 items.* Bar chart showing the number of answers scored above 3 for each MSISQ-19 item, color coded according to the sexual dysfunction domain they contribute to. Data relative to females are shown in panel A, while data regarding males are shown in panel B. MSISQ-19 items: Q1. muscle tightness or spasms in my arms, legs, or body; Q2. bladder or urinary symptoms; Q3. bowel symptoms; Q4. feelings of dependency because of MS; Q5. tremors or shaking in my hands or body; Q6. pain, burning, or discomfort in my body; Q7. feeling that my body is less attractive; Q8. problems moving my body the way I want during sexual activity; Q9. feeling less masculine or feminine due to MS; Q10. problems with concentration, memory, or thinking; Q11. exacerbation or significant worsening of my MS; Q12. less feeling or numbness in my genitals; Q13. fear of being rejected sexually because of MS; Q14. worries about sexually satisfying my partner; Q15. feeling less confident about my sexuality due to MS; Q16. lack of sexual interest or desire; Q17. less intense or pleasurable orgasms or climaxes; Q18. takes too long to orgasm or climax; Q19. inadequate vaginal wetness or lubrication (women)/difficulty getting or keeping a satisfactory erection (men).

an issue documented across neurological disorders (Zorzon et al., 1999; de Rooy et al., 2019). Addressing the presence of SD and identifying the main complaint of each patient would be of utmost importance to implement therapeutic strategies. In our population, the main complaint related to primary SD was difficulty to reach orgasm in women and erectile dysfunction in men, in agreement with previous data (Rees et al., 2007; Sadeghi Bahmani and Motl, 2021). Complaints related to secondary and tertiary SD substantially overlapped (mobility issues and feeling less attractive/less masculine) and could indeed be addressed with medical, rehabilitative and psychological approaches (Afshar et al., 2022).

Our study is not without limitations. First, considering that data collection was web-based, we cannot exclude a selection bias that might have favored younger pwMS or subjects with easier access to smartphones/computers. Second, although we explored a wide range of putative risk factors for SD, we applied tools for global evaluation of disability/mood status and indirect indicators of lifestyle habits (smoking, BMI), which might explain the rather weak associations identified in our analysis. Of note, we applied PDDS, a patient-reported outcome of the impact of MS on walking, as measure of disability. Although PDDS scores are strongly correlated with Expanded Disability Status Scale (EDSS) scores (Learmonth et al., 2013), we cannot exclude that applying EDSS scores would have yielded different results.

Despite these pitfalls, our findings have relevant implications for both research and clinical settings.

As per the research setting, we demonstrated that applying different MSISQ-19 cut-offs influences both the estimated prevalence and the identification of risk factors for SD, underlining the need for careful study planning in future works, and reinforcing the concept that direct comparison of seemingly similar studies should be avoided. Regarding the clinical implications of our work, although several factors related to MS affect the risk of SD, preserved cognition seems to exert a protective effect regardless from the specific study setting (i.e. MSISQ-19 chosen cut-off). This finding, together with the analysis of the main complaints emerging from single-subject MSISQ-19 analysis, should guide the application of preventive and therapeutic strategies for SD in pwMS.

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CRediT authorship contribution statement

M Petracca: Conceptualization, Investigation, Data curation, Writing – original draft, Methodology, Formal analysis. **A Carotenuto:** Methodology, Validation, Visualization, Writing – review & editing. **C Scandurra:** Validation, Visualization, Writing – review & editing, Software, Methodology, Investigation. **M Moccia:** Validation, Visualization, Writing – review & editing. **L Rosa:** Validation, Visualization, Writing – review & editing. **S Arena:** Validation, Visualization, Writing – review & editing. **A Ianniello:** Data curation, Validation, Visualization, Writing – review & editing. **A Nozzolillo:** Data curation, Validation, Visualization, Writing – review & editing. **M Turrini:** Data curation, Validation, Visualization, Writing – review & editing. **LM Streito:** Data curation, Validation, Visualization, Writing – review & editing. **G Abbadessa:** Data curation, Validation, Visualization, Writing – review & editing. **M Cellerino:** Data curation, Validation, Visualization, Writing – review & editing. **S Bucello:** Validation, Visualization, Writing – review & editing. **E Ferraro:** Validation, Visualization, Writing – review & editing. **M Mattioli:** Validation, Visualization, Writing – review & editing. **A Chiodi:** Validation, Visualization, Writing – review & editing. **M Inglese:** Validation, Visualization, Writing – review & editing. **S Bonavita:** Validation, Visualization, Writing – review & editing. **M Clerico:** Validation, Visualization, Writing – review & editing. **C Cordioli:** Validation, Visualization, Writing – review & editing. **L Moiola:** Validation, Visualization, Writing – review & editing. **F Patti:** Validation, Visualization, Writing – review & editing. **L Lavorgna:** Validation, Visualization, Writing – review & editing. **M Filippi:** Validation, Visualization, Writing – review & editing. **G Borriello:** Data curation, Validation, Visualization, Writing – review & editing. **E D'Amico:** Validation, Visualization, Writing – review & editing. **C Pozzilli:** Validation, Visualization, Writing – review & editing. **V Brescia Morra:** Validation, Visualization, Writing – review & editing. **R Lanzillo:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

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