

## ORIGINAL ARTICLE

# Correlation between patient-reported manual ability and three objective measures of upper limb function in people with multiple sclerosis

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## Abstract

**Background and purpose:** Upper limb (UL) function is often affected in people with multiple sclerosis (PwMS) and is typically assessed through objective measures, including the Nine Hole Peg Test (9-HPT), Box and Block Test (BBT), and Hand Grip Strength (HGS). It is important to include the subjective perspective of PwMS in the assessment. This study aims to evaluate associations between Manual Ability Measure-36 (MAM-36) and 9-HPT, BBT, and HGS in MS.

**Methods:** The cross-sectional study included five Italian centers. Inclusion criteria were age  $\geq 18$  years, MS diagnosis, and stable disease course. Exclusion criteria were bilateral UL paralysis, and concomitant orthopedic or neurological diseases.

**Results:** A total of 199 PwMS were included: 128 female, mean age =  $50.7 \pm 13.0$  years, 119 relapsing-remitting MS (RRMS), 31 primary and 49 secondary progressive MS, mean disease duration =  $14.0 \pm 10.4$ , years, mean Expanded Disability Status Scale (EDSS) =  $4.6 \pm 2.0$ .

The MAM-36 showed small correlations with 9-HPT, BBT, and HGS. Correlations between MAM-36 and 9-HPT and BBT were highest among subjects with EDSS  $\geq 6$  and progressive MS. MAM-36 and HGS showed the highest correlations in subjects with EDSS  $\leq 5$  and RRMS. Combining 9-HPT and HGS provided the strongest predictive power over the MAM-36.

**Conclusions:** Correlations between objective measures and MAM-36 were small to moderate, meaning that objective measures do not match subjects' perception of UL function. The combination of 9-HPT and HGS measures can help improve the assessment of UL function in activities of daily living.

## KEYWORDS

multiple sclerosis, objective measures, subjective measures, upper limb

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## INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease affecting white and gray matter in the central nervous system with an unpredictable course. A wide range of neurological symptoms affects several functional systems, resulting in different levels of disability [1, 2].

Upper limb (UL) function is one of the most affected domains in people with MS (PwMS). Holper et al. [3] highlight that 50% of people with MS report self-perceived UL dysfunction. Despite this, in the past, UL dysfunction has often been considered less debilitating than lower limb impairment. Recently, the impact of UL dysfunction on the performance of activities of daily living (ADL) and quality of life has gained attention in the literature [4].

For this reason, the assessment of PwMS cannot be limited to overall disability using the traditional Expanded Disability Status Scale (EDSS) [5], but it may include a specific evaluation of UL function. Among the existing objective UL measures, the most frequently used in clinical trials and practice are the Nine Hole Peg Test (9-HPT), recommended as the gold standard in assessing MS-related UL function [6], the Box and Block Test (BBT) [7], a measure of gross manual dexterity, and Hand Grip Strength (HGS) [8]. In our previous study, a moderate to low correlation was reported among these three measures, indicating that they assess distinct domains of UL function [9].

Due to the complexity of the assessment of UL function, and its influence on ADL [4], researchers and clinicians have to consider subjective perspectives and experiences of PwMS themselves [4]. Patient-reported outcome measures (PROMs) play an increasing role in MS clinical trials and practice and are essential for understanding the effects that MS has on patients' lives, improving patient engagement in their care [10]. The most commonly used self-reported UL performance questionnaires are the Manual Ability Measure-36 (MAM-36) [11], ABILHAND [12], Disabilities of the Arm, Shoulder, and Hand [13], the Motor Activity Log (MAL) [14], and Arm Function in Multiple Sclerosis (AMSQ) [15]. None of these questionnaires was available in Italian at the time of study planning; for this reason, in a previous study, we provided a translation in Italian and validation of the MAM-36 in a large sample of PwMS [11].

In the literature, there are only a few studies that provide information on the correlation between objective and subjective measures of UL in MS. Lamers et al. [14] reported a low correlation between a capacity measure (Action Research Arm Test [ARAT]) and a PROM of UL (MAL). Moreover, moderate correlations were found between 9-HPT, ARAT, and perceived performance (MAM-36) [16]. A study by Solaro and colleagues reported a moderate correlation between 9-HPT for both arms and MAM-36 [11]. Similarly, van Leeuwen et al. [17] found moderate to high correlations among HGS, 9-HPT, ARAT, and AMSQ, in agreement with van Munster et al. [18], who reported a moderate correlation between 9-HPT and AMSQ for both arms.

The present study aims to evaluate the association between three objective UL measures (9-HPT, BBT, HGS) and self-perceived ability to perform manual activities of daily living (MAM-36). We also

explored whether emerging associations between subjective and objective UL function tend to vary according to subjects' disability level and disease course. Finally, we evaluated whether combining multiple objective measures can help improve the prediction of subjects' perception of UL functions over the use of a single objective measure.

Because the assessed UL measures (9-HPT, BBT, HGS) are intended to assess different domains of UL function, we hypothesized that (i) they should show different patterns of associations with self-perceived manual ability in ADLs, conditional on the clinical characteristics of patients; and (ii) they should provide independent contributions in predicting perceived manual ability.

## MATERIALS AND METHODS

### Study design

In this cross-sectional study, data were collected between January 2016 and August 2019 at five Italian centers specializing in MS, the Department of Rehabilitation, CRRF Mons. Luigi Novarese, Moncrivello; Department of Neurology, University of Catania, Catania; Don Carlo Gnocchi Foundation, Milan; Rehabilitation Service of Liguria of the Italian Multiple Sclerosis Society, Genoa; and Saint Andrea Hospital, Rome.

Inclusion criteria were a confirmed diagnosis of MS according to revised McDonald criteria [19], age  $\geq 18$  years, right-hand dominance according to the Edinburgh Handedness Inventory, 18/20 aided or unaided vision, and preserved cognitive functioning (Mini-Mental State Evaluation  $> 24$ ) [20]. Exclusion criteria were relapses or relapse-related treatment in the 3 months before study entry and the presence of orthopedic or other neurological diseases interfering with the use of ULs.

A priori estimation of the required sample size was performed using G\*Power [21]. A sample size of  $N \geq 193$  subjects was deemed sufficient for detecting small correlations with sufficient power [22].

Subjects provided written informed consent before the beginning of the assessments. The study was carried out following the Declaration of Helsinki and approved by the local ethics committee (P.R.196REG2015).

To standardize the administration procedures across five study centers, assessor training was required for study personnel. At each center, neurologists trained for the Neurostatus-EDSS performed the EDSS, whereas occupational or physical therapists performed the objective and subjective UL assessments.

### Instruments

#### Objective measures

The 9-HPT [23] is a brief quantitative test for fine manual dexterity administered according to the Multiple Sclerosis Functional

Composite [24]. It consists in taking nine small pegs from a container, one by one, and placing them into holes on a board, as quickly as possible, then removing each peg from the holes, and placing them back into the container. For each arm, the average time of two trials represents the final score of the test. The time taken to complete each trial was recorded with a maximum time of 180s.

The BBT [7] is a measure of gross manual dexterity. It consists of a box (53.7 × 9 × 25.4 cm) divided by a panel into two spaces (15.2 cm high), filled with 150 blocks. The subject grasps one block at a time, moves the block over the partition, and releases it into the opposite compartment as quickly as possible. The score is the number of blocks moved in 1 min, for each hand separately.

Hand grip strength [8] is evaluated with a Jamar hand dynamometer and quantifies the maximum isometric strength of the hand scored in kilograms. The test was performed in the following position: shoulder abducted and neutrally rotated, elbow flexed at 90°, forearm in a neutral position, wrist between 0° and 30° dorsiflexion and between 0° and 15° ulnar deviation. The mean of three trials was considered for each hand.

## Subjective measure

The MAM-36 consists of 36 items investigating subjects' perceived ability to perform common tasks (e.g., eating, dressing, buttoning clothes), excluding the use of adaptive equipment. Each item is rated on a 4-point scale ranging from 1 (cannot do it) to 4 (easy). Tasks that are rarely performed are scored 0. The MAM-36 was scored by calibrating the Rasch rating scale model using Winsteps (version 3.68), anchoring the item and structure parameters as reported in the validation study for the Italian version of the MAM-36 [11]. The Rasch score is preferable over the raw score because it corrects for individual differences in the number of MAM-36 tasks that are not typically performed by the individual (i.e., 0 responses). The obtained Rasch score is expressed in logit units (Table 2) and show excellent reliability (person reliability = 0.91).

## Data analysis

We computed descriptive statistics on UL measures (i.e., 9-HPT, HGS, and BBT) on each dominant and nondominant arm and their mean, and on the MAM-36 Rasch score. The normality of measures was verified using the Shapiro-Wilk test. We then computed Spearman correlations between the MAM-36 scores and the UL measures (9-HPT, HGS, and BBT) on each arm, as well as their mean values. Correlations were computed on the overall sample ( $N = 199$ ), and by grouping participants according to their EDSS level (mild disability,  $EDSS \leq 3$ ; moderate disability,  $3.5 \leq EDSS \leq 5.5$ ; high disability,  $EDSS \geq 6$ ), and by disease course (relapsing-remitting MS [RRMS] vs. primary progressive MS [PPMS] and secondary progressive MS [SPMS]). The stability of estimated correlations was established by computing 95% confidence intervals using 1000 bootstrap resamples.

As a final analytical step, using multiple linear regression, we evaluated the contribution of each of the three objective measures (i.e., 9-HPT, HGS, and BBT) in predicting the MAM-36 Rasch scores. For this analysis, 9-HPT, HGS, and BBT mean scores were used in place of the measures of each arm to avoid potential collinearity issues. Specifically, we implemented a series of regression models investigating the predictive power over the MAM-36 scores of all possible combinations of the three objective measures (i.e., mean 9-HPT, HGS, and BBT scores). In all models, we controlled for the effect of age, sex (male = 0, female = 1), and a progressive course diagnosis (RRMS = 0; PPMS/SPMS = 1). The Breusch-Pagan test was used to detect potential violations of the homoscedasticity assumption for regression residuals [25]. Histogram and QQ plots of standardized residuals were also assessed to identify relevant deviations from normality of residuals. To determine the predictive power of these models, we used  $R^2$  and adjusted  $R^2$  statistics, and the multiple correlation coefficient  $R$  (i.e., the square root of  $R^2$ ), representing the correlation between observed and predicted MAM-36 (Rasch) scores. A significant change in  $R^2$  ( $p < 0.05$ ) was considered an indication of nonnegligible improvement in predictive power when comparing models sharing at least one common predictor. Except where indicated, all analyses were performed using SPSS, version 23.

## RESULTS

The sample consisted in 199 right-handed PwMS, including 64.3% females ( $n = 128$ ) and 35.7% males ( $n = 71$ ), with a mean age of 50.69 years ( $SD = 13.05$ , median = 52, range = 22–85). The majority of subjects had a relapsing-remitting disease course (59.8%,  $n = 119$ ), 31 (15.6%) had PPMS, and 49 (24.6%) had SPMS. Average disease duration was 13.97 years ( $SD = 10.41$ ). The average EDSS score was 4.58 ( $SD = 1.97$ , median = 5, range = 1–8). All participants completed both questionnaires, and were assessed on all the objective measures.

### Distribution of upper limb and manual ability measures

Table 1 reports information about the distribution of the study measures in our sample. Shapiro-Wilk test indicated that the UL measures (i.e., 9-HPT, HGS, and BBT), as assessed on dominant and nondominant arms and their mean values, all significantly deviated from normality ( $p < 0.05$ ). The MAM-36 also did not comply with the assumption of normality.

### Correlations between UL measures and self-reported manual ability

Table 2 reports the results of Spearman correlations as computed between the MAM-36 scores and objective UL measures. Results

**TABLE 1** Descriptive statistics for objective upper limb measures and patient-reported manual ability measure (MAM-36)

Measure	Mean	SD	Median	Minimum	Maximum
MAM-36					
Raw score	125.53	19.08	131	39	144
Rasch score	3.07	2.17	2.58	-2.04	6.65
9-HPT, s					
Dominant	30.97	17.40	25.00	15.00	130.66
Nondominant	32.34	18.40	26.00	14.00	146.00
Mean	31.65	14.83	26.00	14.50	92.00
HGS, kg					
Dominant	19.38	9.97	18.00	1.28	52.00
Nondominant	18.04	8.71	17.33	1.78	49.33
Mean	18.71	8.76	17.67	2.96	50.67
BBT, blocks					
Dominant	47.08	16.62	46.00	12.00	102.00
Nondominant	46.65	15.86	46.00	13.00	103.00
Mean	46.86	15.62	46.00	13.00	101.00

Abbreviations: 9-HPT, Nine Hole Peg Test; BBT, Box and Block Test; HGS, Hand Grip Strength; MAM-36, Manual Ability Measure-36.

**TABLE 2** Associations between objective upper limb measures and patient-reported manual ability measure (MAM-36): Spearman correlations in the whole sample, by EDSS and disease course

Measure	All subjects, <i>n</i> = 199	Disability, EDSS			Disease course	
		≤3, <i>n</i> = 60	3.5-5.5, <i>n</i> = 53	≥6, <i>n</i> = 86	RR, <i>n</i> = 119	PP/SP, <i>n</i> = 80
9-HPT, s						
Dominant arm	-0.29	0.14	-0.25	<b>-0.30</b>	-0.16	<b>-0.41</b>
Nondominant arm	-0.26	0.09	-0.10	-0.10	-0.12	<b>-0.43</b>
Mean	-0.33	0.12	-0.20	<b>-0.31</b>	<b>-0.19</b>	<b>-0.50</b>
HGS, kg						
Dominant arm	<b>0.33</b>	<b>0.43</b>	<b>0.48</b>	<b>0.23</b>	<b>0.46</b>	0.18
Nondominant arm	<b>0.24</b>	<b>0.34</b>	<b>0.35</b>	0.08	<b>0.28</b>	0.18
Mean	<b>0.31</b>	<b>0.39</b>	<b>0.45</b>	0.19	<b>0.39</b>	0.21
BBT, blocks						
Dominant arm	<b>0.35</b>	0.08	0.10	<b>0.38</b>	<b>0.34</b>	<b>0.26</b>
Nondominant arm	<b>0.26</b>	0.07	0.03	0.09	<b>0.25</b>	0.18
Mean	<b>0.33</b>	0.06	0.07	<b>0.27</b>	<b>0.32</b>	<b>0.24</b>

Note: Correlations in bold are significant at  $p < 0.05$ .

Abbreviations: 9-HPT, Nine Hole Peg Test; BBT, Box and Block Test; EDSS, Expanded Disability Status Scale; HGS, Hand Grip Strength; MAM-36, Manual Ability Measure-36; PP, primary progressive; RR, relapsing-remitting; SP, secondary progressive.

of correlations in the whole group ( $n = 199$ ) showed 9-HPT measures for the dominant and nondominant arms had small significant negative correlations with the MAM-36 scores, whereas the mean 9-HPT score showed a moderate negative association. The BBT and HGS measures showed moderate positive associations with the MAM-36 scores on the dominant arm, and a small positive association with MAM-36 on the nondominant arm. The mean BBT and HGS scores also showed moderate positive associations with MAM-36 scores.

As regards the correlation computed in the EDSS groups, results differed markedly depending on the specific measure examined. In the high disability groups ( $EDSS \geq 6$ ), mean and dominant arm scores for the BBT and 9-HPT showed respectively positive (BBT) and negative (9-HPT) correlations with the MAM-36. No significant correlations between both BBT and 9-HPT measures and the MAM-36 were found in the mild ( $EDSS \leq 3$ ) and moderate ( $3.5 \leq EDSS \leq 5.5$ ) disability groups. Conversely, all HGS measures showed moderate positive correlations with the MAM-36 in the mild ( $EDSS \leq 3$ ) and

moderate ( $3.5 \leq \text{EDSS} \leq 5.5$ ) disability groups, whereas the HGS measures had no significant correlations with the MAM-36 in the high disability group ( $\text{EDSS} \geq 6$ ), except for the HGS score for the dominant arm, which showed a small positive correlation.

We then looked at correlations between UL measures and MAM-36 by disease course (relapsing–remitting vs. progressive course). Among PPMS and SPMS subjects, all 9-HPT measures showed moderate negative correlations with the MAM-36. In relapsing–remitting subjects, a negative correlation emerged between the 9-HPT mean score and the MAM-36. BBT measures showed small to moderate positive correlations with the MAM-36 regardless of patients' disease course, except for the nondominant arm score among subjects with a progressive course, which showed no correlation with the MAM-36. Finally, all HGS measures showed small to moderate positive correlations with the MAM-36 in relapsing–remitting subjects. In turn, among subjects with a progressive course, none of the HGS measures showed significant correlations with the MAM-36.

### Predictive performance of mean UL measures over the MAM-36 (Rasch) scores

On verifying the regression assumption of homoscedasticity of residuals with the Breusch–Pagan test, residuals complied with the homoscedasticity assumption. Visual evaluation of histogram and QQ plots on standardized residuals indicated no relevant deviation from normality. Prediction results are shown in Table 3. Assessing both the  $R^2$  and the adjusted  $R^2$  statistics, a combination of mean 9-HPT and mean HGS scores showed the strongest predictive power over the MAM-36 scores. Interestingly, based on the  $R^2$  change statistic, the model combining all mean score measures (9-HPT, HGS, and BBT) did not improve in predictive power over the model including the mean 9-HPT and HGS scores ( $R^2$  change  $< 0.01$ ,  $p = 0.44$ ). Similarly, when comparing the model including only the mean 9-HPT score, and the model including both the mean 9-HPT and BBT scores, improvement in predictive power was not significant ( $R^2$  change = 0.01,  $p = 0.10$ ). A significant improvement in predictive power was detected when comparing the model including only the mean 9-HPT score and

the model including both the mean 9-HPT and HGS scores ( $R^2$  change = 0.12,  $p < 0.01$ ). A similar effect was found when comparing the model including the mean HGS score with the model with both the mean HGS and BBT scores ( $R^2$  change = 0.11,  $p < 0.01$ ). Finally, the correlation between predicted and observed scores was strong ( $R \geq 0.50$ ) for the models combining mean 9-HPT and HGS scores, or all mean UL measures. For the model including only the BBT mean score among the predictor set (as well as control variables), the correlation between observed and predicted MAM-36 scores was small ( $R = 0.29$ ), whereas for the rest of the models, the correlation was moderate ( $0.30 \leq R < 0.50$ ). Finally, it is worth noting that control variables (i.e., age, sex, and progressive MS) showed limited predictive power over MAM-36 scores ( $R^2 = 0.01$ ). Additionally, adding UL measures into the model, either alone or in combination, resulted in a significant improvement in the predictive power of the model including only control variables ( $R^2$  change  $\geq 0.08$ ,  $p < 0.01$ ).

## DISCUSSION

The present study aimed at investigating the associations between a validated PROM, the MAM-36, and three objective measures, 9-HPT, BBT, and HGS. Overall, the associations between the MAM-36 and each of the three measures are quite small. However, they tend to show a larger effect size when the objective measures are examined on the dominant arm, or when using a mean score for both arms, when compared with the nondominant arm. Our findings are in line with the literature [7, 16, 17, 26, 27], indicating that objective measures and PROMs of UL function show weak associations, as they assess distinct constructs [4, 28]. It is worth noting that these associations appear to be significantly smaller than those reported when correlating PROMs and objective measures of walking ability [29, 30], likely related to the higher complexity of UL activity.

Findings were in line with our hypothesis that the assessed UL measures would demonstrate different associations with manual ability in ADLs depending on the domain of UL function assessed and subjects' clinical characteristics. In line with this hypothesis, the examined UL measures showed different patterns of correlation with the MAM-36. Correlation between the MAM-36 and both 9-HPT and BBT scores tended to be stronger among highly disabled subjects ( $\text{EDSS} \geq 6$ ) and those with a progressive disease course. In turn, MAM-36 and HGS scores showed their strongest association in subjects with mild to moderate disability ( $\text{EDSS} \leq 5$ ), and in subjects with a relapsing–remitting disease course. However, even when examined according to these stratifications, correlations remained moderate at best.

Finally, using multiple linear regression, we looked at the relative contribution of the three objective measures in predicting subjects' perception of their UL function. In line with our hypothesis, we demonstrated that combining the three measures can help improve the overall strength of the association between objective and PROM assessment of UL function. In particular, prediction is strongest when the 9-HPT and HGS measures are combined in a single model; this suggests each of these measures contributes distinct information useful

**TABLE 3** Predictive performance of upper limb measures over the MAM-36 (Rasch) score

Measure	$R^2$	Adjusted $R^2$	$R$
9-HPT	0.16	0.14	0.39
HGS	0.15	0.14	0.39
BBT	0.09	0.07	0.29
9-HPT+HGS	0.27	0.25	0.52
9-HPT+BBT	0.17	0.15	0.41
BBT+HGS	0.19	0.17	0.44
9-HPT+HGS+BBT	0.27	0.25	0.52

Note: Control variables are age, sex, and progressive disease course. Abbreviations: 9-HP, Nine Hole Peg Test; BBT, Box and Block Test; HGS, Hand Grip Strength; MAM-36, Manual Ability Measure-36.

for inferring subjects' UL functioning when managing with ADLs. It is worth noting that we also found a significant overlap between 9-HPT and BBT measures in predicting the MAM-36, insofar that the combining these two measures does not seem to improve prediction over the use of 9-HPT alone. This is not surprising, knowing that the 9-HPT and BBT tend to show stronger associations than those observed when examining associations of the same measures with HGS [9].

A few studies reported in the literature [7, 16, 17, 26, 27] have analyzed the relationship between objective and subjective UL measures, even if using different correlation coefficients. Four studies [7, 17, 26, 27] analyzed correlations between AMSQ and 9-HPT, reporting a coefficient ranging between 0.46 [18] and 0.82 [26], whereas a correlation of  $-0.67$  has been reported between the AMSQ and HGS [17]. One study performed in a smaller sample, with higher mean age, disease duration, disability level, and percentage of SPMS than the present study, reported strong correlations between 9-HPT and HGS, and the MAM-36 [16]. Correlations emerging from the literature appear to be generally higher than those reported in the present study, which ranged from a minimum size of 0.24 (nondominant arm HGS) to a maximum of 0.35 (dominant arm BBT). The strongest correlation found stratifying the sample for EDSS and disease duration was  $-0.50$  for the mean 9-HPT in the progressive MS group.

The reasons for the weak correlation found between subjective and objective measures could be several. First, the MAM-36 assesses overall manual ability in performing both unimanual and bimanual activities and tasks, whereas the objective measures assess the hands separately without considering asymmetry between hands and a global score. Another possible explanation for the weak correlation could be related to the item scoring method of the MAM-36, which is based on a 4-point Likert scale, and probably not ideal for capturing the range of difficulties encountered by the subjects. Therefore, to increase the strength of the correlation, subjective measures should be characterized by bimanual and unimanual subscores with a wider range of item responses. Furthermore, the objective tests should provide a global score corrected for asymmetry in the UL function.

The present study has strengths. First, recruited MS patients were assessed using three objective scales of UL function. Standardization training for administration of the scales among the assessors across centers likely minimized measurement bias, supporting the reliability of the results. Moreover, an EDSS distribution with 50% of participants at  $>5.0$  suggests the results of the study are also applicable to a population with a high level of disability. Nonetheless, the present study is not without limitations. The sample was recruited using a nonprobability, consecutive sampling approach; thus, caution should be applied in generalizing these results to the broader MS population. Furthermore, data were collected at a single point in time, limiting our ability to make causal inferences. Finally, cognitive dysfunction may affect subjects' perception of their ability to perform activities of daily living, which could influence the correlation with objective measures. Therefore, future studies should consider the impact of cognitive function on PROM.

To conclude, the present study demonstrated a small association between the MAM-36 and 9-HPT, BBT, and HGS. However,

9-HPT and BBT appear to provide a more valid assessment of UL functioning in ADL in subjects with higher levels of disability and a progressive disease course, whereas HGS appears to be valid in subjects with lower levels of disability and a relapsing–remitting disease course. Because they appear to provide largely independent information about UL functioning in performing ADL, combining the 9-HPT and HGS measures can improve the assessment of UL functioning in subjects with MS. Furthermore, the lack of a strong overlap between objective and subjective assessments of UL function highlights the need to include both to obtain a comprehensive assessment of UL function.

## AUTHOR CONTRIBUTIONS

Claudio Solaro: Conceptualization, methodology, writing–original draft, writing–review & editing, supervision, project administration, funding acquisition. Rachele Di Giovanni: Investigation, writing–original draft, writing–review & editing. Erica Grange: Investigation, writing–original draft, writing–review & editing. Giampaolo Brichetto: Investigation, project administration. Margit Mueller: Investigation. Andrea Tacchino: Investigation, writing–review & editing. Rita Bertoni: Investigation. Francesco Patti: Investigation, project administration, writing–review & editing. Angelo Pappalardo: Investigation, writing–review & editing. Luca Prosperini: Investigation, project administration, writing–review & editing. Letizia Castelli: Investigation. Rosato Rosalba: Investigation, writing–review & editing. Davide Cattaneo: Investigation, project administration, formal analysis, writing–review & editing. Davide Marengo: Methodology, formal analysis, data curation, writing–original draft, writing–review & editing, visualization.

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## CONFLICT OF INTEREST

None.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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