

# The impact of recurrent Covid-19 waves on patients with Functional Movement Disorders: A follow-up study

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## ABSTRACT

**Background:** Functional Movement Disorders (FMDs) might exacerbate in stressful conditions. As the global health emergency due to Covid-19 rise and multiple waves hit the Italian population, the recurrent severe restrictions' periods imposed could represent important triggers and worsen the symptoms of FMDs. Through a follow-up study, we compare results on Motor Symptoms (MS), Non-Motor Symptoms (NMS), and Global Health Status (GHS) of two surveys, one referred to the first Covid-19 wave and the other to the third Covid-19 wave. **Methods:** 60 FMDs patients responded to an online survey after the first and the third Covid-19 waves in Italy. Questions regarding sociodemographic, clinical and Covid-19 information, MS, NMS, and GHS were collected to assess severity of symptoms and changes in comparison to a period with less severe social restrictions. **Results:** Patients showed minimal to mild motor symptoms' severity, and substantial stability through time in all collected measures, both for severity and changes of MS, NMS, and GHS in comparison at two time points ( $p > 0.050$ ). The worsening of pain resulted as predictor factor for the worsening of Motor Symptoms ( $p = 0.042$ ). **Conclusions:** Patients did not show a vulnerability due to the recurrent restrictions' periods: MS, NMS and GHS did not vary in comparison to the first wave, confirming the previous results and highlighting the role of the social context in those disorders. Further investigations are required to better disentangle the relationship between stressful events, motor symptoms, and pain.

## 1. Short communication

### 1.1. Introduction

Functional movement disorders (FMDs) are disabling neurological conditions that might exacerbate in stressful situations [1]. FMDs are characterized by abnormal movements (Motor Symptoms [MS], e.g., weakness, tremor, dystonia, gait disorders) that are clinically incongruent with those of classical neurological disorders, inconsistent over time and frequently associated to non-motor symptoms ([NMS], e.g., depression, anxiety, pain, physical and mental fatigue) [2,3]. The global health emergency due to the Coronavirus disease 2019 (Covid-19) and the severe restrictions imposed to limit the infection could represent important triggers for the worsening of FMDs. In the general population, the Covid-19 pandemic had a serious impact on mental health, leading to the development of post-traumatic stress symptoms, depression and anxiety [4]. Despite an increased incidence of FMDs during the

pandemic [5] and after the start of the vaccination campaign for Covid-19 [6], it is not clear whether patients with an established diagnosis of FMDs have shown increased vulnerability due to the pandemic.

Since the first case detected on February 21st, 2020, Italy has rapidly become one of the European countries most severely affected by Covid-19. There have been three major repeated outbreaks and different measures to limit the virus' diffusion have been adopted (Fig. 1) [7]. We have recently published the results of a survey-based study on the impact of the first lockdown on our cohort of FMDs patients [8]. We found mild to moderate MS reports in the majority of patients, and levels of NMS comparable to healthy controls (HC). MS, most NMS, and Global Health Status (GHS) remained unchanged in the majority of patients (~60%), except for mental fatigue that worsened in most (~50%). In comparison with HC, pain worsened significantly more in FMDs, whereas anxiety and depression worsened significantly more in HC than FMDs. Our results were in line with previous studies reporting a substantial stability of MS in FMDs during pandemic, despite increased

**Abbreviations:** FMDs, Functional Movement Disorders; MS, Motor Symptoms; NMS, Non-Motor Symptoms; GHS, Global Health Status; HC, Healthy controls.

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anxiety [9]. Through a self-controlled follow-up study, we aimed at investigating the impact of a longstanding pandemic and social restrictions recurrently imposed over time on the same cohort of FMDs patients, investigating MS, NMS, and GHS at the end of the third Covid-19 wave. Given that a stressful situation especially prolonged are thought to exacerbate the symptoms, understanding the long-term impact of social restrictions could shed lights on the understanding of pathophysiology of those disorders.

## 2. Methods

We enrolled 73 patients with an established diagnosis of FMDs based on the Gupta and Lang criteria [10], regularly followed-up every three months at our specialized clinic in Verona, who had previously completed the first survey [8]. They were contacted via phone or mail and given the link for a semi-anonymous Survey and two weeks to complete it. All patients provided informed consent, and the local Ethics Committee approved the study. This is a self-controlled follow-up survey-based study, where we compared data from two time points (as described below).

In May 2021, we asked FMDs patients to retrospectively rate the severity of MS, NMS, and GHS during the two previous months of March-April 2021 (while social restrictions were still quite severe in Italy) and their changes with respect to Summer 2020 (when social restrictions were relatively loose). We compared these results with those obtained from the first survey-based study [8], conducted in October 2020. We will refer to the third wave as T1 and to the first wave as T0 (Fig. 1). The Survey was divided into three sections: i) socio-demographics and Covid-19 related questions (i.e., information related to vaccination, positive testing results, hospitalization or quarantine); ii) patient-estimated severity of symptoms during lockdown: motor and NMS, assessed through a 5-point Likert scale (from 1 = none to 5 = severe) and GHS, assessed using a 5-point scale (from 1 = excellent to 5 = poor); iii) changes in symptoms severity compared to Summer 2020, assessed through a 3-point Likert scale (improved/unchanged/worsened). We also assessed changes in adherence to self-management rehabilitation program. The non-parametric Wilcoxon test for paired data was employed to compare variables at two time points. A composite variable was computed assessing difference in time (T1–T0), which was used to perform both univariable and multivariable logistic regression analyses in order to investigate the relationship in time between changes in MS, NMS (anxiety, depression, physical and mental fatigue, pain), and adherence to rehabilitation.

## 3. Results

60 FMDs patients (85% females) of the 73 contacted (response rate, 82%) with a mean age ( $\pm$ SD) of 40.95 ( $\pm$ 13.15) and a mean disease duration ( $\pm$ SD) of 8.92 ( $\pm$ 10.08) completed the online survey. Main demographics, clinical characteristics, Covid-19 related information and changes in adherence to prescribed rehabilitation are reported in the Supplementary Table 1a. A total of 8% ( $n = 5$ ) of patients had tested positive for Covid-19 during pandemic and 32% ( $n = 19$ ) of them were vaccinated at T1.

MS severity was reported to be minimal to mild in 50% of patients, moderate to severe in 35%, with MS occurring once or more than once a day (continuous phenotype) in 57% of patients.

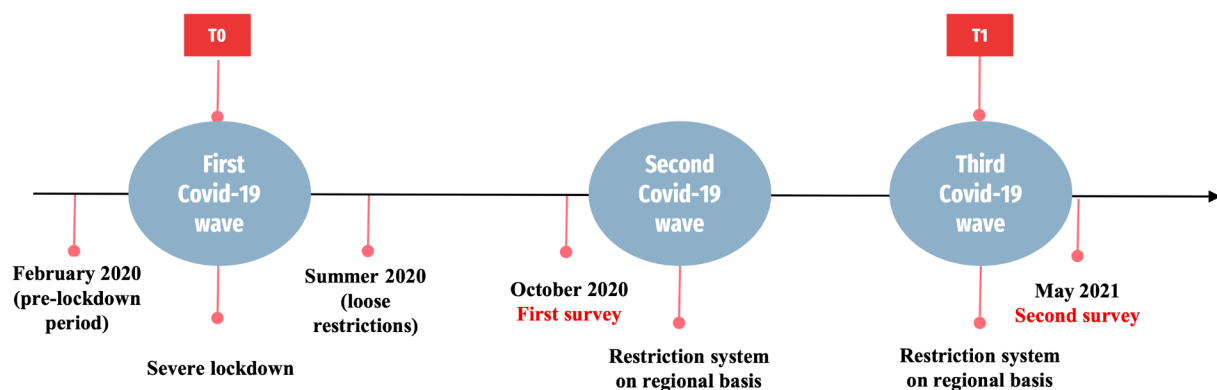
When comparing results at T1 with T0, no significant differences were found between severity and frequency of MS (all,  $p > 0.05$ ). Likewise, NMS severity (depression, anxiety, physical and mental fatigue, demotivation, pain, sleep difficulties) and GHS did not differ at T1 in comparison with T0 (all,  $p > 0.05$ ) (Table 1, section A). Changes of MS, NMS and GHS at T1 compared to T0 did not show any significant difference (all,  $p > 0.05$ ) (Table 1, section B).

Results of univariable logistic regression models with each selected characteristic (anxiety, depression, physical and mental fatigue, pain, adherence to rehabilitation) as independent variable and of a multivariable logistic model with all the independent variables are shown in Table 1 (section C). Worsening of pain significantly predicted MS worsening in both single regression analysis (odds ratio: 7.2,  $p = 0.007$ ), and in the multivariable logistic model (odds ratio: 11.69,  $p = 0.042$ ).

## 4. Discussion

Our findings suggest that patients with an established diagnosis of FMD have shown stability of MS, NMS and GHS over time after a longstanding pandemic and recurrent imposed social restrictions. Notably, to our knowledge this is the first attempt to study the effect of a prolonged psychosocial stressor throughout time on the general health of FMD patients.

MS and NMS were reported minimal to mild in ~50% of patients, and GHS was reported fair in the majority of patients, at T1, all comparable to T0. We also found no differences between changes in MS, NMS and GHS at T1 compared to T0. Mental fatigue was reported equally worsened (~50%) at T1 vs T0. Anxiety and depression levels resulted comparable to T0, where they had been found increased only in HC [4,8]. Pain had worsened in comparison to HC at T0 and remained



**Fig. 1.** Illustrative image of milestone events in the COVID-19 outbreaks in Italy and our study timeline. Since the first case detection on February 21, 2020, Italy has rapidly become one of the more severely affected European countries by the Coronavirus disease (Covid-19). Schematically, there have been three outbreaks of Covid-19 and different measures to limit virus diffusion were adopted. In March-April 2020 a strict lockdown of all unnecessary and social activities has been imposed, followed by a progressive mitigation of restrictions. The second and third waves of COVID-19 have spread in the fall of 2020 and shortly after, during winter/spring 2021. Variable interventions and a three-tiered restriction system were introduced on a regional basis, mainly driven by the burden of the infection. These measures ranged from reduction to closure of bars, restaurants, theaters, gyms, schools and so forth. We administered the two Surveys in two periods of relatively loose restrictions: the beginning of October 2020 (with T0 referring as the first wave) and May 2021 (with T1 referring as the third wave).

**Table 1**  
Clinical variables, changes and regression analyses in FMD in MS, NMS, and GHS during lockdown and after second and third COVID-19 outbreaks.

	FMD at T0	FMD at T1	Test	p-value
<i>Section A: clinical variables</i>				
<b>Severity of Motor symptoms (5-point Likert)</b>			Wilcoxon Signed rank test	0.952
Mean ± SD	3.05 ± 1.08	2.91 ± 1.24		
Median (IQR)	3.00 (2-4)	3.00 (2-4)		
None	5% (n = 3)	15 % (n = 9)		
Minimal	27% (n = 16)	20% (n = 12)		
Mild	40% (n = 24)	30% (n = 18)		
Moderate	15% (n = 9)	23% (n = 14)		
Severe	13% (n = 8)	12% (n = 7)		
I do not Know	-	-		
<b>I felt anxious (5-point Likert)</b>			Wilcoxon Signed rank test	0.079
Mean ± SD	2.65 ± 1.12	2.38 ± 1.14		
Median (IQR)	3.00 (2-3)	2.00 (1.75-3)		
None	18% (n = 11)	25% (n = 15)		
Minimal	25% (n = 15)	31% (n = 19)		
Mild	35% (n = 21)	30% (n = 18)		
Moderate	17% (n = 10)	7% (n = 4)		
Severe	5% (n = 3)	7% (n = 4)		
I do not Know	-	-		
<b>I felt depressed (5-point Likert)</b>			Wilcoxon Signed rank test	0.199
Mean ± SD	2.8 ± 1.27	2.6 ± 1.11		
Median (IQR)	3.00 (2-4)	3.00 (2-3)		
None	15% (n = 9)	17% (n = 10)		
Minimal	32% (n = 19)	31% (n = 19)		
Mild	26% (n = 16)	33% (n = 20)		
Moderate	12% (n = 7)	12% (n = 7)		
Severe	15% (n = 9)	7% (n = 4)		
I do not Know	-	-		
<b>I felt physically fatigued (5-point Likert)</b>			Wilcoxon Signed rank test	0.16
Mean ± SD	3.17 ± 1.15	3.37 ± 1.27		
Median (IQR)	3.00 (2.5-4)	3.00 (3-4)		
None	7% (n = 4)	12% (n = 7)		
Minimal	18% (n = 11)	10% (n = 6)		
Mild	43% (n = 26)	32% (n = 19)		
Moderate	12% (n = 7)	23% (n = 14)		
Severe	18% (n = 11)	23% (n = 14)		
I do not Know	2% (n = 1)	-		
<b>I felt mentally fatigued (5-point Likert)</b>			Wilcoxon Signed rank test	0.623
Mean ± SD	2.98 ± 1.21	3.12 ± 1.34		
Median (IQR)	3.00 (2-4)	3.00 (2-4)		
None	13% (n = 8)	15% (n = 9)		

**Table 1 (continued)**

	FMD at T0	FMD at T1	Test	p-value
Minimal	17% (n = 10)	17% (n = 10)		
Mild	38% (n = 23)	32% (n = 19)		
Moderate	15% (n = 9)	15% (n = 9)		
Severe	13% (n = 8)	21% (n = 13)		
I do not Know	4% (n = 2)	-		
<b>I felt demotivated (5-point Likert)</b>			Wilcoxon Signed rank test	0.21
Mean ± SD	2.56 ± 1.35	2.3 ± 1.17		
Median (IQR)	2.00 (1.5-3)	2.00 (1-3)		
None	25% (n = 15)	30% (n = 18)		
Minimal	30% (n = 18)	32% (n = 19)		
Mild	22% (n = 13)	21% (n = 13)		
Moderate	7% (n = 4)	12% (n = 7)		
Severe	15% (n = 9)	5% (n = 3)		
I do not Know	2% (n = 1)	-		
<b>I felt pain (5-point Likert)</b>			Wilcoxon Signed rank test	0.449
Mean ± SD	2.93 ± 1.23	2.81 ± 1.37		
Median (IQR)	3.00(2-4)	3.00 (2-4)		
None	12% (n = 7)	23% (n = 14)		
Minimal	27% (n = 16)	17% (n = 10)		
Mild	32% (n = 19)	28% (n = 17)		
Moderate	13% (n = 8)	15% (n = 9)		
Severe	15% (n = 9)	15% (n = 9)		
I do not Know	2% (n = 1)	2% (n = 1)		
<b>I had trouble sleeping (5-point Likert)</b>			Wilcoxon Signed rank test	0.932
Mean ± SD	2.66 ± 1.45	2.63 ± 1.39		
Median (IQR)	3.00 (1-3)	2.00 (2-3.5)		
None	30% (n = 18)	23% (n = 14)		
Minimal	15% (n = 9)	32% (n = 19)		
Mild	30% (n = 18)	18% (n = 11)		
Moderate	5% (n = 3)	8% (n = 5)		
Severe	18% (n = 11)	17% (n = 10)		
I do not Know	2% (n = 1)	2% (n = 1)		
<b>Global Health Status (5-point Likert)</b>			Wilcoxon Signed rank test	0.608
Mean ± SD	2.08 ± 0.93	2.17 ± 0.81		
Median (IQR)	2.00(1-3)	2.00 (1-3)		
Poor	33% (n = 20)	29% (n = 17)		
Fair	30% (n = 18)	23% (n = 14)		
Good	32% (n = 19)	3% (n = 2)		
Very good	5% (n = 3)	5% (n = 3)		
Excellent	-	5% (n = 3)		
I do not Know	-	-		

Section B: Symptoms changes

(continued on next page)

Table 1 (continued)

	FMD at T0	FMD at T1	Test	p-value
<b>Severity of Motor symptoms</b>			Wilcoxon Signed rank test	0.097
Worsened	33% (n = 20)	32% (n = 19)		
Unchanged	57% (n = 34)	43% (n = 26)		
Improved	10% (n = 6)	25% (n = 15)		
<b>Frequency of Motor symptoms</b>			Wilcoxon signed rank test	0.403
Worsened	30% (n = 18)	40% (n = 24)		
Unchanged	63% (n = 38)	35% (n = 21)		
Improved	7% (n = 4)	25% (n = 15)		
<b>Anxiety</b>			Wilcoxon signed rank test	0.767
Worsened	35% (n = 21)	40% (n = 24)		
Unchanged	60% (n = 36)	46% (n = 28)		
Improved	5% (n = 3)	14% (n = 8)		
<b>Depression</b>			Wilcoxon signed rank test	0.929
Worsened	42% (n = 25)	43% (n = 26)		
Unchanged	47% (n = 28)	42% (n = 25)		
Improved	12% (n = 7)	15% (n = 9)		
<b>Physical Fatigue</b>			Wilcoxon signed rank test	0.891
Worsened	48% (n = 29)	57% (n = 34)		
Unchanged	45% (n = 27)	30% (n = 18)		
Improved	7% (n = 4)	14% (n = 8)		
<b>Mental Fatigue</b>			Wilcoxon signed rank test	0.742
Worsened	55% (n = 33)	53% (n = 32)		
Unchanged	40% (n = 24)	40% (n = 24)		
Improved	5% (n = 3)	7% (n = 4)		
<b>Demotivation</b>			Wilcoxon signed rank test	0.505
Worsened	35% (n = 21)	30% (n = 18)		
Unchanged	55% (n = 33)	57% (n = 34)		
Improved	10% (n = 6)	14% (n = 8)		
<b>Pain</b>			Wilcoxon signed rank test	0.599
Worsened	38% (n = 23)	42% (n = 25)		
Unchanged	53% (n = 32)	42% (n = 25)		
Improved	8% (n = 5)	16% (n = 10)		
<b>Quality of Sleep</b>			Wilcoxon signed rank test	0.62
Worsened	32% (n = 19)	43% (n = 26)		
Unchanged	62% (n = 37)	43% (n = 26)		
Improved	7% (n = 4)	14% (n = 8)		
<b>Global Health Status</b>			Wilcoxon signed rank test	0.646
Worsened	35% (n = 21)	33% (n = 20)		
Unchanged	57% (n = 34)	55% (n = 33)		
Improved	8% (n = 5)	12% (n = 7)		

Section C: Logistic regression models with changes of Motor Symptoms Severity

Table 1 (continued)

	FMD at T0	FMD at T1	Test	p-value
	Univariable Odds ratio	p-value	Multivariable Odds ratio	p-value
Adherence to rehabilitation	1.2 [0.20–7.3]	0.84	2.96 [0.33–23.3]	0.33
Anxiety (changes)	1.46 [0.33–6.54]	0.62	0.68 [0.02–19.8]	0.82
Depression (changes)	1.97 [0.49–8]	0.34	0.65 [0.01–28.2]	0.82
Physical Fatigue (changes)	2.57 [0.66–9.95]	0.17	0.29 [0.02–4.51]	0.38
Mental Fatigue (changes)	2.54 [0.61–10.6]	0.2	3.32 [0.28–39.9]	0.34
Pain (changes)	7.2 [1.72–30.1]	0.007 **	11.69 [1.09–125]	0.042 *

**Legend:** FMD, Functional Movement Disorders. **Section A:** clinical variables in FMD of MS, NMS, and GHS at T0 and T1. **Section B:** perceived changes in MS, NMS, and GHS at T0 and T1. **Section C:** Regression analyses between changes in Non-Motor Symptoms in FMD and the Severity of Motor Symptoms changes with composite variable T1-T0. Column “Univariable” represents the weight of one single Non-Motor Symptom Changes variable on the Severity of Motor Symptom Changes (i.e., the worsening of pain has a 7.2 risk factor of worsening the severity of Motor Symptoms during lockdown). Column “Multivariable” represents odds ratio of all Non-Motor Symptoms changes on the Severity of Motor Symptoms changes. Pain is the only variable that represents a significant risk factor in increasing the Severity of Motor Symptoms in relation to all others. All variables were classified as 0 or 1 (0 = unchanged, improved; 1 = worsened).

stable in comparison to T1 (reported worsened and unchanged in an equal number of patients, 42%). Contrary to the prevailing view that this pandemic exacerbated FMDs and led to an increased incidence [5,6], our patients with an established diagnosis of FMD reported a stable disease throughout the pandemic. This contrasts with the consistent negative impact on clinical status and the overall well-being of patients with other pre-existing movement disorders, such as Parkinson’s disease [11], further highlighting the uniqueness of FMD pathophysiology and possibly implying a different role of stress in the natural history of this disorder. Importantly, in the framework of the biopsychosocial model, a diverted self-focused attention/monitoring toward the stressful global pandemic might have distracted patients and favored stability of symptoms [8].

Multivariable model has also shown that the proportion of FMD patients who exhibited MS worsening, might have resented from an increased burden of pain and fatigue [8], thus underlining the importance of these NMS in FMDs and their role in exacerbating motor performance. Pain and fatigue are known to be frequent and highly disabling in FMDs [2,12]. These NMS are usually linked to affective and psychological aspects, and could represent the truly profound stress somatization related to pandemic.

Limitations of this study include an inevitable recall bias and self-reported measures. Moreover, we could not retrieve data from 13 patients, losing sample power. Notably, main demographics and clinical characteristics of patients did not significantly differ at the two time-points, except for a longer disease duration at T1 (data not shown, but available on request). Notwithstanding such limitations, we found that patients with FMDs did not show an increase vulnerability at follow-up due to recurrent social restrictions’ periods. To note, an interesting relationship emerged between fatigue and pain and MS, that could shed a light on the understanding of this disorder and better implement intervention programs.

CRedit authorship contribution statement

Angela Sandri: Methodology, Investigation, Data curation, Writing – original draft. Ilaria A. Di Vico: Conceptualization, Methodology,

Investigation, Data curation, Writing – original draft. **Marianna Riello:** Methodology, Investigation, Data curation, Writing – review & editing. **Angela Marotta:** Conceptualization, Methodology, Writing – review & editing. **Michele Tinazzi:** Conceptualization, Supervision, Methodology, Writing – review & editing.

#### Declarations of interest

None.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.prdoa.2022.100139>.

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