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Neurophysiological Profile, Walking Performance Tests and Self-Reported Questionnaires in Spastic Patients with MS: A Pilot Study

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Abstract

Nabiximols is currently being used as an add-on therapeutic option to treat severe forms of multiple sclerosis (MS) spasticity, especially in the progressive phase of the disease.

The aim of this exploratory study is to evaluate the response to Nabiximols therapy and modifications in neurophysiological profile, improvement in walking performance tests and self-reported questionnaires, as possible further outcome measures of spasticity.

8 MS patients were recruited to start Nabiximols therapy, all responders in terms of significant reduction of numerical rating scale (NRS). The patients underwent measurements of lower limbs H-reflex and F wave before treatment (baseline) and after 4 and 8 weeks (T1 and T2) of treatment with Nabiximols titrated to optimal dosage, along with timed 25-foot walk test (T25FW), six-minute walk test (6MWT) and questionnaires evaluating subjectively reported spasticity, fatigue and walking abilities (MSSS-88, MFIS, MSWS-12).

A reduction of the latencies of the H-reflex and F wave was found between baseline and at T1, which was more strongly confirmed at T2 ($P=0.04$ relative to H-reflex; $P=0.05$ and $P=0.007$ relative to minimal and medium F wave latencies). A significant reduction in time to perform T25FW test was observed between baseline and after treatment ($P<0.05$), together with a trend towards an improvement in the 6MWT. After the treatment period significant variations in part of the self-reported questionnaires administered were found, as a reduction of the MSSS-88 and MFIS total scores ($P<0.05$).

Nabiximols treatment might have an impact in different objective measurements, including neurophysiological and walking performance tests and self-reported questionnaires. Latencies reduction in H-reflex and F-wave may reflect modifications in the generation of spasticity mechanisms. Moreover, spasticity control is related with an improvement in quality of life of MS patients as it may have a positive impact on walking abilities and reduction of global perception of fatigue.

Keywords: Multiple sclerosis; Nabiximols; H reflex; F wave; T25FW; MSSS-88; MFIS

Introduction

Spasticity is a severe disabling symptom in patients diagnosed with multiple sclerosis (MS), affecting 40–80% of them, with increasing prevalence and severity as the disease progresses [1]. Spasticity is typically defined as a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from the hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome [2].

The most disturbing characteristic of spasticity likely derives from the permanent and paroxysmal accompanying symptoms. Stiffness and spasms are classified as "positive" symptoms, directly depending from abnormal exaggerated reflex responses. In contrast, muscle weakness and fatigue are seen as the "negative" ones, which widely contribute to the resulting functional loss. The combination of the two aspects is a complex phenomenon, which is difficult to treat by means of therapy and with consequences leading to secondary complications, such as contractures and pain [3]. In light of this evidence, the SPASM consortium (Support Programme for the Assembly of database for Spasticity Measurement) recently extended the definition of spasticity: "Disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" [4].

The pathophysiological mechanisms underlying spasticity in MS are complex and they all contribute to the resulting diversity of symptoms previously described. The accumulation of demyelinating plaques in the central nervous system involves cortical areas connected with maintenance of tone (such as premotor and motor areas; [5]) and different projections to spinal motoneurons, such as corticoreticulospinal fibers [6], with a consequent abnormal descending input. The pathological process is extended to spinal cord circuits, with a deregulation in segmental projections and interneuronal connections, such as reciprocal presynaptic, postsynaptic and recurrent inhibition [7]. The result is a modification of membrane properties of the alpha-motoneuron and consequent changes in the threshold of activation, which eventually contribute to the genesis of abnormal muscle activity.

The degree of spasticity is usually measured via clinical evaluation, assessing the resistance to passive muscle stretch or depending on the purpose and the availability, using neurophysiological tests, biomechanical measures and functional outcome scales.

In clinical practice, the most widely used method is the assessment of stiffness after manual perturbation of the observer, using rating

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scales such as the Modified Ashworth Scale (MAS), grading from 0 to 4 the increasing spastic tone in each limb. Other similar scales are the (modified) Tardieu scale [8] or the Priebe and Penn Scale [9]. However, inter-observer variability and fluctuation of the mechanical properties of the musculoskeletal structures have raised concerns about reliability of the clinical measures [10]. Biomechanical measures are indirect methods, not routinely used in clinical practice, which quantify different features of spasticity such as stiffness, posture at rest and range of movement during a controlled monitored or manual perturbation [11]. Conversely, clinical neurophysiology provide direct measures of the components of the neural stretch reflex; theoretically reflecting altered spinal mechanisms involved in the generation of motoneuronal hyperexcitability in spastic patients. Among them, short-latency stretch reflex measurements (such as H-reflex, F-wave, Stretch reflex and T-reflex studies) have been already investigated extensively by Voerman et al. [7], showing a potential to contribute in the assessment of spasticity.

Another promising tool to monitor patients in clinical practice is performing tests to assess ambulation, considering that patients are slowing the walking pattern according to the severity of spasticity affecting the lower limbs. For instance, leg spasticity, as reported with clinical and self-reported scales, has already been associated with worse walking performance [12]; however these tests are not currently used in clinical practice to evaluate antispastic treatment response.

Finally, there is growing interest on self-reported questionnaires, assessing the impact of peculiar dimensions of disease, such as fatigue and perceived quality of walking in MS patients. Similarly to walking performance tests, questionnaires assessing everyday ambulation have already been correlated to spasticity clinical scales [12]. In addition, dedicated batteries have been developed to investigate specific areas with the intention to quantify quality of life of MS patients, including dedicated questionnaires to evaluate spasticity.

Regarding therapeutic interventions, the rational is to modulate neurotransmission in the spinal and supraspinal mechanisms, using centrally or peripherally acting oral muscle relaxants (baclofen, gabapentin, tizanidine, benzodiazepines and dantrolene). If not satisfactory they should be supported as described by Otero-Romero et al. [13], adding cannabis-based drugs, peripherally acting injected muscle relaxants (botulinum toxin, local phenol injections) or intrathecal therapies (baclofen or phenol), together with a complete rehabilitation program providing continuous physical therapy.

Nabiximols, an oromucosal combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), has been recently approved as a second-line therapy for spasticity treatment in MS patients who have not responded adequately to other antispastic medications. The drug efficacy, evaluated by the subjective measurement validated 11-point Numeric Rating Scale (NRS), was demonstrated in phase III trials by Novotna et al. [14] and confirmed in subsequent observational studies [15,16].

The aim of this pilot study was to describe modifications in neurophysiological tests, walking performance parameters, self-reported questionnaires and spasticity reduction in a cohort of MS patients successfully treated with Nabiximols.

Materials and Methods

Evaluation of patients at the MS Centre of the Fondazione Ca' Granda, IRCCS Ospedale Policlinico, University of Milan, Italy was carried out to select candidates for Nabiximols therapy within one year period, over a global population of around 300 patients. The spasticity-dedicated outpatient facility follows up about 50 patients with MS, especially in the progressive phase of the disease and nearly 60% suffer from spasticity.

Inclusion criteria for the present study were the following: indication of the Italian pharmaceutical regulatory agency to start a second-line antispastic treatment because of sustained spasticity not responding to common oral antispastic treatment (oral baclofen, tizanidine, eperisone, benzodiazepines or gabapentin titrated to maximum dosage) and exclusion of previous psychiatric comorbidities. In addition, only responders to Nabiximols, in terms of a reduction of more than 20% of NRS scale, and only walking patients (EDSS at least less than 7) were recruited.

Eight patients were recruited (5 males and 3 females), with the following characteristics (mean ± SD): Age 50.3 ± 9.2 years; Disease duration 11.8 ± 4.5 years; EDSS 5 ± 1.4; Ambulation index 3 ± 0.9; 4 patients affected by secondary progressive MS, 2 patients from relapsing-remitting MS and 2 patients by primary progressive MS (Table 1). They all were responders to Nabiximols therapy after 4 weeks (mean reduction in NRS 40%; P=0.025, Figure 1) and a significant reduction in the Modified Ashworth Scale was reported (mean reduction 44% in MAS, considering the more affected limb; P=0.0001; Figure 1). Patients enrolled in the study provided informed consent to participate in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with standards of Good Clinical Practice, as described in the ICH Guidelines for Good Clinical Practice, 1996.

The cohort underwent the following neurophysiological tests before and after four weeks trial of Nabiximols therapy (T1): H-reflex, obtained by electrical stimulation of the posterior tibial nerve at the popliteal fossa and recorded from soleus muscle (stimulus duration 1 ms, frequency 0.5 Hz and intensity individually adjusted to obtain maximal responses); F wave study, obtained by 20 consecutive supramaximal stimuli of the posterior tibial nerve at the internal malleolus and recorded at abduttor hallucis (stimulus duration 0,1 ms, frequency 1 Hz and intensity equal to the basal threshold plus 20%). The tests were repeated after eight weeks (T2) of on-going cannabinoid therapy.

Hoffmann reflex (H reflex) has been selected because of its predominantly monosynaptic character, the quite relative stability of the measures (with standardized electrodes location, stimulus duration and frequency) and the monosynaptic nature, with perturbations reflecting modifications occurring directly in the excitability of the motoneurons of the reflex arc. F-wave was selected because previously studied as marker of spasticity by Argyriou et al. [17] and in the present cohort it was registered exclusively at lower limbs in reason of the prevalent spasticity affecting this area in the present cohort.

Timed 25-foot walk (T25FW) and six-minute walk test (6MWT) were similarly performed at baseline, after 4 weeks of therapy (T1) and after 8 weeks (T2), along with multiple sclerosis spasticity scale (MSSS-88), modified fatigue impact score (MFIS) and 12-item MS walking scale (MSWS-12). Walking tests were selected because of the current use in evaluation of MS disability and the questionnaires on the basis of their previous utilization in clinical trials for other symptomatic therapies for MS [2].

Statistical analysis was based on Friedman test with Dunn's post hoc test for the comparison between non parametric distribution of clinical data with regards to walking performance tests and self-reported questionnaires, while RM one way ANOVA (corrected by Dunnett's

Table 1: Clinical and demographic data.

Patient	Age (y)	Gender	Duration of disease (y)	Form of disease	EDSS	Ambulation Index	Puff (n°)	NRS before Sativex	NRS after Sativex	Symptomatic treatment	Disease modifying drugs
1	48	M	15	SP	6.5	4	6	5	3	BAC, 4AM	FTY
2	38	M	18	SP	5.5	3	6	7	5	BAC, 4AM, GAB	FTY
3	45	M	7	SP	6.5	4	6	5	5	BAC, CBZ	IFN
4	45	F	10	RR	2.5	2	5	8	5	BAC, GAB	FTY
5	45	M	14	PP	5	2	8	9	6	BAC, GAB	/
6	64	F	15	RR	4	2	6	7	5	BAC, 4AM	IFN
7	55	F	10	SP	6	3	6	8	2	BAC	IFN
8	62	M	5	PP	4	4	3	7	3	BAC	/

RR: Relapsing-Remitting; SP: Secondary Progressive; PP: Primary Progressive Sympotmatic Treatment; BAC: Baclofen; 4-AM: 4-Aminopiridine; GAB: Gabapentin; CBZ: Carbamazepine Disease Modifying Therapy; FTY: Fingolimod; IFN: Interferon

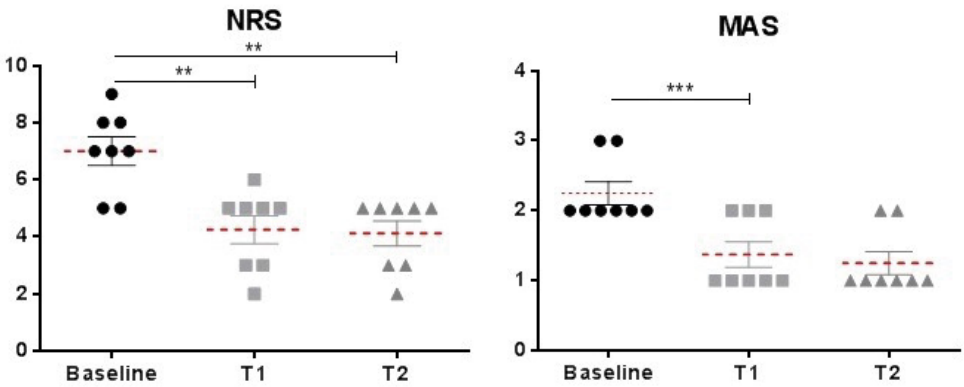


Figure 1: Spasticity scales. Mean numeric rating scale (NRS) at baseline: 7 ± 1.4; at T1: 4.3 ± 1.4 and at T2: 4.1 ± 1.2; **P=0.025. Mean Modified Ashworth Scale (MAS), considering the more affected leg, at baseline: 2.25 ± 0.46; at T1: 1.38 ± 0.52; at T2: 1.25 ± 0.46; ***P=0.0001

post-hoc test) was used for the analysis of parametric distribution of clinical and neurophysiological parameters.

Results

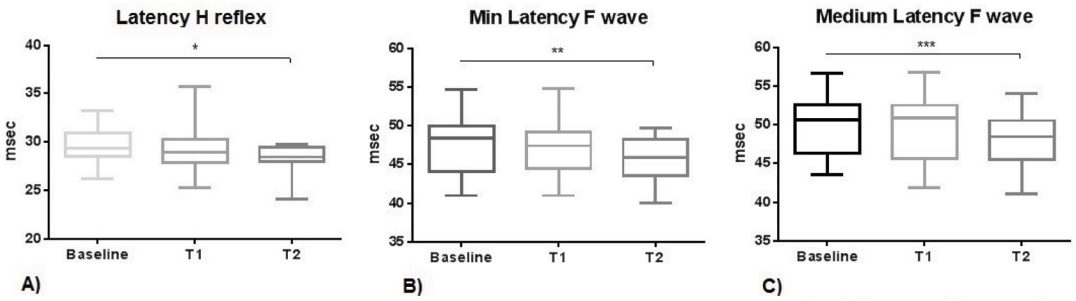
Over 8 weeks follow-up, Nabiximols therapy induced modifications in nearly all the parameters evaluated in the present study. Concerning neurophysiological tests, a reduction of the latencies for both H-reflex (relative reduction 4.4%; P=0.04) and F wave (relative reduction of 3.5% for the minimal latency, P=0.005; relative reduction of 4% for the medium latency, P=0.007) was reported, more evident and significant at T2 (Figure 2). A trend in reduction of H/M ratio was observed, however it was not significant (0.28 ± 0.18 at baseline; 0.23 ± 0.12 at T1; 0.25 ± 0.16 at T2; P>0.05). Considering walking performance tests, we found 21.2% relative reduction of time to perform T25FW at follow-up (mean T25FW at baseline was 12 ± 5.9 s; mean T25FW at T1 was 9.9 ± 4.5 s; mean T25FW at T2 was 9.5 ± 4.2; P<0.05 Figure 3). Better results in 6MWT, with 11.2% relative improvement in distance were found, even though the threshold for statistical significance was not reached (mean 6MWT at baseline was 234 ± 94 mt; at T1 was 284 ± 129 mt; at T2 was 260 ± 86 mt; P>0.05).

Lastly, regarding self-reported questionnaires significant variations were observed in the present cohort before and after Nabiximols treatment in the MSSS-88 total score (mean MSSS-88 score at baseline was 207.1 ± 41.6, at T1 was 174.5 ± 30.6 and at T2 was 177 ± 55.3; P <0.05; Figure 4) and in the MFIS total score comparing the baseline and T2 values (mean MFIS at baseline was 40.7 ± 13.8 and at T2 was 28.5 ± 13.5; P<0.05; Figure 4). There were no differences in the described results between patients treated or not treated with disease modifying drugs.

Discussion

Data showed in this pilot study demonstrate decreased latencies in H-reflexes and F-waves over 8-week efficacious treatment with Nabiximols in 8 MS patients affected by severe spasticity of the lower limbs. Latency of the H-reflex is the time between given electrical stimulus and first deflection in the recorded signal, basically a sum of conduction times between the afferent (1a sensory fibers of the muscle spindle), efferent impulses (α-motoneuron of the corresponding motor unit) in the monosynaptic reflex arc and the synaptic transmission time. In previous reports, a decreased H-reflex latency has been found in spastic patients compared to control subjects, and in this case it was interpreted as a higher excitability and consequently a reduced threshold [18]. Considering other parameters, it is to mention that the amplitude of the H-reflex and the ratio between maximal H-wave and M-wave (H_{max}/M_{max} ratio) are usually significantly increased in spastic patients [7,19].

F-wave is a compound action potential reflecting the activation of a proportion of the anterior horn cells' axons after antidromic stimulation. In MS patients, an increase in amplitude of the F-wave was found in correlation with the degree of spasticity and the duration of the disease, making it feasible as possible surrogate marker of spasticity [17]. We hypothesize that fluctuations observed in neurophysiological parameters, such as latency, after Nabiximols treatment, might reflect the reduction of the global excitability level of the α-motoneuron pool. Modifications in neurophysiological parameters (mainly regarding H reflex) have been described indeed to occur constantly in spastic patients treated with specific medications, such as after baclofen treatment [20].



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	Parameter	Baseline	T1	T2	*P* (Baseline vs T1)	*P* (Baseline vs T2)
H reflex	threshold, mA (± SD)	11.4 ± 5.2	10.4 ± 6.6	10.8 ± 6.8	> 0.05	> 0.05
	latency, ms (± SD)	29.6 ± 1.8	29.3 ± 2.7	28.3 ± 1.5	> 0.05	**0.04***
	amplitude, mV (± SD)	4.1 ± 3.2	3.6 ± 3.0	3.8 ± 3.4	> 0.05	> 0.05
	H / M amplitude ratio (± SD)	0.28 ± 0.18	0.23 ± 0.12	0.25 ± 0.16	> 0.05	> 0.05
F wave	threshold, mA (± SD)	29.7 ± 20.0	30.7 ± 25.5	22.3 ± 10.4	> 0.05	> 0.05
	min. latency, ms (± SD)	47.2 ± 4.0	46.9 ± 3.7	45.6 ± 2.9	> 0.05	**0.05****
	med. latency, ms (± SD)	49.9 ± 4.1	49.3 ± 4.2	47.9 ± 3.6	> 0.05	**0.007*****
	chronodispersion, ms (± SD)	4.3 ± 2.1	4.7 ± 2.2	4.3 ± 2.0	> 0.05	> 0.05
	amplitude, mV (± SD)	0.72 ± 1.36	0.26 ± 0.11	0.35 ± 0.22	> 0.05	> 0.05

Figure 2: Neurophysiological measurements.
A) Mean latency of the H reflex at baseline, at T1 and at T2
B) Mean minimal latency of the F wave at baseline, at T1 and at T2
C) Mean medium latency of the F wave at baseline, at T1 and at T2
D) Table of all neurophysiological measurements
P by RM one way ANOVA; Post-hoc test: Dunn's test

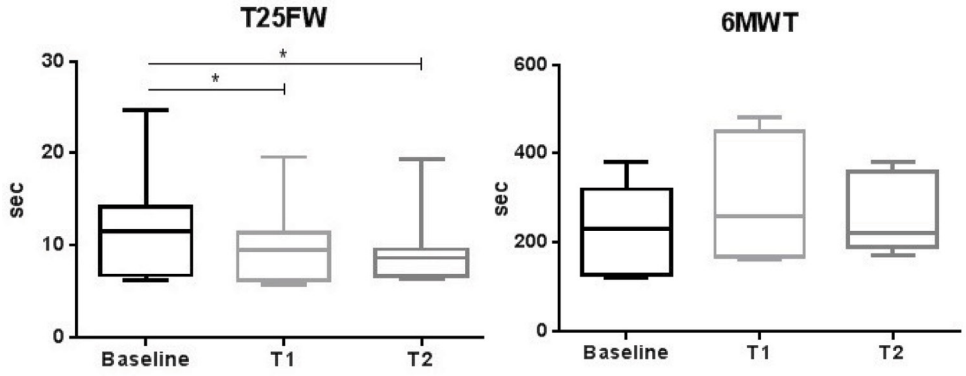

Figure 3: Walking performance tests.
Mean timed 25-foot walk (T25FW) at baseline: 12 ± 5.9 s; at T1: 9.9 ± 4.5 s; at T2: 9.5 ± 4.2 s; *P<0.05
Mean six-minute walk test (6MWT) at baseline: 234 ± 94 mt; at T1: 284 ± 129 mt; at T2: 260 ± 86 mt

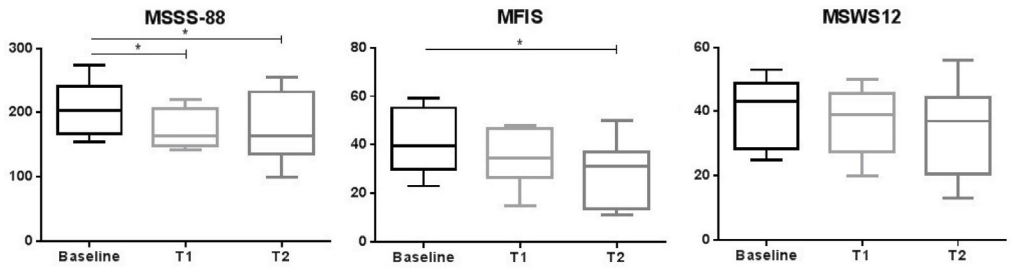

Figure 4: Self-reported questionnaires.
Mean score of the 88-item Multiple Sclerosis Spasticity Scale (MSSS-88) at baseline, T1 and T2, respectively: 207 ± 42; 175 ± 31; 177 ± 55; *P<0.05
Mean score of the Modified Fatigue Impact Scale (MFIS) at baseline and T2, respectively: 41 ± 14; 29 ± 14; *P<0.05
Mean score of the 12-item Multiple sclerosis walking scale (MSWS-12) at baseline, T1 and T2, respectively: 41 ± 10; 37 ± 10; 34 ± 14

The observed modifications may be secondary to modulation of transmission in the pathways involved in spasticity generation, especially at the synaptic level, considering the effects of CB1 receptors activation in retrograde synaptic functions. Descriptions of the effects on excitatory and inhibitory neurotransmitters, such as glutamate and GABA, after the use of cannabinoids have been made on animal models [21,22]. In addition, cannabinoid receptors stimulation, especially the effects on CB1, could contribute to the amelioration of the alterations in spinal circuitry by reducing glutamatergic drive [23]. The fact that in our cohort there is a reduction of the latencies after treatment could signify that cannabinoids contributed to a modification in the spinal mechanism favouring a facilitation of the connections, by increasing synaptic plasticity or reducing intrinsic mechanisms of inhibition.

Neurophysiological tests though could be used as a tool for measuring the degree of spasticity, although correlation between the modifications in these tests and the clinical response to cannabinoids remains controversial [24,25]. Moreover, walking parameters improvement could be related to spasticity reduction since the effect of symptomatic therapies has been previously correlated with the improvement in walking-based measures [26], suggesting that they can be useful as markers of treatment response even for Nabiximols treatment. Finally, self-reported questionnaires, especially MSSS-88 developed with the aim of evaluating spasticity, were useful to assess response to Nabiximols treatment, confirming that the subjective measure is a reliable way of monitoring treatment response to Nabiximols treatment. Unexpectedly, a reduction between baseline and after 8 weeks of Nabiximols treatment of the score in the questionnaire about perceived fatigue (MFIS) was found, thus supporting the notion that spasticity could be associated with a state of reduced energy and a worsened quality of life.

Limitations of the present study are represented by the lack of a control group. Nevertheless, comparing our data with normative values in healthy population [27,28], baseline latency values in H-reflexes and F-waves in our cohort were in the normal range.

We acknowledge that the small size of the cohort studied does not allow generalization of the results proposed and that a confirmatory study in a larger population is needed.

Conclusion

In conclusion, in this pilot study, we describe preliminary data, which suggest that treatment with Nabiximols might have an impact on neurophysiological profile and walking-outcome measures, as well as an improvement in global quality of life of patients. The modifications in latencies of H-reflex and F-wave point out that cannabinoids exert an effect directed to resolution of motoneuronal hyperexcitability typical of spastic patients. Nevertheless, a replication in a larger cohort would be needed to have the power to demonstrate the usefulness of such tools.

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