



## Mild motor signs in major depressive disorder: prevalence and clinical profile

Antonina Luca<sup>a,\*,\*</sup>, Alessandro Serretti<sup>a,b</sup>, Stefano Barlati<sup>c,d</sup>, Lisa Buson<sup>e</sup>,  
Valentina Menesello<sup>e,f</sup>, Anna Magistrali<sup>f</sup>, Rosana Carvalho Silva<sup>f</sup>, Giulia Perusi<sup>e</sup>,  
Gabriele Nibbio<sup>d</sup>, Stefano Bignotti<sup>g</sup>, Giovanni Battista Tura<sup>g</sup>, Raffaele Ferri<sup>b</sup>,  
Massimo Gennarelli<sup>e,f</sup>, Antonio Vita<sup>c,d</sup>, Alessandra Minelli<sup>e,f</sup>, PANDORA study group<sup>#</sup>

<sup>a</sup> Department of Medicine and surgery, Kore University of Enna, Italy

<sup>b</sup> Oasi Research Institute-IRCCS, Troina, Italy

<sup>c</sup> Department of Mental Health and Addiction Services, ASST Spedali Civili of Brescia, Brescia, Italy

<sup>d</sup> Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

<sup>e</sup> Genetics Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

<sup>f</sup> Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

<sup>g</sup> Psychiatry Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

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### ABSTRACT

**Background and objectives:** Motor abnormalities are recognized features of major depressive disorder (MDD). However, subtle forms of motor dysfunction are still largely unexamined in adults with MDD. The aims of the present study were to: 1) assess the prevalence of mild motor signs (MMS) in adults with moderate to severe depression, and 2) evaluate whether patients with MMS exhibit specific depressive symptom profiles.

**Methods:** Two-hundred forty-four participants (172 (70.5 %) women, mean age  $46.8 \pm 14.5$ , mean education  $12.5 \pm 3.6$  years) from the PANDORA trial were enrolled. All the participants were assessed using the Hamilton Depression Rating Scale (HAM-D). MMS were assessed using the UKU Side Effects Rating Scale.

**Results:** Out of the 244 participants, 34 (13.9 %) were MMS+: 20 (58.8 %) had myoclonus, 11 (32.3 %) hyperkinesia, 7 (20.6 %) rigidity, 6 (17.6 %) tremor, and 3 (8.8 %) hypokinesia. The percentage of patients reaching a  $\geq 20$  % improvement in the HAM-D total score was higher in the MMS- group than in the MMS+ (95.1 % vs. 75.0 %, respectively). MMS+ participants had higher HAM-D total score and sub-items exploring work and abilities, psychomotor retardation, agitation, and hypochondriasis. These associations between MMS and depression severity, as well as the specific symptomatology profile, were confirmed in the multivariate analysis, adjusted for age and sex.

**Conclusions:** Our findings suggest that MMS may reflect a distinct subgroup within MDD, potentially characterized by greater sensitivity to motor adverse effects and subtle differences in treatment response.

\* Corresponding author at: Department of Medicine and Surgery, Kore University of Enna, Italy.

E-mail address: [antonina.luca@unikore.it](mailto:antonina.luca@unikore.it) (A. Luca).

<sup>§</sup> Address: Contrada Santa Panasia sn, 94100, Enna, Italy

<sup>#</sup> Members of PANDORA Study Group: Alessandra Minelli, Massimo Gennarelli, Valentina Menesello (Genetic Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli of Brescia; Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy); Beatrice Lana, Chiara Galbiati, Edoardo Giacomuzzi, Erika Vitali, Giulia Perusi, Lisa Buson, Monica Scaglia, Vincenzo Dattilo (Genetic Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli of Brescia); Antonio Vita, Stefano Barlati (Department of Mental Health and Addiction Services, ASST Spedali Civili of Brescia; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy); Alessia Muscarella, Antonio Baglioni, Gabriele Nibbio, Irene Calzavara Pinton, Lorenzo Bertoni, Nicola Necchini, Stefano Paolini, Ughetta Bosco Umbertino (Department of Mental Health and Addiction Services, ASST Spedali Civili of Brescia); Anna Magistrali, Chiara Magri, Mattia Meattini, Rosana Carvalho Silva, Paolo Martini (Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy); Chiara Cobelli, Giovanni Battista Tura, Stefano Bignotti (Psychiatry Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy); Edoardo Spina (Clinical and Experimental Medicine, University of Messina, Messina, Italy)

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## Introduction

Major depressive disorder (MDD) affects >300 million people and accounts for a significant proportion of years lived with disability.<sup>1,2</sup>

Although depressed mood and “anhedonia” are the defining symptoms of MDD,<sup>3,4</sup> motor abnormalities have been recognised as an integral part of the depressive phenotype since its initial description.<sup>5</sup> Yet, symptoms such as psychomotor retardation and agitation are so frequent that remain among the cornerstones of current diagnostic criteria.<sup>4,6</sup> However, subtler forms of motor dysfunction, including mild motor signs (MMS), are still largely unexamined in adults with MDD. MMS (i.e. tremor, myoclonus, bradykinesia, and rigidity) belong to the broader category of neurological soft signs. These minor abnormalities of gait, coordination, balance, muscle tone, and/or involuntary movements are not severe enough to constitute a neurological disorder, and are frequently reported in patients with schizophrenia.<sup>7–9</sup>

Data concerning MMS in patients with depression are less robust. However, previous studies reported a prevalence of MMS in up to 10 % of patients with MDD, regardless of exposure to antidepressants or antipsychotics.<sup>10</sup> We previously assessed a large cohort of patients with treatment-resistant depression (TRD), belonging to the cross-sectional European multicenter Group for the Study of Resistant Depression (GSRD) and reported a prevalence of approximately 40 % of MMS, particularly tremor and rigidity. Interestingly, in that cohort, we found a strong association between several MMS (e.g., dystonia, rigidity, and hypokinesia) and lack of response to treatment, regardless of age or medication. This led us to hypothesise that patients with MMS may have a more severe and less responsive depression phenotype.<sup>11</sup> However, given that over 60 % of participants in the previous study had TRD and were exposed not only to antidepressants, but also to benzodiazepines, mood stabilizers and occasionally to neuroleptics, this could have limited the generalizability of our findings.

On this ground, the aims of the present study were to: 1) assess the prevalence of MMS in adults with moderate to severe depression; 2) evaluate if patients with MMS presented a specific depressive symptomatology profile.

## Material and methods

Participants were collected in the context of the PANDORA trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT04615234), a 12-week, double-blinded, observational prospective randomized controlled trial<sup>12</sup> enrolling patients with MDD referring to psychiatric services to receive a new antidepressant due to current treatment failure or adverse effects. The inclusion criteria were: MDD diagnosed according to DSM-5 criteria; moderate to severe MDD (Hamilton Rating Scale for Depression HAM-D 17 score  $\geq 14$ ); age between 18 and 65. The exclusion criteria were: presence of cognitive impairment (Mini Mental State Examination, MMSE < 24); presence of neurological disorders; psychiatric comorbidity (i.e., psychosis, bipolar I and II disorders, schizophrenia spectrum and other psychotic disorders, obsessive-compulsive disorder, post-traumatic stress disorder); comorbidity with personality disorders (cluster A and/or B), pregnancy, and comorbidity with other severe medical illnesses. Demographic (e.g., age, sex, education), clinical (e.g., depression onset, comorbid anxiety), and treatment data were recorded. Drugs prescribed to <10 participants were considered together as “other antidepressants”. Treatment dose fluoxetine equivalence was calculated.<sup>13</sup>

The Italian versions of the clinician version of the Structured Clinical Interview for DSM-5 disorders (SCID-5-CV) and the Structured Clinical Interview for personality disorders (SCID-5-PD) were used to confirm the diagnosis. Depression was assessed using the HAM-D. Moreover, to ensure that the association between MMS status and depressive severity was not influenced by motor-related items, we computed a *modified HAM-D score* by subtracting the Agitation and Psychomotor Retardation items from the total HAM-D score.

The presence of MMS was assessed with the UKU Side Effects Rating Scale,<sup>14</sup> performed by trained raters at study initiation and at follow-up visits (after 4 weeks, 8 weeks and 12 weeks). Participants with at least one motor sign (i.e., tremor, bradykinesia, hyperkinesia, rigidity, and myoclonus) recorded at any study visit were considered MMS+. Participants without any symptoms of MMS at any study visit were considered MMS-.

Response was defined as  $a \geq 50$  % decrease in HAM-D score at week 12 compared with baseline. Remission was defined as a HAM-D score  $\leq 7$ . In order to capture also mild symptom changes, also  $a \geq 20$  % reduction in the HAM-D total score at 12 weeks was considered.

The study was approved by the Local Ethics Committees (CEIOC IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia N: 43/2018, and Ethics Committee of ASST Spedali Civili of Brescia N: NP 3347) and was performed in accordance with the principles of the Declaration of Helsinki. All patients signed a written informed consent to participate before being enrolled.

The PANDORA trial aimed at carrying out a clinical validation of a combinatorial pharmacogenomics test in patients with MDD. The present study is a secondary analysis exploring a specific symptomatology profile in patients with MDD and MMS.

## Statistical analysis

T-tests and chi-square tests were used to compare continuous and categorical variables, respectively. Each item of the baseline HAM-D, as well as the total score, and the modified HAM-D, were considered for possible associations with MMS. Then, a multivariate analysis was performed, considering MMS as outcome variable, HAM-D items as independent variables (ordinal logistic regression), and age, sex and fluoxetine dose equivalent as potential a priori confounders.

In the PANDORA study,<sup>12</sup> the enrolled patients were not drug-naïve at baseline, as they were already being treated with other antidepressants (which had been substituted due to failure or side effects). Therefore, a statistical analysis to assess the effect of individual molecules on motor signs was not performed, as the effect of the previously taken antidepressant on MMS could not be ruled out. Odds ratio (OR) and 95 % confidence intervals were also reported. Given the confirmatory nature of the study, an alpha level of 0.05 was used.<sup>15</sup> Data were analyzed with STATA v.18 (StataCorp., 2023).

## Results

Two-hundred forty-four participants (172 (70.5 %) women, mean age  $46.8 \pm 14.5$ , mean education  $12.5 \pm 3.6$  years) were enrolled. All patients were treated with antidepressants in monotherapy; Duloxetine, Sertraline, and Venlafaxine were the most frequently prescribed (Table 1). Out of the 244 participants, 34 (13.9 %) were MMS-: 17 (6.9 %) were MMS+ at baseline and 17 (6.9 %) developed MMS during the follow-up visits. Out of the 34 participants MMS+, 20 (58.8 %) had myoclonus, 11 (32.3 %) hyperkinesia, 7 (20.6 %) rigidity, 6 (17.6 %) tremor, and 3 (8.8 %) hypokinesia.

No differences in terms of sex and age were found between MMS+ and MMS- (Table 2). No differences in terms of response or remission prevalence were found between the two groups. However, at week 12, the percentage of patients reaching  $a \geq 20$  % improvement at the HAM-D total score was higher in the MMS- (95.1 %) than in MMS+ (75.0 %). MMS+ participants had higher scores on the HAM-D total score and HAM-D sub-items exploring work and abilities, psychomotor retardation, agitation, and hypochondriasis. In the multivariate analysis, the association between MMS+ and HAM-D total score and each sub-item was confirmed after adjusting for age and sex (Table 3). Modified HAM-D scores, obtained by subtracting the Agitation and Psychomotor Retardation items, remained significantly higher in MMS+ than in MMS- participants ( $p < 0.001$ ), indicating that the association between MMS and depressive severity was not solely driven by motor-related

**Table 1**  
Demographic and clinical characteristics of the sample.

Total sample (n = 244)	
Age at first depressive episode	31.5 ± 14.7
Time since first depressive episode, years	15.7 ± 13.7
Participants with recurrent depression	200 (81.9)
Comorbid anxiety	74 (30.3)
Smoking	76 (31.1)
Suicide attempt in the current depressive episode	26 (10.7)
BMI	25.2 ± 5.4
<b>Current antidepressants</b>	
Duloxetine	51 (20.9)
Sertraline	46 (18.8)
Venlafaxine	37 (15.2)
Escitalopram	25 (10.2)
Vortioxetine	17 (6.9)
Paroxetine	17 (6.9)
Fluoxetine	16 (6.6)
Other antidepressants	35 (14.3)
Fluoxetine dose equivalent	26.4 ± 11.5
HAM-D total score (baseline)	17.8 ± 3.7
HAM-D Depressed mood	2.6 ± 0.6
HAM-D Fell of guilty	1.6 ± 0.7
HAM-D Suicide	0.8 ± 0.9
HAM-D Initial Insomnia	0.7 ± 0.7
HAM-D Middle Insomnia	0.8 ± 0.7
HAM-D Late Insomnia	0.7 ± 0.7
HAM-D Work and activities	2.1 ± 1.1
HAM-D Psychomotor retardation	0.8 ± 0.7
HAM-D Agitation	0.4 ± 0.5
HAM-D Psychic anxiety	2.1 ± 0.9
HAM-D Somatic anxiety	1.5 ± 0.9
HAM-D Gastrointestinal symptoms	0.5 ± 0.5
HAM-D General somatic symptoms	0.8 ± 0.4
HAM-D Genital symptoms	1.3 ± 0.8
HAM-D Hypochondriasis	0.9 ± 0.9
HAM-D Weight loss	0.2 ± 0.5
HAM-D Insight	0.1 ± 0.2
HAM-D improvement ≥ 20 % (obs=215)	198 (92.1)
Response (obs=215)	140 (65.1)
Remission (obs=215)	114 (53.0)

**Legend:** data are expressed as number and percentage and mean and standard deviation. Abbreviation: HAM-D: Hamilton Rating Scale for Depression; obs=observations. It indicates the number of patients with available (non-missing) data for that variable.

items.

## Discussion

Within the PANDORA sample, MMS represent a hybrid construct that cannot be clearly disentangled as either ‘intrinsic’ motor manifestations of depression or purely treatment-emergent side effects. Nevertheless, they appear to identify a clinically relevant subgroup of patients characterized by greater depressive burden and only modest early symptomatic improvement. In the present study, MMS were present in >13 % of patients with MDD, with myoclonus, hyperkinesia, and rigidity being the most frequent. These findings are in line with some previous studies conducted on small samples of patients with MDD.<sup>10,16</sup> As expected, however, the prevalence of MMD in this study was lower than that reported in the GSRD cohort, which primarily included participants with more severe symptoms, including treatment-resistant depression.<sup>11</sup>

Notably, earlier studies found MMS more frequently in older male patients with more severe depression and cognitive impairment,<sup>11,16</sup> supporting the existence of a specific depression phenotype in patients presenting motor signs.

On the contrary, the present study found no age differences between MMS+ and MMS- group. Indeed, although previous studies have linked MMS in depressed individuals to age-related changes in neurotransmitters and fronto-striatal circuits,<sup>17,18</sup> it should be noted that the PANDORA study participants were under 65 years old and therefore probably less at risk of age-related MMS.

**Table 2**  
Demographic and clinical characteristics of participants with and without motor signs.

Total of patients (n = 244)	MMS- (n = 210)	MMS+ (n = 34)	p-value
<b>Sex, women</b>	147 (70.0)	25 (73.5)	0.675
<b>Age, years</b>	46.5 ± 14.7	48.7 ± 13.3	0.410
<b>Education, years</b>	12.5 ± 3.7	12.4 ± 2.5	0.952
<b>Time since first depressive episode, years</b>	15.8 ± 13.8	15.2 ± 13.2	0.827
<b>Participants with recurrent depression</b>	171 (81.4)	29 (85.3)	0.587
<b>Comorbid anxiety</b>	68 (32.4)	6 (17.6)	0.083
<b>Smoking</b>	64 (30.5)	12 (35.3)	0.574
<b>Suicide attempt in the current depressive episode</b>	23 (10.9)	3 (8.8)	0.709
<b>BMI</b>	25.3 ± 5.5	24.1 ± 4.8	0.224
<b>Fluoxetine dose equivalent</b>	26.7 ± 12.1	24.4 ± 6.2	0.265
<b>HAM-D total score (baseline)</b>	17.4 ± 3.3	20.7 ± 4.6	<0.001
HAM-D Depressed mood	2.6 ± 0.7	2.8 ± 0.5	0.111
HAM-D Fell of guilty	1.6 ± 0.7	1.8 ± 0.6	0.102
HAM-D Suicide	0.8 ± 0.9	0.7 ± 0.9	0.815
HAM-D Initial Insomnia	0.7 ± 0.7	0.9 ± 0.8	0.189
HAM-D Middle Insomnia	0.8 ± 0.7	0.9 ± 0.8	0.191
HAM-D Late Insomnia	0.7 ± 0.7	0.9 ± 0.8	0.121
HAM-D Work and activities	2.1 ± 1.1	2.5 ± 0.9	<b>0.037</b>
HAM-D Psychomotor retardation	0.7 ± 0.7	1.3 ± 0.8	<0.001
HAM-D Agitation	0.4 ± 0.5	0.7 ± 0.5	<b>0.001</b>
HAM-D Psychic anxiety	2.0 ± 0.8	2.1 ± 0.8	0.851
HAM-D Somatic anxiety	1.4 ± 0.9	1.7 ± 0.8	0.093
HAM-D Gastrointestinal symptoms	0.5 ± 0.5	0.5 ± 0.5	0.876
HAM-D General somatic symptoms	0.8 ± 0.4	0.8 ± 0.4	0.459
HAM-D Genital symptoms	1.2 ± 0.8	1.4 ± 0.7	0.181
HAM-D Hypochondriasis	0.8 ± 0.9	1.4 ± 1.0	<b>0.003</b>
HAM-D Weight loss	1.2 ± 0.5	1.1 ± 0.4	0.395
HAM-D Insight	0.1 ± 0.1	0.1 ± 0.3	0.320
<b>Modified HAM-D</b>	16.3 ± 3.2	18.7 ± 4.1	<0.001
<b>HAM-D improvement ≥ 20 % (obs=215)</b>	174 (95.1)	24 (75.0)	<0.001
<b>Response (obs=215)</b>	118 (65.5)	22 (68.7)	0.640
<b>Remission (obs=215)</b>	99 (54.1)	15 (48.9)	0.450

**Legend:** data are expressed as number and percentage and mean and standard deviation. Abbreviation: HAM-D= Hamilton Rating Scale for Depression; obs=observations. It indicates the number of patients with available (non-missing) data for that variable.

**Table 3**  
Depression characteristics of participants with and without motor signs: multi-variate analysis.

Variables	OR	95 %CI	p-value
<b>HAM-D total score (baseline)</b>	1.2	1.12–1.35	<0.001
HAM-D Work and activities	1.5	1.02–2.12	<b>0.038</b>
HAM-D Psychomotor retardation	2.9	1.76–4.83	<0.001
HAM-D Agitation	2.7	1.44–4.93	<b>0.002</b>
HAM-D Hypochondriasis	1.7	1.15–2.42	<b>0.007</b>

**Legend:** data are expressed as number and percentage and mean and standard deviation. Abbreviation: HAM-D= Hamilton Rating Scale for Depression; obs= observations; OR= Odd ratio; CI= confidence intervals. All models were adjusted for age, sex, and fluoxetine dose equivalent; fluoxetine-equivalent dose was not significantly associated with MMS status.

Although the presence of MMS was not significantly associated with treatment response or remission, a significantly larger proportion of MMS+ patients showed at least a 20 % reduction in HAM-D scores (95.1 %) compared to those MMS+ (75.0 %). This pattern may indicate that depression in patients MMS+ may have a different clinical phenotype. Indeed, patients with MMS not only had more severe depression, as reflected by the total score on the HAM-D, but also had higher scores on some specific sub-items, including difficulties in work and abilities, psychomotor retardation and agitation. This finding is particularly interesting considering that the higher HAM-D total score observed in

MMS+ patients were mainly due to the sub-items “agitation” and “psychomotor retardation”, which might not reflect more severe depression but rather be manifestations of MMS itself.

The difficulties experienced at work and in everyday activities are no less important. Previous epidemiological studies have reported that >70 % of individuals with depression continued working despite experiencing cognitive impairment associated with depression, such as indecisiveness, difficulty concentrating, and impaired problem solving.<sup>19–21</sup>

In this context, the presence of motor signs may further limit work functioning in individuals with depression.<sup>22</sup> Subtle bradykinesia, tremor, or impaired fine-motor coordination could slow typing speed, hinder handwriting, and reduce overall psychomotor efficiency. Crucially, occupational functioning is a key determinant of quality of life, financial independence, and social integration; persistent under-performance or absenteeism can trigger a vicious cycle of job insecurity, self-stigma, and further mood deterioration. Recognizing and treating MMS may thus have direct economic and psychosocial benefits, helping individuals maintain productivity.<sup>23</sup>

The study has some limitations. First, participants were not drug-naïve and it was not possible to define if MMS were a “non-mood” symptom of depression or an antidepressant side effect. Indeed, a high percentage of patients (17 out of 34 MMS+, 50 %) were already MMS+ at baseline, suggesting that in some cases these signs may pre-exist treatment. However, an alternative explanation is the existence of a subgroup of patients who are “biologically” more sensitive to motor adverse effects, a potentially relevant phenotype that warrants further investigation. Indeed, because all participants were already on antidepressant therapy at baseline—and had heterogeneous treatment histories prior to inclusion—the motor signs observed in this study cannot be causally attributed either to the underlying depressive disorder or to medication exposure. Consequently, distinguishing between intrinsic motor abnormalities and treatment-emergent side effects was not possible. Moreover, considering the small size of MMS+ participants ( $n = 34$ ), to avoid generating potentially misleading subgroup findings, a sensitivity analysis was not conducted, limiting both interpretability and reliability of the results.

Moreover, the use of a 20 % reduction in HAMD total score as an indicator of minimal clinical improvement represents another limitation. Indeed, although this threshold was selected to capture modest yet meaningful changes in symptom severity, it deviates from the more conventional 25–50 % reduction typically used to define partial response. As such, the generalizability of our findings to studies adopting standard response criteria may be limited.

In addition, patients were classified as MMS+ if motor symptoms emerged at any visit between week 4 and week 12. Because some participants dropped out shortly after the onset of symptoms, it was not possible to reliably evaluate differences according to the exact week of appearance. For this reason, the occurrence of MMS was considered irrespective of timing, and our findings should be interpreted accordingly.

The use of  $a \geq 20$  % reduction in HAM-D total score as an indicator of minimal clinical improvement was chosen to capture subtle changes in symptom severity; however, it deviates from the more conventional 25–50 % thresholds typically adopted for partial or full response. As such, the comparability of our findings with studies using standard response criteria is limited.

Furthermore, a methodological limitation of our study is that mild motor signs were assessed using UKU motor items, a scale primarily developed to quantify psychotropic side-effects rather than intrinsic motor phenomena. Although UKU captures extrapyramidal features that align with the construct of mild motor signs, it does not represent a dedicated instrument for such phenomena.

Finally, item-by-item analyses were not corrected for multiple comparisons. This choice was made to preserve exploratory sensitivity; however, it increases the likelihood of Type I errors. Therefore, the item-level findings should be interpreted with caution.

However, the PANDORA study enrolled a relatively large cohort of adults with MDD. By excluding older adults, it reduced the potential confounding effect of age-related parkinsonism or dementia. Moreover, the diagnosis of MDD and comorbidities was confirmed with validated and structured clinical interviews, ensuring diagnostic accuracy and sample homogeneity.

In conclusion, our findings suggest that MMS, independently from age and short-term antidepressant outcome, could constitute a significant clinical dimension of MDD. Instead, MMS appears to indicate a subgroup with greater baseline severity, regardless from motor symptoms, and greater functional impairment in the workplace — a profile that may require specific therapeutic and rehabilitative strategies.<sup>24–27</sup>

## Author s' roles

1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

AL: 1A, 2A, 2B, 2C, 3A; AS: 1A, 2C, 3B; SB: 1A, 1B, 1C, 3B; LS: 1C, 3B; VM: 1C, 3B; AM: 1C, 3B; RCS: 1C, 3B; GP: 1C, 3B; GN: 1C, 3B; SB: 1C, 3B; PANDORA study group: 1C, 3B; GBT: 1C, 3B; RF: 2C, 3B; MG: 1A, 1B, 1C, 3B; AV: 1C, 3B; AM: 1A, 1B, 1C, 3B

## Ethical considerations

The study was approved by the Local Ethics Committees (CEIOC IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia N: 43/2018, and Ethics Committee of ASST Spedali Civili of Brescia N: NP 3347) and was performed in accordance with the principles of the Declaration of Helsinki. All patients signed a written informed consent to participate before being enrolled.

## Conflict of interest

A Luca has served as speaker for PIAM, and Eli Lilly. S Barlati received advisory board, lecture, or consulting fees, outside the present work, from: Angelini, Janssen, Lundbeck, Otsuka, and Rovi. A Serretti has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier and Taliaz. The other authors reported no conflict of interest.

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