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PsiOvi Staging Model for Schizophrenia (PsiOvi SMS): A New Internet Tool for Staging Patients with Schizophrenia

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Research Article

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Abstract

Background. One of the challenges of psychiatry is the staging of patients, especially those with severe mental disorders. Therefore, we aim to develop an empirical staging model for schizophrenia.

Methods. Data were obtained from 212 stable outpatients with schizophrenia: demographic, clinical, psychometric (PANSS, CAINS, CDSS, OSQ, CGI-S, PSP, MATRICS), inflammatory peripheral blood markers (C-reactive protein, interleukins-1RA and 6, and platelet/lymphocyte [PLR], neutrophil/lymphocyte [NLR], and monocyte/lymphocyte [MLR] ratios). We used machine learning techniques to develop the model (genetic algorithms, support vector machines) and applied a fitness function to measure the model's accuracy (% agreement between patient classification of our model and the CGI-S).

Results. Our model includes 12 variables from 5 dimensions: 1) psychopathology: positive, negative, depressive, general psychopathology symptoms; 2) clinical features: number of hospitalizations; 3) cognition: processing speed, visual learning, social cognition; 4) biomarkers: PLR, NLR, MLR; and 5) functioning: PSP total score. Accuracy was 62% (SD = 5.3), and sensitivity values were appropriate for mild, moderate, and marked severity (from 0.62106 to 0.6728).

Discussion. We present a multidimensional, accessible, and easy-to-apply model that goes beyond simply categorizing patients according to CGI-S score. It provides clinicians with a multifaceted patient profile that facilitates the design of personalized intervention plans.

Introduction

Increasing schizophrenia research studies are providing important insights into some of its main challenges, such as genetic, neurobiological, and neuroimaging biomarkers [1, 2]. However, another significant challenge yet to be achieved is developing a staging model for this disorder. Staging models allow us to integrate clinical information with biomarkers, comorbid conditions, and other significant variables [3]. Thus, they offer a unitary framework for providing effective interventions adapted to the stages of the disorder [4–6] and reducing heterogeneity in clinical practice [5, 7].

The first staging model for schizophrenia was proposed by Fava and Kellner in 1993 [8]. Since then, different theoretical staging models have been proposed, ranging from the simplest, which includes only psychotic psychopathology and functioning [8], to the most complex, which also comprises affective symptoms, cognition, neuroimaging, and biological and endophenotypic markers [9, 10]. In this regard, the recently developed models based solely on the Positive and Negative Syndrome Scale (PANSS) deserve a separate mention [11–13]. Additionally, we have noticed a growing interest in validating some of the proposed theoretical models [6] for the purpose of establishing their validity and/or improving them [14–22]. However, despite these above-mentioned efforts, practically all of these models have significant limitations [6]. According to the literature, most were theoretical proposals, only partially validated at best, and have rarely been integrated into routine clinical practice.

In this context, our study aims to develop a staging model for schizophrenia that overcomes the limitations of those already proposed, using machine-learning methodologies from information on different dimensions relevant to this disorder.

Methods

This is a naturalistic and cross-sectional study of patients with schizophrenia in outpatient treatment. The study was developed according to the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo also approved the study protocol (Ref. 36/2012, Ref. 25/2014). Before enrollment, written informed consent was obtained from all subjects.

Participants

A total of 212 patients with stable schizophrenia were recruited. Inclusion criteria were (1) outpatients with a confirmed diagnosis of schizophrenia according to the International Classification of Diseases 10th Edition (ICD-10) criteria in treatment at any of the participating centers (La Eria and La Corredoria mental health centers in Oviedo, Spain)]; (2) age > 17 years; and (3) written informed consent to participate in the study.

Exclusion criteria were designed to be minimal to obtain a representative and heterogeneous sample. Therefore, only patients with an intellectual developmental disability or acquired brain injury were excluded from the study.

Evaluations

Extensive evaluations were performed for all subjects where demographic and clinical data were collected, such as length of illness, number of hospitalizations, and physical comorbidities. In addition, we also included pragmatic variables, which are an indirect measure of functionality, such as educational level, marital status, employment status, and official disability status.

The assessment was developed by trained clinicians and also included the Spanish versions of the following instruments:

Psychopathology. Positive and Negative Syndrome Scale (PANSS) [23], Clinical Assessment Interview of Negative Symptoms (CAINS) [24], and Calgary Depression Scale for Schizophrenia (CDSS) [25]. The presence of sleep disturbances was also assessed through the Oviedo sleep questionnaire (OSQ) [26]. Although the OSQ comprises three subscales (subjective satisfaction, insomnia, and hypersomnia), we used only the subjective satisfaction subscale for this study. In addition, we included the items that assessed sleep latency (OSQ3) and efficiency (OSQ6), and the use of pharmacotherapy or other sleep remedies (OSQ11).

As for negative symptoms, the PANSS negative subscale (PANSS-N) and Marder Negative Factor (PANSS-MNF) scores were calculated. The PANSS-MNF includes the items of the PANSS-N, except difficulty in abstract thinking and stereotyped thinking, plus two items from the PANSS general psychopathology subscale of the (PANSS-GP): motor retardation and active social avoidance. In addition, due to the psychometric limitations of existing instruments to evaluate negative symptoms [27], we used the CAINS scale, which focuses on the patient's subjective experience of the negative signs and symptoms instead of the patient's functioning. This scale comprises two subscales: motivation and pleasure (MAP), which evaluates the severity of abulia and anhedonia, and emotional expression (EXP), which measures the severity of alogia and blunted affect. It provides scores for each subscale and a total score obtained by combining the scores on the two subscales, where higher scores reflect greater symptom severity.

Cognition. We used the measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery (MATRICS-CCB) [28], which consists of 10 tests that are grouped into seven cognitive domains: Processing Speed (Trail Making Test: Part A; Brief Assessment of Cognition in Schizophrenia: Symbol Coding and Category Fluency Test: Animal Naming); Attention/Vigilance (Continuous Performance Test: Identical Pairs); Working Memory (Wechsler Memory Scale Spatial Span-III, and Letter Number Span Test); Visual Learning (Brief Visuospatial Memory Test-Revised); Verbal Learning (Hopkins Verbal Learning Test-Revised); Reasoning/Problem-Solving (Neuropsychological Assessment Battery: Mazes); and Social Cognition (Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions [D and H sections]). First, the raw score was obtained for each of the subtests,

Table 1. Sociodemographic and clinical characteristics of the sample

Sociodemographic characteristics	Mean (SD)
Age	40.30 (13.05)
Sex, males [n (%)]	135 (63.70)
Marital status [n (%)]	
Never married	157 (74.10)
Married[a]	55 (25.9)
Educational level [n (%)]	
Primary school	46 (21.70)
Secondary school	125 (59.50)
University	41 (19.30)
Work status [n (%)]	
Working (full–/part–time)	31 (14.60)
Not working[b]	152 (71.70)
Homemaker or student	29 (13.70)
Recognized disability, yes [n (%)]	80 (37.70)
Clinical characteristics	Mean (SD)
Length of illness, years	11.97 (12.02)
Number of hospitalizations	1.62 (1.89)
Suicide attempts	
Yes [n (%)]	34 (16.00)
No. of suicide attempts	1.71 (1.50)
Use of substances	
Coffee (current) [n (%)]	122 (57.50)
No. of cups	2.68 (1.78)
Tobacco (current) [n (%)]	91 (42.90)
No. of cigarettes	17.88 (9.63)
Alcohol (current) [n (%)]	60 (28.30)
Cannabis (lifetime) [n (%)]	110 (51.90)
Metabolic Syndrome	
Yes [n (%)]	70 (33.02)
No. of criteria	1.89 (1.40)
Physical disease (Yes) [n (%)]	145 (68.39)
Physical treatment (Yes) [n (%)]	62 (29.25)

Abbreviation: SD, standard deviation.
[a]Married includes married, cohabiting, widowed, and divorced.
[b]Not working includes permanently disabled due to health conditions, temporarily disabled, retired, and unemployed.

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Table 2. Psychometric, cognitive, functional, and laboratory results for the total sample

Psychometric scores	Mean (SD)
PANSS–positive	12.90 (5.10)
PANSS–negative	18.21 (5.59)
PANSS–marder negative factor	18.14 (6.12)
PANSS–general psychopathology	29.382 (7.44)
CAINS–MAP	20.81 (8.98)
CAINS–EXP	6.95 (4.56)
CDSS	3.17 (4.03)
CGI–S	4.18 (0.93)
OSQ–satisfaction	4.55 (1.64)
OSQ3	2.21 (1.21)
OSQ6	1.87 (1.28)
OSQ11	2.49 (1.79)
Cognition scores	Mean (SD)
MATRICS–CCB subtest raw scores	
TMT A	52.75 (35.09)
BACS	38.23 (14.30)
HVLT–R	21.92 (6.66)
WMSIII	14.13 (4.08)
LNS	12.36 (4.12)
NAB:MAZES	11.66 (8.02)
BVMT–R	16.88 (9.42)
CF	17.85 (5.95)
MSCEIT ME	88.95 (14.69)
CPT–IP	1.91 (0.83)
MATRICS–CCB domain scores	
Speed of processing	32.68 (15.04)
Attention/vigilance	34.06 (11.19)
Working memory	38.70 (12.93)
Visual learning	36.46 (13.73)
Verbal learning	38.78 (10.31)
Reasoning/problem–solving	37.17 (9.46)
Social cognition	41.46 (16.36)
MATRICS–CS	259.34 (63.02)
Functioning scores	Mean (SD)
PSP–Total	53.54 (17.67)
Laboratory results	Mean (SD)
Hematology	
RBCs (μl)	4.88 (0.48)
Hemoglobin (g/dl)	14.67 (1.54)
Platelets (μl)	229.67 (57.34)
PLR (μl)	198.78 (41.47)
NLR (μl)	1.96 (1.02)
MLR (μl)	0.26 (0.11)
Hormones	
Insulin (μU/ml)	16.23 (12.60)
Inflammatory and oxidative biomarkers	
CRP (ml/dl)	0.43 (0.66)
IL_1RA (pg/ml)	209.12 (142.85)
IL_6 (pg/ml)	1.40 (0.82)

Abbreviations: SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; EXP, expression subscale; MAP, motivation and pleasure subscale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, clinical global impression-schizophrenia severity; PSP, personal and social performance; OSQ, Oviedo sleep questionnaire; MATRICS-CCB, measurement and treatment research to improve cognition in schizophrenia-consensus cognitive battery; TMTA, Trail Making Test A; BACS, brief assessment of cognition in schizophrenia: symbol coding; HVLT-R, Hopkins Verbal Learning Test-Revised; WMSIII, Wechsler Memory Scale Spatial Span-III; LNS, letter number span; NAB:MAZES, neuropsychological assessment battery: mazes; BVMT-R, brief visuospatial memory test revised; CF, category fluency; MSCEIT ME, Mayer-Salovey-Caruso emotional intelligence test: managing emotions; CPT-IP, continuous performance test: identical pairs; CS, composite score; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; CRP, C-reactive protein; IL, interleukin; RBCs, red blood cells.

where higher scores reflect better cognitive performance, except for Trail Making Test A, where higher scores reflect greater impairment. Secondly, we transformed the raw scores, according to age and sex, into *t*-scores. Finally, we summed the *t*-scores from each domain test and transformed them into the final score using the tables provided by the MATRICS.

Real-world functioning. The personal and social performance (PSP) scale [29] was employed, and its total score was used. We chose this instrument due to the well-known difficulties associated with the GAF [30, 31] and because it was available in several languages.

Global severity. We used the score on the clinical global impression-schizophrenia severity scale (CGI-S) [32] as the "best current gold standard" to determine the performance of each of the models generated by genetic algorithms. We decided to use this scale because, as reported in previous studies [32–34], it demonstrates high interrater reliability when raters are specifically trained in the use of this instrument. Consistent with the inclusion criteria, the percentage of people recruited with CGI-S scores of 1 (normal, not ill), 2 (minimally ill), 6 (severely ill), or 7 (among the most severely ill) was inadequate. Therefore, we regrouped these CGI-S scores: 1 and 2 into the same dimension and 6 and 7 into the same category.

Biological assessment. A physical examination of the patients was also performed, in which height, weight, waist circumference, heart rate, and blood pressure were recorded. In addition, blood samples were collected to perform laboratory tests (hematology, biochemistry, and hormones) after a confirmed overnight fast. Additionally, the following blood biomarkers of inflammation were obtained: C-reactive protein (CRP), interleukin (IL) 1RA and IL6, and platelet/lymphocyte (PLR), neutrophil/lymphocyte (NLR), and monocyte/lymphocyte (MLR) ratios (Table 2). In addition, we used the NHANES criteria [35] to determine the presence of metabolic syndrome.

Machine-learning Model

Genetic algorithms.

Genetic algorithms (GAs) are a methodology based on the natural selection process and are suitable for solving optimization problems. These algorithms simulate natural selection processes

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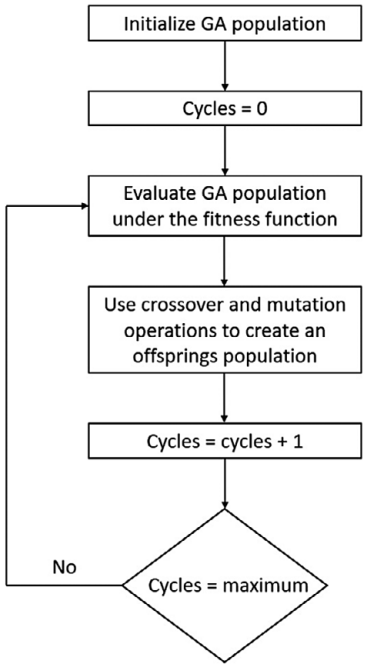

Figure 1. Flowchart of the algorithm employed in this research. *GA Genetic Algorithm.*

such as inheritance, mutation, crossover, and selection [36]. Every genetic algorithm uses an initial population from which the algorithm will start searching for optimum values. A fitness function is applied to the initial population to assess how suitable each initial population's elements are as the solution to the problem under study.

The solutions that are deemed to be the best, as determined by the fitness function, will be chosen to transmit knowledge to the following generation. This knowledge transmission is performed with the help of the genetic operators' mutation, crossover, and elitism applied to create a new generation that achieves better values when assessed with the fitness function.

Support-vector machines.

Support-vector machines (SVMs) are supervised learning models for classification problems. Given a set of training data, each marked with the category to which it belongs, an SVM model can assign new examples in one category or another. Using the kernel method, SVM can efficiently perform linear and nonlinear classifications [37]. This implicitly assumes mapping its inputs into high-dimensional feature spaces. The original SVM algorithm was created by Vapnik and Chervonenkis [38]. Years later, Boser et al. [39] suggested creating nonlinear classifiers by applying the kernel method to maximum margin hyperplanes. Currently, the most widely used implementation of this method is the one proposed by Cortes and Vapnik [40].

The proposed algorithm.

The algorithm proposed for the variable selection made use of GA and SVM. Their steps are presented as a flowchart in Figure 1. The first step consists of initialization of the GA population. Each population's member is formed by a string of '0s' and '1s' with a length of 61, which is the total number of possible input variables of the model. The criteria for including/excluding data from the analysis were the subject of our previous systematic review [6] and the team discussion. Each '0' means that the variable will not be present in the model under study, and each '1' means that the variable will be employed for training the model.

To evaluate the performance of all the trained models, we used the CGI-S patient classification as the "best current gold standard." We applied a fitness function to measure the model's accuracy: the percentage of concordance between the classification of patients according to our model and the CGI-S.

To avoid the selected subsets influencing the model's performance, a three-fold cross-validation was applied [41]. This means that the data set was randomly divided into three parts, two of which were employed for the model training and the other for the validation. Three-fold cross-validation is a particularization of the k-fold cross-validation methodology, also known as out-of-sample testing, for $k = 3$. This methodology is frequently applied in machine-learning studies to reduce bias, with good performance [42], suggesting that it is beneficial in minimizing data-testing uncertainties and overfitting issues [43].

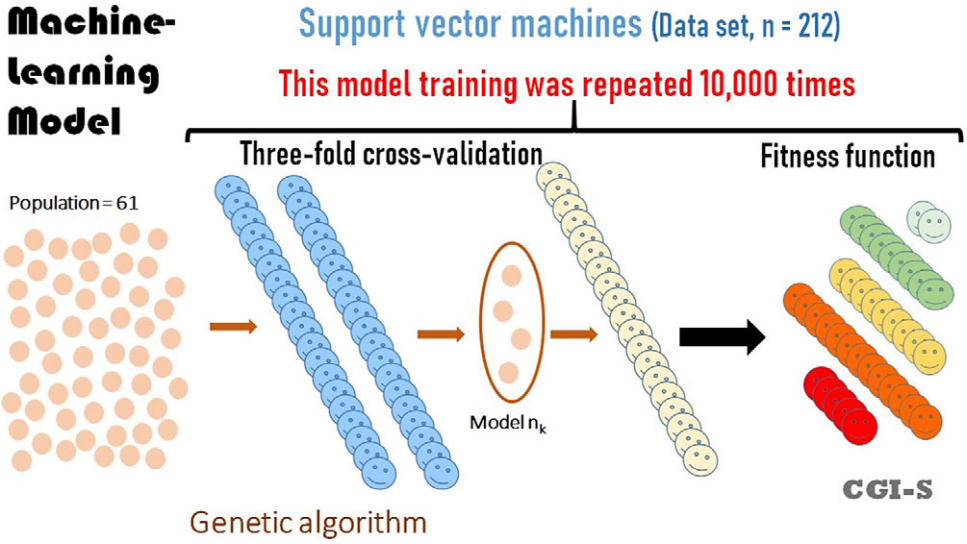

Figure 2. Development of our model using Machine-Learning techniques. *CGI-S Clinical Global Impression-Schizophrenia Severity*.

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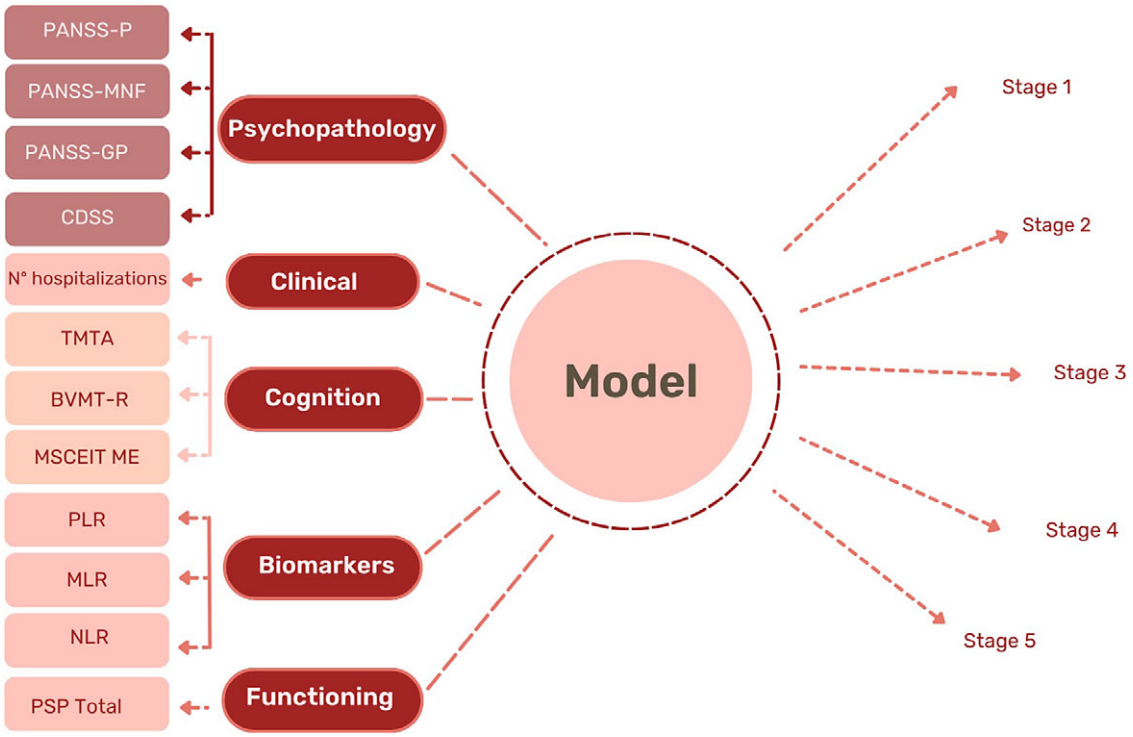

Figure 3. Variables included in the staging model. *PANSS Positive and Negative Syndrome Scale, PANSS-P Positive, PANSS-MNF Marder Negative Factor, PANSS-GP General Psychopathology, CDSS Calgary Depression Scale for Schizophrenia, TMT A Trail Making Test A, BVMT-R Brief Visuospatial Memory Test Revised, MSCEIT Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions, PLR Platelets/lymphocytes Ratio, MLR Monocytes/lymphocytes Ratio, NLR Neutrophils/lymphocytes Ratio; PSP-Total: Personal and Social Performance Total score.*

The three-fold cross-validation process was repeated 10,000 times for each model (see Figure 2). Therefore, the value of the fitness function is the average of the model performance of all models trained for each variable's subset. The stop criterion employed in this research was for the algorithm to stop after 100 cycles where none of the individuals in the population improved the percentage of patients classified in the correct category according to the CGI-S classification.

The population size for the GA was 10,000. For the mutation, the value of 1% was chosen; for the crossover, it was 100%, and for elitism, it was 5%. Please note that these values have shown good performance in previous research studies by the authors [44, 45]. The classification version of SVM was applied in this algorithm, using the radial basis function kernel and a gamma value equal to the inverse of the number of input variables of the model. The tolerance values of the models were 0.001 with an epsilon of 0.1, as those values showed good performance in previous research [46, 47].

Results

Demographic and clinical characteristics

The mean age of our sample was 40.3 (SD = 13.1) years, 63.7% were males, 74.1% were never married, and 37.7% received disability benefits due to schizophrenia. The rest of the sociodemographic characteristics are shown in Table 1.

The mean age at diagnosis was 28.3 (SD = 8.2) years, the mean length of the disorder was 12.0 (SD = 12.0) years, and 16% had a comorbid mental disorder. Regarding the use of substances, while cannabis was the substance with the highest reported consumption (51.9%), tobacco (43.4%) and alcohol (28.3%) were currently the most used. On average, our sample's mean severity level was 4.2 (SD = 0.9) (Table 2). The patients' psychometric scores and laboratory results are shown in Table 2. Concerning physical health, 68.4% had at least one comorbid physical disease, and 70 (33.3%) patients had metabolic syndrome.

Development of the "PsiOvi Staging Model for Schizophrenia (PsiOvi SMS)"

The best SVM model used the following 12 variables as input variables: PANSS-Positive subscale, PANSS-MNF subscale, PANSS-GP subscale, Calgary Depression Scale, number of hospitalizations, Trail Making Test – Part A, Brief Visuospatial Memory Test-Revised, Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions (D and H sections), PLR, NLR, MLR and total PSP (Figure 3).

Concerning the performance of PsiOvi SMS, we found a percentage of concordance of 62% (SD = 5.3) between the CGI-S and our model's classifications. Its specificity and sensitivity (mean and standard deviation) are shown in Table 3. As can be seen, in general,

Table 3. Model specificity and sensitivity of patient classification according to CGI-S category

	Model specificity		Model sensitivity	
CGI-S category	Mean	SD	Mean	SD
Stage 1	0.96692	0.01920	0.22331	0.30293
Stage 2	0.91212	0.03675	0.62106	0.13500
Stage 3	0.79897	0.06656	0.63647	0.07970
Stage 4	0.83270	0.05222	0.67284	0.09089
Stage 5	0.95384	0.02211	0.36334	0.32796

Abbreviations: SD, standard deviation; CGI-S, clinical global impression-schizophrenia severity.

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the specificity values are quite high, but depending on the characteristics of the model and the problem under study, the sensitivity values seem to be of greater interest. In this regard, the sensitivity values are satisfactory for patients classified as Mildly ill, Moderately ill, and Markedly ill by the CGI-S (values ranging from 0.62106 to 0.6728). In contrast, they are moderate and low for the minimally ill and severely ill groups, respectively.

Discussion

Our work provides clinicians with a staging model, PsiOvi SMS, that is easily and directly transferable to daily clinical practice to classify patients with schizophrenia according to the severity of their disorder. This model is aligned with personalized medicine, the prevailing trend in the 21st century across most medical specialties. In addition to classifying patients by severity, our model provides clinicians with a comprehensive profile, including symptomatology, cognition, functionality, and biological factors for each patient. This will allow clinicians to design specific interventions aimed at enhancing the strengths of each individual and reducing, as much as possible, their deficits.

Although we used a large number of psychometric and biological assessments, our final model comprises only 12 easily obtainable profilers. Profilers include positive, negative, depressive, and general psychopathology symptoms, number of hospitalizations, processing speed, visual learning, social cognition, PLR, MLR, NLR, and real-world functioning.

In the past few years, the use of machine-learning methodologies has become common in healthcare. These methodologies have proved their interest in other fields of science and engineering [48, 49]. They have also been adopted in the healthcare field, and their performance has been tested in very different applications, e.g., exploitation of electronic health record data [50], training and validation of models able to prevent cardiovascular diseases [51], and improvement of patient outcomes in dermatology [52].

The specialty of psychiatry is no stranger to such emergence of new techniques. According to some authors, these methodologies would promote a paradigm shift in the diagnosis, prognosis, monitoring, and treatment of mental illnesses [53]. One of the most recent research studies in this field is the one performed by Ramos-Lima et al. [54], which investigated the viability of a predictive model to support posttraumatic stress disorders (PTSDs). In that study, a model with four stages suitable for PTSD staging was developed.

In the present research, we have developed a machine-learning-based staging model for patients with schizophrenia. The proposed model uses genetic algorithms and SVM for patient classification. Although the sensitivity values can be considered adequate globally, values for the CGI-S minimally ill and severely ill categories, 0.22331 and 0.36334, respectively, can be regarded as low. However, it must be taken into account that, according to the inclusion criteria, both categories are composed of a very small set of individuals, which makes the process of training and validating the model more complex.

One of the benefits of this work is the neutrality and absence of bias when generating the models. This is achieved thanks to the three-fold cross-validation [55], and the 10,000-fold repetition of each randomly selected subset of variables – the methodology used in the development and validation process. Although this way of working reduces specificity and sensitivity, not using this methodology can lead to severely inflated performance indicators [56]. Furthermore, it means that certain machine-learning models may appear to predict well when they do not if they have not been overtrained [57]. Please note that this practice is sometimes hidden in some research studies testing different machine-learning models until one seems to predict well enough for the problem under study [58, 59].

As stated in the Methods section, our model was trained against the CGI-S patient classification. We may face criticism for our decision to use the CGI-S, as it has been suggested that our methodology is tautological and that the CGI-S is easier to use and requires minimal administration time. First, we do recognize that our model requires greater effort on the part of clinicians in terms of patient assessment. They will need to become familiar with the 12 profilers, which represent the patient's scores on specific instruments and the results of a complete blood count. Although incorporating the model into routine clinical practice may seem laborious, we firmly believe that this effort is justified. Schizophrenia is one of the most severe mental disorders associated with poor prognosis and substantial variability in intervention outcomes. Therefore, not performing fundamental assessments of core symptomatology, cognition, functioning, and basic laboratory tests could be considered negligent. Second, as noted in the Methods section, with specific training, this instrument can be considered the "best current gold standard" grading system. However, psychiatrists lack it. Generally speaking, then, the CGI-S should be viewed as a "black box," as the dimensions of the disorder that clinicians take into consideration and the scoring anchors used when assessing severity are unknown [60, 61]. It is also important to highlight the conceptual change schizophrenia has undergone since the CGI-S scale was developed. In these almost 50 years, schizophrenia has gone from being considered an exclusively mental illness to a disease underlying chronic subclinical inflammation and presenting high rates of somatic comorbidity, mainly endocrine-metabolic and cardiovascular diseases [62]. In line with the results of Dunlop et al. [63], we doubt that these changes are borne in mind by clinicians when using the CGI-S. Finally, since it provides a single index rather than a profile of a patient's strengths and deficits, it does not help design personalized intervention plans to enhance strengths and reduce deficits as much as possible.

The 12 profilers included in PsiOvi SMS pertain to the following five dimensions: psychopathology, clinical features, functioning, cognition, and biomarkers. Although other authors have also proposed these dimensions and primarily psychopathology [4, 11-13, 64], and functioning [8, 9, 10, 16, 65, 66], most models do not provide information on how to evaluate them.

Regarding the psychopathology dimension, our model includes positive, negative, depressive, and general symptoms. It seems logical that psychotic symptoms should be part of the model since they are the disorder's core symptoms. However, traditionally, the literature has placed less importance on depressive symptoms. Specifically, in the theoretical model of McGorry et al. [9], they were included only in the premorbid and prodromal phases of the disorder. However, recent studies have analyzed the impact of depressive symptoms on the long-term evolution of the disorder, finding that depressive symptoms play a significant role in functional remission and personal recovery [67, 68]. Our model also includes the number of hospitalizations, which refers to relapses requiring hospitalization. It makes sense to include this profile due to its demonstrated negative impact on the disorder's prognosis [69, 70].

In cognition, significant domains emerged: processing speed and visual learning assessed with Trail Making Test – Part A and Brief Visuospatial Memory Test-Revised, respectively. Different cognitive dimensions have also been included in previous staging models [4, 9, 10-13, 16, 18, 21, 64]. However, it is worth noting the

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findings of Lin et al. [71], who demonstrated that processing speed and visual learning and memory tests were the best predictors of global cognition in schizophrenia. Therefore, their results may explain why processing speed and visual learning were the only cognitive domains that emerged in our model. Thus, it might be possible to obtain an approximation of the global cognitive function of these patients only through the Trail Making Test – Part A and Brief Visuospatial Memory Test-Revised tests. On the other hand, we would point out that the model does not include pure dimensions of cognition only, since social cognition has also emerged as a significant variable. Although several authors mentioned social deficits and impairment of social functioning [9, 64, 65], only Hickie et al. [10] included social cognition in their staging model. Social cognition consists of the fundamental ability to engage in social interactions, such as recognizing other people's feelings, perceiving their intentions, and understanding social and cultural norms [72, 73]. For this reason, development of social cognition is crucial for appropriate psychosocial and work-related adjustment of these patients [74, 75].

Another important finding is that PLR, MLR, and NLR have emerged as profilers within PsiOvi SMS. Other authors had previously included biomarkers in their theoretical models [9, 10], but they were not empirically validated. Specifically, Godín et al. [16], whose objective was to empirically validate and improve the model of McGorry et al. [9], found no association between CRP and the severity stages of the model. Therefore, to the best of our knowledge, our model is the first to include specific empirically validated biomarkers associated with the severity of the disorder. Furthermore, in keeping with the present results, a previous study by Özdin and Bökeb [76] found that NLR, PLR, and MLR increased significantly in the relapse period. Additionally, MLR and PLR were found to be significantly higher in the remission period of patients with schizophrenia compared with the control group. Therefore, these results support the possibility that PLR, MLR, and NLR could be biomarkers of schizophrenia severity. Furthermore, although our model did not include any somatic comorbidities, these would be indirectly indicated by peripheral inflammation biomarkers, underlying metabolic syndrome, and obesity.

Finally, functioning also emerged as a significant variable in our staging model. Previous theoretical models also included this variable; even McGorry et al. [9] and Hickie et al. [10] proposed specific psychometric ranges of the Global Assessment of Functioning (GAF) scale [77]. However, we use the PSP to assess functioning since its scores include objective indicators and do not overlap with psychopathology [30, 31] as occurs with the GAF scale.

Strengths and limitations

From a methodological point of view, using the CGI-S to train and obtain the best model might be viewed as the main limitation, and even a tautology, of the study. We have explained our point of view extensively and discussed this topic in the "Discussion" section. Another significant limitation is the small sample size of each CGI-S group, which may affect the generalization of our results. However, as stated before, we consider our sample a good fit with the typical severity distribution found in outpatient clinical practice. Thus, we would point out that the PsiOvi SMS is applicable only to patients with schizophrenia in outpatient treatment, and the prodromal and extremely severe phases are outside the scope of the model. However, since people with schizophrenia will spend most of their lives in outpatient treatment, as very severe acute phases are rare and brief, our model can be used in virtually all patients.

Our study had several strengths. First, we developed an empirical staging model to classify patients in a standardized manner, based on psychometric and biological parameters, that is easily translatable into clinical practice. The required biological parameters are available in almost all settings, easy to obtain, and inexpensive. A second strength is the transparency in the data and selection criteria employed in the model development. Thus, readers can check their strengths and limitations. A third strength is that the raters were extensively trained in psychometric assessments, including the CGI-S. This allowed us to correctly assess the patient's level of severity for training and obtaining an accurate staging model. Its final strengths are its neutrality, absence of bias, and reproducibility. Furthermore, in addition to the previously mentioned clinical advantages, the "PsiOvi SMS" is associated with a calculator (https://test2023.shinyapps.io/res_patient/) that automatically generates the patient's stage, which makes our model truly transferable to clinical practice.

Therefore, the next step after developing our model will be to follow patients over time and evaluate the effectiveness of the interventions implemented at each stage. This will allow us to verify and propose interventions that are truly useful to improve patient outcomes depending on the stage in which they are located, which could represent progress in the standardization of clinical practice and the implementation of personalized medicine.

Conclusion

To the best of our knowledge, ours is the first development of an empirical multidimensional staging model for schizophrenia using machine learning. Our model constitutes a unique, accessible, inexpensive, and easy-to-apply tool to help doctors manage the heterogeneity of schizophrenia, facilitate the transfer of information between professionals, and implement personalized therapeutic interventions. Therefore, they should be aware of these results, as they represent a further step towards implementing patient-centered precision medicine.

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Competing interest. The authors declare no conflict of interest related to the submitted work.

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