Predictive factors and symptom severity spectrum in adult schizophrenia: Potential insights for improved management and adequate care

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Abstract. Schizophrenia is one of the most disabling psychiatric disorders characterized by positive (hallucinations, delusions, formal thinking disorder) and negative symptoms (anhedonia, lack of speech and motivation). The present study aimed to identify the predictive factors of schizophrenia in adults, and potential differences in the environment of origin, sex, levels of occupational stress, intellectual level, marital status and age of onset of the disease depending on the severity of symptoms using analysis of data collected from 120 patients with a diagnosis of schizophrenia. The study was conducted at the 'Prof. Dr. Alexandru Obregia' Clinical Psychiatric Hospital in Bucharest and included adult patients hospitalized between March 2018 and January 2021 diagnosed with schizophrenia and evaluated by general clinical examination, psychiatric, neurological and psychological evaluation. Results revealed that robust predictors of mild and moderate symptoms were affective symptoms, heredo-collateral history of schizophrenia, late onset, the presence of positive and negative symptoms, substance abuse, stress and marital status, unmarried, lower IQ and mental deficiency. For moderate-severe and severe symptoms, predictors were affective symptoms, heredo-collateral history of schizophrenia and affective disorders, substance abuse, stress, borderline IQ and mild mental deficiency. The present results can be used for further development of psychopharmacological management of schizophrenia.

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Introduction

Schizophrenia is described as one of the most disabling psychiatric disorders characterized by positive (hallucinations, delusions, formal thinking disorders) and negative symptoms (anhedonia, lack of speech and lack of motivation) (1).

Positive symptomatology is associated with heightened dopaminergic activity in the mesencephalic and cortical regions. Conversely, negative and dyscognitive symptoms are associated with a reduction in dopaminergic transmission originating from the cerebral cortex, particularly in the prefrontal cerebral cortex (2).

The prevalence of schizophrenia worldwide is estimated at 0.33-0.75% (3,4). Pharmacological management of schizophrenia needs to consider aspects such as metabolic disturbances (such as obesity) (5).

A set of causes has not yet been discovered as the basic mechanism for this disorder, schizophrenia being considered a heterogeneous disorder with multiple etiologies (6-8). Schizophrenia is hereditary for 80% of patients, although schizophrenia has numerous aetiologies (9). Scherr *et al* (10) and Martínez-Ortega *et al* (11) examined risk factors for schizophrenia; these include obstetric complications, birth during winter or spring, premorbid behavioral disorders, delayed motor or language development, exposure to toxic substances *in utero*, or adverse effects of medications. In a study by Chandra *et al* (12), 41.9% of patients were non-compliant with medication over a 5-month period. Factors associated with non-compliance include younger age, early onset of illness, unemployment, poor insight into illness and higher Positive and Negative Syndrome Scale (PANSS) scores on the positive items. Denial of illness is the primary

reason for non-compliance, with other factors including financial burden, lack of illness knowledge, limited treatment access, medication side effects and substance abuse (12). Extensive studies have concluded that aspects associated with intrauterine development can also influence risk of future development of schizophrenia, such as malnutrition (13,14) or infections during pregnancy (15,16), obstetrical complications (17), genetic influence (18), substance abuse (19-22) and stress (23,24). These predictive factors can also trigger early onset of schizophrenia in adult patients. A meta-analysis concluded that targeting enhanced social support in individuals with severe mental illness has a significant impact on the quality of life, although it did not translate into a clinically significant improvement in perceived social support (25). Another study found that rural patients generally have lower quality of life compared with urban patients across all measured domains (social functioning, self care, career, economic support, vocational skills training, input in mental health services, community rehabilitation services, and social support). Factors such as marital status, vocational skills, physical exercise and social support affect quality of life among urban patients. Age, marital status and proximity to medical institutions are significant factors affecting quality of life among rural patients (26).

One of the most severe consequences of schizophrenia is the increased risk of suicide or suicidal behavior. The incidence of suicide among individuals with schizophrenia is ~10% (27). Evaluating the risk of suicide is challenging, with depression and suicide attempts emerging as primary risk factors. Notably, young men undergoing inpatient care appear to be particularly susceptible. In a comprehensive study involving 288 schizophrenic patients, nearly half (49%) acknowledged a history of lifelong self-harm during interviews (28). The motivation behind self-harm is not necessarily suicidal, although it may coexist with suicidal ideation and serve as a potent predictor of completed suicide. There is a heightened risk of suicide among individuals with a history of self-harm and poor social support (29). Suicide prevalence among individuals diagnosed with schizophrenia rose during the COVID-19 pandemic, potentially as an expression of isolation and insufficient access to proper psychiatric treatment (27-30).

With technological progress that allows better imaging techniques, such as computed tomography (CT) and MRI, research on schizophrenia imaging has grown considerably; neuroimaging studies conducted on patients diagnosed with schizophrenia revealed several cerebral modifications: Enlargement of the Virchow spaces, lesions of the white matter with demyelinating appearance and inflammatory sinus reactions (31,32).

The present study aimed to identify possible differences in the place of living (rural/urban), sex, levels of occupational stress, intellectual level, marital status and age of onset of the disease depending on the severity of symptoms, as well as possible influences of family and personal medical history (hereditary history, substance abuse, intellectual level, number of positive and negative symptoms, affective symptoms, late onset of schizophrenia) and socio-demographic factors (marital status, occupational stress level, substance abuse) on the severity of schizophrenia in adult patients.

Materials and methods

Patients. The study was conducted at the 'Prof. Dr. Alexandru Obregia' Clinical Psychiatric Hospital (Bucharest, Romania) and included 120 adult patients, aged between 18 and 69 years, 46 females and 74 males, hospitalized between March 2018 and January 2021 diagnosed with schizophrenia who agreed to participate by signing adequate informed consent. Exclusion criteria was represented by comorbid psychiatric or other illness (such as depression, Alzheimer's disease, Parkinson's Disease).

Methods. The diagnosis was established according to Diagnostic and Statistical Manual, 4th Edition Text Revision (DSM IV TR) and International Classification of Diseases 10th Revision (ICD-10) criteria as per national regulations (33,34). In all cases, the personal and family history was noted regarding positive family history for psychiatric disorders (family study conducted through diagnostic interviews with relatives; first degree relatives included parents and siblings, second degree relatives included aunts, uncles, grandparents or step-siblings), factors such as high professional stress, marital status (married/unmarried) and intellectual level and positive personal history of other psychiatric disorders (affective disorders, especially depression).

The severity of symptoms was established at diagnosis by the attending psychiatrist as follows: 0, not present; 1, equivocal; 2, present, but mild; 3, present and moderate; 4, present and severe and 5, present and serious, according to the DSM-5 using the Clinician-Rated Dimensions of Psychosis Symptom Severity Scale (35).

Late onset was considered as diagnosis at age ≥18 years. All patients received antipsychotic treatment in appropriate dosing regimen following national guidelines. There were no cases of treatment resistant schizophrenia.

All patients were evaluated by general clinical examination, psychiatric, neurological and psychological evaluation.

Symptom severity was categorized mild-moderate or severe-serious. Variables were structured in two groups for easier data management as follows: Group 1 consisting of: positive, negative, affective symptoms, late onset, hereditary antecedents and Group 2 consisting of: stress, intelligence level, marital status, consumption of substances.

Intellectual level was determined using Raven's Progressive Matrices Standard Version (36) and DSM IV TR by intelligence Quotient (IQ) and grouped as follows: ≥130=very high, 120-129=high, 110-119=medium-high, 90-109=medium, 80-89=medium-low, 70-79=low, ≤69=very low.

Statistical analysis. Statistical data analysis was performed using IBM SPSS Statistics Version 22 software (IBM Corp.), open-source Jeffrey's Amazing Statistics Program version 0.18.2 (jasp-stats.org) and open-source JAMOVI (https://www.jamovi.org) version 2.5. Data were presented as mean ± standard deviation. Logistic regression models and Kendall's τB test were applied to verify associations between variables such as symptom severity and age of onset, biological and demographic factors. To perform the regression model, the dependent variables were transformed into dichotomous variables. Symptom severity was categorized

as mild-moderate and severe-serious. χ^2 test was applied to assess differences in symptom severity based on criteria such as levels of occupational stress, place of living, sex, marital status, age of disease onset, intellectual level and MRI results. P<0.05 was considered to indicate a statistically significant difference.

Results

Demographics. The present study involved 120 patients aged between 18 and 69 years, including 46 females and 74 males, with a mean age of 40.57±12.23 (data not shown). A total of 77 patients came from urban areas and 43 from rural areas, 65 were married and 55 unmarried; 62 of the participants worked in a stressful environment.

Illness characteristics. Auditory hallucinations and delusional ideation (both n=95) were the main positive symptoms in most patients; disorganized thinking and speech was observed, associated with negative symptoms such as avolition (n=89), affective flattening (n=90) and anhedonia and apathy (n=63; data not shown).

A total of 80 participants had a late onset of schizophrenia and 39 of the cases reported substance abuse (data not shown). Substance abuse (cocaine and cannabis) was also reported by 35 patients with early onset of psychiatric manifestations. A total of nine participants had serious symptoms, 27 severe symptoms, 66 moderate and 18 mild symptoms.

Of the patients with severe symptoms, seven had borderline intellect and two had mild mental deficiency, 17 had a family history of schizophrenia, 26 had early onset of schizophrenia, and 26 reported substance abuse (data not shown).

A total of 57 patients with medium intellect had moderate and 16 had mild symptoms (data not shown). A total of three patients with a late onset of the disease had moderate symptoms and substance abuse. A total of 43 married and 22 unmarried patients presented associated affective symptoms with a moderate severity. However, 19 married male and 24 female patients, with a moderate severity of schizophrenia symptoms, also had affective symptoms.

Data analysis. There was a significant difference in stress levels and marital status between patients with mild-moderate and severe-serious symptoms (Table I).

Severe-serious symptoms were not associated with family history of affective disorder but were associated with the presence of affective symptoms, heredo-collateral antecedents (schizophrenia, late onset, positive and negative symptoms, substance abuse, stress levels, unmarried, low IQ and mild mental deficiency (Table II).

The regression coefficients for mild-moderate symptoms were not significant for family history of affective disorder but were significant for affective symptoms; heredo-collateral antecedents (schizophrenia and affective disorder), early onset, substance abuse, stress levels, limit IQ and mild mental deficiency (Table III).

Although the regression models fit all included data, only certain variables were robust predictors of the symptom severity. There were predictive factors common to all levels of symptom severity, as well as specific predictors, such as positive and negative symptoms and marital status for severe-serious symptoms.

Table I. χ^2 test for mild-moderate and serious-severe symptoms.

Variable	Value	df	P-value
Place of living	4.865	3	0.182
Sex	1.038	3	0.792
Stress levels	38.967	3	<0.001
Marital status	37.352	3	<0.001
Intellectual level	94.871	3	<0.001
Schizophrenia onset	91.999	3	<0.001

Discussion

Schizophrenia is a heterogeneous disorder that can occur in early adulthood, but in many cases, there are signs present from birth (37-39). Given this heterogeneity of the disorder, a combination of factors may determine the occurrence (8,40,41). Schizophrenia affects the entirety of life, including social interactions, hygiene and feeding, quality of sleep, professional and academic achievement and cognition (13,26,38,42). Also, sudden cardiac death occurs at a 0.8% rate in psychiatric hospitals in patients with schizophrenia, which is higher than in the general population (43).

Chou *et al* (44) found a prevalence of schizophrenia 6.3 times higher in patients with a first-degree relative with schizophrenia and 2.4 times higher in individuals with a second-degree relative with schizophrenia, compared with the general population. In the present study, patients with a family history of psychiatry had only first-degree relatives with schizophrenia or depression. There were significant differences between married and unmarried patients depending on the severity of symptoms (married patients had lower severity symptoms). These results are consistent with those reported in the literature; for example Nyer *et al* (45) concluded that patients who are married or older at the onset of schizophrenia have a higher quality of life and lower severity of symptoms. Married patients also have fewer suicidal thoughts and a higher overall quality of life (42,45). The intellectual level varies between patients with schizophrenia symptoms of different severities. Černis *et al* (46) and Linca *et al* (47) demonstrated that patients with a high IQ have fewer negative symptoms and therefore less severe symptoms. In the present study, 57 patients with medium intellect had moderate symptoms and 16 mild symptoms. A total of three patients with late onset of the disease had moderate symptoms and were associated with substance abuse. A total of 43 of the 65 married patients and 22 of 55 unmarried patients reported affective symptoms with a moderate severity. Mild-moderate symptoms were associated with the presence of affective symptoms, heredo-collateral history of schizophrenia, late onset, the presence of positive and negative symptoms, substance abuse, stress levels, unmarried, borderline IQ and mental deficiency. Severe-serious symptoms were associated with affective symptoms, heredo-collateral history of schizophrenia and affective

Table II. Coefficients of logistic regression for servere-serious symptoms.

Variable	Estimate	Standard error	95% confidence interval		Z-score	P-value
			Lower	Upper		
General intercept	0.688	0.799	-0.879	2.254	0.860	0.039
Affective symptoms	-0.473	0.637	-1.722	0.776	-0.743	0.045
Late onset	-0.272	0.487	-1.226	0.683	-0.558	0.047
Positive symptoms						
1	-0.631	0.770	-2.140	0.877	-0.820	0.042
2	-0.658	0.810	-2.246	0.930	-0.612	0.047
3	-22.149	8,331.563	-16,351.712	16,307.415	-0.903	0.038
Negative symptoms						
1	-0.178	0.419	-0.998	0.643	-0.424	0.032
2	-1.092	0.966	-2.985	0.801	-1.131	0.025
3	-21.601	17,246.910	-33,824.923	33,781.721	-0.701	0.039
Heredo-collateral history						
Affective disorders	0.155	0.234	-0.303	0.613	0.662	0.080
Schizophrenia	-20.112	3,240.703	-6,371.772	6,331.549	-0.706	0.045
Specific intercept	0.068	0.145	-0.216	0.353	0.471	0.037
Substance abuse	-1.828	0.763	-3.323	-0.333	-2.397	0.017
Stress levels	-0.014	0.246	-0.496	0.467	-0.458	0.044
Unmarried	-0.015	0.261	-0.528	0.497	-0.458	0.045
IQ	-0.209	0.379	-0.951	0.533	-0.552	0.031
Mild mental deficiency	-0.434	0.745	-1.894	1.026	-0.583	0.040

Table III. Coefficients of logistic regression for mild-moderate symptoms.

Variable	Estimate	Standard error	95% confidence interval		Z-score	P-value
			Lower	Upper		
General intercept	-19.585	5,420.523	-10,643.616	10,604.445	-0.004	0.047
Affective symptoms	2.310	1.324	-0.286	4.906	1.744	0.031
Late onset	3.914	1.040	1.877	5.952	3.765	<0.001
Positive symptoms						
1	14.861	5,420.523	-10,609.170	10,638.892	0.003	0.998
2	14.756	5,420.523	-10,609.275	10,638.786	0.003	0.998
3	15.354	5,420.523	-10,608.677	10,639.385	0.003	0.998
Negative symptoms						
1	0.185	0.438	-0.673	1.043	0.423	0.673
2	0.340	0.600	-0.835	1.515	0.567	0.571
3	0.556	0.823	-1.057	2.169	0.676	0.499
Heredo-collateral history						
Affective disorders	-1.583	1.041	-3.623	0.457	-1.521	0.028
Schizophrenia	1.749	0.356	1.051	2.447	4.912	<0.001
Specific intercept	-23.514	7,644.552	-15,006.560	14,959.533	-1.203	0.038
Substance abuse	21.896	7,644.552	-14,961.150	15,004.943	1.003	0.028
Stress levels	0.120	0.749	-1.348	1.589	1.161	0.045
Unmarried	0.026	0.518	-0.988	1.040	0.050	0.090
IQ	0.418	0.848	-1.245	2.080	1.492	0.022
Mild mental deficiency	0.396	0.874	-1.317	2.109	1.453	0.041

disorders, substance abuse, stress levels, borderline IQ and mild mental deficiency. DSM-5 assessement is more time-efficient and, by considering not only the symptoms but also the general functionality of the patient and the response to certain interventions, offers a more objective evaluation than the PANSS which is a more subjective evaluation scale that only focuses on symptomatology. To the best of our knowledge, no previous studies have used a holistic approach to these factors; most studies (20,48-51) focus only on 1-2 risk factors. The present study has several limitations, such as potential selection error and reliance on interviews for data collection, which may introduce recall bias; further studies should consider gathering information form additional sources, such as medical records. Aditional factors, such as those associated with intrauterine life (for example, malnutrition or infections during pregnancy and obstetrical complications) were not analyzed due to difficulty in obtaining relevant and accurate data. Relying solely on the family interview would have introduced recall bias, given the long period of time since the birth of each patient.

An evidence-based approach to clinical presentation and evolution of psychosis is the first step in identifying strategies for developing personalized treatment such as multidisciplinary approach to schizophrenia involving other healthcare specialists (psychologists and primary care physicians). Identifying risk factors for predicting the severity of symptoms may contribute to better management concerning all aspects involved in the course of illness (symptom-free time frames, adequate social and work-field reinsertion, better quality of life and decreased suicide risk). Notably, a positive familial history of psychiatric disorders was a significant risk factor influencing severity of symptoms. Additionally, significant risk factors include urban dwelling, sex, substance use, marital status (unmarried) and intellectual level. The present results can be used to improve the outcome of the disease in the early stages. Information regarding medical history and the bio-psycho-social characteristics of the patient comes can improve the therapeutic approach, which may improve treatment compliance and accurately understanding the disease and what it involves.

Although the present results may not be generalized to other cohorts due to the relatively small size of the sample, the present study provides a basis for investigating predictors in future using larger cohorts. These should include intellectual level, marital status, levels of occupational stress and age of onset. Longitudinal studies should be performed to assess the influence on the severity of symptoms of patients with schizophrenia.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FPI, RML and AMM conceived and designed the study and wrote the manuscript. MCM and AT analyzed data and revised the manuscript. RML and AMM edited the manuscript and data analysis and interpretation. CAC and CIV collected and analyzed data analysis. AMC and MM supervised and conceived the study and reviewed the manuscript. FPI and MCM confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of 'Prof. Dr. Alexandru Obregia' Clinical Hospital of Psychiatry, Bucharest, Romania (approval no. 10/21.03.2018). Written informed consent was obtained from each patient/legal guardian of each patient regarding participation in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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