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*Research Article*

# Development of a Prognostic Stratification Scale for Cardiovascular Death in Patients with Schizophrenia

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## ABSTRACT

**Introduction:** Patients with schizophrenia have a 15-20 year reduced life expectancy compared to the general population, with cardiovascular diseases being the leading cause of death. Conventional cardiovascular risk scales (Framingham, SCORE, REGICOR) have significant limitations as they do not include specific variables for mental illness and are not validated for the Cuban socioeconomic and healthcare context.

**Objective:** To develop and validate a prognostic model and cardiovascular death risk stratification scale specific for patients with schizophrenia in Sancti Spíritus province, Cuba.

**Methods:** An observational analytical study for prognostic model development with prospective cohort design was designed. 350 patients with schizophrenia diagnosis (ICD-10) from "Camilo Cienfuegos" Provincial General Hospital in Sancti Spíritus will be recruited, with 24-month prospective follow-up. Study variables will include demographic dimensions (age, sex, disease evolution time), clinical (BMI, blood pressure, smoking, sedentary behavior), psychiatric (schizophrenia subtype, antipsychotic treatment), hemochemical parameters (lipid profile, blood glucose, creatinine) and socio-environmental factors (social support, family functioning, educational level). Statistical analysis will follow a sequential strategy: descriptive analysis, univariate analysis (Chi-square, t-Student tests), survival analysis using Cox regression to identify independent prognostic factors, prognostic model development based on Beta coefficients, scoring scale elaboration, and internal validation through bootstrapping with 1,000 resamples.

**Expected results:** Based on reviewed literature, independent prognostic factors anticipated include: age > 50 years (expected RR: 2.1; 95%CI: 1.8-2.5), schizophrenia evolution time > 10 years (RR: 1.8; 95%CI: 1.5-2.2), use of high metabolic risk atypical antipsychotics (RR: 1.5; 95%CI: 1.2-1.9), HDL cholesterol < 40 mg/dL (RR: 2.2; 95%CI: 1.8-2.7), and low family social support (RR: 1.9; 95%CI: 1.6-2.3). The final model will include 6-8 significant predictor variables ($p < 0.05$) and demonstrate adequate discriminatory capacity (Harrell's C-index > 0.75) and calibration.

**Conclusions:** These findings confirm the existing idea that alcohol makes a significant contribution to the burden of suicide mortality in the European region. These results also suggest that alcohol is a key predictor of the East-West gap in suicide rates.

**KEYWORDS**

Schizophrenia, Cardiovascular disease, Risk stratification, Prognosis, Cuba, Premature mortality.

## Introduction

Cardiovascular diseases (CVD) constitute one of the main challenges for health systems globally. According to World Health Organization reports, CVD were responsible for approximately 19.8 million deaths in 2022, representing a significant increase compared to the 12.4 million registered in 1990 [1]. In the Cuban context, this problem acquires particular relevance when analyzing specific mortality rates. During 2022, Cuba reported an adjusted CVD mortality rate of 129.6 per 100,000 inhabitants, with a crude rate of 296.7 [2]. The province of Sancti Spíritus, the geographical scope of this study, showed even higher indicators, with a crude mortality rate of 359.6 and an adjusted rate of 148.1 per 100,000 inhabitants [2].

Concurrently, schizophrenia represents a severe mental health condition affecting approximately 1% of the world population [3]. Patients diagnosed with this disorder present a particularly high vulnerability for developing medical comorbidities and experiencing premature mortality. Robust epidemiological studies have demonstrated that patients with schizophrenia have a 2-3 times greater risk of dying than the general population [4]. While initially this excess mortality was attributed to external causes such as suicides, homicides, or accidents, contemporary evidence identifies cardiovascular diseases as the leading cause of death in this population [5].

The association between schizophrenia and CVD has been the subject of growing scientific interest in recent decades. Recent systematic reviews and meta-analyses have confirmed this relationship, particularly for coronary heart disease and cerebrovascular disease [6]. An emerging hypothesis postulates that schizophrenia *per se* constitutes an independent risk factor for CVD, not completely explainable by traditional cardiovascular risk factors, lifestyles, or medication iatrogenesis [7]. This intrinsic vulnerability could be mediated by alterations in neuroendocrine systems, chronic inflammatory processes, autonomic dysfunction, and shared genetic factors [8].

In routine clinical practice, cardiovascular risk stratification in patients with schizophrenia is predominantly performed using scales designed for the general population, such as Framingham, SCORE, REGICOR, or WHO charts [9]. However, these tools have fundamental limitations when applied to this specific population. Firstly, they were developed and validated in cohorts that systematically excluded patients with severe mental illness [10]. Secondly, they do not incorporate specific variables relevant to schizophrenia, such as the type and duration of antipsychotic treatment, particular symptomatic characteristics, or specific psychosocial dimensions [11]. Finally, these scales were calibrated for populations with epidemiological, genetic, and socioeconomic characteristics different from those of the Cuban population [12].

In the international context, some specific instruments for populations with severe mental disorders have been developed. The PRIMROSE model developed in the United Kingdom stands out, which includes variables such as prescription of antipsychotics, antidepressants, and social deprivation [13]. However, its applicability in the Cuban health system is limited due to structural differences in the organization of health services, distinct epidemiological profiles, and differential availability of diagnostic and therapeutic resources [14].

In Cuba, care for patients with schizophrenia is governed by treatment guidelines and action protocols that, unfortunately, prioritize the management of psychotic symptoms over cardiovascular prevention [15]. Risk stratification is performed using tools extrapolated from other regions, without evidence of their validity in this specific population. This care gap becomes more relevant considering that, according to WHO data, deaths attributed to schizophrenia in Cuba reached 68 in 2020, placing the country 12th worldwide in terms of disease burden from this disorder [16].

The creation of a specific cardiovascular risk stratification tool for patients with schizophrenia, adapted to the Cuban context, would allow not only the early identification of individuals with greater vulnerability but also the optimization of limited health resource allocation and guide personalized preventive interventions. This study is based on the premise that incorporating specific clinical, psychiatric, and socio-environmental variables of this population will significantly improve predictive accuracy compared to conventional scales.

Therefore, the **general objective** of this research is to develop and validate a prognostic model and a scale for the stratification of cardiovascular death risk in patients with schizophrenia from the

province of Sancti Spíritus, Cuba. To address this, we proceeded to describe the baseline characteristics of the study population and the variables related to cardiovascular risk; identify prognostic factors that allow estimation of the probability of cardiovascular death; then determine a prognostic model of cardiovascular mortality based on the identified predictors; to develop a risk scale for prognostic stratification and proceed to validate the obtained risk scale.

## Methods

**Study design:** An observational analytical study for the development and validation of a prognostic model, with a prospective cohort design, was designed. This design is appropriate for the stated objectives, as it allows establishing temporal relationships between predictor variables and the outcome of interest, as well as calculating association measures such as relative risks. The study will follow the recommendations of the TRIPOD statement (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) to guarantee methodological quality and transparency in reporting [17].

**Setting and period:** The study will be developed at the "Camilo Cienfuegos" Provincial General Hospital in Sancti Spíritus, Cuba, and in the outpatient psychiatry services associated with this institution. This hospital is the main referral center for mental health in the province, serving an approximate population of 465,000 inhabitants. The recruitment period will extend from January 2024 to December 2025, with a prospective follow-up of 24 months for each included patient. The study completion is planned for December 2027, allowing for complete data analysis and model validation.

**Population and sample:** The target population consists of approximately 1,200 patients with a diagnosis of schizophrenia (codes F20.x according to ICD-10) registered in the psychiatry services of the study setting. The sample size calculation was performed considering the following parameters: statistical power of 80%, significance level of 0.05, expected relative risk of 2.0, proportion of exposed of 40%, and event rate of 15% in the highest risk group. Using the Schoenfeld formula for proportional hazards models, a minimum sample size of 298 patients was determined. Anticipating a possible 15% loss during follow-up, the final sample size was set at 350 patients.

### Inclusion criteria

- Confirmed diagnosis of schizophrenia according to ICD-10 criteria
- Age equal to or greater than 18 years
- Expected permanence in the province during the study period
- Written informed consent from the patient or legal representative

### Exclusion criteria

- Established cardiovascular disease at study start (previous acute myocardial infarction, cerebrovascular accident, coronary revascularization, symptomatic heart failure)
- Life expectancy less than 1 year due to concomitant medical conditions
- Refusal to participate in the study
- Inability to complete baseline evaluations due to clinical or cognitive conditions

### Study variables

- **Primary outcome variable:** Death from cardiovascular cause, defined as death attributable to acute myocardial infarction, cerebrovascular accident, sudden cardiac death, or heart failure, confirmed through review of death certificates and medical records.
- **Predictor variables:** Organized into five dimensions:
  1. *Demographic:* age (completed years), sex (male/female), time since schizophrenia onset (years since first diagnosis)
  2. *Clinical:* body mass index (kg/m$^2$), systolic and diastolic blood pressure (mmHg), smoking status (never smoker/former smoker/current smoker), alcohol consumption (absent/mild/moderate/severe according to AUDIT), sedentary behavior (hours/day in sedentary activities)
  3. *Psychiatric:* schizophrenia subtype (paranoid/hebephrenic/catatonic/undifferentiated/residual), antipsychotic treatment (type, chlorpromazine equivalent dose, duration of current treatment), current symptomatology (assessed using PANSS)
  4. *Hemochemical:* fasting glucose (mmol/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), creatinine (µmol/L)
  5. *Socio-environmental:* social support (assessed using MOS scale), family functioning (family APGAR), educational level (years of formal education), employment status (employed/unemployed/disabled)

### Data collection

Data collection will be performed using a structured form designed specifically for this study. This instrument will include sections for: (a) data from psychiatric and medical records; (b) structured clinical interview with the patient; (c) interview with family member or primary caregiver; (d) clinical laboratory results. Hemochemical variables will be determined in the hospital's clinical laboratory using standardized and automated methods. All blood pressure measurements will be performed following the protocol established by the Cuban Society of Arterial Hypertension, with calibrated sphygmomanometers and by trained personnel.

### Ethical aspects

The study protocol was approved by the Research Ethics Committee of the University of Medical Sciences of Sancti Spíritus (Minutes No. 15/2023). Written informed consent will be obtained from all participants after a detailed explanation of the objectives, procedures, potential benefits, and risks of the study. In cases of patients with diminished capacity to consent, consent will be obtained from the legal representative as established by current Cuban legislation. Data confidentiality will be guaranteed through

the use of identification codes and secure database storage. The study will be conducted in accordance with the principles of the Declaration of Helsinki and Cuban ethical regulations for research in humans.

## Statistical analysis

Data analysis will follow a sequential strategy:

1. *Descriptive analysis:* Measures of central tendency and dispersion will be calculated for continuous variables, and frequencies and percentages for categorical variables. The normality of distributions will be assessed using Kolmogorov-Smirnov tests.
2. *Univariate analysis:* Chi-square tests for categorical variables and Student's t-tests or ANOVA for continuous variables, as appropriate, will be used to identify preliminary associations with the outcome.
3. *Survival analysis:* Cox regression will be used to identify independent prognostic factors. The proportional hazards assumption will be verified using Schoenfeld residual analysis.
4. *Prognostic model development:* The Beta coefficients from the Cox regression will be transformed into points to create a scoring scale. Both full models and simplified models using backward stepwise selection will be considered.
5. *Scale elaboration:* Points will be assigned proportionally to the Beta coefficients, creating risk categories (low, moderate, high) based on clinically significant cut-off points.
6. *Internal validation:* Will be performed using bootstrapping with 1,000 resamples to correct model optimism and obtain more robust estimates of its performance.
7. *Performance evaluation:* Harrell's C-index will be calculated for discrimination and a calibration plot will be constructed to assess the agreement between predicted and observed probabilities.

Data management and analysis will be performed with SPSS v.25 and R v.4.0 with the rms and survival packages.

## Expected Results

Based on the exhaustive review of the literature and the epidemiological characteristics of the Cuban population with schizophrenia, the following results are anticipated:

## Baseline population characteristics

A cohort of 350 patients is expected to be recruited with a sex distribution similar to that reported in previous national studies (approximately 55% male, 45% female). The anticipated mean age is 45±12 years, with a mean time since schizophrenia onset of 15±8 years. Regarding the distribution by diagnostic subtypes, a predominance of the paranoid subtype (≈60%) is expected, followed by undifferentiated (≈25%) and residual (≈15%).

## Prevalence of cardiovascular risk factors

According to international literature and previous Cuban studies, a high prevalence of modifiable cardiovascular risk factors is anticipated: active smoking (≥60%), sedentary behavior (≥70%, defined as <150 minutes of moderate physical activity/week), metabolic syndrome according to ATP-III criteria (≥30%), abdominal obesity (≥40%), arterial hypertension (≥35%), and dyslipidemias (≥50%)[18]. The antipsychotic treatment profile will likely show a predominance of atypical antipsychotics (≈70%), with olanzapine and risperidone being the most frequently prescribed.

**Identified prognostic factors:** In the multivariate analysis using Cox regression, the following are anticipated to be identified as independent prognostic factors for cardiovascular death:

- Age > 50 years (expected RR: 2.1; 95%CI: 1.8-2.5; p<0.001)
- Time since schizophrenia onset > 10 years (RR: 1.8; 95%CI: 1.5-2.2; p=0.003)
- Use of high metabolic risk atypical antipsychotics (olanzapine, clozapine) (RR: 1.5; 95%CI: 1.2-1.9; p=0.012)
- HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women (RR: 2.2; 95%CI: 1.8-2.7; p<0.001)
- Active smoking (≥10 cigarettes/day) (RR: 1.6; 95%CI: 1.3-2.0; p=0.008)
- Low family social support (APGAR score < 7) (RR: 1.9; 95%CI: 1.6-2.3; p=0.005)
- Systolic blood pressure > 140 mmHg (RR: 1.7; 95%CI: 1.4-2.1; p=0.010)

## Final prognostic model

The final model is anticipated to include between 6-8 statistically significant predictor variables ($p < 0.05$). The model will demonstrate adequate global fit (likelihood ratio test, $p<0.001$) and compliance with the proportional hazards assumption (Schoenfeld test, $p>0.05$). The model equation will have the form: Risk Score = $\Sigma(\beta i \times Xi)$, where $\beta i$ represents the Cox regression coefficients and Xi the values of each predictor variable.

## Risk stratification scale

The scale derived from the model will allow stratifying patients into three risk categories based on the total score:

- **Low risk:** score <20, 5-year risk <5%
- **Moderate risk:** score 20-35, 5-year risk 5-15%
- **High risk:** score >35, 5-year risk >15%

## Model validation

Internal validation through bootstrapping is expected to show good model performance, with an optimism-corrected Harrell's C-index >0.75, indicating adequate discriminatory capacity. The calibration plot is expected to demonstrate good agreement between predicted and observed probabilities, with a calibration slope close to 1 and a non-significant Hosmer-Lemeshow test ($p>0.05$).

## Discussion

The development of a specific scale for cardiovascular risk stratification in patients with schizophrenia represents a necessary response to an identified care gap in the Cuban health system. The expected results of this study align with findings reported in the international literature, which consistently highlight the importance of specific factors in this population, such as the

type of antipsychotic, the time since illness onset, and particular psychosocial dimensions [19].

The anticipated identification of time since schizophrenia onset as an independent prognostic factor reinforces the hypothesis that the cumulative burden of mental illness contributes significantly to cardiovascular risk. This finding would be consistent with previous studies that have documented a dose-response relationship between the duration of schizophrenia and all-cause mortality [20]. Underlying mechanisms could include cumulative neurobiological effects, prolonged exposure to psychotropic medications, and progressive deterioration of psychosocial functioning.

The inclusion of socio-environmental variables, particularly family social support, constitutes a significant innovation compared to conventional cardiovascular risk scales. Scientific literature has consistently demonstrated that family functioning and social support are crucial determinants in the clinical evolution of patients with schizophrenia, influencing treatment adherence, lifestyles, and access to health services [21]. In the Cuban context, where the family traditionally plays a central role in supporting people with mental illness, this variable could have particularly high relevance.

The emphasis on low-cost hemochemical parameters widely available in the Cuban health system (such as HDL cholesterol) responds to the need to develop feasible and sustainable tools in resource-limited contexts. This approach is consistent with WHO recommendations for the development of risk assessment instruments in middle- and low-income countries [22].

The potential limitations of the study deserve consideration. Firstly, the observational design prevents establishing definitive causal relationships between predictor variables and the outcome. However, the prospective nature of the cohort and adjustment for multiple confounding factors will allow robust inferences about prognostic associations. Secondly, being conducted in a single Cuban province, the generalization of the results will require external validation in other regions of the country. Nevertheless, the selection of Sancti Spíritus, with its epidemiological characteristics representative of the Cuban context, increases the likelihood that the findings will be extrapolable. Finally, possible loss to follow-up constitutes a methodological concern that will be addressed through active participant tracking and retention strategies.

The practical implications of this research are multifaceted. At the individual clinical level, the resulting scale will allow psychiatrists and family physicians to identify high-risk patients requiring intensive preventive interventions, optimize the selection of antipsychotics according to individual metabolic risk profile, and improve coordination between psychiatry and cardiology services. At the public health level, it will facilitate the efficient allocation of limited resources towards the most vulnerable population, prioritizing cost-effective interventions in high-risk subgroups. Additionally, the scale could serve as an evaluation tool in future research on preventive interventions in this population.

The scientific novelty of this study lies in several aspects: (1) It is the first development of a specific cardiovascular risk scale for patients with schizophrenia in Cuba; (2) It incorporates dimensions traditionally omitted in conventional scales, such as specific psychiatric variables and socio-environmental factors; (3) It uses a robust methodology for the development and validation of prognostic models; (4) It responds to the particularities of the Cuban health system and its socioeconomic context.

Future studies should evaluate the impact of the implementation of this scale on relevant clinical outcomes (cardiovascular mortality, non-fatal events, quality of life) and on the efficiency of health resource use. Likewise, it would be valuable to explore the possible utility of the scale in other severe mental disorders with high cardiovascular mortality, such as bipolar disorder.

## Conclusions

1. The development of a specific scale for cardiovascular risk stratification in patients with schizophrenia is methodologically feasible and addresses an unmet clinical need in the Cuban health system.
2. The proposed scale will incorporate clinical, psychiatric, and socio-environmental variables not considered in conventional tools, which will potentially improve its predictive accuracy in this specific population.
3. The anticipated prognostic factors (age, time since onset, antipsychotic treatment, metabolic parameters, and social support) reflect the multifactorial nature of cardiovascular risk in schizophrenia.
4. The implementation of this tool could contribute significantly to reducing premature cardiovascular mortality in this vulnerable population through the early identification of high-risk individuals and the optimization of preventive strategies.
5. External validation of the scale in other regions of Cuba is recommended once developed, as well as implementation studies that evaluate its impact on clinical and organizational outcomes.

## Ethical Aspects

Approved by the Research Ethics Committee of the University of Medical Sciences of Sancti Spíritus (Minutes No. 15/2023). Informed consent will be obtained from all participants.

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