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Stability of schizophrenia diagnosis in a ten-year longitudinal study on first episode of non-affective psychosis: conclusions from the PAFIP cohort

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ABSTRACT

Objective: To evaluate the ten-year stability of schizophrenia diagnosis in a cohort of first-episode psychosis (FEP) patients and the factors associated with it.

Methods: Changes in diagnosis of 209 FEP patients were described during ten years of follow-up. Related factors with maintenance or change of schizophrenia diagnosis were evaluated in prospective and retrospective approaches through Binary Logistic Regressions, ROC and survival curves.

Results: Out of the 209 patients, 126 were diagnosed of schizophrenia six months after their inclusion in the clinical program. Prospective analyses showed that eight of those 126 schizophrenia patients had changed to a different diagnosis after ten years, and predictors of change were better childhood premorbid adjustment, less severity of clinical global impression at baseline, and diagnosis of comorbid personality disorder during follow-up. Retrospectively, out of the 154 patients with schizophrenia in the ten-year assessment, 36 had a different diagnosis at baseline, and those factors related with a different prior diagnosis than schizophrenia were better socioeconomic status and shorter duration of untreated psychosis (DUP). A survival analysis on the timing of schizophrenia diagnosis showed that male gender and longer DUP were predictors of earlier definite diagnosis.

Conclusions: Diagnostic stability of schizophrenia in our FEP sample is high, especially prospective stability, and the group of patients with diagnostic change corresponded to a milder psychopathological profile before and at the onset of disease. Moreover, we observed a cautious attitude in the diagnosis of schizophrenia in patients with shorter DUP who had schizophrenia diagnosis after ten years.

Keywords: Schizophrenia; first-episode psychosis; cohort; follow-up; diagnosis.

Significant outcomes:

- A detailed assessment of FEP patients focused on premorbid adjustment and comorbidity with personality disorders may lead to high diagnostic stability of schizophrenia.
- Certain factors regarded as classical predictors for schizophrenia prognosis, such as gender and DUP, influence the time until definite schizophrenia diagnosis.

Limitations:

- Given the high prospective stability of schizophrenia diagnosis, the number of patients who changed to a different diagnosis at ten-year assessment was small (N=8), thus reducing the statistical power.

Data Availability Statement

- Data will be available upon request

1. INTRODUCTION

Schizophrenia spectrum disorders (SSD) are a heterogenous group of diseases characterized by abnormalities in one or more of the following features: delusions, hallucinations, disorganized thinking, abnormal or peculiar motor behaviour and negative symptoms (1). Although exhibiting an important overlap of symptoms, this group of disorders differs in terms of type, complexity and duration of psychopathology, varying in their long-term prognosis. Within them, schizophrenia is a complex mental disorder that affects approximately 1% of the general population and whose diagnosis represents a challenge for both, clinicians and patients. Challenges for clinicians concern the absence of pathognomonic symptoms, the poor understanding of the neuropathology and pathophysiology, and the multifactorial etiology (2,3). In this vein, schizophrenia diagnosis is also difficult because approximately half of schizophrenia patients has comorbidity with at least one psychiatric or medical condition (4); and symptoms sometimes resemble clinical manifestations of other mental diseases such as personality disorders (5) or substance-induced psychosis (6). Besides, for patients, receiving a diagnosis of schizophrenia may be a life-changing experience, sometimes leading to disabling consequences and self-stigma (7), as it is considered a lifelong illness that may convey long-term cognitive or functional impairments (8). However, an early intervention during first episode of psychosis (FEP) may reduce the duration of untreated psychosis (DUP), hospital admissions, relapse rates and symptom severity (9,10). Moreover, the increased contact between health staff and patients and families enhances adherence and longitudinal diagnostic assessments (11). Taken together, these considerations highlight the need for caution in schizophrenia diagnosis but, at the same time, an early identification of symptoms in at-risk patients, or those who have already experienced a FEP, is crucial for the prognosis over functional and clinical outcomes (12,13). In order to establish a precise balance between diagnostic cautiousness and assertiveness, it is important to have an accurate knowledge of the premorbid adjustment, clinical and

sociodemographic factors that have been associated to a revision of the diagnosis in patients presenting with early psychosis (14).

However, the proportion of schizophrenia diagnosis in FEP cohorts varies across different studies in function of the employed diagnostic system. The two main systems used at present are the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), proposed respectively by the American Psychiatric Association (APA) and the World Health Organization (WHO). When defining schizophrenia, the main difference between both systems is the symptom duration criterion (six months for DSM-IV and one month for ICD-10). On the one hand, the longer duration criterion for symptoms according to DSM-IV establishes the diagnosis in a more conservative framework, which theoretically, confers a greater predictive validity. On the other hand, the use of ICD-10 criteria for schizophrenia diagnosis yields a greater statistical power (15).

During the diagnostic process, the apparent prevalence of schizophrenia rises over time in people with psychotic disorders (16), as the diagnostic shift from any other psychotic disorder to schizophrenia occurs significantly more often than the shift in the opposite direction (17). In line with this, several authors have investigated the middle to long-term stability of schizophrenia diagnosis in FEP samples. The maintenance of DSM-IV baseline schizophrenia diagnosis (i.e. prospective stability) was 95-99% after one year (18,19); 97% after 18 months (11) and between 87 and 99% after two years (19–21). Two studies exploring prospective stability of schizophrenia diagnosis after three years found rates of 91% using DSM-IV at baseline (17), and 80% irrespective of the employed system (ICD-10 and DSM-IV)(22). After ten years, between 73 and 93% of schizophrenia patients retained their schizophrenia diagnosis made following DSM-IV criteria at baseline (23,24), whereas 75% of patients maintained their diagnosis of schizophrenia when first diagnosis was made using ICD-10 criteria (23,25). Regarding retrospective stability of schizophrenia diagnosis (i.e., what proportion of patients with a final diagnosis of schizophrenia had received the same diagnosis at baseline), two studies explored diagnostic change during two years finding rates between 63 and 79%, using DSM-IV (20,21). Similarly, after ten years, retrospective stability ranged between 60 and 69%, depending on the employed diagnostic classification system (DSM-IV and ICD-10, respectively)(23). Although studies showed heterogenous results, it seems evident that retrospective stability of schizophrenia diagnosis was lower than the prospective one. Furthermore, a quantitative synthesis of studies found no significant differences between ICD-10 *vs* DSM-IV systems in terms of prospective stability (26).

Aims of the study

The aim of this research was to evaluate the ten-year stability of schizophrenia diagnosis in a large cohort of FEP patients (N=209), exploring the diagnostic shift toward and away from schizophrenia during the follow-up (retrospective and prospective stability, respectively). Diagnostic stability was studied between baseline (six months since first contact) and a reassessment visit at ten years. Prospective stability referred to the proportion of individuals initially diagnosed with schizophrenia who retained the same diagnosis after ten years of follow-up, which would correspond to the positive predictive value of a schizophrenia diagnosis at baseline. Meanwhile, retrospective stability was the proportion of subjects, within the total number with schizophrenia diagnosis at the ten-year visit, who had received the same diagnosis at baseline, and this would correspond to sensitivity (21). As another of the main goals, factors that predicted diagnostic *instability* were sought by means of Binary Logistic Regression, wherein the effect of sociodemographic and clinical modulators was ascertained. In order to better guide diagnostic decisions, significant predictors were subsequently explored by means of Receiver Operating Characteristic (ROC) curves, to determine the optimal cut-off point for diagnostic accuracy (sensitivity and specificity). Finally, by using survival analyses, we aimed to explore the time until acquisition of a definite schizophrenia diagnosis.

2. MATERIAL AND METHODS

2.1. Subjects, study setting and design

The present study was performed over a large cohort of non-affective FEP patients (N=307) from an early intervention program; participants were intensively followed during the first three years after onset, and re-evaluated at ten years. Assessments were broad and structured at the main time points: first contact (T0), six months (T6m) -this is considered the 'baseline' time point for the analyses on diagnostic stability in this study-, three years (T3y) and ten years (T10y) of follow-up; data about symptoms, functioning, outcomes, substance consumption, quality of life and cognition were collected at these main time points.

Patients were recruited from February 2001 to July 2008 and treated during the first three years after initial presentation as part of a longitudinal clinical program for early psychosis (known as PAFIP, Spanish abbreviations) at the University Hospital Marqués de Valdecilla, Cantabria, Spain. This hospital is the only medical institution with 24-hour Psychiatric Emergency Services and with inpatient unit in the province of Cantabria, covering a catchment area of 550,000 inhabitants. A detailed description of the program is available in previous articles (27,28). Patients recruited for the program came from hospital Emergencies, the inpatient unit and mental health outpatients clinics and they met the following inclusion criteria: 1) aged 15-60 years at the time of first evaluation; 2) living in the catchment area; 3) experiencing a non-

affective first episode of psychosis (FEP); 4) neuroleptic-*naïve* patients or, if previously treated, the life-time treatment duration was less than six weeks; and 5) meeting diagnostic criteria for schizophrenia, schizophreniform disorder, brief psychotic disorder, not otherwise specified (NOS) psychosis or schizoaffective disorder according to DSM-IV criteria. Patients were excluded for any of the following reasons: 1) intellectual disability ('mental retardation') according to DSM-IV criteria; 2) history of brain injury or neurological disease; and 3) meeting criteria for drug dependence (except nicotine dependence). Conforming to international standards for research ethics, this study was approved by the local research ethics committee and patients provided written informed consent to be included in the PAFIP clinical program.

Patients who contacted with the program were evaluated by a psychiatric nurse and a consultant psychiatrist who carried out a formal interview to confirm the presence of FEP. At this point, clinical scales were administered with the patient alone. The program provided an intensive medical and multidisciplinary management during the first three years after FEP. After this period, patients were referred to their corresponding mental health outpatient unit. For the present longitudinal study (PAFIP-10 study), all patients included in the PAFIP program between 2001 and 2008 were invited for a reassessment about ten years after their first contact (actually between 8 and 12 years).

2.2. Assessments

Only the specific variables used for this study are described in this section. A detailed description of the collected variables for PAFIP and PAFIP-10 studies has been described elsewhere (27,29).

2.2.1. Diagnosis

A provisional diagnostic impression was made at the initial presentation (T0), and was reviewed six months later (T6m) by means of the Structured Clinical Interview for DSM-IV Disorders axis I (SCID-I) (30) and axis II, personality disorders (SCID-II) (31). For this study we used the T6m diagnosis as 'baseline' because of the chronological criterion for diagnosis of schizophrenia according to DSM-IV, requiring 'at least six months of continuous signs of perturbance'. Diagnoses were also reviewed at the end of the PAFIP program (T3y) and at ten years of follow-up (T10y) by psychiatrists blind to previous diagnosis, using SCID-I and SCID-II. For those patients who received a schizophrenia diagnosis between the last standard PAFIP visit (T3y) and the ten-year reassessment (T10y), a thorough review of medical records was performed in order to establish the time point when schizophrenia diagnosis is reached. Comorbid

personality disorders diagnosed by treating clinicians after T3y were also assessed through retrospective examination of the patient´s medical records.

2.2.2. Sociodemographic variables

The following sociodemographic information was collected from patients, relatives and medical records on admission (T0) and at T10y: gender, family history of psychosis (1. Yes/2. No), socioeconomic status derived from parents 'occupation (1. Low-skilled worker/ 2. other) and employment status (1. Unemployed/2. Other, including students).

2.2.3. Clinical variables prior to inclusion

Clinical variables previous to inclusion in the program considered for the study were: 1) duration of untreated psychosis (DUP), defined as the time from the first continuous psychotic symptoms to the introduction of appropriate neuroleptic treatment; 2) age of psychosis onset, defined as the age when the first continuous psychotic symptoms appeared, and 3) premorbid adjustment measured with Premorbid Adjustment Scale (PAS), that evaluates the degree of achievement of developmental goals at several stages in a subject's life before the onset of schizophrenia (childhood: up to 11 years old (y.o.); early adolescence: 12-15 y.o.; late adolescence: 16-18 y.o.; and adulthood: 19 y.o. and beyond), higher scores in PAS mean poorer adjustment (32).

2.2.4. Clinical variables posterior to inclusion

The following clinical variables measured at T0 were used: Negative and positive psychotic symptoms were respectively measured by the Scale for the Assessment of Negative Symptoms (SANS) (33) and the Scale for the Assessment of Positive Symptoms (SAPS) (34). General psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS) (35). Depression was measured with the Calgary Depression Scale for Schizophrenia (CDSS) (36) and manic symptomatology using the Young Mania Rating Scale (YMRS) (37). Higher scores in SANS, SAPS, CDSS and YMRS imply worse psychopathology. Severity of the patient's illness at the time of assessment was measured with the Clinical Global Impression-Severity (CGI-S) rating scale (38), a 7-point scale to rate the severity regarding clinician's past experience with patients with same diagnosis. The possible rating is: 1. Normal, not at all ill; 2. Borderline mentally ill; 3. Mildly ill; 4. Moderately ill; 5. Markedly ill; 6. Severely ill; 7. Among the most extremely ill patients.

At T10y, we considered the following factors: if patient had any psychotic relapse during the follow-up after reaching clinical stability according to Andreasen´s criteria (39), whereas relapse is defined by any of

the following criteria for at least one week: 1) ≥5 on any BPRS key symptoms; 2) CGI-I (CGI-improvement) score ≥6 and change in the CGI to "much worse" or "very much worse"; 3) hospitalization due to psychosis; 4) suicide (40–42).

2.3. Statistical analysis

For the study of each prospective and retrospective stability, a dichotomous variable was created named 'diagnostic change' which assigned a value of 1 once a patient experienced a diagnosis shift, and 0 for those patients who retained the same diagnosis during the ten years of follow-up (i.e., between T6m and T10y). Diagnostic change was employed as dependent variable in our analyses. For prospective and retrospective stability, separately considered, two multivariate analyses using stepwise logistic regression were performed to assess the relative contribution of each potential predictor of diagnosis change during the ten-year follow-up. Variable selection for models was based on evidence from previous studies of diagnostic stability in psychosis, lack of missing data and results of previous exploratory univariate analyses. As such, the following were explored as independent variables: 1. Sociodemographic factors (gender, family history of psychosis, socioeconomic status, employment); 2. Clinical variables previous to study inclusion (DUP, age of psychosis onset, PAS childhood); 3. Clinical variables at study onset (BPRS, SAPS, SANS, CDSS, YMRS, CGI-S); 4. Clinical variables during the ten-year follow-up (Psychosis relapse and personality disorder diagnosis). For each approach (prospective and retrospective diagnosis stability), two models were created: the first only contained variables that were already available at baseline, while the second also incorporated information from the period of follow-up (i.e., subsequence diagnosis of personality disorder and psychotic relapses). Alternative models employing variables with higher proportion of missing data (e.g., psychopathological scales administered at T10y) were conducted as sensitivity analysis.

Once established the significant predictors of diagnosis stability by logistic regression, Receiver Operating Characteristic (ROC) curves were performed on each of the significant quantitative predictors, and on the entire logistic regression model. The optimal cut-off point for those quantitative predictors was decided by visual inspection and the maximum value of Youden index in the ROC curves (43).

Finally, factors associated to time of stabilization of schizophrenia diagnosis were sought by means of multiple Cox survival regression analyses. Time to stabilization of schizophrenia diagnosis was defined as the time between initial diagnosis (six-month visit) and the date of definite schizophrenia diagnosis (this time could be 0 if the patient has received schizophrenia diagnosis from the start). The time was determined retrospectively through examination of the patient´s medical records, including PAFIP

assessments (T6m, T3y, T10y), and diagnostic impression by the treating clinician at the outpatient units or hospital reports of admissions (in cases of relapse). The event variable was defined as 1 if patient had a schizophrenia diagnosis by the ten-year visit, and 0 if they did not. Independent variables employed for survival analyses were the same as for logistic regression analysis; likewise, two survival models were run, one including only information available at baseline, and another also having follow-up data. Furthermore, Kaplan-Meier analyses were performed for separated categories of significant predictors, contrasting survival time with Log-rank tests. Statistical analyses were carried out using IBM SPSS Statistics version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

3. RESULTS

3.1. Description of the study sample

Initially, 307 patients were enrolled in the three-year PAFIP clinical program (2001-2008). Out of them, 209 patients (68.1%) provided written consent to participate in the ten-year follow-up study. The other 98 patients were lost during follow-up, mainly because they refused a re-evaluation (N=34; 11.1%) or they were unreachable (N= 22; 7.2%). See Figure 1 for the detailed patient´s flow-chart.

Descriptive statistics for the 209 patients who participated in the ten-year reassessment are presented in Table 1. Briefly, the mean age of psychosis onset was 28.14 (SD=8.35) and 54.5% (114 patients) were male. The 'baseline' diagnoses (provided at the six-month visit, T6m) were as follows: 126 had been characterized as schizophrenia (60.3%), 17 brief psychotic disorder (8.1%), 16 NOS psychosis (7.7.%), 46 schizophreniform disorder (22%) and 4 schizoaffective disorder (1.1%). At the T10y reassessment visit (average follow-up: 135.5 months, SD=19.7), the diagnoses were: 154 schizophrenia (73.7%), 10 brief psychotic disorder (4.8%), 12 NOS psychosis (5.7%), 12 schizophreniform disorder (5.7%), 19 schizoaffective disorder (9.1%), 1 delusional disorder (0.5%) and 1 bipolar disorder (0.5%).

Patients lost to follow-up did not differ from the analysed sample in terms of gender, age, clinical features or initial diagnosis. However, drop-outs had poorer premorbid adjustment, lower educational attainment and higher frequency of drug consumption. A summary table detailing baseline differences between both groups is presented in Supplementary table 1.

3.2. Diagnostic stability between secondary time points

3.2.1. T0 - T6m

At patient´s first contact (T0), provisional diagnostic impressions were provided, being schizophrenia the most frequent (N=83; 39.7%), followed by schizophreniform disorder (N=73; 34.9%), whereas 27 were diagnosed with brief psychotic disorder (12.9%) and 26 with NOS psychosis (12.4%). There was a considerable shift between T0 and T6m diagnoses, as shown in Table 2. Forty-three patients received a diagnosis of schizophrenia for the first time at T6m (20.6%), most of them changing from a diagnosis of schizophreniform disorder at T0. By contrast, out of the 83 patients who had been diagnosed with schizophrenia at T0, only one was revised at T6m (changing to schizophreniform disorder).

Insufficient DUP according to DSM-IV criteria was the main reason for re-evaluation of the diagnosis at six months. Approximately, one fourth of patients (26.8%) with DUP under six months at T0 acquired schizophrenia diagnosis at the six-month visit (T6m).

3.2.2. T3y-T10y

Out of the 144 patients diagnosed with schizophrenia at T3y, five changed their diagnosis between T3y and T10y, two of them toward schizoaffective disorders. Conversely, five patients newly acquired schizophrenia diagnosis between T3y and T10y, three changing from schizophreniform disorder and two from brief psychotic disorder. Thus, both prospective and retrospective stability between these time points was 96.5%. Seventeen patients lacked information at T3y but were recaught at T10y.

3.3. Overview of prospective and retrospective stability of schizophrenia diagnosis

Table 3 presents the specific numbers for transfer between each possible T6m diagnosis and T10y diagnoses. As shown, the prospective stability of schizophrenia diagnosis was very high, as 118 of the 126 patients who received that diagnosis at baseline, retained the same in the ten-year visit (93.7%). Conversely, the retrospective stability of schizophrenia diagnosis was not that high, as only 118 out of 154 patients with schizophrenia diagnosis at the ten-year visit (76.6%) had already received that diagnosis at baseline.

Out of the eight patients who lost schizophrenia diagnosis during follow-up, four (50%) shifted to schizoaffective disorder. On the other hand, the vast majority of the 36 patients who acquired schizophrenia diagnosis during follow-up (28, i.e., 77.8%) were initially diagnosed with schizophreniform disorder, while six (16.7%) had brief psychotic disorder, and two (5.6%) had NOS psychotic disorder.

3.4. Logistic regression for prospective stability

Univariate comparisons regarding prospective stability are presented in the Supplementary table 2. The results of the logistic regression models are collected in Table 4. For the ten-year prospective stability

model, only the 126 patients who initially received schizophrenia diagnosis were included. Due to missing data for some variables, the final N for the model was 117 (109 remained with schizophrenia diagnosis and 8 had changed).

First, the model was run including only information available at the baseline visit. The significant variables after stepwise selection were PAS in childhood and CGI-S at baseline. Specifically, each additional point in the PAS childhood score (indicating poorer adjustment) involved 4.76 times less likelihood of changing diagnosis of schizophrenia to something different during the ten years of follow-up. Likewise, each additional point in CGI-S at baseline (meaning worse clinical impression) reduced likelihood of changing diagnosis from schizophrenia to other by 6.90 times.

Subsequently, variables pertaining to the ten-year follow-up evaluation were added to the model. This model had the same two predictors as before (childhood PAS and baseline CGI-S, with slightly different coefficients), plus diagnosis of comorbid personality disorder during the follow-up , which, increased the likelihood of modifying the initial schizophrenia diagnosis by almost 60 times. This result is based on six diagnoses of comorbid personality disorders.

Repeating the model after adding the psychopathological scores of clinical scales collected at the ten-year reassessment, the final N of the model was smaller due to some participants not having these data (N=106), with only six patients changing their diagnosis, but the resulting significant predictors were the same and had similar coefficient values.

3.5. Logistic regression for retrospective stability

For the retrospective approach, only those patients who had schizophrenia diagnosis at the ten-year visit were considered (N=154); in this case, change of diagnosis established whether patients had received a different initial diagnosis than schizophrenia. Univariate comparisons are collected in the Supplementary table 3.

Due to missing data, the final N for this model was 140. Out of this, 31 patients had changed from a different T6m diagnosis to schizophrenia. The significant predictors of the model and their coefficient values were the same regardless of inclusion of follow-up variables, namely low socioeconomic status of parents and DUP (Table 4). Among patients with schizophrenia at reassessment, those with low socioeconomic status -of parents- were 3.11 times more likely to have been diagnosed with schizophrenia from the start. Likewise, each additional month of DUP at baseline entailed 1.18 times more likelihood of

receiving schizophrenia diagnosis at the initial (T6m) visit. These results were the same regardless of inclusion of ten-year follow-up variables. When adding the ten-year psychopathological scales (N=125), these were not found to be significant predictors.

3.6. ROC Curves

Figure 2a presents the ROC curves for the two quantitative predictors of prospective diagnostic change (childhood PAS and baseline CGI-S). The ROC curve for childhood PAS had an area under the curve (AUC)=0.822; 95%CI=0.716-0.928, indicating good diagnostic value. The optimal cut-off point, as defined by the maximum Youden J statistic, was 1.875, with a sensitivity=1 and specificity=0.587; in other words, 100% of patients who changed their schizophrenia diagnosis into something else, but only 41.3% those who retained such diagnosis had a childhood PAS ≤ 1.875. Baseline CGI-S also conveyed a good diagnostic value (AUC=0.766; 95%CI=0.580-0.951). The optimal cut-off point was 5, corresponding to "Markedly ill", with very high specificity (0.915), meaning that 91.5% of patients who retained the schizophrenia diagnosis had a CGI-S score above 5; conversely, sensitivity was moderate (0.500), suggesting that 50% of patients with CGI-S below or equal 5 change their diagnosis. Moreover, receiving a diagnosis of personality disorder during follow-up had 37.5% sensitivity and 97.5% specificity for detecting those patients who lost their diagnosis of schizophrenia. A ROC curve was run for the entire equation of the logistic regression model (Figure 2b):

$$Y = \frac{1}{1 + e^{-((-1.876 * Baseline\ CGI) + (-2.071 * Child\ PAS) + (4.085 * Personality\ Disoder) + 10.765)}}$$ where Y represents the probability of schizophrenia diagnostic change given by the logistic regression model of the prospective approach. The full logistic regression model was very good, with AUC of 0.950; 95% CI=0.893-1. Because of the very few people who changed their diagnosis, the model was more effective in predicting those who did not change; thus, the optimal cut-off value of the logistic function was not 0.5 (for predicting whether an individual changes their diagnosis according to the model), but 0.092, with a sensitivity of 0.875 and a specificity of 0.899.

Likewise, for retrospective diagnostic change, ROC curves were run for the individual numeric predictors and the full model. The predictive value for DUP, in terms of identifying patients who change from some other initial diagnosis to schizophrenia, was good: AUC=0.784; 95% CI=0.706-0.862 (Figure 2c). The optimal cut-off point was 5.5 months (sensitivity: 0.833; specificity:0.636), i.e., 83.3% of patients who changed their diagnosis toward schizophrenia had DUP below 5.5 months, whereas 63.6% of those who already started and retained a schizophrenia diagnosis had DUP longer than that time. Low parental

socioeconomic status had a sensitivity of 58.3% and 57.6% of specificity. A ROC curve was performed on the full logistic function (Figure 2d).

$$Y = \frac{1}{e^{-((-1.136 \, * \, Low \, SE \, status) \, + \, (-0.163 \, * \, DUP) \, + \, 0.439)}}$$

The AUC for the ROC curve of the full logistic function indicated good diagnosis value: 0.800; 95% CI=0.722- 0.879. The optimal cut-off point (sensitivity 0.694, specificity 0.754) was 0.297 meaning 29.7% probability of changing diagnosis towards schizophrenia, given the model results; again, the model is biased toward identifying those individuals who do not change diagnosis.

3.7. Survival analysis

Due to missing data, the N for survival analysis was 186, with 140 having a final diagnosis of schizophrenia. According to multivariate Cox regression analysis, based only on information available at baseline, significant predictors for the event 'stable schizophrenia diagnosis' were: male gender (B=0.528; p=0.003; HR=1.696 95%CI 1.197-2.404) and (longer) DUP (B= 0.005, p=0.016; HR=1.005 95%CI 1.001-1.009). When information related to follow-up was incorporated to the model (subsequent diagnosis of personality disorder and psychotic relapses), results were similar.

The mean time for stabilization of schizophrenia diagnosis was 52.96 months (95%IC=42.315-63.606). However, median time was 0 months as most people were diagnosed with schizophrenia from the start. Figure 3a presents the survival curve for the entire sample.

Considering gender, the median time to diagnosis for males and female was 0 and 29 months respectively (Log-rank test= 14.06, df=1, p<0.001). Separated Kaplan-Meier curves are shown in figure 3b. As for DUP, the median time to diagnosis in patients with DUP ≤4 months at inclusion in the program (i.e., ten months at the six-month initial visit) was 30 (95%CI 11.581-48.419), whereas for DUP >4, it was 0 (Log-rank test 26.840, df=1, p<0.001) (see Figure 3c).

4. DISCUSSION

In this cohort study, diagnostic stability of schizophrenia in patients with FEP was high after ten years of follow-up, especially prospective stability (~94%), whereas retrospective stability of schizophrenia diagnosis was lower (~77%). Some significant predictors for prospective and retrospective stability have

been found, and interestingly, they had been previously reported as prognosis factors for schizophrenia. Hence, the group of patients with prospective diagnostic *instability* over time (i.e., those who changed from schizophrenia diagnosis to another different disorder during follow-up) corresponded to a milder psychopathological profile, before and at the onset of disease, with significantly better premorbid childhood adjustment and less severe clinical global impression at baseline. In addition, this group of patients were more likely to be diagnosed with comorbid personality disorder during follow-up. Regarding retrospective stability, a cautious attitude in the initial diagnosis of schizophrenia was observed for those patients with shorter DUP and better parental socioeconomic status, showing, in those patients who finally achieve schizophrenia diagnosis over ten years, higher rates of retrospective instability of the diagnosis. To the best of our knowledge, this is the first study exploring the timing of stabilization of schizophrenia diagnosis in relation to certain factors, finding male gender and longer DUP as predictors for an earlier diagnosis of schizophrenia.

High rates of prospective consistency of schizophrenia diagnosis have been previously reported during similar periods of follow-up (23,24). This shows that schizophrenia is usually a reliable and consistent diagnosis, as also seen in our cohort, where only 6% of patients were re-diagnosed from schizophrenia to other psychotic disorders after ten years. The low rate of false positive diagnosis of schizophrenia reflects certain, but appropriate, caution before diagnosis making at first time. Our findings show that a better premorbid adjustment and less severity in the clinical global impression at first evaluation predicted prospective diagnostic instability of schizophrenia. This seems consistent with other studies, reporting poorer adolescent adjustment and worse premorbid functioning as predictors of future change to a diagnosis of schizophrenia from another initial diagnosis (18,20). Better premorbid adjustment and clinical impression have also been related with better longitudinal course and functioning during the follow-up of patients with schizophrenia (44,45). Furthermore, a recent study on FEP patients has found that those patients diagnosed with schizophrenia since first contact, together with those changing to schizophrenia diagnosis during follow-up, had worse clinical and functional outcome than those patients who had never been diagnosed with schizophrenia and those who changed from schizophrenia to other psychotic disorder (25). The variability in the prognosis of patients diagnosed with schizophrenia suggests a psychopathological *continuum*, ranging from brief psychosis, to other psychotic disorders, to schizophrenia, with little qualitative gap between diagnostic entities. This notion has been put forward by the APA, in its latest version of the DSM (DSM-5) (46). In light of this, it has been suggested that during the therapeutic process, clinical decisions should not be exclusively based on diagnosis, but rather on symptom predominance (47).

Besides, another factor related with prospective change of schizophrenia diagnosis to a different entity in our cohort was the comorbidity with personality disorders during the follow-up. At this point, it is important to highlight that although hallucinations constitute one of the characteristic symptoms of psychotic disorders, the majority of clinical features of hallucinations in schizophrenia are shared with other psychiatric conditions, including personality disorders, and also with medical or neurological diseases, considering hallucinations as a transdiagnostic phenomenon (48). Moreover, personality disorders, specifically of borderline type, may lead to psychotic-like experiences, such as voice hearing, that may be partly explained by the "psychotic-reactivity-to-stress" model, in relation to a hyperactivity of the hypothalamic-pituitary-adrenal axis and of the dopaminergic system under stress (49). Furthermore, it should be noted that psychiatric comorbidities in general are common among patients with schizophrenia, and some authors advocate examining whether these comorbidities might represent distinct phenotypes of schizophrenia (50). Therefore, we recommend that, in order to increase diagnostic specificity and accuracy, first assessments for FEP patients should be exhaustive, focusing in premorbid adjustment and considering axis II diagnosis since the first contact and during the entire follow-up.

With regard to retrospective stability of schizophrenia diagnosis in the present cohort, around 23% of patients that were diagnosed with schizophrenia over ten years had a different baseline diagnosis. Elsewhere, retrospective schizophrenia instability has been reported between 21 and 37% during two-year of follow-up, by using DSM-IV (20,21). Moreover, after ten years, between 30 and 40% of FEP patients shifted to schizophrenia diagnosis from another initial disorder, depending on the employed diagnostic system for baseline evaluation (DSM-IV or ICD-10, respectively) (23). Overall, although different rates of retrospective stability of schizophrenia diagnosis were found depending on the diagnostic criteria or the period of follow-up, retrospective consistency of schizophrenia diagnosis seems not as high as the prospective consistency. In this context, our results demonstrate that out of the 36 patients who received a different diagnosis at first contact (T0) and later acquired schizophrenia diagnosis, 28 had been initially diagnosed with schizophreniform disorder, by using DSM-IV criteria (~78%). Previous authors have reported that most of individuals who later get a schizophrenia diagnosis mainly shift from schizophreniform disorder, followed by NOS psychosis and brief psychotic disorders (19). Taken together, these results may indicate that those patients who change to a diagnosis of schizophrenia from schizophreniform disorder probably do not meet the diagnostic threshold at the baseline. Our results also showed that those patients with schizophrenia diagnosis at the ten-year assessment, but also having schizophrenia diagnosis from the start, were more likely to belong to a low socio-economic status and had significantly longer DUP before program admission compared to those

whose baseline diagnosis shifted toward schizophrenia during follow-up. On the one hand, in previous studies, a longer DUP has been associated to change to schizophrenia from other baseline diagnosis (i.e., predictor of retrospective instability of schizophrenia diagnosis) (20,21,23), but there are not enough studies to establish a clear effect of DUP, according to a meta-analysis about diagnostic stability in FEP patients (26). The higher probability of receiving schizophrenia diagnosis from the start among patients with longer DUP may be explained because the establishment of a definite schizophrenia diagnosis may require longer time-frame due to an ambiguous initial presentation or the need of an ulterior evaluation for a final diagnosis. Regarding our findings about the effect of socioeconomic level on retrospective stability, it may constitute a Bayesian bias applied at the time of the initial diagnosis of schizophrenia in relation to the influence of deprived environments over schizophrenia risk. It is well-known that contextual effects of low socioeconomic status, such as urban environment, minor group position and cannabis use, are associated with higher risk of schizophrenia development (51). In other words, clinicians seem to be cautious and likely to assign non-schizophrenia diagnoses in those patients without specific risk factors for schizophrenia. This may be partly explained as a diagnosis of schizophrenia may carry a significant stigma burden, even among mental health professionals (52).

In regard to the timing for stabilization of schizophrenia diagnosis (i.e., the time until schizophrenia diagnosis is given that remains valid at ten-year follow-up), we observed influence of certain factors that are also considered as classical predictors for schizophrenia outcomes. Thus, stabilization of schizophrenia diagnosis occurred significantly earlier in male patients and in those with longer DUP. Elsewhere, longer DUP has been associated with overall poor prognosis (53,54) and gender effects have been reported quite consistently in schizophrenia, with male patients having an earlier age of onset and more severe negative symptoms (55) and less probability of symptomatic and functional remission (14). The higher likelihood of acquiring schizophrenia diagnosis in our cohort, at any time-point, is in line with the results of several studies on FEP patients, where longer DUP was associated to more frequent shift toward schizophrenia diagnosis over one (18), two (20,21) and ten years of follow-up (23). Moreover, we found differences between gender in the median timing of diagnosis consistency (29 months in women and 0 months in men). Although evidence between gender and diagnosis stability of schizophrenia is scarce, some authors found that being female is a significant factor in those patients with schizophreniform disorder keeping their diagnosis over time, compared to those shifting to schizophrenia (19); in this line, male gender has been showed as a strong predictor of change to schizophrenia from another DSM-IV diagnosis for psychosis (23). Despite the fact that the general mean time for stabilization of schizophrenia diagnosis in our cohort was 52.96 months, the median time was 0 months, meaning that more than half of

schizophrenia patients were diagnosed from the start; this fact, together with the high prospective stability of schizophrenia diagnosis (94%) pointed to a rapid and accurate diagnostic process.

This study is subject to some limitations that are worth of note. First, affective psychoses were not included; however, this is not a disadvantage by itself, as affective psychotic disorders may be considered a subgroup displaying specific characteristics in terms of clinical course, functional outcomes and psychopharmacological treatment (56), and therefore, our cohort ensure more homogeneous sample diagnoses. Second, regarding prospective stability of schizophrenia diagnosis (as given at T6m), the number of patients who changed diagnosis by the ten-year assessment was small (N=8), reducing the statistical power of the analyses. In this context, the optimal cut-off points for quantitative predictors of schizophrenia stability, explored by ROC curves, should be interpreted with caution. However, the fact that different statistical analyses exploring the prospective stability in our study (regression including different sets of predictors, ROC curves and survival analyses) yielded consistent results, increases our confidence in their internal validity. At any rate, these results may help to advise about adequate diagnostic attitude toward different patient profiles. Third, there was a noticeable proportion of patients lost to follow-up (31.9%) with a few significant differences compared to those who were reassessed at ten years. Specifically, the higher frequency of drug use observed among drop-outs might have caused an overestimation of diagnostic stability in our cohort, given the reported inverse association between drug abuse or dependency and stability of schizophrenia diagnosis (14). Fourth, the present work only considered diagnostic stability regarding DSM criteria; interestingly, no ICD / DSM significant differences regarding diagnostic stability in FEP have been found in a quantitative synthesis comprising 42 studies (26), although some individual studies have found such notorious differences (15,23). Among the strengths of this study, first, its large time frame of follow-up is worth considering. Second, raters at ten years were different and blind to baseline, one year and three-year evaluations, avoiding an artificial enlargement of diagnosis stability. Finally, to the best of our knowledge, this is the first study to examine so many potential predictors of diagnostic change considering time until definite schizophrenia diagnosis through survival analysis and optimal cut-off point obtained by ROC curves.

In conclusion, diagnostic stability of schizophrenia observed in our FEP sample was high, especially the prospective stability of initial diagnosis of schizophrenia; and the group of patients with diagnostic change corresponded to a less severe psychopathological profile before and at the onset of disease. In this sense, schizophrenia may be considered as a part of a psychopathological *continuum* among schizophrenia spectrum disorders. Moreover, a cautious attitude was observed in the diagnosis of schizophrenia in patients with shorter DUP who finally have schizophrenia diagnosis after ten years. Therefore, during the

diagnostic process, clinicians should balance prudence and precision, regarding the diagnosis as subject to revision at ulterior evaluations. A thorough first assessment of FEP patients and family by mental health professionals, regarding previous history, premorbid adjustment and comorbidity with other psychological disorders may lead to high diagnostic stability in schizophrenia.

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N=209	First contact to PAFIP	End of follow-up (10 year)
Sociodemographic variables		
Sex (males)	114 (54.5%)	
Age of onset (years)	28.14 *(8.35)*	
Low socioeconomic status	113 (54.6%)	
Education level (elementary or less)	92 (44.0%)	
Unemployed	94 (45.0%)	142 (67.9%)
Living with parents	109 (52.2%)	86 (41.1%)
Unmarried	158 (75.6%)	119 (59.9%)
Clinical variables		
Family history of psychosis	46 (22.1%)	
DUI (months)	27.5 *(40.07)*	
DUP (months)	14.05 *(30.18)*	
Index hospitalization	133 (63.6%)	
CGI-S		
Normal, not at all ill	0 (0%)	61 (29.2%)
Borderline ill	0 (0%)	35 (16.7%)
Mildly ill	0 (0%)	39 (18.7%)
Moderately ill	3 (1.4%)	19 (9.1%)
Markedly ill	31 (14.8%)	14 (6.7%)
Severely ill	91 (43.5%)	11 (5.3%)
Among the most extremely ill	84 (40.2%)	4 (1.9%)
Not evaluated	0 (0%)	26 (12.4%)
Psychopathology [^]		
YMRS	10.30 *(5.18)*	1.95 *(3.56)*
CDSS	2.62 *(3.42)*	0.80 *(2.27)*
BPRS	61.94 *(13.20)*	32.21 *(9.58)*
SAPS	13.28 *(4.60)*	1.64 *(3.36)*
SANS	7.78 *(6.38)*	4.68 *(5.28)*
Positive dimension	7.44 *(2.38)*	1.04 *(2.07)*
Negative dimension	5.97 *(5.82)*	4.17 *(4.71)*
Disorganized dimension	5.85 *(3.62)*	0.60 *(1.70)*
DAS	1.17 *(1.41)*	1.01 *(1.18)*
GAF	54.03 *(28.31)*	82.63 *(17.63)*
Diagnosis [+]		
Schizophrenia	126 (60.3%)	154 (73.7%)

Brief psychotic disorder	17 (8.1%)	10 (4.8%)
NOS psychotic disorder	16 (7.7%)	12 (5.7%)
Schizophreniform disorder	46 (22.0%)	33 (35.5%)
Schizoaffective disorder	4 (1.9%)	19 (9.1%)
Delusional disorder	0 (0%)	1 (0.5%)
Bipolar disorder	0 (0%)	1 (0.5%)

Table 1. Characteristics of study participants (N=209)

For categorical variables, the absolute frequency (and %) is provided; quantitative variables present the mean *(SD)*.

BPRS: Brief Psychiatric Rating Scale; CDSS: Calgary Depression Scale for Schizophrenia; CGI -S: Clinical Global Impression-Severity; DAS: The Disability Assessment Scale; DUI: Duration of untreated illness; DUP: duration of untreated psychosis; GAF: Global Assessment Functioning; NOS: not otherwise specified; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; YMRS: Young Mania Rating Scale.

^ Psychopathological scales at the 10-year assessment were not available for the entire sample, with an available N ranging between 169 and 183 participants.

+ The diagnoses are those given at 6 months since the first contact to the program.

			Diagnosis at T6m					
			Schizophrenia	Brief psychotic disorder	NOS Psychosis	Schizophreniform disorder	Schizoaffective disorder	
Diagnosis at first contact (T0)		Schizophrenia	82	0	0	1	0	**83 (39.7%)**
		Brief psychotic disorder	7	12	3	5	0	**27 (12.9%)**
		NOS Psychosis	5	5	11	4	1	**26 (12.4%)**
		Schizophreniform disorder	32	0	2	36	3	**73 (34.9%)**
			126 (60.3%)	**17 (8.1%)**	**16 (7.7%)**	**46 (22.0%)**	**4 (1.9%)**	**209 (100%)**

Table 2. Cross-tabulation of diagnostic impression at first contact (T0) and six-month diagnosis (T6m).

NOS: Not otherwise specified psychosis

The total numbers and percents given at the rightmost column correspond to frequencies at T0, whereas the ones reported at the lowest row apply to T6m.

				Diagnosis at 10-year follow-up						
				Schizophrenia	Brief psychotic disorder	NOS Psychosis	Schizophreniform disorder	Schizoaffective disorder	Delusional disorder	Bipolar disorder
		N=209 **(100%)**		154 (73.7%)	10 (4.8%)	12 (5.7%)	12 (5.7%)	19 (9.1%)	1 (0.5%)	1 (0.5%)
				% within 10-year diagnosis (retrospective stability)						
Diagnosis at six months (T6m)	Schizophrenia	126 (60.3%)	% within 6-month diagnosis (prospective stability)	**118** 93.7% 76.6%	**0** 0% 0%	**2** 1.6% 16.7%	**1** 0.8% 8.3%	**4** 3.2% 21.1%	**1** 0.8% 100%	**0** 0% 0%
	Brief psychotic disorder	17 (8.1%)		**6** 35.3% 3.9%	**9** 52.9% 90%	**1** 5.9% 8.3%	**0** 0% 0%	**1** 5.9% 5.3%	**0** 0% 0%	**0** 0% 0%
	NOS Psychosis	16 (7.7%)		**2** 12.5% 1.3%	**1** 6.3% 10%	**9** 56.3% 75%	**1** 6.3% 8.3%	**3** 18.8% 15.8%	**0** 0% 0%	**0** 0% 0%
	Schizophreniform disorder	46 (22%)		**28** 60.9% 18.2%	**0** 0% 0%	**0** 0% 0%	**10** 21.7% 83.3%	**7** 15.2% 36.8%	**0** 0% 0%	**1** 2.2% 100%
	Schizoaffective disorder	4 (1.1%)		**0** 0% 0%	**0** 0% 0%	**0** 0% 0%	**0** 0% 0%	**4** 100% 21.1%	**0** 0% 0%	**0** 0% 0%

Delusional disorder	0 (0%)		**0**	**0**	**0**	**0**	**0**	**0**	**0**
			0%	0%	0%	0%	0%	0%	0%
			0%	0%	0%	0%	0%	0%	0%
Bipolar disorder	0 (0%)		**0**	**0**	**0**	**0**	**0**	**0**	**0**
			0%	0%	0%	0%	0%	0%	0%
			0%	0%	0%	0%	0%	0%	0%

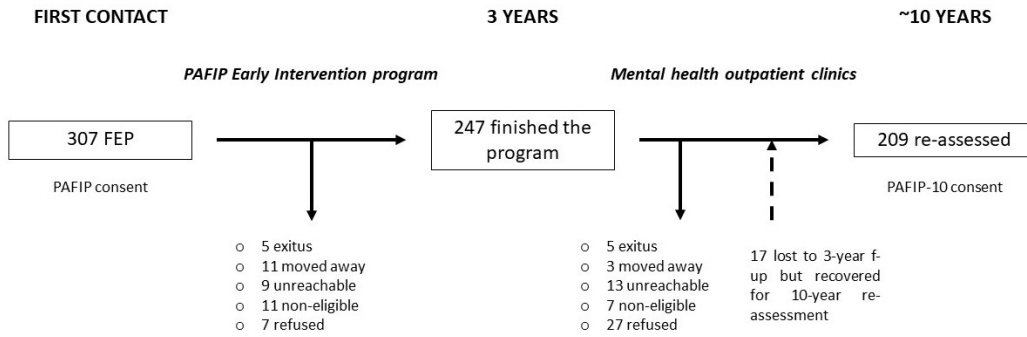**Table 3. Cross-tabulation of 6-month and 10-year diagnosis in the PAFIP cohort**

NOS: Not otherwise specified psychosis

Shaded rows mean % of retrospective stability, it is calculated over the diagnosis at 10-year follow-up
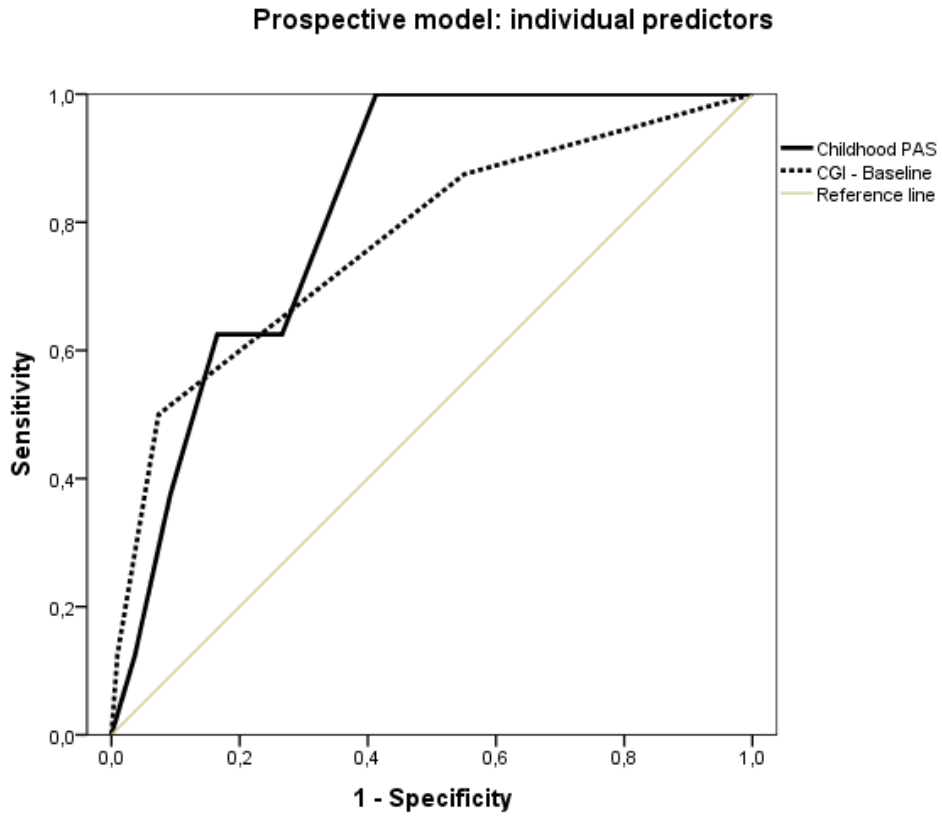
Prospective change of schizophrenia diagnosis				
With baseline variables only				
Model fit: χ2=22.07; df=2; p<0.001; Nagelkerke R^2=0.438				
	B	p value	OR	95% CI
PAS childhood	-1.562	0.008	0.21	0.066-0.663
CGI baseline	-1.931	0.003	0.145	0.041- 0.513
Including follow-up variables				
Model fit: χ2=30.64; df=3; p<0.001; Nagelkerle R^2 =0.587				
	B	p value	OR	95%CI
PAS childhood	-2.071	0.012	0.126	0.025-0.633
CGI baseline	-1.876	0.009	0.153	0.037-0.630
Personality disoder diagnosis in the follow-up	4.085	0.008	59.44	2.97-1189.71
Retrospective change of schizophrenia diagnosis				
Baseline and including follow-up				
Model fit: χ2=33.48; df=2; p<0.001; Nagelkerke R^2 = 0.326				
	B	P value	OR	95% CI
Low socioeconomic level	-1.136	0.014	0.321	0.129-0.797
DUP	-0.163	0.001	0.850	0.774-0.933

Table 4. Results of stepwise logistic regression model for prospective and retrospective change in schizophrenia diagnosis.
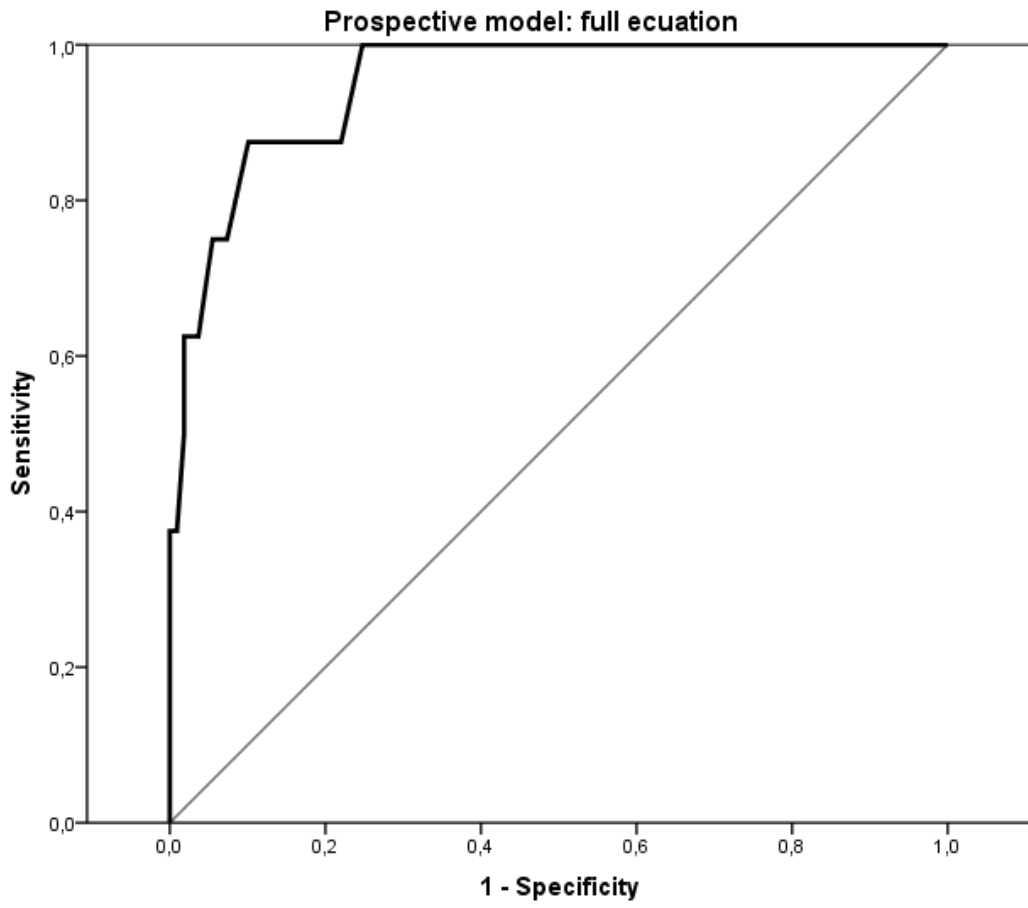
CGI: Clinical Global Impression; DUP: Duration of Untreated Psychosis; PAS: Premorbid Adjustment Scale; B: Regression Coefficient; CI: Confident Interval; PR: Odd Ratio.
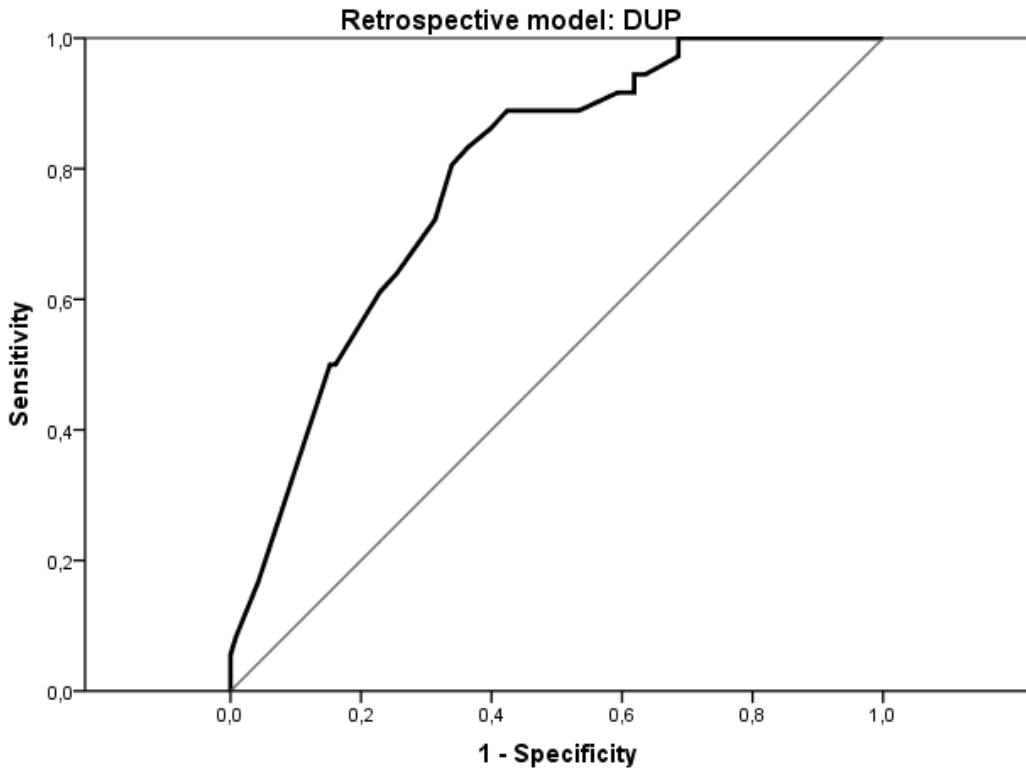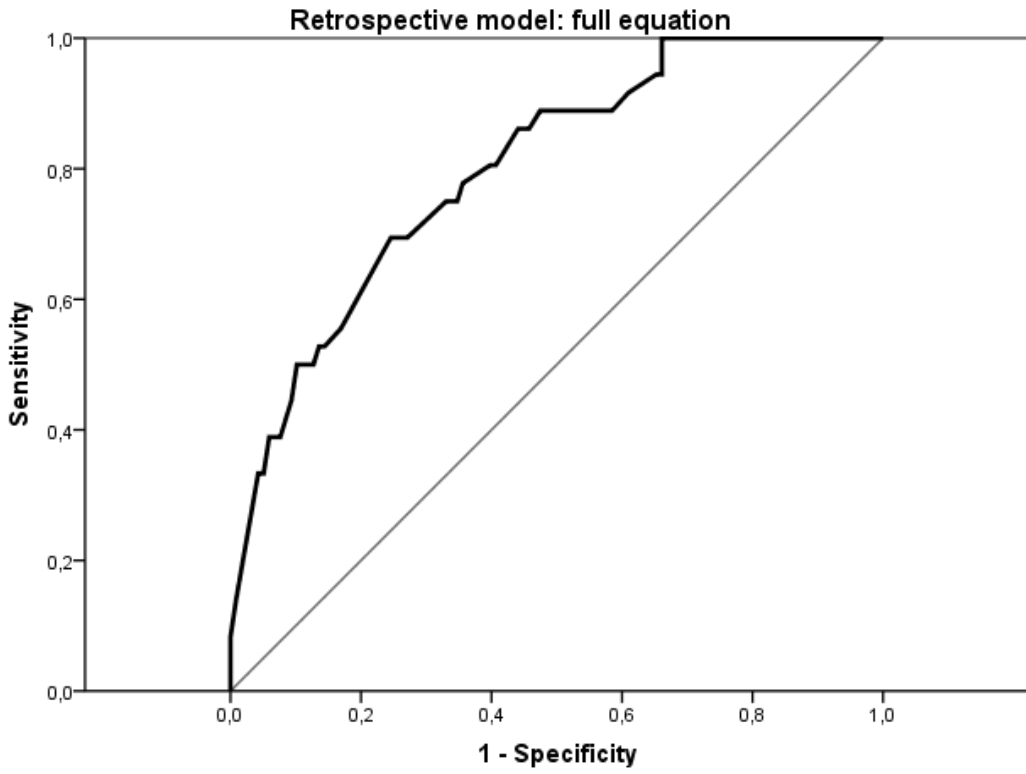
FIRST CONTACT		3 YEARS		~10 YEARS

PAFIP Early Intervention program   *Mental health outpatient clinics*

307 FEP	→	247 finished the program	→	209 re-assessed

PAFIP consent   PAFIP-10 consent

- o 5 exitus
- o 11 moved away
- o 9 unreachable
- o 11 non-eligible
- o 7 refused

- o 5 exitus
- o 3 moved away
- o 13 unreachable
- o 7 non-eligible
- o 27 refused

17 lost to 3-year f-up but recovered for 10-year re-assessment

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Prospective model: individual predictors

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Prospective model: full ecuation

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Retrospective model: DUP

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acps_13344_f2d.png

Survival curve for stable schizophrenia diagnosis
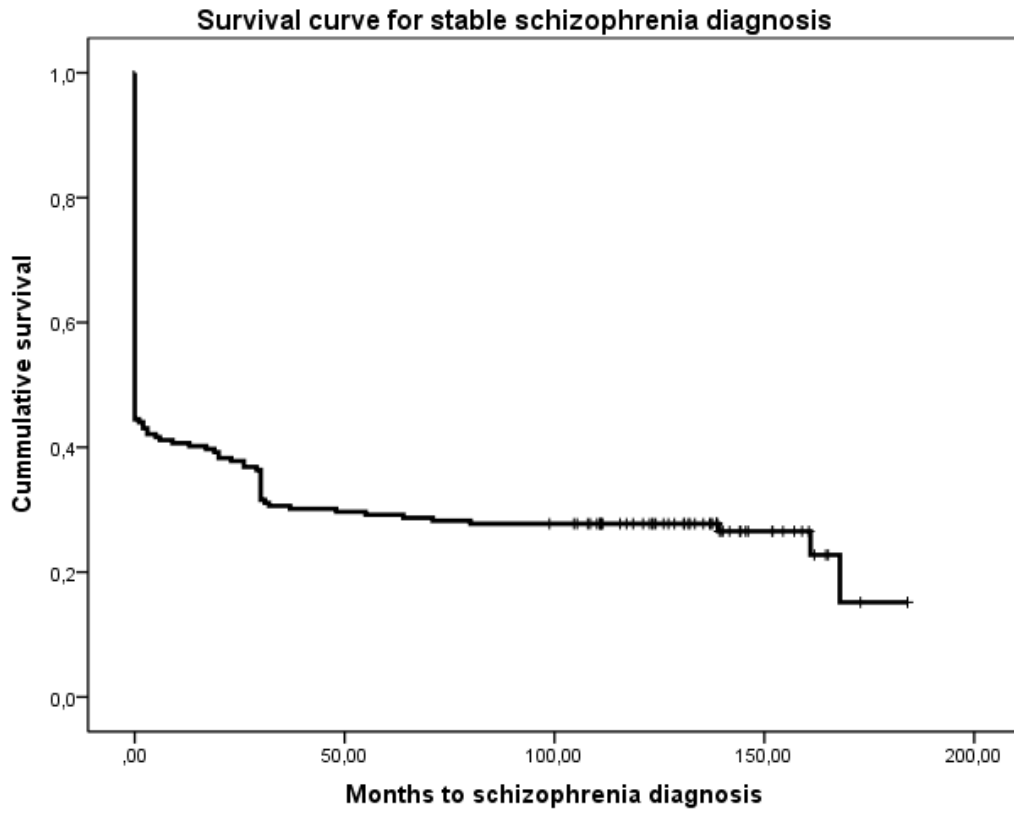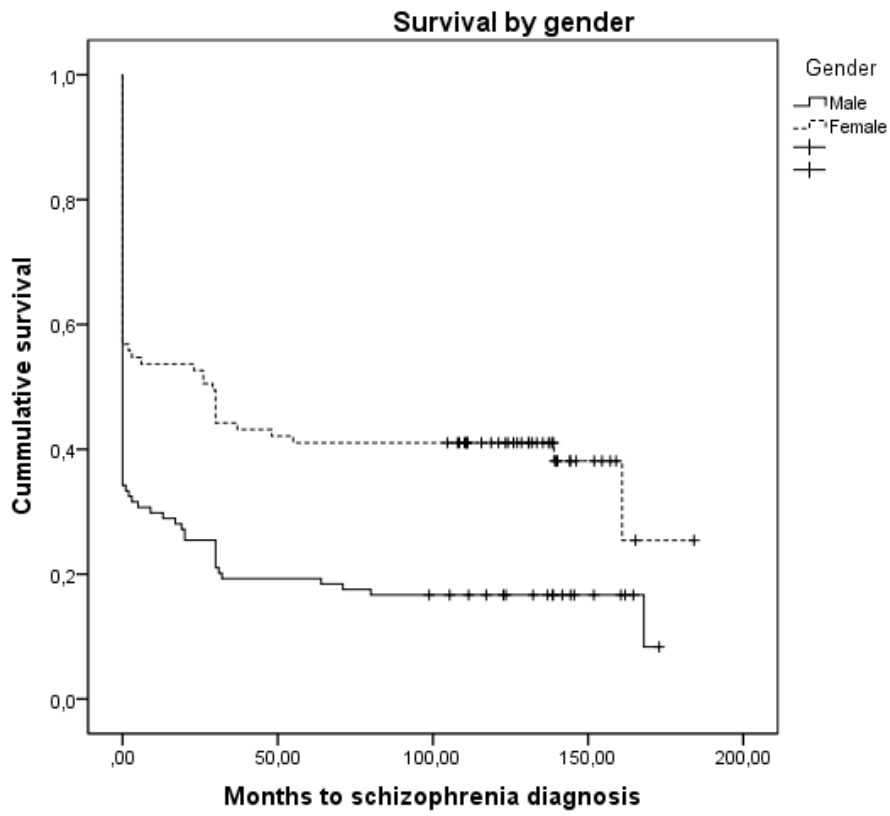
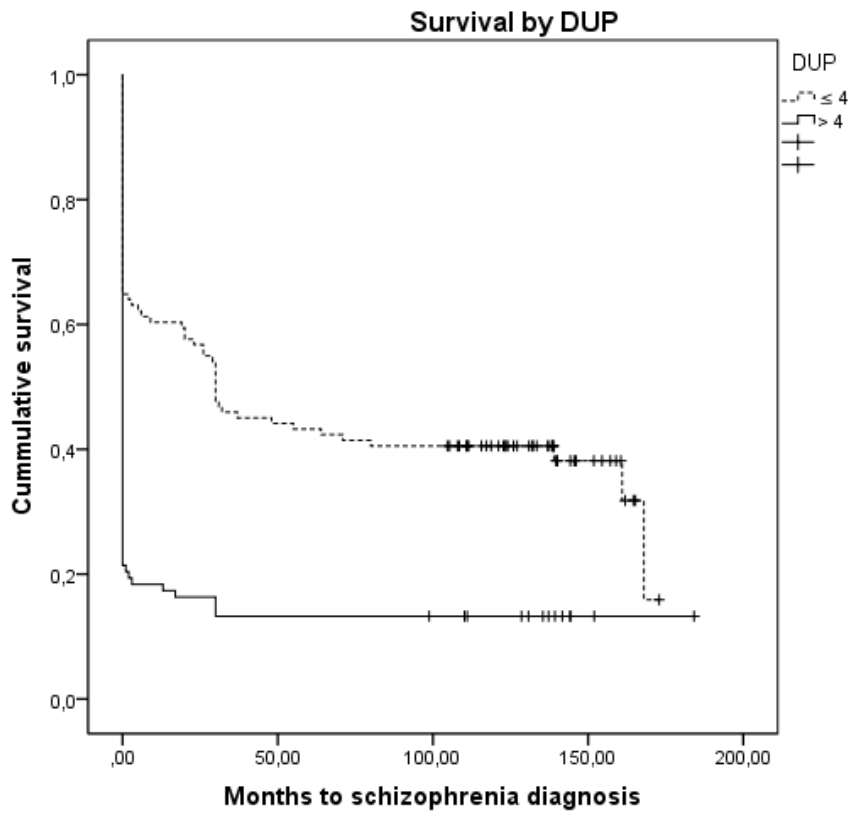acps_13344_f3a.png

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