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Evaluation of a few discrete clinical markers may predict categorization of actively symptomatic non-acute schizophrenia patients as treatment resistant or responders: A study by ROC curve analysis and multivariate analyses

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ABSTRACT

Here, we used Receiver Operating Characteristic (ROC) curve analysis to determine whether clinical factors may aid predicting the categorization of schizophrenia patients as Treatment Resistant (TRS) or antipsychotic responsive schizophrenia (ARS). Patients with an established condition of TRS or ARS were assessed for: clinical presentation and course; neurological soft signs (NES); psychopathology by PANSS; cognitive performances; quality of life scale (QLS); functional capacity; social functioning (PSP and SLOF scales). In ROC curve analysis, significance indicated that the Area under curve (AUC) allowed distinguishing between TRS and ARS. Multivariate analyses were additionally used to provide independent predictive analysis. Multiple clinical variables showed significant AUCs. The largest significant AUCs were found for: NES total score; SLOF Area2; QLS subscale; antipsychotic doses. The highest sensitivity was found for NES total score, the highest specificity for previous hospitalizations. The highest Odds Ratio of being included within the TRS category were found for: NES total score (7.5); QLS total score (5.49); and previous hospitalizations (4.76). This same circumscribed group of variables was also found to be predictive of TRS when adopting stepwise logistic regression or discriminant analysis. We concluded that the evaluation of few clinical factors may provide reliable and accurate predictions on whether one schizophrenia patient may be categorized as a TRS.

1. Introduction

Treatment resistant schizophrenia (TRS) is defined as the partial or complete non-response to antipsychotic treatments against the symptoms of schizophrenia, which afflict approximately 30% of patients suffering from the disease (Howes et al., 2017). Non-response to treatments prevents symptomatic and functional remission and it is a major challenge to gain recovery from schizophrenia (Englisch and Zink, 2012). For these reasons, TRS represents a prominent current issue in mental health both for the burden of suffering the patients face and for direct and indirect economic costs deriving from unsuccessful ordinary therapeutic management (Kennedy et al., 2014). Given the poor prognosis and high disability associated with TRS (Iasevoli et al., 2016), this schizophrenia subtype should be tackled with proper therapeutic approaches as soon as possible.

Factors affecting antipsychotic response should be carefully investigated to identify cases of the so-called pseudo-resistance (Dold and Leucht, 2014; Iasevoli et al., 2016), and eliminated where possible. Clozapine should be offered early to TRS patients, although delay has frequently been described (Howes et al., 2012; Nielsen et al., 2012; Wheeler et al., 2014) and may predispose to poor response to the drug (Ucok et al., 2015). Agents acting on the glutamatergic system should also be taken into account (Shim and Nadeem, 2014), since dysfunctions in this system have been indicated among causative factors of schizophrenia and possibly TRS (Errico et al., 2013; Mouchlianitis et al., 2016). Combination and augmentation pharmacological strategies, mostly with clozapine, should also be taken into account to treat the most resistant patients (Arumugham et al., 2016; Lally et al., 2016b;

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Rayikanti et al., 2017; Zheng et al., 2017).

However, recognizing of TRS is underpowered even in patients with intermediate-to-long duration of illness (Howes et al., 2012; Ucok et al., 2015), mostly for clinician-related factors. Also, these patients are in high percentage exposed to polypharmacy or higher-than-recommended antipsychotic doses (Ucok et al., 2015). Therefore, one of the major challenges that clinicians are required to face when treating schizophrenia patients with a relatively long-lasting history of disease, multiple pharmacological treatments, and non-controlled symptoms is to promptly classify them as treatment resistant or treatment responders, to rapidly switch to the most appropriate therapeutic strategy. Despite the expected relevant impact that tools allowing this distinction may have, there is still little evidence on which feature may be more representative in separating TRS from non-TRS patients with high specificity and sensitivity. In a recent study, we observed that high rate of neurological soft signs (NSS) was significantly predictive of being categorized as TRS (de Bartolomeis et al., 2018). In earlier works, it has been reported that TRS patients have more impaired cognitive functioning (de Bartolomeis et al., 2013; Frydecka et al., 2016), and suffer from more severe social disabilities (Iasevoli et al., 2016) compared to non-TRS schizophrenia patients. In a recent 10-year longitudinal study that followed first-episode psychosis patients from their antipsychotic initiation, factors predicting treatment resistance from illness onset were negative symptoms, younger age at onset, and longer duration of untreated psychosis (Demjaha et al., 2017). These previous reports indicated a set of factors that may be predictive of TRS, however, several other variables still need to be taken into account.

The aim of this study was to evaluate whether and at what specificity/sensitivity level it may be possible to distinguish TRS from antipsychotic responder schizophrenia (ARS) on the basis of discrete clinical factors, in a population of schizophrenia patients with intermediate duration of illness, prolonged and documented previous antipsychotic treatments, active psychotic symptoms, and whose putative condition of TRS had neither been previously recognized nor systematically assessed. To address this aim, we adopted the Receiver Operator Characteristic (ROC) curve analysis, that allowed determining optimal cut-offs for predicting TRS or ARS status. Multivariate analysis by stepwise logistic regression and descriptive discriminant analysis were additionally used to provide additional predictive information on putative clinical markers of TRS.

2. Patients and methods

2.1. Patients

Patients were collected at the Outpatient Unit on Treatment Resistant Psychosis, Section of Psychiatry, Department of Neuroscience, University "Federico II" of Naples, from January 2016 to July 2017. All patients signed a written informed consent form, approved by the local Ethical Committee of the participating Institution. All procedures carried out in the present study complied with the principles laid down by the Declaration of Helsinki, revised Hong Kong 1989. Inclusion criteria were: i) age within the 18–65 years range; ii) diagnosis of schizophrenia; iii) stabilized symptoms, including persistent psychotic symptoms with no evidence of actual or recent (i.e. in the last 3 months prior assessments) worsening; iv) duration of illness exceeding 5 years. Exclusion criteria were: i) intellectual disability; ii) severe medical diseases; iii) non-schizophrenia psychotic disorders (including brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, schizotypal personality disorder, affective psychosis); iv) psychiatric disorders due to another medical condition or to substances/medications. All diagnoses were made by two raters (FI and LDA) based on SCID-I. Interrater reliability was tested on half of the patients and showed excellent agreement ($k = 0.89$).

The sample included in this study partially overlapped the ones included in two recent studies from our group that were aimed at assessing whether Neurological Soft Signs were more frequent and severe in TRS vs. ARS patients (de Bartolomeis et al., 2018) and whether functional capacity may differ in severity and clinical determinants between the two populations (Iasevoli et al., 2018). None of these already-published studies had the specific goal to investigate whether it may be possible to distinguish TRS from ARS patients on the basis of discrete clinical factors (including but not limited to NSS and functional capacity), which was the aim of the present study by specifically adopting the ROC curve analysis and multivariate analyses. As described in more details elsewhere, in the study on NSS a logistic regression was carried out with the binary dichotomous TRS/ARS variable as the dependent one. However, that analysis was only deemed to evaluate the relative role of NSS subtypes and associated clinical variables to predict the inclusion within the TRS group (de Bartolomeis et al., 2018).

The samples for these studies derived from the same eligible population, i.e. patients suffering from psychotic symptoms and referred to our outpatient unit. Screening procedures started on January 2016, however timing of recruitment differed in the studies due to the different primary aims of each of these and to the different power required. All patients underwent the same panel of assessments, with the same methodological rules. The procedures for categorization of patients as TRS or ARS were the same in all these studies. Therefore, composition of TRS and ARS groups were consistent across the studies, although with some differences depending on the different recruitment period and inclusion/exclusion criteria of each one.

In conclusion, the populations included in these studies show substantial, albeit not complete overlapping. However, since the aims of the studies were different and preventively established, power analysis appropriately calculated and met, we may exclude selection/detection or otherwise source of bias and considered reliable the data obtained from assessments and statistical analyses carried out.

2.2. Diagnostic procedures for defining TRS and ARS patients' group

2.2.1. Actual severity criterion

The Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of overall psychotic symptoms (Kay et al., 1987; Rossi et al., 2009). According to previous reports (Kozma et al., 2010), we considered a patient as actively symptomatic when PANSS score trespassed a cut-off score of 70. Since standard PANSS rating could underestimate response, we adopted the rescaling in the prospective trial (Obermeier et al., 2011).

2.2.2. Historical criterion

Medication history was reconstructed based on clinical information and previous medical records. According to published algorithms (Lehman et al., 2004), actively symptomatic patients (i.e. PANSS score >70) were considered as "possible TRS" if they did not respond to at least three different antipsychotics in the past five years, given for an adequate period of time (i.e. four-to-six consecutive weeks) and at appropriate doses (i.e. 300–600 mg/day chlorpromazine equivalents for all the four-six weeks) (Conley and Kelly, 2001). These patients were still defined possible TRS because we wanted to rule out possible causes of pseudo-resistance, as described in the next step.

2.2.3. Exclusion criterion

Pseudo-resistance was defined as the lack of antipsychotic response that may depend on modifiable/not modifiable factors beyond putative lack of efficacious pharmacological action of the antipsychotic compound (Dold and Leucht, 2014). Factors of pseudo-resistance were: i) incorrect diagnosis; ii) incorrect antipsychotic prescription (i.e. under/over-dosing; insufficient duration of treatment); iii) drug-drug interactions; iv) lack of compliance; v) concomitant substance abuse; vi) medical disorders affecting antipsychotic pharmacokinetics/pharmacodynamics; vii) adverse and detrimental psychosocial conditions.