ORIGINAL ARTICLE

Modelling and forecasting Positive and Negative Syndrome Scale scores to achieve remission using time series analysis

Alka Sabharwal¹ | Gurprit Grover² | Sakshi Kaushik² | K. E. Sadanandan Unni³

¹Department of Statistics, Kirori Mal College, University of Delhi, New Delhi, India

²Department of Statistics, Faculty of Mathematical Sciences, University of Delhi, New Delhi, India

³Department of Psychiatry & Drug Deaddiction Centre, Lady Hardinge Medical College & Smt. S.K. Hospital, New Delhi, India

Correspondence

Sakshi Kaushik, Department of Statistics, Faculty of Mathematical Sciences, University of Delhi, New Delhi, India.
Email: sakshi2007@gmail.com

Abstract

Objectives: Schizophrenia is a chronic mental condition. The objective of this study is to apply time series modelling to Positive and Negative Syndrome Scale scores of outpatients with schizophrenia, observed at regular intervals of time, and hence forecast the number of visits required to reach remission.

Methods: A retrospective data of outpatients diagnosed with chronic paranoid-type schizophrenia were extracted from the records of outpatient department of a tertiary hospital in New Delhi, India. Autoregressive integrated moving average (ARIMA) and ARIMAX models (ARIMA with explanatory variable as Clinical Global Impression Severity scale) are fitted to the data. The best fit models are employed to forecast the number of visits required to reach remission for the outpatients who did not achieve remission by the end of study. Prediction accuracy of the two models is compared using mean absolute percentage error and mean absolute deviation.

Results: The ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models are identified to be suitable models after a series of statistical tests.

Conclusions: ARIMA and ARIMAX models are suitable to predict number of visits required to reach remission. Further, ARIMAX model performed better than ARIMA model.

KEYWORDS

ARIMA, ARIMAX, forecasting, remission, schizophrenia

1 | INTRODUCTION

Schizophrenia is a severe chronic mental condition with long-term impairment. Definition of remission in schizophrenia has been a very ambiguous notion. The Remission in Schizophrenia Working Group (RSWG) defined remission as a combination of two components: (a) the symptom severity component or resolution in which eight items selected from the Positive and Negative Syndrome Scale (PANSS) should score 3 or less and (b) the time component that suggests that this score should be maintained for a period of 6 months (Andreasen et al., 2005; Kay, Fiszbein, & Opler, 1987). Assessment of remission in practice raises question regarding time required by a patient to reach either resolution or relapse (Yeomans et al., 2010). The best predictions arise from statistical methods that fit precise data to valid models

describing how the relevant variables contribute to the outcome (McMahon, 2014).

Time series analysis is a statistical methodology appropriate for prediction in longitudinal research designs involving a single subject or research units that are measured repeatedly at regular intervals of time. There are two main goals of time series analysis: (a) identifying the nature of the phenomenon represented by the sequence of observations (i.e., evaluating the behavioural trend) and (b) forecasting or predicting future values of the behaviour based on the most recent observation (StatSoft, 2004). Most time series models are defined for stationary time series. However, in practice, most time series are nonstationary in nature. The concept of stationarity of a stochastic process can be visualized as a form of statistical equilibrium (Hipel & McLeod, 1994).

The most popular and frequently used stochastic time series models are as follows: (a) the autoregressive integrated moving average (ARIMA) model (Box & Jenkins, 1970) and (b) ARIMA with exogenous variable (ARIMAX) model with an added advantage of capturing the influence of independent variable on the dependent variable. This model has the capacity to identify the underlying patterns in time series data and to quantify the impact of environmental influences simultaneously (Victor-Edema & Essi, 2016). Time series analysis has been used previously for predicting emergency department visits, daily hospital attendance, and admissions, forecasting haemorrhagic fever with renal syndrome incidence, and evaluating patterns of tobacco, alcohol, and marijuana use and disease management (Dierker et al., 2009; Liu, Liu, Jiang, & Yang, 2011; Rathlev et al., 2007; Sato, 2013; Soyiri & Reidpath, 2012; Sun, Heng, Seow, & Seow, 2009). Moore, Little, McSharry, Geddes, and Goodwin (2012) used time series analysis to forecast depression in patients with bipolar disorder. Walther, Ramseyer, Horn, Strik, and Tschacher (2013) predicted severity of positive syndrome, excitement, and disorganization in schizophrenia using time series analysis. Jäger et al. (2009) used logistic regression to determine the rates of remission during inpatient treatment and explored predictors of remission based on PANSS scores in schizophrenia.

The aim of this study is to apply time series modelling on PANSS scores of outpatients of schizophrenia, visiting the outpatient department (OPD) at regular intervals of time, and hence forecast the number of visits required to reach remission. To achieve our aim, we fitted ARIMA (p, d, q) model on data of outpatients consisting of PANSS scores measured at various visits. The modelling consisted of two important procedures: (a) identifying the best fit model among the various ARIMA models applied to the data and (b) validating the fitted model by comparing estimated data obtained from fitted model with the actual data. Next, we applied ARIMAX model to the available data with Clinical Global Impression Severity (CGI-S) scale scores of patients as exogenous variable. The above-mentioned procedure of modelling and forecasting is repeated with ARIMAX model as well.

In this study, the threshold for resolution or symptom severity criteria of remission is assumed to be a total score of PANSS less than or equal to 45 (indicating "very mild" category by Levine, Rabinowitz, Engel, Etschel, & Leucht, 2008) from the perspective of forecasting. The data consisted of two categories of patients: (a) who had achieved remission by the end of study period (i.e. total PANSS score less than or equal to 45 and a score less than or equal to 3 for selected eight items of PANSS as given by RSWG; Andreasen et al., 2005) and (b) who had not achieved remission by the end of study period. The data of patients belonging to the first category are used for model selection only as forecasting is not required for them. For patients belonging to the second category, we forecasted number of visits required to achieve remission on the basis of PANSS scores using selected models. Finally, the performance of ARIMA and ARIMAX models is compared on the basis of mean absolute percentage error (MAPE) and mean absolute deviation (MAD) of the fitted models. The accuracy of forecasts derived from two models is also compared using Diebold–Mariano (DM) test (Diebold & Mariano, 1995).

The outline of the rest of the paper is as follows: In Section 2, data and methodology used have been discussed. Section 3 describes the

application of time series analysis to the data along with the results obtained. The paper is concluded with a discussion in Section 4.

2 | METHODS

2.1 | Material used

A retrospective data of 14 outpatients diagnosed with chronic paranoid-type schizophrenia (in accordance with American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* and the World Health Organization *International Classification of Diseases*) were extracted from the records of OPD of a tertiary hospital in New Delhi, India. The data were gathered for a duration of 18 months consisting of 21 visits of each patient. The data included information on variables age, gender, number of episodes, duration of illness, and course and onset of illness, and scores on psychiatric rating scales, namely, PANSS (Kay et al., 1987), Brief Psychiatric Rating Scale (Overall & Gorham, 1962), CGI-S scale, Clinical Global Impression-Improvement scale (Guy, 1976b), Simpson–Angus Rating Scale (Simpson & Angus, 1970), Montgomery–Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979), Behavioural Activation for Depression Scale (Kanter, Mulick, Busch, Berlin, & Martell, 2007), and Abnormal Involuntary Movement Scale (Guy, 1976a), as recorded by psychiatrists were available. The patients were receiving antipsychotic medications. Out of 14 patients, four patients could not achieve remission at the end of 18 months. It was observed that the remaining 10 patients who achieved remission had minimal severity of symptoms, that is, had scored 3 or less on the eight items of PANSS as given by RSWG and also maintained the same for a duration of 6 months. The mean and standard deviation of age and duration of illness of patients were found to be (30 years, 5.6140) and (9.5 years, 4.2083), respectively. The descriptive statistics of PANSS and CGI-S scale of patients are given in Table 1.

TABLE 1 Descriptive statistics of PANSS and CGI-S scale scores for all patients

Patient code	PANSS (mean, SD)	CGI-S (min, max)
PAT01	(73.0476, 25.5568)	(1, 5)
PAT02	(67.8571, 17.2374)	(2, 5)
PAT03	(62.5238, 24.1632)	(2, 5)
PAT04	(89.8095, 12.9947)	(4, 6)
PAT05	(76.2381, 15.3392)	(3, 5)
PAT06	(102.2381, 7.2312)	(5, 6)
PAT07	(64.4762, 18.0128)	(2, 4)
PAT08	(95.0952, 9.7412)	(4, 6)
PAT09	(56.8571, 18.0091)	(2, 5)
PAT10	(66.9048, 17.8771)	(2, 5)
PAT11	(49.3810, 12.6431)	(2, 4)
PAT12	(69.5238, 22.8071)	(2, 6)
PAT13	(54.1905, 19.6510)	(2, 5)
PAT14	(70.6667, 19.6503)	(2, 6)

Note. PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression Severity; SD: standard deviation; min: minimum; max: maximum.

2.2 | Time series model

2.2.1 | ARIMA model

A time series is a sequential set of data points measured over successive times. In this study, the PANSS scores of each patient at different visits are treated as an individual time series. Let $y_{k,t}$ represent the PANSS score of k th patient at visit t with $y_{k,(t-p)}$ being the lagged value of $y_{k,t}$ at some previous visit $(t-p)$. An ARMA (p, q) model at visit t is given as

$$y_{k,t} = \mu + \varphi_{k,1}y_{k,(t-1)} + \varphi_{k,2}y_{k,(t-2)} + \dots + \varphi_{k,p}y_{k,(t-p)} + \varepsilon_{k,t} + \theta_{k,1}\varepsilon_{k,(t-1)} + \theta_{k,2}\varepsilon_{k,(t-2)} + \dots + \theta_{k,q}\varepsilon_{k,(t-q)} \quad (1)$$

where $\varphi_{k,i}$ ($i = 1, 2, \dots, p$) and $\theta_{k,j}$ ($j = 1, 2, \dots, q$) are model parameters of autoregressive and moving average part of the model with $\varepsilon_{k,t}$ being error terms for k^{th} patient at visit t ($t = 1, 2, \dots, 21$) and μ is a constant. Equation (1) can also be written as

$$\begin{aligned} y_{k,t} - \varphi_{k,1}y_{k,(t-1)} - \dots - \varphi_{k,p}y_{k,(t-p)} \\ = \mu + \varepsilon_{k,t} + \theta_{k,1}\varepsilon_{k,(t-1)} + \dots \\ + \theta_{k,q}\varepsilon_{k,(t-q)} \Rightarrow (1 - \varphi_{k,1}L - \varphi_{k,2}L^2 - \dots - \varphi_{k,p}L^p)y_{k,t} \\ = \mu + (1 + \theta_{k,1}L + \theta_{k,2}L^2 + \dots + \theta_{k,q}L^q)\varepsilon_{k,t}, \Rightarrow \varphi(L)y_{k,t} \\ = \theta(L)\varepsilon_{k,t} \end{aligned} \quad (2)$$

where $\varphi(L) = 1 - \sum_{i=1}^p \varphi_{k,i}L^i$, $\theta(L) = 1 - \sum_{j=1}^q \theta_{k,j}L^j$, and L is the lag operator.

The random errors, $\varepsilon_{k,t}$ are assumed to be a white noise process (Box & Jenkins, 1970), that is, a sequence of independent and identically distributed random variables sampled from a normal distribution with zero mean and a constant variance. If the time series is not stationary (i.e. mean and variance of the series are not constant), it is transformed into stationary series by applying appropriate differencing scheme. If d is the order of differencing, the resulting stationary series $y_{k,t}$ may be represented by an ARIMA (p, d, q) model as (Box & Jenkins, 1970)

$$\varphi(L)(1-L)^d y_{k,t} = \theta(L)\varepsilon_{k,t} \quad (3)$$

where (p, d, q) refer to the order of the model. p is the order (number of time lags) of the autoregressive model, d is the degree of differencing, and q is the order of the moving average model.

2.2.2 | ARIMAX model

The ARIMA model can be extended to ARIMAX model by incorporating an explanatory variable X . In this study, CGI-S scale score for a patient is assumed to be the independent variable. Let $x_{k,t}$ represent the CGI-S scale score for k^{th} patient ($k = 1, 2, \dots, 14$) at visit t ($t = 1, 2, \dots, 21$); then an ARIMAX (p, d, q) model can be represented as (Victor-Edema & Essi, 2016)

$$\varphi(L)(1-L)^d y_{k,t} = \beta_k x_{k,t} + \theta(L)\varepsilon_{k,t}, \quad (4)$$

where β_k are coefficients of $x_{k,t}$ and (p, d, q) are as defined in ARIMA model.

2.3 | Augmented Dickey-Fuller test for stationarity

The augmented Dickey-Fuller (ADF) test is used to check the stationarity of a time series. The regression model employed by Dickey and Fuller (1979) is given by

$$\Delta y_{t,k} = \alpha + \lambda_{k,t}t + \delta_k y_{k,(t-1)} + \sum_{i=1}^p \lambda_{k,i} \Delta y_{k,(t-i)} + \varepsilon_{k,t}, \quad (5)$$

where $\Delta y_{t,k} = y_{t,k} - y_{k,(t-1)}$, α is a constant, $\lambda_{k,t}$ is the coefficient of time trend, p is the lag order of the autoregressive process, and $\varepsilon_{k,t}$ is the error term for k^{th} patient. The ADF test statistic is given by

$$ADF_k = \frac{\hat{\delta}_k}{SE(\hat{\delta}_k)},$$

where $SE(\hat{\delta}_k)$ is the standard error of the least squares estimate of δ_k , to test the null hypothesis (the time series contains a unit root, i.e. $\delta_k = 0$) against the hypothesis that the time series is stationary. The ADF test statistic follows t distribution.

2.4 | Ljung-Box test for autocorrelation

It is a prerequisite for the transformed series to not exhibit significant autocorrelation for applying ARIMA/ARIMAX models. The significance of the autocorrelation of the transformed time series is tested using Ljung-Box test (Ljung & Box, 1978). Under this test, the null hypothesis (the autocorrelation at lag h is zero, i.e. $\rho_{k,h} = 0$) is tested against the hypothesis that the autocorrelation at lag h is nonzero, that is, $\rho_{k,h} \neq 0$, and the test statistic is given by

$$Q_k = n(n+2) \sum_{h=1}^m \frac{\hat{\rho}_{k,h}^2}{n-m},$$

where n is the number of usable data points after differencing operation, $\hat{\rho}_{k,h}$ is the sample autocorrelation at lag h , and m is the number of lags being tested for k^{th} patient. The statistic Q_k follows a χ_m^2 distribution.

2.5 | Granger causality test

Granger causality test is used to verify the significance of the causal relationship of the exogenous variable (CGI-S scale) with the dependent variable (PANSS) prior to application of ARIMAX model (Granger, 1969). Consider the equation

$$y_{k,t} = \alpha + \sum_{i=1}^p \varphi_{k,i} y_{k,(t-i)} + \sum_{l=1}^n \beta_{k,l} x_{k,(t-l)} + \varepsilon_{k,t},$$

where α is a constant, $\beta_{k,l}$ is coefficient of $(t-l)^{\text{th}}$ lagged value of x variable (CGI-S scale) for k^{th} patient, and $\varphi_{k,i}$, $y_{k,(t-i)}$ and $\varepsilon_{k,t}$ are as defined in Section 2.2.1. The null and alternative hypotheses are given as follows:

Null hypothesis: $x_{k,t}$ (CGI-S scale) does not Granger cause $y_{k,t}$ (PANSS), that is, $\beta_{k,1} = \beta_{k,2} = \dots = \beta_{k,n} = 0$, versus the hypothesis H_a : At least one $\beta_{k,l} \neq 0$. The test statistic is given by

$$F_k = \frac{\left\{ \frac{SSR_r - SSR_u}{n} \right\}}{\left\{ \frac{SSR_u}{T - (p + n + 1)} \right\}},$$

where SSR_r is restricted sum of squared residuals obtained by regressing $y_{k,t}$ on its past values excluding $x_{k,t}$ whereas SSR_u is unrestricted sum of squared residuals obtained by regressing $y_{k,t}$ on its past values and lagged values of $x_{k,t}$ and T is the total number of observations. The statistic F_k follows $F_{n, (T - (p + n + 1))}$ distribution.

2.6 | DM test for comparing accuracy of forecasts

This test is used for comparing the accuracy of forecasts derived from two models. Let $\hat{y}_{k,t,arima}$ and $\hat{y}_{k,t,arimax}$ denote forecasts of the time series $y_{k,t}$ of k^{th} patient at visit t ($t = 1, 2, \dots, T$) by ARIMA and ARIMAX models. Let the associated forecast errors be $\epsilon_{k,t,arima}$ and $\epsilon_{k,t,arimax}$. Denote the loss functions associated with forecast errors $\epsilon_{k,t,arima}$ and $\epsilon_{k,t,arimax}$ as $g(\epsilon_{k,t,arima})$ and $g(\epsilon_{k,t,arimax})$, respectively. The loss differential between the two forecasts for k^{th} patient is defined as $d_{k,t} = g(\epsilon_{k,t,arima}) - g(\epsilon_{k,t,arimax})$. Then the hypotheses of test are given as follows:

Null hypothesis: The two forecasts from ARIMA and ARIMAX models have the same accuracy, that is, $E(d_{k,t}) = 0 \forall t$, versus the hypothesis that the two forecasts from ARIMA and ARIMAX models have different levels of accuracy, that is, $E(d_{k,t}) \neq 0$. The test statistic is given as (Diebold & Mariano, 1995)

$$S_k = \frac{\bar{d}_k}{\hat{\sigma}_{\bar{d}_k}} \rightarrow N(0, 1),$$

where $\bar{d}_k = \frac{1}{T} \sum_{t=1}^T d_{k,t}$ is the sample mean loss differential and $\hat{\sigma}_{\bar{d}_k}$ is a consistent estimate of the standard deviation of $\bar{d}_k$.

2.7 | Procedure for application of ARIMA/ARIMAX models

The procedure followed to apply ARIMA and ARIMAX models is described as follows:

- Check stationarity of time series.
- Obtain value of d component of ARIMA/ARIMAX model for non-stationary series.
- Inspect causal influence of exogenous variable (CGI-S scale) on dependent variable (PANSS)—applicable for ARIMAX model only.
- Test significance of autocorrelation of time series.
- Determine the components p and q of model using autocorrelation function (ACF) and partial autocorrelation function (PACF).
- Fit the candidate models.
- Select a model using Akaike information criteria (AIC) and Bayesian Information Criterion (BIC).
- Test autocorrelation of residuals for significance.
- Assess normality and homoscedasticity of residuals.

- Compare ARIMA and ARIMAX models.
- Forecast number of visits required to reach remission using selected model.

3 | RESULTS

In this study, the total scores of PANSS measured at 21 visits for all 14 patients are treated as separate time series and are denoted as PANSS1 for the first patient with patient code PAT01, PANSS2 for the second patient with patient code PAT02, ..., and PANSS14 for the 14th patient with patient code PAT14. The PANSS total score plot for PAT02 with respect to 21 visits to OPD is shown in Figure 1. There is a consistent downward trend over the visits. A time series with a trend is nonstationary in nature. The process of model selection and forecasting is demonstrated stepwise as discussed in Section 2.7 using PANSS scores of a single patient PAT02, whereas results are presented for all 14 patients.

Step 1 Stationarity: Stationarity of time series is tested using ADF test (Dickey & Fuller, 1979). The value of ADF statistic and corresponding p value for PAT02 (PANSS score) are found to be -1.0869 and 0.9078 , which does not support the rejection of the null hypothesis of nonstationarity. Next, a finite differencing of order 1 is applied to this series. We failed to reject the null hypothesis again on this series using ADF test. Further, we observed that this time series

FIGURE 1 Time series plot of PANSS scores with respect to 21 visits for PAT02. PAT02 refers to the code for the second patient. PANSS2 is the time series of total scores of PANSS measured at 21 visits for PAT02. PANSS: Positive and Negative Syndrome Scale

FIGURE 2 Time series plot of PANSS scores with respect to 21 visits for the second patient PAT02 after differencing twice. PAT02 refers to the code for the second patient. DPANSS2 represents the transformed time series of total scores of PANSS measured at 21 visits for PAT02 after applying differencing of order 2. PANSS: Positive and Negative Syndrome Scale

TABLE 2 Results on application of ADF test to the transformed time series

Patient code	Series	ADF statistic	p value
PAT01	DPANSS1	-5.5993	0.01
PAT02	DPANSS2	-4.2048	0.0161
PAT03	DPANSS3	-4.3686	0.0104
PAT04	DPANSS4	-6.6104	0.01
PAT05	DPANSS5	-3.6939	0.0433
PAT06	DPANSS6	-3.7214	0.0413
PAT07	DPANSS7	-5.5023	0.01
PAT08	DPANSS8	-3.7602	0.0386
PAT09	DPANSS9	-6.9936	0.01
PAT10	DPANSS10	-4.7111	0.01
PAT11	DPANSS11	-5.7446	0.01
PAT12	DPANSS12	-3.7824	0.0370
PAT13	DPANSS13	-12.078	0.01
PAT14	DPANSS14	-3.728	0.04086

Note. DPANSS represents the transformed time series of total scores of PANSS measured at 21 visits for patients after applying differencing of order 2. This table gives the ADF statistic value and corresponding *p* value obtained on applying ADF test to the time series after differencing it twice. ADF: augmented Dickey-Fuller; PANSS: Positive and Negative Syndrome Scale.

is found to be stationary on applying a finite difference of order 2. The transformed series is represented as DPANSS2 for PAT02. From Figure 2, it is obvious that the trend component present in

nonstationary series has been removed by differencing. The series appears to be more stabilized as compared with Figure 1. Similar procedure was followed for PANSS scores of all 14 patients, and series were found to be stationary after applying differencing of order 2. Thus, the *d* component for both ARIMA and ARIMAX models is observed to be 2 for all patients. Table 2 presents results obtained on applying ADF test to all 14 transformed series (after differencing) represented as DPANSS1 for PAT01, DPANSS2 for PAT02, ..., and DPANSS14 for PAT14. It can be seen from Table 2 that series are stationary at 5% level of significance corresponding to all patients.

Step 2 Checking causality (applicable to ARIMAX model only): The causal influence of the exogenous variable (CGI-S scale) with the dependent variable (PANSS) is checked using Granger causality test (Granger, 1969). For PAT02, the test resulted in a highly significant *p* value of 0.0020 concluding that the null hypothesis of no Granger causality is rejected. Likewise, Granger causality test is verified for all patients, and results obtained were found to be congruent with this result.

Step 3 Autocorrelation check: The Ljung-Box test is employed to test the significance of the autocorrelation of the transformed time series DPANSS2 (Ljung & Box, 1978). As the *p* value was less than 0.05, it can be concluded that the null hypothesis is rejected indicating that AR and/or MA terms must be added into the model to remove the serial correlation. The same results were observed for all the patients. The ACF and PACF values up to Lag 6 for all patients are summarized in Table 3.

TABLE 3 The ACF and PACF values of differenced series up to Lag 6 for all patients

Patient code	Series		Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6
PAT01	DPANSS1	ACF	-0.60	0.24	-0.28	0.28	-0.15	0.05
		PACF	-0.60	-0.21	-0.39	-0.13	-0.05	-0.10
PAT02	DPANSS2	ACF	-0.79	0.50	-0.32	0.11	0.05	-0.08
		PACF	-0.79	-0.36	-0.21	-0.43	-0.24	-0.05
PAT03	DPANSS3	ACF	-0.56	-0.39	0.28	-0.11	-0.31	0.34
		PACF	-0.56	-0.41	-0.31	-0.07	-0.17	0.01
PAT04	DPANSS4	ACF	-0.60	0.05	0.06	0.08	0.02	-0.33
		PACF	-0.60	-0.50	-0.41	-0.15	0.29	-0.16
PAT05	DPANSS5	ACF	-0.49	0.09	-0.16	-0.10	0.10	0.21
		PACF	-0.49	-0.20	-0.27	-0.44	-0.40	-0.04
PAT06	DPANSS6	ACF	-0.51	0.10	0.03	-0.16	0.15	-0.10
		PACF	-0.51	-0.22	-0.02	-0.18	-0.04	-0.07
PAT07	DPANSS7	ACF	-0.64	0.16	-0.05	0.02	0.06	-0.14
		PACF	-0.64	-0.41	-0.34	-0.29	-0.10	-0.20
PAT08	DPANSS8	ACF	-0.49	0.01	0.01	-0.08	0.02	-0.11
		PACF	-0.49	-0.30	-0.19	-0.24	-0.24	-0.42
PAT09	DPANSS9	ACF	-0.64	0.38	-0.02	-0.26	0.17	-0.13
		PACF	-0.64	-0.05	0.35	-0.22	-0.40	-0.03
PAT10	DPANSS10	ACF	-0.52	-0.29	0.21	0.02	-0.09	0.11
		PACF	-0.52	-0.35	-0.30	-0.19	-0.15	0.06
PAT11	DPANSS11	ACF	-0.62	-0.29	0.19	-0.17	0.03	0.09
		PACF	-0.62	-0.31	-0.19	-0.24	-0.17	-0.06
PAT12	DPANSS12	ACF	-0.57	0.20	-0.17	-0.02	0.24	-0.45
		PACF	-0.57	-0.18	-0.20	-0.30	0.13	-0.40
PAT13	DPANSS13	ACF	-0.65	0.15	0.01	0.02	-0.01	-0.01
		PACF	-0.65	-0.47	-0.36	-0.24	-0.14	-0.10
PAT14	DPANSS14	ACF	-0.66	0.33	0.07	0.05	-0.14	-0.25
		PACF	-0.66	0.28	-0.31	0.13	-0.35	0.09

Note. DPANSS represents the transformed time series of total scores of PANSS measured at 21 visits for patients after applying differencing of order 2. ACF: autocorrelation function; PACF: partial autocorrelation function; PANSS: Positive and Negative Syndrome Scale.

Step 4a Model selection—ARIMA model: The final ARIMA model is selected on the basis of ACF and PACF values of the given transformed time series. Figure 3 presents the ACF and PACF plots for DPANSS2 series for PAT02. It is evident from the figure that the autocorrelation spikes at Lags 1 and 2 and partial autocorrelation spike at Lag 1 are beyond confidence region. From the ACF plot of residuals, the highly significant correlations at Lags 1 and 2 (-0.79 and 0.50) suggest that MA1 and MA2 terms should be included in the ARIMA model. The PACF provides evidence that an AR1 term with a correlation (-0.79) is also significant and should be included in the model. To select the final ARIMA model, two models, one with only MA1 and AR1 terms and other with MA1, MA2, and AR1 terms, were compared. The AIC and Bayesian information criterion (BIC) values of the two models were (92.47, 97.3074) and (94.47, 100.2478), respectively. The coefficients in both the models were highly significant. Based on AIC and BIC values, the final ARIMA model selected for DPANSS2 series was AR1 and MA1, that is, ARIMA model with $p = 1$, $d = 2$, and $q = 1$. Thus, ARIMA (1, 2, 1) model equation for PAT02 is represented as

$$\hat{y}_{2,t} = -0.5561 y_{2,(t-1)} - 0.8125 \varepsilon_{2,(t-1)} \quad (6)$$

Similar procedure was performed for all patients resulting in ARIMA (1, 2, 1) as the final model. Table 4 summarizes the coefficients of AR1 and MA1 terms along with their standard errors and AIC values of the fitted ARIMA (1, 2, 1) model to time series data of all patients.

The significance of coefficients of AR1 and MA1 terms of ARIMA (1, 2, 1) model is tested using z test and is found to be highly significant (p value < 0.05) for all patients.

Step 4b Model selection—ARIMAX model: As an extension of ARIMA (1, 2, 1) model, ARIMAX model with parameters $p = 1$, $d = 2$, and $q = 1$ is fitted to data of PAT02 with CGI-S scale score as exogenous variable. Because there is only one independent variable present in the model, multicollinearity is not a concern. Thus, ARIMAX (1, 2, 1) model equation for PAT02 is represented as

$$\hat{y}_{2,t} = 0.9250 x_{2,t} - 0.5734 y_{2,(t-1)} - 0.7801 \varepsilon_{2,(t-1)} \quad (7)$$

Similarly, ARIMAX (1, 2, 1) model with CGI-S scale score as exogenous variable is fitted to all patients' data. Table 5 summarizes the coefficients of AR1, MA1, and x variables along with their standard errors and AIC values of the fitted ARIMAX (1, 2, 1) model to time series data of all patients.

FIGURE 3 The ACF and PACF plots of transformed series DPANSS2 for PAT02. PAT02 refers to the code for the second patient. DPANSS2 represents the transformed time series of total scores of PANSS measured at 21 visits for PAT02 after applying differencing of order 2. ACF: autocorrelation function; PACF: partial autocorrelation function; PANSS: Positive and Negative Syndrome Scale

TABLE 4 Coefficients of AR1 and MA1 terms of ARIMA (1, 2, 1) model along with their standard errors (SE) and AIC values

Patient code	Dependent series	AR1 (SE)	MA1 (SE)	AIC
PAT01	DPANSS1	-0.2809 (0.1338)	-0.9032 (0.2060)	115.67
PAT02	DPANSS2	-0.5561 (0.1869)	-0.8125 (0.1634)	92.47
PAT03	DPANSS3	0.2744 (0.1348)	-1.0000 (0.1572)	165.27
PAT04	DPANSS4	-0.5316 (0.1947)	-1.0000 (0.1433)	167.73
PAT05	DPANSS5	0.2214 (0.1124)	-1.0000 (0.1856)	90.08
PAT06	DPANSS6	-0.2819 (0.1411)	-1.0000 (0.1651)	127.23
PAT07	DPANSS7	-0.4198 (0.2073)	-1.0000 (0.1536)	147.53
PAT08	DPANSS8	0.2479 (0.1201)	-1.0000 (0.1593)	136.53
PAT09	DPANSS9	-0.5868 (0.2548)	-0.2799 (0.1387)	115.57
PAT10	DPANSS10	-0.2965 (0.1474)	-0.8455 (0.1674)	111.44
PAT11	DPANSS11	0.3642 (0.1760)	-0.8539 (0.2786)	119
PAT12	DPANSS12	-0.2902 (0.1391)	-1.0000 (0.2175)	111.59
PAT13	DPANSS13	-0.4820 (0.219)	-0.7866 (0.1528)	148.2
PAT14	DPANSS14	0.4968 (0.2125)	-0.9999 (0.1633)	93.34

Note. DPANSS represents the transformed time series of total scores of PANSS measured at 21 visits for patients after applying differencing of order 2. This table presents the results obtained on applying ARIMA (1, 2, 1) model to the transformed time series DPANSS. AR1 and MA1 terms represent autoregressive and moving average terms of order 1. AR: autoregressive; MA: moving average; ARIMA: autoregressive integrated moving average; AIC: Akaike information criteria; PANSS: Positive and Negative Syndrome Scale.

The significance of coefficients of AR1, MA1, and x variables of ARIMAX (1, 2, 1) model is tested using z test and is found to be highly significant (p value < 0.05) for all patients.

Step 5 Autocorrelation check of residuals: The Ljung–Box testing is performed again to check if there exists significant autocorrelation among residuals obtained from ARIMA (1, 2, 1)

TABLE 6 Ljung–Box statistic and corresponding p value for residuals from ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models

Patient code	Series	Model ^a	Statistic	p value
PAT01	DPANSS1	1	6.653	0.5750
		2	6.762	0.4540
PAT02	DPANSS2	1	5.5069	0.7023
		2	6.5135	0.4812
PAT03	DPANSS3	1	7.634	0.4260
		2	6.520	0.6420
PAT04	DPANSS4	1	8.040	0.3870
		2	11.36	0.1240
PAT05	DPANSS5	1	10.28	0.2460
		2	8.600	0.3420
PAT06	DPANSS6	1	3.627	0.8890
		2	7.280	0.4000
PAT07	DPANSS7	1	3.851	0.8700
		2	2.589	0.9200
PAT08	DPANSS8	1	6.146	0.6310
		2	8.615	0.2810
PAT09	DPANSS9	1	10.57	0.2270
		2	10.63	0.1560
PAT10	DPANSS10	1	4.859	0.7730
		2	11.76	0.1120
PAT11	DPANSS11	1	2.298	0.9700
		2	7.424	0.3860
PAT12	DPANSS12	1	10.57	0.2270
		2	7.017	0.4270
PAT13	DPANSS13	1	1.689	0.9890
		2	6.162	0.5210
PAT14	DPANSS14	1	12.83	0.1180
		2	11.58	0.1150

Note. DPANSS represents the transformed time series of total scores of PANSS measured at 21 visits for patients after applying differencing of order 2. ARIMA: autoregressive integrated moving average; ARIMAX: autoregressive integrated moving average with exogenous variable; CGI-S: Clinical Global Impression Severity; PANSS: Positive and Negative Syndrome Scale.

^aModel 1: ARIMA (1, 2, 1) model. Model 2: ARIMAX (1, 2, 1) model with CGI-S scale scores of patients as exogenous variable.

TABLE 5 Coefficients of AR1, MA1, and x variables of ARIMAX (1, 2, 1) model along with their standard errors (SE) and AIC values

Patient code	Dependent series	AR1 (SE)	MA1 (SE)	x (SE)	AIC
PAT01	DPANSS1	-0.4972 (0.2311)	-0.8056 (0.1700)	4.5203 (2.2195)	116.33
PAT02	DPANSS2	-0.5734 (0.1850)	-0.7801 (0.1615)	0.9250 (0.367)	94.03
PAT03	DPANSS3	0.2751 (0.1357)	-1.0000 (0.1572)	0.7172 (0.3060)	167.26
PAT04	DPANSS4	-0.6460 (0.1906)	-1.0000 (0.1980)	7.9373 (2.3474)	152.6
PAT05	DPANSS5	0.5189 (0.2323)	-1.0000 (0.1675)	5.2339 (1.0402)	76.27
PAT06	DPANSS6	-0.5978 (0.2787)	-0.8905 (0.2362)	4.5228 (1.8883)	122.24
PAT07	DPANSS7	-0.7851 (0.2055)	-1.0000 (0.1469)	3.6828 (1.2869)	148.86
PAT08	DPANSS8	-0.4367 (0.2054)	-1.0000 (0.1812)	5.3053 (1.8183)	127.35
PAT09	DPANSS9	-0.5874 (0.2596)	-0.8354 (0.3532)	2.6337 (0.8273)	117.57
PAT10	DPANSS10	0.8449 (0.2823)	-0.9022 (0.2047)	4.8390 (2.2402)	109.34
PAT11	DPANSS11	0.8713 (0.2256)	-1.0000 (0.2164)	6.1300 (2.2666)	107.76
PAT12	DPANSS12	-0.8698 (0.2417)	-1.0000 (0.1707)	5.1637 (2.2651)	111.79
PAT13	DPANSS13	0.7473 (0.1731)	-0.8624 (0.3014)	5.9151 (1.5085)	121.88
PAT14	DPANSS14	0.5393 (0.2408)	-1.0000 (0.1582)	3.1379 (1.1463)	94.39

Note. DPANSS represents the transformed time series of total scores of PANSS measured at 21 visits for patients after applying differencing of order 2. This table presents the results obtained on applying ARIMAX (1, 2, 1) model with CGI-S scale scores of patients as exogenous variable to the transformed time series DPANSS. AR1 and MA1 terms represent autoregressive and moving average terms of order 1. The x variable represents the exogenous variable CGI-S scale. AR: autoregressive; MA: moving average; ARIMAX: autoregressive integrated moving average with exogenous variable; AIC: Akaike information criteria; PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression Severity.

FIGURE 4 Plots of standardized residuals, ACF, normal Q-Q plot, and p values for Ljung-Box statistic for PAT02 for residuals estimated from ARIMA (1, 2, 1) model. PAT02 refers to the code for the second patient. ACF: autocorrelation function; Q-Q plot: quantile-quantile plot; ARIMA: autoregressive integrated moving average

and ARIMAX (1, 2, 1) models. The results provided little evidence that autocorrelation remained in the residuals. Thus, ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models appeared to be strong. Table 6 summarizes the Ljung-Box statistic and p value for residuals from ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models. Figure 4 shows plots of standardized residuals plotted for 20 lags, ACF of residuals, normal Q-Q plot of standardized residuals, and plot of p values for Ljung-Box statistic for 20 lags for PAT02 for residuals estimated from ARIMA (1, 2, 1) model. It is evident from the ACF plot of residuals that autocorrelation at all lags stands within the confidence interval and hence is insignificant, which has been already confirmed by Ljung-Box test presented earlier. The p values of Ljung-Box statistic at different lags appear to be above the confidence region.

Hence, our model has captured all the structure of the time series for PAT02. Similar results were observed for all patients with both ARIMA and ARIMAX models.

Step 6 Normality and homoscedasticity check of residuals: In addition to testing for independence of the residuals, the assumptions of normality and homoscedasticity of residuals are also validated using Kolmogorov-Smirnov (K-S) and White's tests (Massey, 1951; White, 1980). The K-S test statistic value for the residuals from ARIMA (1, 2, 1) model for PAT02 is calculated to be 0.095 with a p value of 0.982, which does not support rejection of the null hypothesis of normally distributed residuals. This can also be verified from the normal Q-Q plot of standardized residuals shown in Figure 4. Similarly, the residuals estimated from both

FIGURE 5 Comparison of fit estimates from ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models with actual PANSS scores for PAT02. PAT02 refers to the code for the second patient. CGI-S scale is the exogenous variable used for ARIMAX model. ARIMA: autoregressive integrated moving average; ARIMAX: autoregressive integrated moving average with exogenous variable; PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression Severity

TABLE 7 MAPE, MAD, and AIC values of the fitted ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models

Patient code	Series	Model ^a	AIC	MAPE	MAD
PAT01	DPANSS1	1	115.67	3.9074	2.7674
		2	116.33	4.2759	2.9892
PAT02	DPANSS2	1	92.47	2.6733	1.8165
		2	94.03	2.5310	1.7123
PAT03	DPANSS3	1	165.27	15.1154	10.3224
		2	167.27	15.1050	10.3165
PAT04	DPANSS4	1	167.73	17.8496	12.0954
		2	152.6	9.5212	6.4672
PAT05	DPANSS5	1	90.08	2.5337	1.6600
		2	76.27	1.6687	1.1394
PAT06	DPANSS6	1	127.23	5.4393	3.6553
		2	122.24	3.9506	2.6872
PAT07	DPANSS7	1	147.53	7.8858	5.0541
		2	148.86	7.6808	4.9118
PAT08	DPANSS8	1	136.53	8.4684	5.8859
		2	127.35	5.5827	3.8523
PAT09	DPANSS9	1	115.57	4.4896	2.9881
		2	117.57	4.4909	2.9891
PAT10	DPANSS10	1	111.44	4.0192	2.6956
		2	109.34	3.7575	2.5770
PAT11	DPANSS11	1	119.00	4.1976	2.8166
		2	107.76	2.8325	1.9190
PAT12	DPANSS12	1	111.59	4.2534	2.9458
		2	111.79	3.8452	2.6538
PAT13	DPANSS13	1	148.20	9.0184	5.9425
		2	121.88	4.3486	2.9488
PAT14	DPANSS14	1	93.34	2.4554	1.6397
		2	94.39	2.3170	1.5445

Note. DPANSS represents the transformed time series of total scores of PANSS measured at 21 visits for patients after applying differencing of order 2. MAPE: mean absolute percentage error; MAD: mean absolute deviation; AIC: Akaike information criteria; ARIMA: autoregressive integrated moving average; ARIMAX: autoregressive integrated moving average with exogenous variable; CGI-S: Clinical Global Impression Severity; PANSS: Positive and Negative Syndrome Scale.

^aModel 1: ARIMA (1, 2, 1) model. Model 2: ARIMAX (1, 2, 1) model with CGI-S scale scores of patients as exogenous variable.

ARIMA and ARIMAX models for all patients were found to be normally distributed using K-S test. The significance of heteroscedasticity among residuals was assessed for all patients for both ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models using White's test. The results indicated that the residuals do not exhibit heteroscedasticity at 0.05 level for all patients.

FIGURE 6 Comparison of MAPE estimated from ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models. MAPE: mean absolute percentage error; ARIMA: autoregressive integrated moving average; ARIMAX: autoregressive integrated moving average with exogenous variable CGI-S scale; CGI-S: Clinical Global Impression Severity; PANSS: Positive and Negative Syndrome Scale

Step 7 Comparison between ARIMA and ARIMAX models: In this study, ARIMA and ARIMAX models are compared in four ways. First, their fit performance is compared by plotting the fitted ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models against actual data. Second, they are compared in terms of MAPE and MAD produced by them. Third, the AIC values derived from fitted models are compared, and lastly, the accuracy of forecasts derived from two models is compared using DM test (Diebold & Mariano, 1995).

Figure 5 compares the fit estimates produced by each model with actual PANSS scores for PAT02 all at 21 visits. Both the models perform equally well in estimating the actual PANSS scores. The MAPE, MAD, and AIC values of the fitted ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models are presented in Table 7. From Table 7, it is observed that the ARIMAX (1, 2, 1) model's average MAPE and MAD are lower as compared with the ARIMA (1, 2, 1) model except for PAT01. AIC values of ARIMAX model are also lower than that of ARIMA model except for few cases where they are comparable. The plots comparing ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models in terms of MAPE and MAD are shown in Figures 6 and 7. It is evident from the figures that ARIMAX model is preferable to the ARIMA model when compared with respect to MAPE and MAD. Finally, DM test is used for comparing accuracy of two models. For PAT02, the DM statistic and p value are observed to be 0.2465 and 0.596, which does not support rejection of null hypothesis. Thus, for PAT02, there exists no significant difference in the forecasting accuracy of ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models. Similar results were observed for two other patients as well.

Step 8 Forecasting: Finally, we forecasted the number of visits required to reach resolution (first step of remission) for the outpatients, who did not achieve remission by the end of study. We predicted the PANSS scores with ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models for the next visits until the symptom severity becomes "very mild" (i.e., the PANSS score becomes less than or equal to 45; Levine et al., 2008). The CGI-S scale scores supplied for forecasting are based on the relationship between PANSS and CGI-S scale as described in the study (Levine et al., 2008). Table 8 presents PANSS scores and number of visits forecasted from fitted ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models with CGI-S scale scores of patients as exogenous variable.

All calculations were performed in R version 3.4.0.

FIGURE 7 Comparison of MAD estimated from ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models. MAD: mean absolute deviation; ARIMA: autoregressive integrated moving average; ARIMAX: autoregressive integrated moving average with exogenous variable CGI-S scale; CGI-S: Clinical Global Impression Severity; PANSS: Positive and Negative Syndrome Scale

TABLE 8 PANSS scores and number of visits forecasted from fitted ARIMA and ARIMAX models

Patient code	Model ^a	CGI score	PANSS score	Number of visits
PAT04	1	Nil	68, 66, 63, 60, 58, 55, 52, 50, 49, 47, 46, 44	12
	2	5, 4, 4, 4, 4, 4	68, 51, 48, 47, 45	5
PAT05	1	Nil	52, 50, 48, 45	4
	2	3, 3, 3, 2	53, 51, 49, 42	4
PAT06	1	Nil	85, 82, 79, 75, 71, 67, 63, 59, 54, 52, 49, 45	12
	2	4, 4, 4, 4, 4, 4, 4, 4, 3, 3	71, 69, 68, 66, 65, 64, 62, 61, 46, 43	10
PAT08	1	Nil	63, 62, 60, 58, 57, 55, 53, 52, 50, 48, 47, 45	12
	2	4, 4, 4, 3, 3, 3, 3, 3, 3, 2	63, 62, 60, 54, 53, 51, 50, 48, 47, 41	10

Note. In this table, PANSS scores and number of visits are forecasted from fitted ARIMA (1, 2, 1) and ARIMAX (1, 2, 1) models with CGI-S scale scores of patients as exogenous variable. The CGI-S scale scores supplied for forecasting are based on the relationship between PANSS and CGI-S scale as described in the study (Levine et al., 2008). ARIMA: autoregressive integrated moving average; ARIMAX: autoregressive integrated moving average with exogenous variable; CGI-S: Clinical Global Impression Severity; PANSS: Positive and Negative Syndrome Scale.

^aModel 1: ARIMA (1, 2, 1) model. Model 2: ARIMAX (1, 2, 1) model with CGI-S scale scores of patients as exogenous variable.

4 | DISCUSSION

Schizophrenia is a chronic and severe mental disorder affecting more than 21 million people worldwide (World Health Organization, 2018). PANSS has served to measure the presence and severity of positive and negative symptoms of schizophrenia. Many people continue to experience residual symptoms after the first episode. Some suffer relapses, or remain ill and functionally impaired. Remission is a new research outcome indicating long-term wellness (Yeomans et al., 2010). Time to remission is the time to resolution with an added duration of 6 months during which the minimal severity of symptoms is maintained with respect to the definition of remission given by RSWG (Andreasen et al., 2005). Forecasting can be used to predict the time required by a patient to achieve resolution.

Time series analysis is a very useful tool to forecast number of visits required to achieve remission on the basis of the remission criteria whenever data of outpatients are recorded at regular

intervals of time irrespective of the disease. ARIMA and ARIMAX models are important and widely used models because they provide a basic methodology to model the effects of dependency from the data series and allow valid statistical testing (Velicer & Fava, 2003).

In this paper, first, we have used ARIMA model to forecast the number of visits required to reach resolution (first step of remission) for the outpatients who did not achieve remission by the end of study on the basis of the PANSS scores. The criterion used for remission is a total score of PANSS less than or equal to 45 (belonging to “very mild” category by Levine et al., 2008) along with a score less than or equal to 3 for selected eight items of PANSS as given by RSWG (Andreasen et al., 2005). Second, a similar procedure of forecasting is performed with ARIMAX model with CGI-S scale as exogenous variable. We have used CGI-S scale as independent variable as previous studies suggest that it is possible to extrapolate from a CGI-S scale to a PANSS severity score (Levine et al., 2008). The PANSS and CGI-S scale are used together to measure severity of psychotic illness, and the CGI-S scale shows overlap with the core symptoms of schizophrenia. Previous studies found them to be correlated but not synonymous (Rabinowitz, Mehnert, & Eerdeken, 2006).

We observed that ARIMAX model performed better than ARIMA model (which is in accordance with a previous study; Taweasin, Seeboonruang, & Saraphirom, 2018) in terms of MAPE, MAD, and AIC values of the fitted models, whereas according to DM test (Diebold & Mariano, 1995), the accuracy of the two models was found to be similar for some cases. We suggest to prefer ARIMAX model over ARIMA whenever information on exogenous variable can be supplied as additional information results in a better model.

Forecasting is also beneficial in regulating the treatment adherence by a patient. This study will not only facilitate the clinicians in efficient prognosis by projecting an approximate time to symptom remission for the patient but also assist them in management of appropriate interventions and resources. Further, it has an implication of instilling hope in patients and their families as a major step towards recovery.

DECLARATION OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ORCID

Sakshi Kaushik <https://orcid.org/0000-0002-4219-1488>

REFERENCES

- Andreasen, N. C., Carpenter, W. T., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: Proposed criteria and rationale for consensus. *The American Journal of Psychiatry*, 162(3), 441–449. <https://doi.org/10.1176/appi.ajp.162.3.441>
- Box, G., & Jenkins, G. (1970). *Time series analysis: Forecasting and control*. San Francisco: Holden-Day.
- Dickey, D. A., & Fuller, W. A. (1979). Distribution of the estimators for autoregressive time series with a unit test. *Journal of the American Statistical Association*, 74(366), 427–431.
- Diebold, F. X., & Mariano, R. S. (1995). Comparing predictive accuracy. *Journal of Business & Economic Statistics*, 13(3), 253–263.
- Dierker, L., Stolar, M., Lloyd-Richardson, E., Tiffany, S., Flay, B., Collins, L., ... (TERN), T. E. (2009). Tobacco, alcohol, and marijuana use among first-year U.S. college students: A time series analysis. 43 2008(5), Pages 680–699.
- Granger, C. W. (1969). Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*, 37(3), 424–438. <https://doi.org/10.2307/1912791>
- Guy, W. A. (1976a). Abnormal Involuntary Movement Scale (AIMS). In W. A. Guy (Ed.), *ECDEU assessment manual for psychopharmacology* (pp. 534–537). Washington, DC: U.S. Department of Health Education and Welfare.
- Guy, W. A. (1976b). Clinical global impressions. In W. A. Guy (Ed.), *ECDEU assessment manual for psychopharmacology—Revised* (pp. 218–222). Rockville: U.S. Department of Health, Education, and Welfare; Public Health Service, Alcohol; Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs.
- Hipel, K. W., & McLeod, A. I. (1994). *Time series modelling of water resources and environmental systems* (1st ed.), (Vol. 45). Amsterdam: Elsevier.
- Jäger, M., Riedel, M., Schmauss, M., Laux, G., Pfeiffer, H., Naber, D., ... Möller, H.-J. (2009). Prediction of symptom remission in schizophrenia during inpatient treatment. *The World Journal of Biological Psychiatry*, 10(4–2), 426–434. <https://doi.org/10.1080/15622970701541054>
- Kanter, J. W., Mulick, P., Busch, A. M., Berlin, K. S., & Martell, C. R. (2007). The Behavioral Activation for Depression Scale (BADS): Psychometric properties and factor structure. *Journal of Psychopathology and Behavioral Assessment*, 29, 191–202. <https://doi.org/10.1007/s10862-006-9038-5>
- Kay, S. R., Fiszbein, A., & Opler, A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, 13(2), 261–276. <https://doi.org/10.1093/schbul/13.2.261>
- Levine, S. Z., Rabinowitz, J., Engel, R., Etschel, E., & Leucht, S. (2008). Extrapolation between measures of symptom severity and change: An examination of the PANSS and CGI. *Schizophrenia Research*, 98(1–3), 318–322. <https://doi.org/10.1016/j.schres.2007.09.006>
- Liu, Q., Liu, X., Jiang, B., & Yang, W. (2011). Forecasting incidence of hemorrhagic fever with renal syndrome in China using ARIMA model. *BMC Infectious Diseases*, 11, 218. <https://doi.org/10.1186/1471-2334-11-218>
- Ljung, G. M., & Box, G. E. (1978). On a measure of a lack of fit in time series models. *Biometrika*, 65(2), 297–303. <https://doi.org/10.1093/biomet/65.2.297>
- Massey, F. J. Jr. (1951). The Kolmogorov–Smirnov test for goodness of fit. *Journal of the American Statistical Association*, 46(253), 68–78. <https://doi.org/10.1080/01621459.1951.10500769>
- McMahon, F. J. (2014). Prediction of treatment outcomes in psychiatry—Where do we stand? *Dialogues in Clinical Neuroscience*, 16(4), 455–464.
- Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, 134, 382–389. <https://doi.org/10.1192/bjp.134.4.382>
- Moore, P. J., Little, M. A., McSharry, P. E., Geddes, J. R., & Goodwin, G. M. (2012). Forecasting depression in bipolar disorder. *IEEE Transactions on Biomedical Engineering*, 59(10), 2801–2807. <https://doi.org/10.1109/TBME.2012.2210715>
- Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, 10, 799–812. <https://doi.org/10.2466/pr0.1962.10.3.799>
- Rabinowitz, J., Mehnert, A., & Eerdeken, M. (2006). To what extent do the PANSS and CGI-S overlap? *Journal of Clinical Psychopharmacology*, 26(3), 303–307. <https://doi.org/10.1097/01.jcp.0000218407.10362.6e>
- Rathlev, N. K., Chessare, J., Olshaker, J., Obendorfer, D., Mehta, S. D., Rothenhaus, T., ... Litvak, E. (2007). Time series analysis of variables associated with daily mean emergency department length of stay. *Annals of Emergency Medicine*, 49(3), 265–271. <https://doi.org/10.1016/j.annemergmed.2006.11.007>
- Sato, R. C. (2013). Disease management with ARIMA model in time series. *Einstein (Sao Paulo)*, 11(1), 128–131. <https://doi.org/10.1590/S1679-45082013000100024>
- Simpson, G. M., & Angus, J. W. (1970). A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*, 212, 11–19.
- Soyiri, I. N., & Reidpath, D. D. (2012). Evolving forecasting classifications and applications in health forecasting. *International Journal of General Medicine*, 5, 381–389.
- StatSoft. (2004). How to identify patterns in time series data: Time series analysis. Retrieved from StatSoft Electronic Statistics Textbook: <http://www.statsoft.com/Textbook/Time-Series-Analysis#1general>
- Sun, Y., Heng, B. H., Seow, Y. T., & Seow, E. (2009). Forecasting daily attendances at an emergency department to aid resource planning. *BMC Emergency Medicine*, 9(1). <https://doi.org/10.1186/1471-227X-9-1>
- Taweessin, K., Seeboonruang, U., & Saraphirom, P. (2018). The influence of climate variability effects on groundwater time series in the lower central plains of Thailand. *Water*, 10(3), 290. <https://doi.org/10.3390/w10030290>
- Velicer, W. F., & Fava, J. L. (2003). Time series analysis. In J. A. Schinka, W. F. Velicer, & I. B. Weiner (Eds.), *Handbook of psychology, research methods in psychology* (Vol. 2) (pp. 581–606). New York: John Wiley & Sons. <https://doi.org/10.1002/0471264385.wei0223>
- Victor-Edema, U. A., & Essi, I. D. (2016). Autoregressive integrated moving average with exogenous variable (ARIMAX) model for Nigerian non-oil export. *European Journal of Business and Management*, 8(36), 29–34.
- Walther, S., Ramseyer, F., Horn, H., Strik, W., & Tschacher, W. (2013). Less structured movement patterns predict severity of positive syndrome, excitement, and disorganization. *Schizophrenia Bulletin*, 40(3), 585–591. <https://doi.org/10.1093/schbul/sbt038>
- White, H. (1980). A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica*, 48(4), 817–838. <https://doi.org/10.2307/1912934>
- World Health Organization. (2018). Schizophrenia. Retrieved from World Health Organization: <http://www.who.int/news-room/fact-sheets/detail/schizophrenia>
- Yeomans, D., Taylor, M., Currie, A., Whale, R., Ford, K., Fear, C., ... Burns, T. (2010). Resolution and remission in schizophrenia: Getting well and staying well. *Advances in Psychiatric Treatment*, 16(2), 86–95. <https://doi.org/10.1192/apt.bp.108.006411>

How to cite this article: Sabharwal A, Grover G, Kaushik S, Unni KES. Modelling and forecasting Positive and Negative Syndrome Scale scores to achieve remission using time series analysis. *Int J Methods Psychiatr Res*. 2019;28:e1763. <https://doi.org/10.1002/mpr.1763>