An Interrupted Time Series Analysis Method for Healthcare Data Using the INGARCH Model: An Application to Psychotropic Drug Prescription Data in Japan

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Abstract

Interrupted time series analysis (ITSA) is generally performed in evaluating the effect of a health policy. Although segmented regression analysis methods are the standard methods for ITSA and are used to fit linear models to the data, these methods are oversimplified for real data. Further, ITSA data are often count time series data that total the number of cases of interest. Although several methods of analysis have been proposed and used for an ITSA, methods using a count time series model have merely been discussed and used. Thus, we propose to use a count time series model, the integer-valued generalized autoregressive conditional heteroscedastic (INGARCH) model, as an ITSA to evaluate a health policy. The INGARCH model is a count time series model which can model more complicated time series data than linear regression models; moreover, it has not been compared with segmented regression analysis methods. We applied the INGARCH model and segmented regression analysis methods (Poisson regression analysis (PREG) and generalized least squares (GLS)) to real psychotropic drug prescription data in Japan and then discussed the statistical behavior of these methods. We used psychotropic drug prescription data from a hospital in Japan for the ITSA. Several administrative policies for the prevention of multidrug use of psychotropic drugs have been enforced in recent years, and we evaluated the effects of the policies on the four types of psychotropic medicines (antidepressants, antipsychotic drugs, anxiolytics, and sleeping drugs). The test results differed according to the methods of analysis used. Segmented regression analysis methods by GLS and PREG fit linear regression models to the data but did not necessarily model the real time series data well. Conversely, INGARCH could model the more complicated time series behavior; thus, the results suggested that INGARCH can model more various types of count time series than segmented regression analysis.

[Keywords] interrupted time series analysis, INGARCH, segmented regression analysis, psychotropic drugs, prescription drug data, multidrug use

1. Introduction

Interrupted time series analyses (ITSAs) are often conducted as a statistical method for evaluating the effect of a medical policy or intervention[1]. ITSA is a method investigating the change in an outcome value before and after an intervention using time series data. Several statistical methods have been proposed for ITSAs[2-8], and a few methods are most commonly used[9-12]. The ITSA results change depending on the methods of analysis used; thus,

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it is important to consider what methods will be used for ITSA.

According to a systematic review of ITSAs on drug utilization research or healthcare[2], segmented regression analysis is by far the most well-known method. Segmented regression analysis fits linear regression models to time series data, and a few methods have been proposed[3,5,6]. This analysis is easy to implement with any statistical software and is also easy for clinicians to understand. However, ITSA deals with time series data, and time series data are usually accompanied by the autocorrelation of observed values. Although segmented regression analysis methods that take autocorrelation into account have been also used[3], ITSA is not designed for count or proportion data that are not numeric. Moreover, segmented regression analysis fits linear models, but time series data are usually not linear; thus, more advanced time series models are required for modeling more complicated time series behavior. Further, ITSAs for health data often deal with count data, such as the number of incidents or the number of patients. Although numeric data can represent continuous values from minus infinity to infinity, count data can represent integer values that are zero or higher. Therefore, when data are count time series data, a count time series model can be more useful. Although Poisson regression is used as a segmented regression analysis method for count time series data[1], count time series models for an ITSA are, however, merely discussed or used. Among the several count time series models already proposed, in this study, we focus on the integer-valued generalized autoregressive conditional heteroscedastic (INGARCH) model[13]. Although INGARCH is not well known in the fields of medicine or healthcare, its autoregressive structure is similar to autoregressive moving average (ARMA) model[14]. Therefore, it can be used as a substitute for ARMA when using count time series data. To our knowledge, INGARCH has not been previously used to evaluate a health policy. Therefore, comparing it with segmented regression analysis methods will provide beneficial information.

To compare methods, we conducted an ITSA on psychotropic drug prescription data in Japan. Multidrug use is a serious problem in Japan, and it leads to adverse drug reactions, particularly in older people[15,16]. The multidrug use of psychotropic medicines is regarded as a serious problem[17,18], leading to the enforcement of several administrative policies. Beginning in 2012, there has been a reduction in the reimbursement rate for continuous outpatient support and guidance fees when three or more types of these medicines were prescribed simultaneously for anxiolytics and sleeping drugs. Since 2014, prescription charges and drug fees for antidepressants and antipsychotic drugs have been reduced when four or more types of these medicines were prescribed simultaneously, in addition to a similar policy for three or more types of anxiolytics and sleeping drugs. Additionally, reimbursement for continuous outpatient support and guidance fees is no longer provided when three or more types of these medicines are prescribed simultaneously for anxiolytics and sleeping drugs, or when four or more types of these medicines are prescribed simultaneously. Since 2016, prescription charges and drug fees for all four kinds of psychotropic drugs (antidepressants, antipsychotic drugs, anxiolytics, and sleeping drugs) have been reduced when three or more types of the same kind of medicines were prescribed simultaneously. It is important to investigate whether the simultaneous prescription of multiple psychotropic drugs decreased after the introduction of these policies. If we focus on the number of patients who were simultaneously prescribed more than a certain number of types of medicines, data used for the ITSA become count time series data. Furthermore, in this study, we applied the INGARCH model and other ITSA methods to real psychotropic drug prescription data in Japan and then compared the statistical behavior of the analysis methods.

2. Methods

In this section, we describe the ITSA methods used in this study and explain the data that were used.

2.1 ITSA Methods

We implemented three types of ITSA methods in this study.

2.1.1 Segmented Regression Analysis

We conducted the segmented regression analysis by the ordinary least squares (OLS) method. We considered

the following linear model:

$$y_t = \beta_0 + \beta_1 x_t + \beta_2 t + \varepsilon_t$$

where y_t represents the outcome value at time t and x_t represents a dummy variable of whether time t is before or after an intervention. β_0, β_1, and β_2 represent regression coefficients. ε_t follows a normal distribution with variance σ^2.

$$\varepsilon_t \sim N(0, \sigma^2)$$

When we test for changes in a level for the mean value of the observed values, we focus on β_2.
For count time series data, a Poisson regression model can be used:

$$\mu_t = \beta_0 + \beta_1 x_t + \beta_2 t + \log(n_t)$$

$$y_t \sim poisson(\mu_t)$$

where μ_t is the mean of y_t at time t and n_t is the total count of time t. Offset term $\log(n_t)$ is included in the model when we focus on the ratio of y_t to n_t. We call this method PREG.
If we want to test a change in a trend rather than in a level, an interaction term of the intervention effect and time effect is included:

$$\mu_t = \beta_0 + \beta_1 x_t + \beta_2 t + \beta_3 x_t t + \log(n_t)$$

where β_3 is the coefficient of the interaction term.

2.1.2 Segmented Regression Analysis by Generalized Least Squares

Although OLS and PREG are easy to understand, these methods do not take into account the autocorrelation of the time series. Depending on the values used, the values of sequential time series data are usually correlated.

Segmented regression analysis by generalized least squares (hereafter, GLS) is an analysis method that takes the autocorrelation into account. The regression model is the same as that of OLS. However, GLS assumes a time series model for the error term ε_t.[19]

$$\varepsilon_t = \sum_{i=1}^{p} \varphi_i \varepsilon_{t-i} + w_t + \sum_{j=0}^{q} \psi_j w_{t-j}$$

where w_{t-j} represents white noise at time $t-j$, φ_i represents coefficients of ε_{t-i}, and ψ_j represents coefficients of w_{t-j}. w_t is assumed to be normal random error.

$$w_t \sim N(0, \sigma_w^2)$$

Orders(p, q) are often determined by AIC. $\sum_{i=1}^{p} \varphi_i \varepsilon_{t-i}$ represents an autoregressive process, and $\sum_{j=0}^{q} \psi_j w_{t-j}$ represents a moving-average process. Furthermore, the model assumes an autoregressive moving average (ARMA) model for the error term. By using this model, we can take into account the correlation among errors. Although a Poisson regression model whose error term follows the time series process can be constructed using a Bayesian statistical model, it is not usually used in practice and is not proposed for an ITSA. To take into account the total count n_t, we include n_t as an explanatory variable.

2.1.3 INGARCH

GLS assumes that observed values follow a normal distribution that can represent continuous values from minus infinity to infinity. However, the values of count data include integer values that can be zero or higher. Depending on the data, it may be preferable to use a count data analysis method if count data are used.

The following model was used for INGARCH:[13]

$$\mu_t = \sum_{i=1}^{p} \varphi_i y_{t-i} + \sum_{j=1}^{q} \psi_j \mu_{t-j} + \beta_0 + \beta_1 x_t$$

$$y_t \sim poisson(\mu_t)$$

where φ_i and ψ_j are coefficients for past outcome values and past mean values and α is the coefficient. In INGARCH, the mean value of a certain time μ_t is affected by the past outcome values y_{t-i} and the past mean values μ_{t-j}. In INGARCH, the past values are used for explanatory variables for the mean rather than a simple linear time effect; thus, it can model time series data that do not necessarily follow linear models. Additionally, the interpretation of the intervention effect is relatively straightforward. The values of orders (p, q) can be selected by the AIC. Similar to GLS, we also include $\log(n_t)$ as an explanatory variable.

2.2. Data Analysis

We evaluated the effects of the policies for psychotropic drug prescriptions by the three ITSA models using electronic medical records (EMR) data. Additionally, we used real-world data from the EMR of one university hospital and extracted prescription drug data. The research subjects were patients who have been prescribed a psychotropic medication from April 2008 to March 2019. We classified each psychotropic medicine into one of the four types of psychotropic medicines (antipsychotic drugs, anxiolytics, antidepressants, and sleeping drugs) based on the chart for the medical service fees in Japan.[20] We used the data of patients who were at least 20 years old.

Although several policies have been introduced for psychotropic medicines, it is often difficult to distinguish the effects of these multiple policies. Therefore, in this study, we focused on the first policies implemented for the four types of psychotropic medicines. Afterward, we used a dummy variable of after or before 2014 as the intervention effect for antipsychotic drugs and antidepressants and a dummy variable of after or before 2012 for anxiolytics and sleeping drugs. We totaled the number of patients who were simultaneously prescribed three or more types of anxiolytics and sleeping drugs in one day per month and four or more types of antipsychotic drugs and antidepressants. To check the autocorrelation of the time series data, we plotted autocorrelation plots for the time series of the four types of psychotropic medicines. We then fitted the three methods to each type of psychotropic medicine and evaluated the effect of the policy. Furthermore, we plotted the fitted values by the models in order to confirm the goodness of fit for the models. Although we tested the change in a level of the observed values by not including the interaction term for PREG and GLS, the model fit can be improved by including the interaction term. Therefore, we also plotted the fitted values of the models including the interaction term for PREG and GLS. For all the fitted models, we calculated the sum of squared residuals in order to evaluate the goodness of fit for the models.

R3.5.1[21] was used for all the analyses. GLS was conducted with R: package nlme[22]. Orders of GLS and INGARCH were determined based on the AIC. INGARCH was conducted using R: package tscount[23]. Statistical significance was assessed at the probability level of 0.05.

3. Results

Table 1 presents a summary of the data. A total of 2,767,277 prescriptions were analyzed. Additionally, 20,741, 39,968, 18,910, and 57,201 patients were prescribed antipsychotic drugs, anxiolytics, antidepressants, and sleeping drugs, respectively.

Figure 1 shows the time series for the number of patients who were simultaneously prescribed three or more types of anxiolytics and sleeping drugs in one day per month and the number of patients who were prescribed four or more types of antipsychotic drugs and antidepressants. The number for antipsychotic drugs began to decrease around April 2014 and that for anxiolytics and antidepressants began to decrease beginning around 2012. With regard to sleeping drugs, the number abruptly decreased around 2014 and remained relatively stable from around the middle of 2014.

Figure 2 shows the autocorrelation plot for the four types of psychotropic medicines. Obviously, the autocorrelation of observations exists for the four types of psychotropic medicines. Therefore, a method that takes autocorrelation into account must be used.

Table 2 summarizes the results of the ITSAs. For all four types of medicines, the p value for PREG was statistically significant. Although the effects of the interventions were not statistically significant for GLS, downward effects by the interventions were suggested from the estimates. Based on the INGARCH results, the estimates suggested the downward effect except for sleeping drugs.

Figures 3, 4, and 5 show the fitted values of the models. Obviously, the fitted values of PREG and GLS are relatively linear, and they do not necessarily capture the time series trend of observed values. Conversely, the fitted values of INGARCH display a better fit to the observed values.

Figures 6 and 7 show the fitted values of PREG and GLS including the interaction term of both the intervention effect and time effect. The model fits improved by including the interaction term; for anxiolytics, the models accurately captured the time series behavior. However, they did not accurately capture the time series behavior of relatively complicated time series such as antidepressants or sleeping drugs.

Table 3 shows the results of the sum of squared residuals for the fitted models. The sum of squared residuals for INGARCH were the lowest of the fitted models regardless of the type of psychotropic drugs.

Table 1. Summary statistics for the data

Item	Psychotropic drugs				
	Antipsychotic drugs	Anxiolytics	Antidepressants	Sleeping drugs	Total
Number of prescriptions*	509077	742929	510750	994521	2757277
Number of patients*	20741	39968	18910	57201	83239
Age†	44.88(15.76)	51.40(16.51)	48.55(15.91)	54.07(16.56)	50.63(16.63)
Sex‡	40.46	37.63	37.06	42.57	39.83
Number of types of prescribed drugs*	20	14	16	17	67

*Number of cases

†Mean(standard deviation)

‡Proportion of male

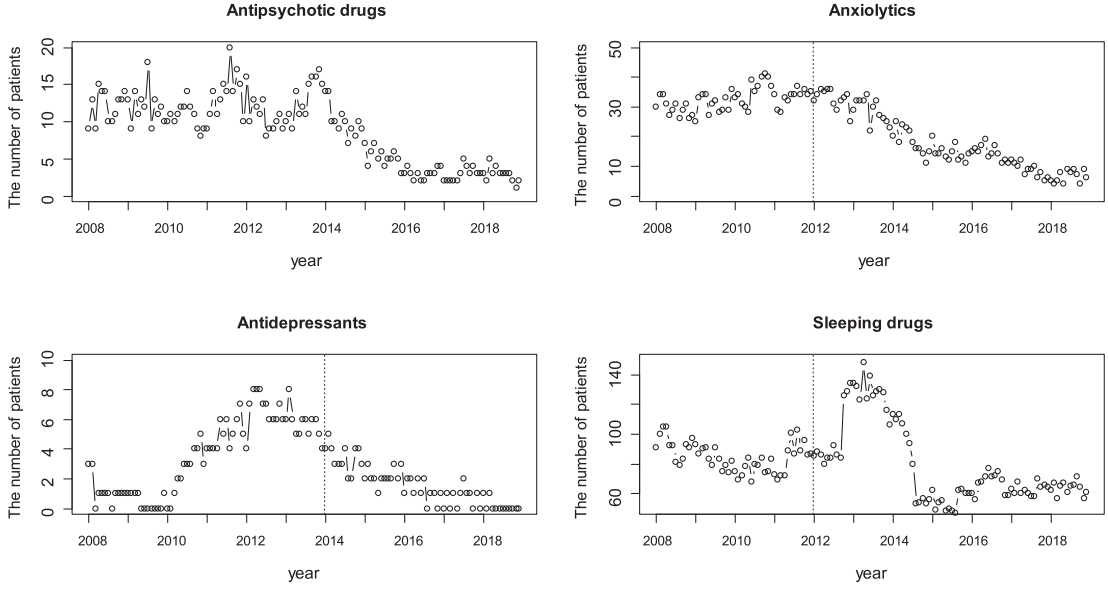

Figure 1. Time series of the number of patients who received simultaneous prescriptions.

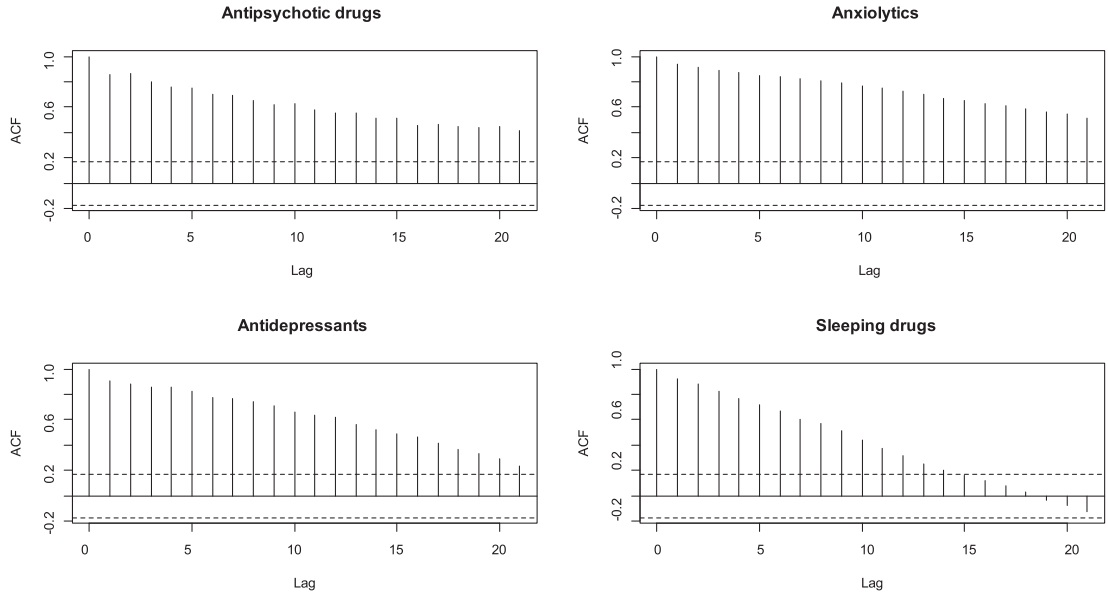

Figure 2. Autocorrelation plot of the four types of psychotropic medicines.

Table 2. The ITSA results

Drug	Model	Order*	Coefficients β_0	β_1	β_2	95%CI †	Pvalue ‡
Antipsychotic drugs	PREG	-	-4.083	-0.544	-0.006	(-0.777, -0.311)	<0.001
	GLS	(3,3)	5.242	-2.175	-0.065	(-4.999, 0.649)	0.13
	INGARCH	(3,2)	0.064	-0.032	-	(-0.077, 0.012)	0.154
Anxiolytics	PREG	-	-3.712	0.27	-0.011	(0.137, 0.403)	<0.001
	GLS	(3,3)	12.065	-1.363	-0.125	(-5.947, 3.222)	0.558
	INGARCH	(2,1)	0	-0.024	-	(-0.052, 0.004)	0.101
Antidepressants	PREG	-	-6.383	-1.887	0.016	(-2.307, -1.467)	<0.001
	GLS	(1,1)	-0.081	-0.462	-0.013	(-2.064, 1.003)	0.552
	INGARCH	(1,2)	0.001	-0.124	-	(-0.272, 0.024)	0.104
Sleeping drugs	PREG	-	-2.424	0.487	-0.008	(0.417, 0.558)	<0.001
	GLS	(3,0)	2.174	-1.67	-0.152	(-16.483, 13,143)	0.824
	INGARCH	(1,0)	0.534	0.022	-	(-0.019, 0.063)	0.294

* Order (p,q) for GLS and INGARCH

† 95% confidence interval for β_1

‡ Pvalue for β_1

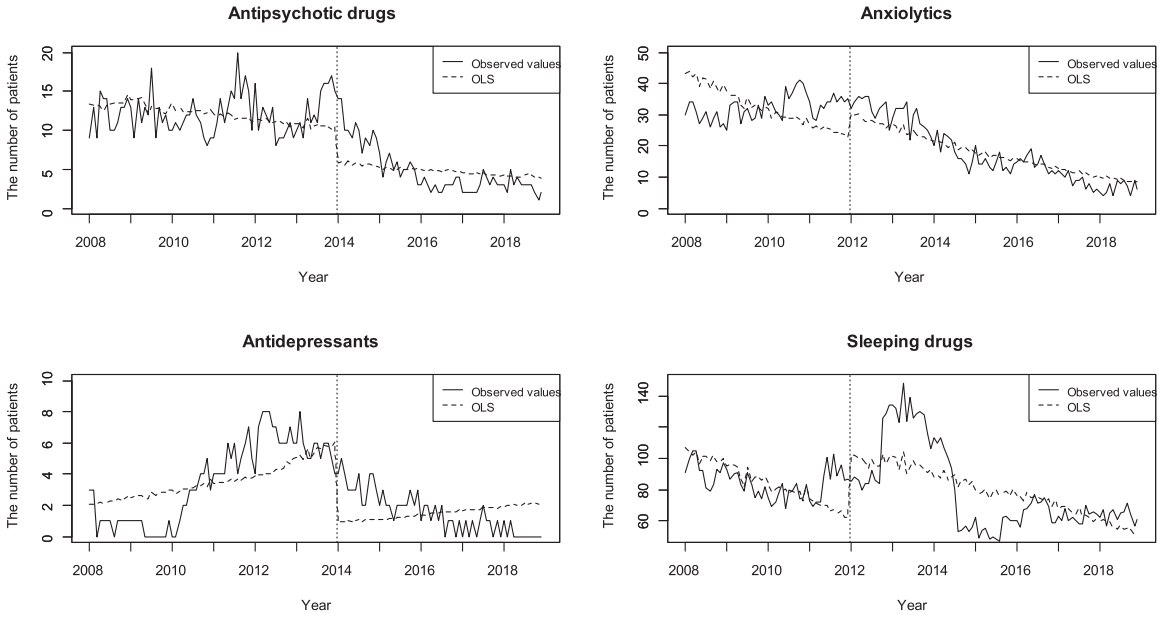

Figure 3. Fitted values of PREG for the four types of psychotropic medicines.

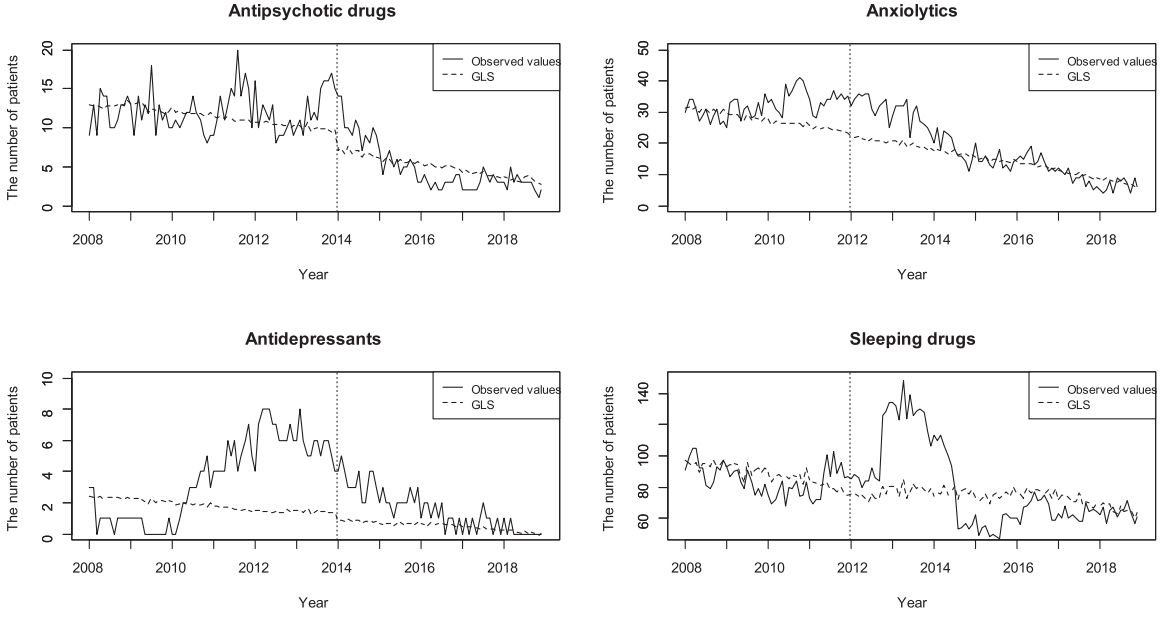

Figure 4. Fitted values of GLS for the four types of psychotropic medicines.

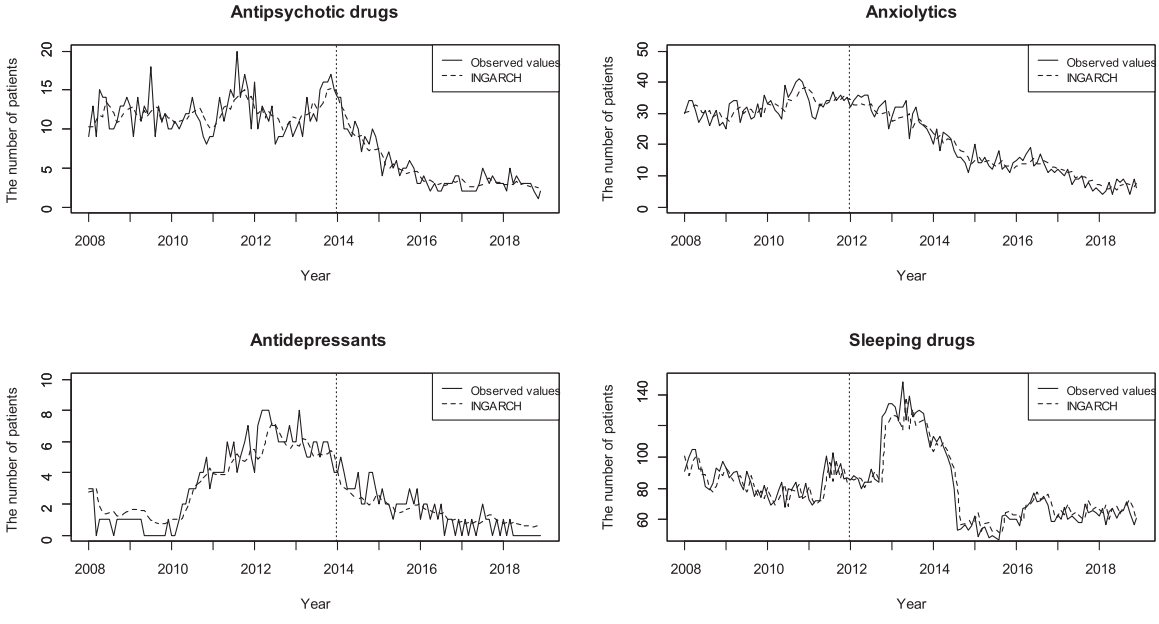

Figure 5. Fitted values of INGARCH for the four types of psychotropic medicines.

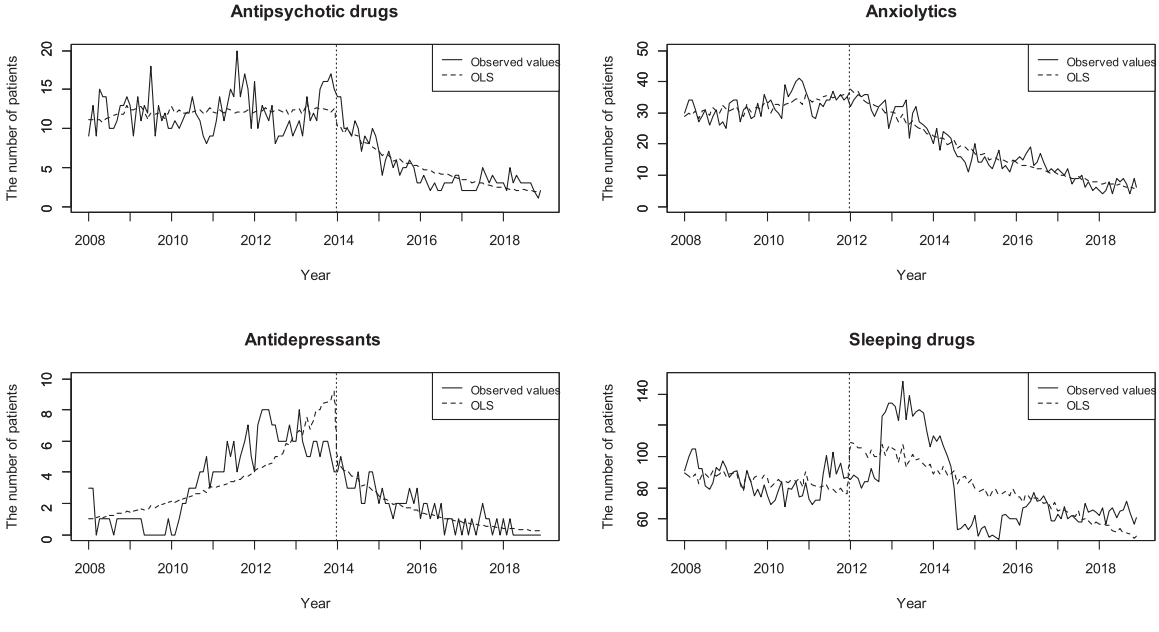

Figure 6. Fitted values of PREG including the interaction term for the four types of psychotropic medicines.

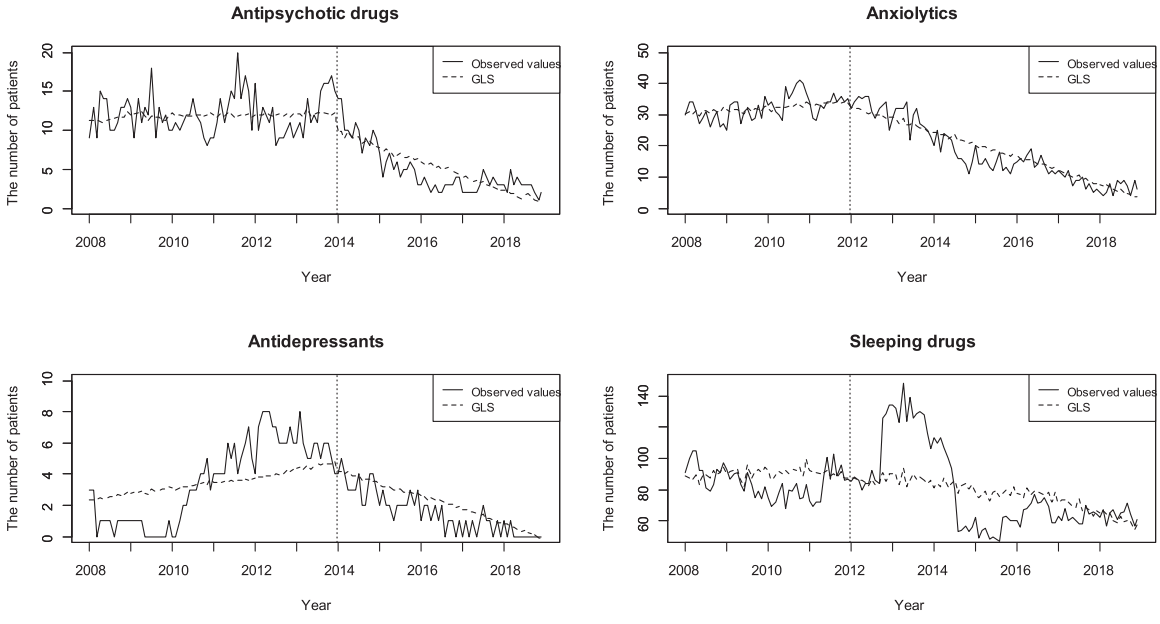

Figure 7. Fitted values of GLS including the interaction term for the four types of psychotropic medicines.

Table 3. Results of the sum of squared residuals

	Psychotropic drugs			
Model	Antipsychotic drugs	Anxiolytics	Antidepressants	Sleeping drugs
PREG	1000.9	4870.4	420.3	42006.2
GLS	908.1	5804.1	949.7	60635.4
INGARCH	385.5	1197.7	116.3	9999.6
PREG with the interaction term	593.5	1234.0	258.0	36717.8
GLS with the interaction term	683.0	1642.2	360.2	49611.0

4. Discussion

We compared the ITSA methods using the psychotropic drug prescription data. As shown in Figure 1, there was an obvious decrease in the observed values after the interventions for antidepressants and anxiolytics were introduced. However, the test results differ depending on the methods of analysis. Although the estimates of the intervention effects for PREG were statistically significant for all four types of psychotropic drugs, autocorrelation of the observations exists, as indicated in Figure 2. Therefore, the standard errors of the estimates for PREG may be underestimated. Although GLS and INGARCH both had test results that were not statistically significant, as Figures 4 and 5 show, the models fitted by these methods are completely different. GLS did not model the time series trend well because it fitted almost straight lines to the data, and as Table 3 shows, the goodness of fit

improves by using INGARCH.

The goodness of fit for PREG and GLS can be improved by including the interaction term of the intervention effect and time effect, as shown in Figures 6 and 7, and in Table 3. However, in that case, the intervention effect indicates the difference between the intercepts of the two regression models rather than the difference between the means of the observations, and the change in a level by the intervention cannot be detected. Even if we test the change in a trend rather than the change in a level by including the interaction term, fitting straight lines to the data we analyzed is oversimplified because time series data are generally not linear either before or after an intervention. Further, as the results of antidepressants and sleeping drugs of Figures 6 and 7 show, even if we include the interaction term, it is uncertain whether these models accurately model the time series trend of the data. Testing a change in a trend by incorrectly fitted models can lead to a wrong conclusion. Conversely, a drawback of INGARCH is that detecting a change in trend becomes more complicated and difficult. Although including the interaction in the model is one option, it can lead to the same problem as the segmented regression analysis methods. Therefore, if we want to capture the change in a trend by INGARCH, mixture models such as the Markov switching model or structural break model may need to be constructed to consider the change of the coefficients caused by the intervention.

There are some limitations of this data analysis. The data may not reflect the overall trends in Japan because they are obtained from an acute care hospital. A study using nationwide data (e.g., NDB) should be conducted using an appropriate statistical method. Furthermore, this analysis focused on the number of patients who were simultaneously prescribed multiple medicines. However, various outcome measures can be used for evaluating the policy effects, such as the number of patients who were prescribed a certain type of medicine per month or the number of prescriptions for the four types of psychotropic medicines. Analyses using other types of outcome measures may also be necessary.

As the test results of this study show, the analysis results change depending on the analysis methods used. The analytical methods should be determined based on the time series behavior of the data or the variable type of the observed values. For example, if proportion data that can represent values from zero to one are used, other types of time series models should also be considered. Therefore, it is important to be able to utilize multiple analytical methods rather than just one method. If the data analyzed are count time series data, INGARCH is a possible option. Although INGARCH is not known well in the field of healthcare, it can be fitted to broad count time series data such as the data we analyzed.

5. Conclusion

We proposed using the INGARCH model for an ITSA of healthcare data and compared it with segmented regression models using psychotropic drug prescription data. As a result, the INGARCH model displayed a better fit to the data compared with a segmented regression analysis. Therefore, INGARCH can be used as an ITSA for various types of count time series data.

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7. Ethics approval

The data analysis was conducted after receiving the approval from the ethics committee of the hospital.

8. Conflict of Interest

The authors declare no conflicts of interest associated with this manuscript.