

# Factors Associated With Low Relapse Rates of Schizophrenia In Southern Thailand: A University Hospital-Based Study

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## Research Article

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# Abstract

**Background:** Schizophrenia is a chronic disease that has residual symptoms and relapse. Relapse prevention research will provide useful knowledge for the employment of an effective caring process. This study aims to explore factors associated with relapse rates in hospital where there are comparatively low relapse rates for schizophrenia.

**Method:** Medical records of patients who had their first schizophrenia diagnosis, in the Songklanagarind hospital's inpatient psychiatric unit, were retrospectively reviewed for the period from January 2007 to December 2019. This yielded data outlining demographic information, profiles of schizophrenia and treatment. Descriptive statistical analysis was utilized to process all data; and factors associated to relapse were investigated using bivariate and multivariate analyses.

**Results:** Reviewed medical records identified a sample size of 156 schizophrenias. The majority were male (50.6%), Buddhist (85.9%), unmarried (80.1%), unemployed (50.6%) and living with their families (90.4%). Their mean age was 39.2 years. Relapse was defined as readmission to a psychiatric unit within 5 years after their first psychotic episode. From the 156 patients, 53.8% featured relapse whereas 46.2% were in remission. Cumulatively, the first to the fifth-year relapse rate was 22.4%, 35.3%, 44.9%, 50.0%, and 53.8% respectively. Multivariate analysis indicated that patients having stressful life events, non-adherence to medication, prescription changes and lack of insight were all factors with a statistically significant association to relapse rates.

**Conclusions:** Stressful life events, adverse events, medical non-adherence, change prescription, and lack of insight were related to relapse. Emphasizing multimodality of treatment could be key to successful relapse prevention for schizophrenia.

## Background

Schizophrenia is a mental illness affecting about 7 per 1,000 adults globally [1] or approximately 1% of the world's population [2]. In addition, schizophrenia is a long-term debilitating chronic disease that has residual symptoms, including functional impairment, and requires lifelong medical care and supervision [1–3]. Therefore, biological treatment and psychiatric rehabilitation are necessary to improve patients' quality of life [4] and lessen the burden for their families [5, 6].

Historically, the core strategy in the management of schizophrenia has been a combination of medication, ensuring patients gain insight about their condition and the teaching of essential community-living skills as integrating patients back into society and engaging in employment and other meaningful activities can reduce social stigma [7]. Although some schizophrenic patients can gain insight well, the reality of their condition causes them emotional pain due to social stigmatization. This often leads to them refusing to take their medication, leading to relapse.

Relapse in schizophrenia is broadly defined as the reemergence or the worsening of psychotic symptoms [2]. Furthermore, this definition can include the aggravation of positive or negative symptoms, hospital admission, more intensive management and/or changes in medication [8].

Systematic review and meta-analytic studies found that at least 80% of first diagnosed schizophrenic patients had a relapse of symptoms within a minimum 12-month follow-up period [6]. Nevertheless, some studies identified that relapse rates vary from 50–92% globally [9–10]. Furthermore, most schizophrenic patients in treatment relapse within 5 years and suicide might occur in up to 10% of them [3]. Several studies suggest that there is an association between suicidal ideation and the likelihood of relapse with the probability of relapse being 9.1 times larger than schizophrenic patients without suicidal ideation [11, 12]. Additionally, the factors commonly associated with relapse are poor or non-adherence to medication, ranging from 26–44%, as many as two-thirds of patients were at least partially poorly adherent, resulting in an increased risk of hospitalization [1, 7]. However, persistent substance use disorder [13, 14], poorer premorbid adjustments, co-morbid psychiatric illness [15], co-morbid medical or health-related problems [16, 17], poverty, unemployment [13], stressful life events, family' criticism, or low family support [9, 13], patient-provider relationships or the treatment setting [18, 19], and aging are also significantly predisposing the risk for relapse in schizophrenia [20]. In other words, relapse among schizophrenic patients from non-adherence to medication may be due to factors that are related to: patients (forgetfulness, anxiety about adverse effects, inadequate knowledge, lack of insight and motivation and fear of stigma) [20–22]; healthcare (poor patient-health care provider relationship, poor service and access to services, poor staff training) [23]; socioeconomic aspects (low level of education, unemployed, cultural and social attitudes, belief systems) [6]; and treatment strategy (poly-pharmacology, complex treatment regimens) [24]. In addition, there is some evidence suggesting that drug treatment regimen history, drug administration route, and antipsychotic drug adverse effects can also contribute to schizophrenia relapse [25, 26]. Nowadays, antipsychotic medication plays an effective role regarding symptom control in the management of schizophrenia, but continuous long-term treatment is required to ensure medication adherence, control symptoms, and prevent relapse and its consequences [27]. However, schizophrenic patients often relapse, even during treatment [2]. This makes a compelling case for the importance of promptly identifying relapse associated factors, their contribution to relapse rates and the significance of relapse prevention strategies in schizophrenia management [3, 7].

Successive relapse control can reduce the degree and duration of the next remission, worsen disability, and increase refractoriness to future treatment [28]. Relapse control has been a concern and an area of focus for many years in our healthcare setting, Songklanagarind hospital. Our prior studies of relapse prevention were done aiming to assist in the maintenance of life quality and to lessen the burden and stigma for the families of schizophrenic patients [4, 5]. Additionally, our goals of social de-stigmatization were to boost social or community recognition and positive attitudes towards schizophrenic patients [29]. As a result, our schizophrenic patients has good medication adherence and relapse rate has been low compared to other countries [30]. Thus, this study aimed to evaluate the relapse rate among patients with schizophrenia, within a five-year period, and to identify factors associated with relapse in comparison with a group on remission.

## Methods

The study protocol was performed in accordance with the relevant guidelines. After being approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC: 63-523-3-4), a retrospective study was conducted at Songklanagarind Hospital, Thailand, which is an 800-bed university hospital serving as a tertiary referral center in Southern Thailand. A review was conducted of all the information in the medical records of schizophrenic patients from the hospital computer system; the inclusion criteria was that patients had a first episode of schizophrenia as per the ICD-10 code F 20.0 to 20.9, they had a diagnosis by a psychiatrist, had medical registration at the psychiatric inpatient unit from January 2007 to December 2019, and their age ranged from 18-60 years old. Meanwhile, patients with schizophrenia and co-morbidity with other mental illness (mood disorder, anxiety disorder) and having diagnosis changes were excluded. The patients were divided into 2 groups, the relapse group and the remission group.

The relapse group contained the cases of patients with schizophrenia who had a symptom relapse within 5 years after the first episode of psychosis. Therefore, we viewed information from their first episode of schizophrenia until their next relapse episode. The remission group had the schizophrenic patients who did not have a history of symptom relapse within 5 years after the first episode of psychosis. We viewed the information from their first episode of schizophrenia until the next relapse episode occurred. The factors associated with relapse as well as the protective factors found between the 2 groups were compared and analyzed.

Relapse was identified in cases of patients with schizophrenia who had documented evidence of re-emergence or aggravation of psychotic symptoms and hospitalization to a psychiatric unit within 5 years after the first episode of psychosis. Planned hospital admission for a non-related illness or special investigation was not deemed to be a relapse [8].

Remission applied to patients with schizophrenia who did not have a history of relapse within 5 years after the first episode of psychosis.

## Measures

Data records were reviewed by 5 psychiatrists and a content validity analysis was performed; the content validity index (CVI) score was 0.8. They were composed of 2 parts:

1. Personal and demographic information inquiry consisting of questions related to age, gender, religion, marital status, education level, occupation, patient income, supporting system, health coverage, physical illness, and substance usage.
2. Profile of schizophrenic disorder and treatment information included residual symptoms, insight, stressful life event, suicidal ideation, psychiatric family history, cause of discontinuing antipsychotic drugs due to factors of patient-related or healthcare-related or socio-economically-related, number and duration of readmission, follow-up interval, the regimen of treatment, type and route of drug

administration, antipsychotic adverse events, and history of changing type or dose of antipsychotic drugs.

## **Statistical methods**

Descriptive statistics such as percentage, frequency, proportion, mean, and standard deviation (SD) were calculated. Bivariate and multivariate analyses were utilized to identify factors associated with symptom relapse.

# **Results**

## **Demographic characteristics**

According to the study period, there were 156 schizophrenic patients, who were first diagnosed with schizophrenia and admitted to the psychiatric inpatient unit. The majority of them were male (50.6%), Buddhist (85.9%), unmarried (80.1%), unemployed (50.6%), and staying with family (90.4%). For all of the participants, their mean age was 39.2 years, and 44 (28.2%) patients had a history of substance use. (Table 1) The most common substances that the schizophrenic patients used was cigarettes (59.1%), alcohol (29.5%), stimulants (25%), marijuana (22.7%), and kratom (11.4%). Additionally, some patients (19.9%) had a physical illness, such as hypertension (32.3%), and diabetes (19.4%).

## **Schizophrenic characteristics**

Of all schizophrenic patients in the study, 84 (53.8%) reported symptom relapse within five years after the first episode of psychosis, relapse group, whereas 72 (46.2%) patients were in the remission group. The median (IOR) length of patients being symptoms free, prior to relapse was 17 (6.5, 28) months. Cumulatively, the first to fifth year relapse rate was 22.4%, 35.3%, 44.9%, 50%, 53.8%, respectively. Additionally, the first to fifth relapse rate was 22.4%, 12.8%, 9.6%, 5.1%, 3.8%, respectively.

Nevertheless, some schizophrenic patients showed residual symptoms (39.1%) and a lack of insight (38.8%). Most residual symptoms were hallucinations (52.5%), delusions (45.9%), and disorganized or catatonic behavior (16.4%). In regards to problems, patients found to be burdensome, they reported having stressful life events (32.7%) and suicidal ideation (10.9%). (Table 2) The most common stressful life events that the schizophrenic patients identified were relationship problems (47.1%), work stress (27.5%), and the loss of a person significant to them (9.8%).

According to patients in the relapse group, half had residual symptoms (48.8%) and more than half of the patients reported poor insight (60.7%), having stressful life events (56%) and suicidal ideation (19%). There was a statistically significant difference in residual symptoms, insight, stressful life events and suicidal ideation between relapse and remission groups ( $p < 0.05$ ). (Table 2)

## **Treatment information**

In regards to all schizophrenic patients, their median (IQR) length of hospital stay was 17 (12.8, 25) days. The median (IQR) number of types and amounts in regards to their oral medication prescriptions, tablets, were 3 (2,5), and 5 (3,8) respectively. Most of the patients self-administered tablets 1-2 times per day (65.4%) via the oral route (88.5%). Two-thirds (64.1%) had no adverse effects and demonstrated good medical adherence (62.2%) (Table 2). About half of the patients (51.3%) had follow-ups by a physician visiting them at an interval of every 1-3 months.

According to relapse patients, two-thirds (59.5%) had a history of medical non-adherence. The most common cause of medical non-adherence was patient-related factors (53.6%) such as; lack of insight (62.2%); anxiety about the adverse events of antipsychotic medication (24.4%), and factors associated with patient's socio-economic status (14.3%). However, a few patients reported being medical non-adherent due to not having sufficient knowledge, being forgetful, and feeling stigmatized due to having a prescription. There was a statistically significant difference in adverse event, medical non-adherence, and history of change prescription between the relapse and the remission groups ( $p < 0.001$ ). (Table 2) Additionally, no statistically significant difference was found regarding the length of hospital stay between relapse and remission groups ( $p < 0.001$ ).

Focusing on the adverse events of antipsychotic drugs, schizophrenic patients mainly reported no adverse effects (64.1%). Furthermore, more than half of all patients received second-generation antipsychotic drugs; pure second-generation antipsychotic drugs (37.2%); and/or a combination of first and second-generation antipsychotic drugs (18.6%). (Table 2) Extrapyramidal symptoms (EPS) (56.7%) were the most common adverse event among the relapse group. Schizophrenic patients who had received first-generation antipsychotics developed EPS more than patients taking second-generation antipsychotic drugs. (Figure 1 and Figure 2) However, no statistically significant difference in EPS between the relapse and remission group was detected. Viewing this from a different perspective, the adverse event could be related to medical adherence. A statistically significant association between the group of patients who developed adverse events during treatment and the history of poor drug compliance was detected ( $p < 0.001$ ). (Figure 3)

### **The association between demographic and schizophrenic characteristics, treatment, and symptom relapse**

Multivariate analysis indicated that having stressful life events, medical non-adherence, history of change prescription, and lack of insight were all factors statistically significantly associated to symptom relapse. The schizophrenic patients who had stressful life events had a higher rate of relapse than the remission group, the adjusted odds ratio (AOR) was 23.5 and the 95% confidence interval (CI) was 5.2 to 107.1 The same was true when comparing them with those who had medical non-adherence, prescription changes, and poor insight; AOR (95%CI) was 5 (1.3,19.7), 10.9 (1.2, 100.9), and 22.6 (4.1, 123.5) respectively. (Table 3)

## **Discussion**

This survey indicated that the first-year relapse rate and cumulative relapse rate in five years among patients with schizophrenia were 22.4% and 53.8% respectively. Patients from the relapse group reported having lack of insight (60.7%), stressful life events (56%), residual symptoms (48.8%), and suicidal ideation (19%). Moreover, two-thirds (59.5%) demonstrated medical non-adherence due to patient-related factors (53.6%) such as lack of insight and experiencing anxiety about the adverse events of antipsychotic drugs as well as due to socio-economic factors (14.3%). The factors with a statistically significant association to relapse risk were stressful life events, medical non-adherence, prescription changes and a lack of insight

Regarding the rate of relapse, some studies identified that relapse rates vary from 50–92% globally [9, 10]. Our study features a lesser relapse rate vs. the general international levels: much lower than studies in Birmingham [31] and New York [18] that found first-year relapse rates of 67%, and 81.9% respectively. These findings corroborated previous studies in which Asian ethnicity tended to have lower relapse rates compared to white and Afro-Caribbean patients [31]. This may be due to Thai and Asian culture in general being more collectivist vs. European and American culture that tends to be more individualistic [32, 33].

In our study, 90.4% of patients stayed with family and it appeared that they had good family support without feeling like a burden in family or experiencing stigma in schizophrenic patients [4, 5]. In a previous study in our healthcare setting 73.2% of the caregivers report non-severe or nil burden as a result of being with the patient [5]. This information highlighted that there is a collectivist system in Southern Thailand where there is a whole-family sense of duty to care for the schizophrenic patient and family member. Furthermore, the ability to access our health care system seems easier when compared to other countries [34]. Comprehensive psychoeducation appears to be important in aiding relatives and patients to better understand treatment guidelines, potentially reducing relapse rates and any burden on the family.

About factors associated with relapse, our findings support those from previous reports from Australia as non-adherence to medication and psychosocial stressors were commonly noted as clinical precipitants of relapse [35]. Furthermore, discontinuing antipsychotic drug therapy increased the risk of relapse by almost 5 times [18]; and it was found that relapse was common after the discontinuation of antipsychotic medication post recovery from the first episode of psychosis. Patients who wished to discontinue their medication needed to be informed of the high relapse rates and the associated risks. Furthermore, male patients who had previous hospital admissions potentially require closer monitoring [36]. However, this study identified no statistically significant difference in gender between the relapse and remission groups. The reason for this might be the fact that most schizophrenic patients stayed with their family and they equally received caring from their caretakers [4, 5].

In addition, this study revealed that psychosocial stressors were a factor noted as a clinical precipitant of relapse. According to guidelines from the National Institute for Health and Care Excellence in the United Kingdom and the Schizophrenia Patient Outcomes Research Team in the United States, psychotherapeutic treatments have the potential to improve the therapeutic change in schizophrenia

spectrum disorder [37]. Psychotherapeutic treatment is potentially an essential component for the treatment of schizophrenic patients; aiming to reduce suicidal ideation and the impact of stressful life events, which are both precipitating factors.

In regards to adverse effects of antipsychotic drugs associated with medical non-adherence, optimum dosing with the lowest level of adverse effects would be our paramount concern. Even though the type and route of administration of antipsychotic drugs was not a significant factor in our research; the new generation of antipsychotic drugs have shown that they cause fewer adverse events, especially in regards to EPS as compared with the first generation of drugs. Furthermore, real-world data suggest that long-acting injections tend to reduce the occurrence of EPS and/or neuroleptic malignant syndrome but there is other adverse effect with similar risks to oral antipsychotics [38]. According to this information, atypical antipsychotic long-acting injections could be an interesting choice due to reducing the risk of adverse events, medical non-adherence, and any fluctuations of the concentration of the drug in the system of schizophrenic patients. If the conventional antipsychotic is necessary, balancing optimum dosing to control symptoms with the least amount of side effects should be considered. A shared decision-making process between physician and patient may be one of the main ways to reduce patient distress.

As per the low relapse rate that was shown in this study, Songklanagarind Hospital has continued creating relapse prevention programs and to work through various aspects accentuating the quality of life of schizophrenic patients. A previous study identified that most schizophrenia outpatients at Songklanagarind Hospital had good medication adherence and high scores of meaning in their lives. Furthermore, results indicated that the presence of a sense of meaning in life and engaging in something that increased patients' lives feel meaningful and purposeful could reduce social stigma and promote insight. Therefore, most schizophrenic outpatients had good medication adherence being associated to their sense of a meaning in their lives [30]. Additionally, a destigmatization program was created by our homestay program to rehabilitate and engage patients by boosting their social skills. This program enables the community and the patient's family to understand the patient's disease, decreasing stigma and making the patient's relationship with society more harmonious [29]. One study found that schizophrenic patients (62%) perceived a low level of stigma and that only 1.8% of patients experienced a high level of stigma in our healthcare setting [4]. All our inpatients with a first episode of schizophrenia would engage in a discussion with our staff, aiming to discover positive meaning in their lives; and would participate in our rehabilitation program. Potentially, the reduction of patient perceived stigma and the boosting of insight could improve their adherence to the pharmacological component of their treatment plans and reduce levels of distress.

Finally, this study was one of the first studies showing that substance use or inadequate knowledge resulted in no increase of relapse risk; not corroborating prior reports from Australia [35]. This may be because our study had a low sample size in regards to substance use and a relatively small number of patients with insufficient knowledge. Therefore, psychoeducation and co-morbidity prevention for patients with a first episode of schizophrenia should be highlighted accordingly.

This study had a number of noteworthy strengths and limitations. To our knowledge, this is the first study that explored the rate of schizophrenia relapse and its associated factors in southern Thailand. Furthermore, it involved an adequately large participant sample size. Nevertheless, it was a retrospective study reviewing computer medical records which have limitations and the potential of bias. Furthermore, the study used only quantitative data and the sample size was restricted to schizophrenic inpatients only from our hospital instead of including other areas of Thailand. Hence, this dataset may not be representative of schizophrenic patients across the whole of Thailand.

## **Conclusions**

Our results suggest that half of patients relapse within 5 years of their first diagnosis of schizophrenia and that the factors heightening the risk of relapse were: stressful life events, medical non-adherence, prescription changes, and lack of insight by the patient. Although our study has some methodological limitations, the results provided interesting information that can inform additional therapeutic intervention strategies. Furthermore, they emphasize the importance of implementing a multimodality of treatment such as managing adverse events and reducing the like hood of relapse by combining optimum dosing, type, and route of antipsychotic drug administration. Furthermore, at the same time, integrating pharmacological strategies with effective psychotherapeutic methods aiming to reduce stress, gain insight, increase patient perceived life meaning and boost social integration and community acceptance.

## **Declarations**

We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

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## **Authors' contributions**

JP: conception and design of the study, analysis of data, drafting of the manuscript, tables and figures; PR: acquisition and analysis of data, drafting of the manuscript tables and figures; TT: conception and design of the study. All authors approved the final manuscript.

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## **Availability of data and materials**

The datasets used and/or analyzed during the current study available from the corresponding author upon reasonable request.

### **Ethics approval and consent to participate**

All stages of research were conducted following the Declaration of Helsinki and the Ethical Statements of the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. This study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC: 63-523-3-4). Throughout the process, patients could not be identified, therefore the informed consent was waived by the Medical Ethics Committee.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no conflicts of interest.

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## Tables

**Table 1 Demographic characteristics (N = 156)**

| Demographic characteristics  | Number (%) |           |           | $\chi^2$<br>P-value |
|--|------------|-----------|-----------|---------------------|
|  | Total      | Relapse   | Remission |                     |
|  | (n=156)    | (n=84)    | (n=72)    |                     |
| <b>Gender</b>  |            |           |           | 0.203               |
| Male   | 79 (50.6)  | 47 (56.0) | 32 (44.4) |                     |
| Female   | 77 (49.4)  | 37 (44.0) | 40 (55.6) |                     |
| <b>Religion</b>  |            |           |           | 0.763               |
| Buddhism   | 134 (85.9) | 71 (84.5) | 63 (87.5) |                     |
| Others (Islam, Christ, others)                                     | 22 (14.1)  | 13 (15.5) | 9 (12.5)  |                     |
| <b>Marital Status</b>  |            |           |           | 0.859               |
| Single/separated/widowed   | 125 (80.1) | 66 (79.5) | 59 (81.9) |                     |
| Married  | 30 (19.2)  | 17 (20.5) | 13 (18.1) |                     |
| Not specify  | 1 (0.6)    |           |           |                     |
| <b>Education level</b>   |            |           |           | 0.007               |
| Secondary school/ below  | 19 (12.2)  | 13 (15.5) | 6 (8.3)   |                     |
| High school/ diploma   | 38 (24.4)  | 28 (33.3) | 10 (13.9) |                     |
| Bachelor's degree or more  | 46 (29.5)  | 21 (25)   | 25 (34.7) |                     |
| Not specify  | 53 (34.0)  | 22 (26.2) | 31 (43.1) |                     |
| <b>Occupation</b>  |            |           |           | 0.267               |
| Unemployed/ student/ monk  | 79 (50.6)  | 47 (56)   | 32 (44.4) |                     |
| Self-employed/ agriculture   | 41 (26.3)  | 19 (22.6) | 22 (30.6) |                     |
| Government officer/<br>state enterprise employee/ company employee | 18 (11.5)  | 11 (13.1) | 7 (9.7)   |                     |
| Merchant/ personal business  | 18 (11.5)  | 7 (8.3)   | 11 (15.3) |                     |
| <b>Patient income</b>  |            |           |           | 0.341               |
| No income  | 79 (50.6)  | 46 (54.8) | 33 (45.8) |                     |
| Yes  | 77 (49.4)  | 38 (45.2) | 39 (54.2) |                     |
| <b>Supporting system</b>   |            |           |           | 0.060               |
| Stay with family   | 141 (90.4) | 74 (89.2) | 67 (97.1) |                     |

| Demographic characteristics  | Number (%)       |                   |                     | $\chi^2$<br>P-value |
|--|------------------|-------------------|---------------------|---------------------|
|  | Total<br>(n=156) | Relapse<br>(n=84) | Remission<br>(n=72) |                     |
| Alone  | 11 (7.1)         | 9 (10.8)          | 2 (2.9)             |                     |
| Not specify  | 4 (2.6)          |                   |                     |                     |
| <b>Health coverage</b>   |                  |                   |                     | 0.036               |
| Civil Servant Medical Benefit Scheme (CSMBS)/ Provincial Administrative Organization | 19 (12.2)        | 12 (14.3)         | 7 (9.7)             |                     |
| Universal Coverage Scheme (UCS)/ Social Security Scheme (SSS)                        | 103 (66.0)       | 48 (57.1)         | 55 (76.4)           |                     |
| Out-of-pocket  | 34 (21.8)        | 24 (28.6)         | 10 (13.9)           |                     |
| <b>Physical illness</b>  |                  |                   |                     | 0.467               |
| No   | 125 (80.1)       | 65 (77.4)         | 60 (83.3)           |                     |
| Yes  | 31 (19.9)        | 19 (22.6)         | 12 (16.7)           |                     |
| <b>Substance usage</b>   |                  |                   |                     | 0.773               |
| No   | 112 (71.8)       | 59 (70.2)         | 53 (73.6)           |                     |
| Yes  | 44 (28.2)        | 25 (29.8)         | 19 (26.4)           |                     |

**Table 2 Schizophrenic characteristics and treatment information (N=156)**

| Schizophrenic characteristics            | Number (%) |           |           | $\chi^2$<br>P-value |
|--|------------|-----------|-----------|---------------------|
|  | Total      | Relapse   | Remission |                     |
|  | (n=156)    | (n=84)    | (n=72)    |                     |
| <b>Residual symptoms</b>                 |            |           |           | < 0.012             |
| No                                       | 95 (60.9)  | 43 (51.2) | 52 (72.2) |                     |
| Yes                                      | 61 (39.1)  | 41 (48.8) | 20 (27.8) |                     |
| <b>Insight</b>                           |            |           |           | < 0.001             |
| True emotional                           | 27 (19.4)  | 7 (8.3)   | 20 (27.8) |                     |
| Intellectual                             | 22 (15.8)  | 19 (22.6) | 3 (4.2)   |                     |
| Poor                                     | 54 (38.8)  | 51 (60.7) | 3 (4.2)   |                     |
| Not specify                              | 53 (34.0)  | 7 (8.3)   | 46 (63.9) |                     |
| <b>Stressful life event</b>              |            |           |           | < 0.001             |
| No                                       | 105 (67.3) | 37 (44.0) | 68 (94.4) |                     |
| Yes                                      | 51 (32.7)  | 47 (56.0) | 4 (5.6)   |                     |
| <b>Suicidal ideation</b>                 |            |           |           | 0.001               |
| No                                       | 139 (89.1) | 68 (81.0) | 71 (98.6) |                     |
| Yes                                      | 17 (10.9)  | 16 (19.0) | 1 (1.4)   |                     |
| <b>Having psychiatric family history</b> |            |           |           | 0.068               |
| No                                       | 116 (74.4) | 57 (67.9) | 59 (81.9) |                     |
| Yes                                      | 40 (25.6)  | 27 (32.1) | 13 (18.1) |                     |
| <b>History of medical non-adherence</b>  |            |           |           | < 0.001             |
| No                                       | 97 (62.2)  | 34 (40.5) | 63 (87.5) |                     |
| Yes                                      | 59 (37.8)  | 50 (59.5) | 1. (12.5) |                     |
| <b>1. Patient-related</b>                |            |           |           |                     |
| No                                       | 5 (3.2)    | 5 (6.0)   | 0 (0.0)   |                     |
| Yes                                      | 54 (34.6)  | 45 (53.6) | 1. (12.5) |                     |
| <b>2. Health care-related</b>            |            |           |           |                     |

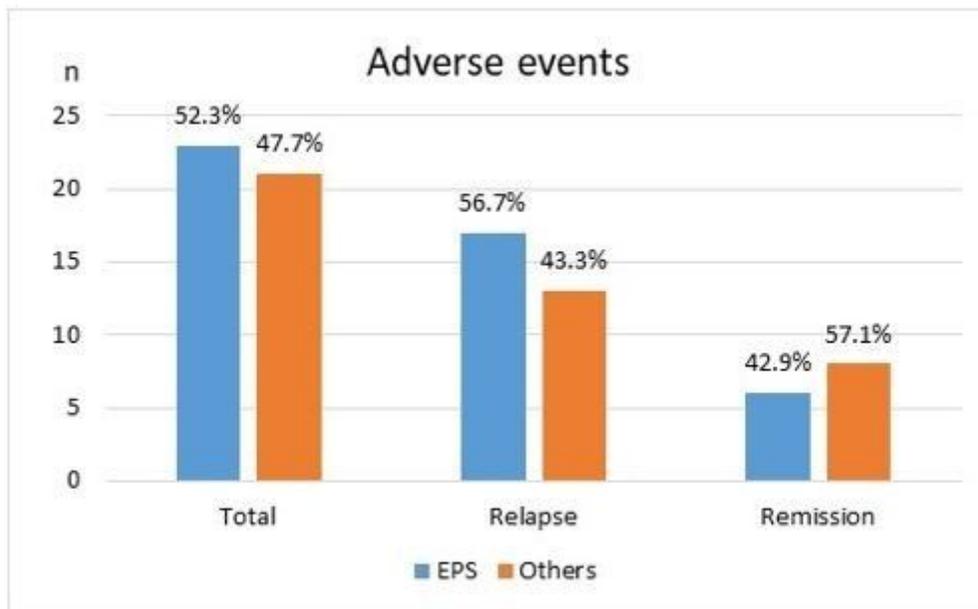
| Schizophrenic characteristics                            | Number (%) |           |           | $\chi^2$<br>P-value |
|--|------------|-----------|-----------|---------------------|
|  | Total      | Relapse   | Remission |                     |
|  | (n=156)    | (n=84)    | (n=72)    |                     |
| No   | 55 (35.3)  | 46 (54.8) | 9 (12.5)  |                     |
| Yes  | 4 (2.6)    | 4 (4.8)   | 0 (0.0)   |                     |
| <b>3. Socio-economically-related</b>                     |            |           |           |                     |
| No   | 46 (29.5)  | 38 (45.2) | 8 (11.1)  |                     |
| Yes  | 13 (8.3)   | 12 (14.3) | 1 (1.4)   |                     |
| <b>Amount of type of antipsychotic drugs</b>             |            |           |           | 0.391               |
| 1  | 87 (55.8)  | 50 (59.5) | 37 (51.4) |                     |
| 2-4  | 69 (44.2)  | 34 (40.5) | 35 (48.6) |                     |
| <b>Type of antipsychotic</b>                             |            |           |           |                     |
| First generation antipsychotic                           |            |           |           | 0.295               |
| No   | 101 (64.7) | 58 (69.0) | 43 (59.7) |                     |
| Yes  | 55 (35.3)  | 26 (31.0) | 29 (40.3) |                     |
| Second generation antipsychotic                          |            |           |           | 0.565               |
| No   | 98 (62.8)  | 55 (65.5) | 43 (59.7) |                     |
| Yes  | 58 (37.2)  | 29 (34.5) | 29 (40.3) |                     |
| Combination first & second generation                    |            |           |           | 1                   |
| No   | 127 (81.4) | 68 (81.0) | 59 (81.9) |                     |
| Yes  | 29 (18.6)  | 16 (19.0) | 13 (18.1) |                     |
| <b>Amount of time that administration per day (time)</b> |            |           |           | 0.886               |
| 1-2  | 102 (65.4) | 54 (64.3) | 48 (66.7) |                     |
| 3-4  | 54 (34.6)  | 30 (35.7) | 24 (33.3) |                     |
| <b>Route of administration</b>                           |            |           |           | 0.363               |
| Oral medication  | 138 (88.5) | 72 (85.7) | 66 (91.7) |                     |

| Schizophrenic characteristics                 | Number (%) |           |           | $\chi^2$<br>P-value |
|---|------------|-----------|-----------|---------------------|
|   | Total      | Relapse   | Remission |                     |
|   | (n=156)    | (n=84)    | (n=72)    |                     |
| Oral medication & long-acting injection       | 18 (11.5)  | 12 (14.3) | 6 (8.3)   |                     |
| <b>Adverse events</b>                         |            |           |           | <0.001              |
| No  | 100 (64.1) | 43 (51.2) | 57 (79.2) |                     |
| Yes   | 44 (28.2)  | 30 (35.7) | 14 (19.4) |                     |
| Not specify                                   | 12 (7.7)   | 11 (13.1) | 1 (1.4)   |                     |
| <b>History of changing type of medication</b> |            |           |           | 0.004               |
| No  | 138 (88.5) | 68 (81.0) | 70 (97.2) |                     |
| Yes   | 18 (11.5)  | 16 (19.0) | 2 (2.8)   |                     |

**Table 3 Factors related to relapse: multivariate analysis**

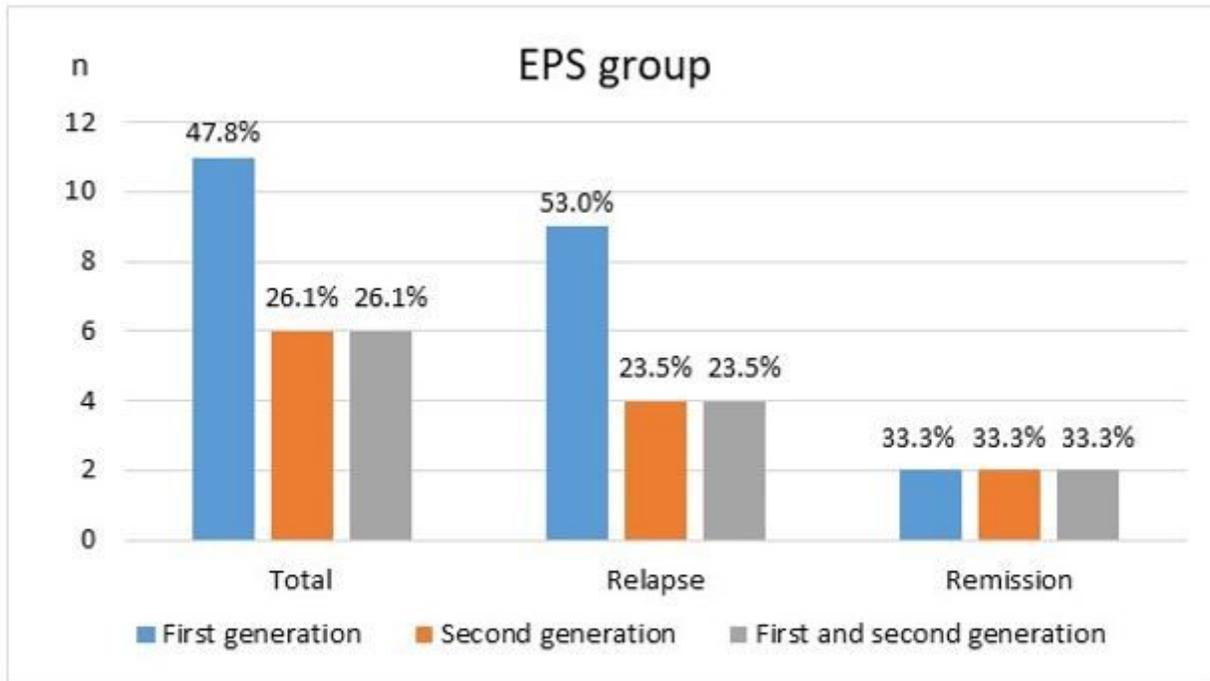
| Factors                                       | Crude OR<br>(95%CI) | Adjusted OR (95%CI) | P-value<br>LR-test |
|---|---------------------|---------------------|--------------------|
| <b>Stressful life event</b>                   |                     |                     | <0.001             |
| No  | Reference           | Reference           |                    |
| Yes   | 21.6 (7.2, 64.6)    | 23.5 (5.2, 107.2)   |                    |
| <b>Insight</b>                                |                     |                     | <0.001             |
| True emotional                                | Reference           | Reference           |                    |
| Intellectual                                  | 18.1 (4.1, 80.4)    | 10.3 (1.6, 68.6)    |                    |
| Poor  | 48.6 (11.4, 206.6)  | 22.6 (4.1, 123.5)   |                    |
| Not specify                                   | 0.4 (0.1, 1.4)      | 0.4 (0.1, 1.6)      |                    |
| <b>History of medical non-adherence</b>       |                     |                     | 0.021              |
| No  | Reference           | Reference           |                    |
| Yes   | 10.3 (4.5, 23.4)    | 5.0 (1.3, 19.7)     |                    |
| <b>History of changing type of medication</b> |                     |                     | 0.023              |
| No  | Reference           | Reference           |                    |
| Yes   | 8.2 (1.8, 37.2)     | 10.9 (1.2, 100.9)   |                    |

## Figures



**Figure 1**

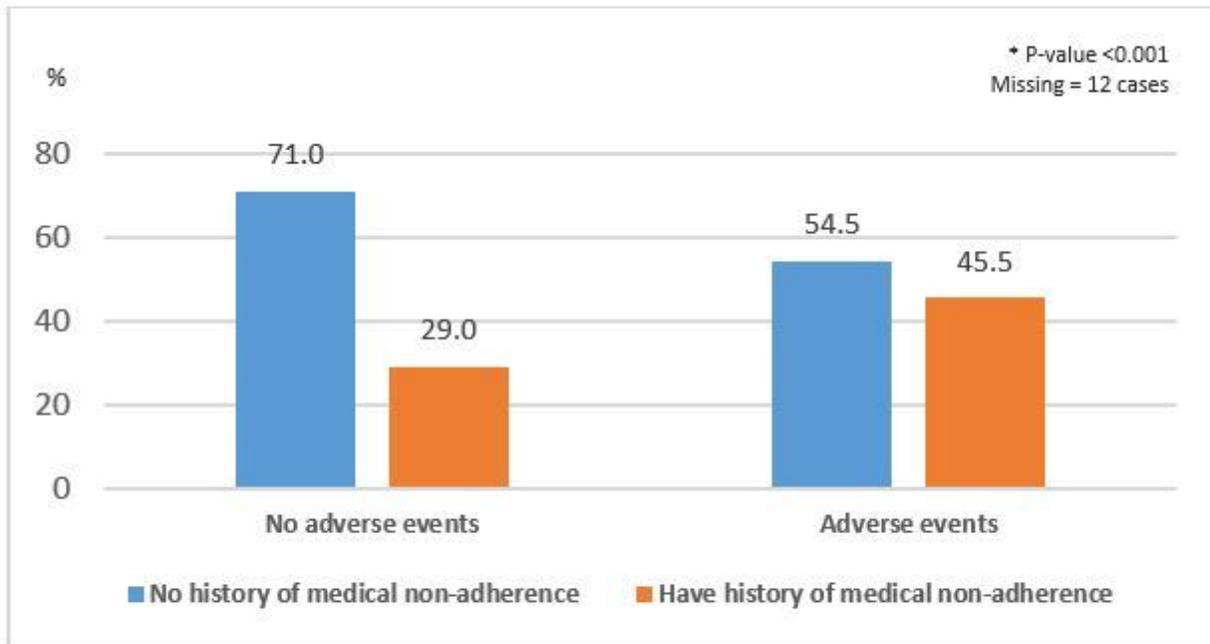
Comparison of the adverse event of antipsychotic drug between EPS and other adverse effect among relapse and remission group. (N=44)



\*Non-statistically significant

**Figure 2**

Comparison of the type of antipsychotic drugs among schizophrenic patient who developed EPS. (N=23)



\*Statistically significant

**Figure 3**

Association between adverse events of antipsychotic drug and history of medical non-adherence (N=156)