

## Research Article

# Time to Relapse and Relapse Predictors in Patients with Schizophrenia at Ayder Comprehensive Specialized Hospital, Northern Ethiopia

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**Background.** Rehospitalization, treatment resistance, and impairment are all possible outcomes of a schizophrenia relapse, which has a severe impact on patients, families, and the healthcare system. However, little is known regarding the time to relapse and relapse predictors in Ethiopia and in the study settings. Therefore, the aim of this study was to determine the time to relapse and relapse predictors in patients with schizophrenia at Ayder Comprehensive Specialized Hospital, Northern Ethiopia. **Methods.** A retrospective cohort study was carried out among 273 schizophrenia patients discharged from Ayder Comprehensive and Specialty Hospital between January 2015 and January 2019. The data was taken from the patient's medical record and was chosen using a systematic random sampling procedure. A standardized data collection checklist was employed. The survival experiences of participants were compiled using a life table. Both univariate and multivariate Cox regression models were used for variable selection. Finally, after confirming the model's diagnosis and assumptions, factors with a  $p$  value of less than 0.05 were declared to be statistically significant predictors of schizophrenia relapse. **Results.** In this study, the incidence of relapse was 2.9 per 100 person-months (PMs) and the median time to relapse of 13 months (interquartile range: 6–23 months). Being divorced (AHR = 2.50, 95% CI: 1.18–5.28), not adhering to treatment (AHR = 5.7, 95% CI: 3.03–10.74), and substance abuse (AHR = 1.8, 95% CI: 1.01–3.22) were risk factors for increasing schizophrenia relapse. Age (AHR = 0.65, 95% CI: 0.34–0.88) and length of first hospitalization (AHR = 0.69, 95% CI: 0.57–0.86) were factors that decreased schizophrenia relapse. **Conclusion and Recommendation.** In this study, out of 100 patients with schizophrenia followed up for a month, three had a relapse, and the highest risk factor for relapse was treatment nonadherence, followed by being divorced and substance misuse. As a result, it is advised that all parties involved focus on early detection and taking preventive measures against schizophrenia relapse, as well as providing regular psychoeducation about the significance of treatment adherence and connecting patients with substance misuse to substance rehabilitation centers.

## 1. Introduction

Schizophrenia is a severe mental and neurological disorder that manifests as a variety of symptoms, such as hallucinations, delusions, disordered speech or behavior, and cognitive impairment. It affects 1.1% of the population on average, and around 80% of patients have multiple relapses

throughout the course of their illness [1–3]. Relapse in schizophrenia is the recurrence of symptoms and return to initial psychotic episodes. Schizophrenia relapse is frequently accompanied by rehospitalization and medication adjustments and is typically characterized as the worsening of both positive and negative psychotic symptoms. Additionally, a few specific criteria are used to describe it, such

as the escalation of either positive or negative symptoms, a hospital admission within the previous six months, more extensive case management, and/or a change in medication [4, 5]. Risk factors for schizophrenia are influenced by both environmental and genetic factors. Yet, the precise kind, location, and timing of this illness are still unknown [6].

According to the World Health Organization (WHO) reports, schizophrenia patients had a two- to threefold higher risk of dying than the general population, and their burden was nearly four times greater in low-income nations than it was in high-income ones [7]. Schizophrenia is linked to frequent hospitalizations and contributes significantly to high expenses in mental healthcare [7, 8]. In many cases, hospitalization is advised when schizophrenia recurs since the psychiatric symptoms manifest frequently. Hospitalization following treatment might be seen as an indication of relapse because the readmission rate is directly related to the rate of relapse [9, 10]. As a result, the probability of the disease becoming chronic with substantial functional impairment appears to be higher with an increase in the frequency of relapses [11].

Relapses from schizophrenia can have a negative impact on a patient's quality of life, limit their ability to perform daily tasks, and place a greater burden on national economies in terms of lost productivity from long periods of unemployment, school dropout, inadequate school adaptation in early life and the early twenties, and mortality [12–14]. Moreover, the relapse of schizophrenia is accompanied by disability, depression, and low self-esteem, all of which can impair quality of life and cause social isolation [15]. Due to more frequent hospitalizations, consultations, and therapies, the expense of treating individuals with schizophrenia who have relapsed has increased compared to those who have not [16, 17]. Studies have also shown that the most prominent factors associated with schizophrenia relapse include the frequency of psychotic episodes, comorbid psychiatric diseases, substance misuse, treatment nonadherence, treatment side effects, unemployment, stressful life events, and psychotic stress [18–21].

Few studies have demonstrated that after 1 to 3 years of episodes, patients with schizophrenia have a relapse rate that ranges from 19% to 65% [10, 21–25]. Estimating relapse is important for the treatment plan and for future research; in a study from Germany, it was found that 50% of the patients experienced relapses [23] and that nearly 40% of patients who received the appropriate antipsychotic medication experienced relapses within a year of being discharged from the hospital [26]. A further estimate places the probability of relapse at 77% in the first year and up to 90% in the following two, although it is only approximately 3% in patients who continue to take medication [27]. According to a Federal Minister of Health (FMOH) report from 2010, over 60% of mental hospitalizations in Ethiopia were related to schizophrenia, which has a greater level of impairment, family hardship, stigma, death, and human rights abuses. In addition, a few recent cross-sectional studies that assessed prevalence discovered that relapses occurred in 24%–88% of patients who were admitted with schizophrenia [20, 26–30]. Preventing relapse in schizophrenia has gained importance

since it is associated with a high financial and human cost. The time to relapse and relapse predictors in Ethiopia and specifically in the study setting, however, received little attention despite the significant burden they imposed. Determining the time to relapse and relapse predictors was therefore one of the objectives of this research in order to offer recommendations for early detection and relapse prevention in patients with schizophrenia.

## 2. Materials and Methods

*2.1. Study Area, Design, and Period.* The study was conducted at Ayder Comprehensive Specialized Hospital (ASCH), which is a medical facility that can be found in Mekelle, the capital of the Tigray regional state, which is located 778 kilometers north of Addis Ababa, Ethiopia. Situated in Mekelle City's Ayder subdistrict, over 80 specialists were employed at the institution. The hospital serves as a research and teaching facility in addition to providing clinical services. One of the main services offered by the hospital is mental healthcare, which is available in the psychiatric outpatient unit and two admission wards (one for men and one for women) with rehabilitation facilities. Inpatient psychiatric departments saw 1468 cases of mental and behavioral disorders, including undefined diseases, from 2015 to 2019. Of these, 823 cases involved schizophrenia, with 480 male patients and 343 female patients, respectively. To determine the time to relapse and predictors of relapse, a retrospective cohort study design was carried out among patients with schizophrenia at Ayder Comprehensive and Specialized Hospital, Mekelle, Ethiopia, from April 19 through May 3, 2019.

*2.2. Source Population.* All patients with a confirmed diagnosis of schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria, are the source population.

*2.3. Study Population.* Patients with confirmed DSM-IV-TR diagnoses of schizophrenia who received treatment and underwent follow-up at ACSH between January 2015 and January 2019 are the study population.

*2.4. Study Unit.* Randomly chosen medical charts of schizophrenia patients from January 2015 to January 2019 who were discharged from their initial admission to ACSH are the study unit.

### 2.5. Inclusion and Exclusion Criteria

*2.5.1. Inclusion Criteria.* Patients with schizophrenia who were discharged after their initial hospitalization and had "completed recovery" and were receiving follow-up service for at least six months were included because symptomatic remission is expected to occur within six months of beginning medication or follow-up [31], and those who received follow-up care at the Ayder Specialized Hospital beginning with their second visit and continuing throughout the study period were included in the study.

*2.5.2. Exclusion Criteria.* Patients with newly diagnosed individuals with a DSM-IV-TR diagnostic of schizophrenia and patients with “partially or poorly recovered” after their initial hospital release were excluded.

*2.6. Study Variables.* The dependent variable, which was measured in months, was the amount of time it took for schizophrenia to relapse after being discharged from the first admission to ACSH. However, the event of interest is relapse. As a result, the relapse was given the number 1, and censored data was given the number 0, which was considered when a patient with schizophrenia was lost to follow-up, transferred, or passed away before experiencing the event of interest, as well as those patients with schizophrenia who had not yet experienced the event of interest throughout the follow-up periods. The independent variables were social and demographic characteristics (such as sex, age, place of residence, religion, occupation, marital status, education, and living condition), behavioral factors (such as substance misuse, suicidal attempts, and stressful life events), and clinical predictors (such as drug nonadherence, depression, duration of first hospitalization, comorbid medical disorders, family history of psychiatric illness, and past psychiatric history).

*2.7. Sample Size Determination and Sampling Techniques.* The sample size was calculated using a double population proportion formula under the following assumptions: a statistical power of 90%, a degree of confidence of 95%, and the cumulative relapse rate from the previous study on predictors of relapse in schizophrenia and associated factors [25].  $n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 / (\log(\text{HR}))^2 pq P(E)$ , where 95% confidence level  $Z_{1-\alpha/2}$  is 1.96; power 90%  $Z_{1-\beta}$  is 1.28; HR is 2.36;  $p$  is the proportion of nonadherence, which is 13% (0.13);  $q$  is the proportion of medication adherents, which is 87% (0.87); and  $P(E)$  is the cumulative relapse rate, which is 48.1% (0.481) from similar study. Finally, 273 schizophrenia patients were included in the study.

A systematic sampling technique was applied to select patients' medical records that met the inclusion criteria. From January 2015 through January 2019, the patient's medical record contained information on 823 schizophrenia patients. Out of the 823 admissions that were reviewed, 749 follow-ups had full documentation available. The sampling interval was calculated by dividing the total number of eligible patients' medical records (749) by the calculated optimal sample size of 273 patients. Using the lottery method, the first patient's medical card was chosen at random. Thereafter, until the sample size was reached, the next patient's medical card was chosen every third interval.

*2.8. Data Collection Techniques, Procedures, and Quality Control.* To extract data from the patient's medical record and registration book, structured data collection checklists were used. The data collection checklist, which includes sociodemographic, behavioral, and clinical characteristics, was developed by reviewing earlier, related studies [10, 19, 21, 29, 32]. To maintain uniformity, the checklist was written in English, translated into Amharic, and then translated

back into English. Prior to beginning the data collection, the medical record (registration book) was identified by the patient's card number. Four psychiatry bachelor's degree holders extracted the data from the participants' medical records, and one master's degree holder in the field of psychiatry supervised the data collection. The data extraction process took place between April 19 and May 3, 2019. Before the collection of data, a pretest was done on 5% of the calculated sample size with this information; the variable family histories of psychiatric illness were included, and the family's expressed emotions were excluded. Then, the data gathering tools were adjusted accordingly. Data collectors were trained and supervised, and the primary investigator checked the data gathering tools for consistency, completeness, and accuracy in day-to-day activities.

*2.9. Operational Definitions.* *Schizophrenia relapse:* we assessed relapse as rehospitalization in a mental health facility, the recurrence or aggravation of psychotic symptoms, and acute clinical worsening that requires additional treatment are all indications of schizophrenia relapse, according to a physician's diagnosis [33], made by reviewing the patient's medical file. Or patients with schizophrenia who were initially admitted to ACSH, discharged with improvements, and then readmitted with recurring or worsening symptoms after a period of progress or recovery were noted by the doctor as having relapsed in the patient's medical records.

*Follow-up (period of observation):* the number of months the schizophrenia patients were followed from the discharge of their first hospitalization to the ACSH psychiatric ward until they developed the event of interest was from January 2015 to January 2019.

*Recovered:* schizophrenia patients are considered “recovered” when their psychotic symptoms subside and they resume their prior level of psychosocial functioning [34], as confirmed by their doctor and documented in the patient's medical records.

*Nonadherence:* patients with schizophrenia stop taking the prescribed medications and refuse to take them, or when the clinician records a treatment discontinuation on the patient's medical record.

*Substance misuse:* patients with schizophrenia who use any of the following substances during treatment and follow-up care—cigarettes, illegal drugs, and others—as documented in their medical records by a psychiatrist's diagnosis are regarded as substance misusers.

*Stressful life event:* patients with schizophrenia who go through any of the following: loss of a loved one, divorce, loss of employment, etc. According to the patient's profile, a stressful life event is noted.

*Suicidal attempts:* suicidal attempts are defined as any self-inflicted acts committed by schizophrenia patients that are recorded in patient medical records and are associated with a desire to die or the use of a potentially fatal means, as determined by psychiatric professionals.

*2.10. Statistical Data Processing and Analysis.* Data was cleaned, edited, labeled, and entered using EP-Info version 17 software, transferred to STATA version 14 for analysis,

and then declared to be survival time data. In the descriptive statistics, to summarize categorical variables, percentage and frequency were used, while for continuous variables, median and interquartile range (IQR) were used. To summarize the experience of the participants, a life table (actuarial) was used [35], and the Kaplan-Meier (KM) curve and log-rank test were used to compare the probability of events (failure) and/or survival of two or more groups [36]. To identify candidate variables, univariate Cox regression analysis was used, in which every variable was tested against the dependent variable at a  $p$  value of 0.25, and those variables that had a  $p$  value of less than 0.25 were considered in multivariate Cox regression analysis [35].

In fitting the Cox model, it is assumed that the hazard ratio between two subjects with different covariate information is constant over time, i.e., proportionality of hazards. This implies that predictors are time-independent. The Cox proportional hazard assumption was checked on significant predictors by the Schoenfeld global test; a  $p$  value  $> 0.05$  implies that it fulfills the criteria [37]. We investigated the interactions between the variables. No significant interactions were found; hence, they were not taken into account in the final Cox model [35]. The Cox-Snell residuals were used to evaluate the fit of the Cox proportional hazard model. The plot of the graph of the cumulative hazard function conditional on covariate vectors had an exponential distribution with a hazard rate of one, which indicates the model fits the data well [37]. Hence, we concluded that our final model fits the data well. After conducting interaction and model diagnostics, factors with a  $p$  value of less than 0.05 were deemed statistically significant predictors of relapse in patients with schizophrenia in the multivariate Cox regression model. Finally, the adjusted hazard ratio (AHR) and 95% confidence interval (CI) were utilized to interpret the significant predictors.

### 3. Result

**3.1. Sociodemographic Characteristics.** In total, 273 patient medical records with diagnoses of schizophrenia were reviewed for this study. More than half of the participants (55%) came from urban areas; more than three-fifths (61.5%) of the patients were men; and over two-thirds (41%) of the patients were between the ages of 25 and 34, with a mean age of 29 years across participants. Moreover, 233 (85.4%) of the population lived with family, 209 (76.5%) were unemployed, and nearly half (48.7%) were single (Table 1).

**3.2. Behavioral and Clinical Characteristics.** According to behavioral and clinical features, of the total 273 participants, nearly half (48.7%) of patients with schizophrenia had less than two weeks of hospitalization, with a mean period of hospitalization of 15 days, and one-third (33%) had stressful life events. In addition, more than one-third (35.9%) of all schizophrenia patients did not adhere to their prescribed course of therapy (Table 2).

**3.3. The Incidence of Schizophrenia Relapse.** The incidence of relapse among patients with schizophrenia was determined to be 2.9 per 100 person-months (PMS) [95% CI: 2.3–3.6].

TABLE 1: Sociodemographic characteristics of patients with schizophrenia ( $n = 273$ ).

Predictors	Frequency	Percent (%)
<i>Sex of the patient</i>		
Female	105	38.5
Male	168	61.5
<i>Age of the participants</i>		
15-24	67	24.5
25-34	112	41.0
35-44	69	25.27
$\geq 45$	25	9.16
<i>Residence</i>		
Rural	122	44.7
Urban	151	55.3
<i>Religion</i>		
Orthodox	220	80.6
Muslim	42	15.3
Others <sup>a</sup>	11	4.1
<i>Marital status</i>		
Single	133	48.7
Married	83	30.3
Divorced	49	17.9
Widowed	8	2.1
<i>Occupational status</i>		
Employed	44	16.1
Nonemployed	209	76.5
Private job	20	7.3
<i>Educational status</i>		
Unable to read and write	32	11.7
Primary	89	32.6
Secondary	94	34.4
College and above	58	21.3
<i>Living condition</i>		
With family	233	85.4
Living alone	40	14.6

Others<sup>a</sup>: Catholics/Protestants.

During the entire follow-up period, 83 out of 273 (or 30.4%) of schizophrenic patients relapsed.

According to the selected characteristics, 53 (63.86%) males out of 83 experienced a relapse for schizophrenia at a rate of 2.9 per 100 per month. The incidence of relapse among schizophrenia patients aged 25 to 34 was 3.2 per 100 per month, accounting for nearly 48% of all cases of relapse. Twenty-one of 83 patients (25.3%) who were divorced in their marital status experienced relapse, and a 4.3 incidence of relapse per 100 patients per month was noted. Additionally, nearly half of patients with schizophrenia relapsed among those who misused substances, with an incidence of relapse of 4 per 100 per month. Over six-fifths (84.3%) of relapsed patients had not adhered to their treatment, and this group had a relapse rate of 7.3 per 100 patients per month (Table 3).

TABLE 2: Clinical and behavioral characteristics of patients with schizophrenia ( $n = 273$ ).

Predictors	Frequency	Percent (%)
<i>Stressful life events</i>		
Yes	90	32.9
No	183	67.1
<i>Suicidal attempt</i>		
Yes	77	28.2
No	196	71.8
<i>Substance misuse</i>		
Yes	98	35.1
No	175	64.9
<i>Duration of first hospitalization</i>		
<2 week	133	48.7
≥2 week	140	51.3
<i>Treatment adherence</i>		
Adhered	175	64.1
Not adhered	98	35.9
<i>History of comorbid depression</i>		
Yes	50	18.3
No	223	81.7
<i>History of discharge with comorbid medical illness</i>		
Yes	47	17.2
No	226	82.8
<i>Family history of psychiatric illness</i>		
Yes	47	17.2
No	226	82.8

**3.4. Time to Schizophrenia Relapse.** In this study, patients with schizophrenia had a 13-month median time to relapse (IQR: 6 months to 23 months). The life table estimate indicates that the cumulative relapse rate was 64% during the first five months of follow-up and 17.4% during the subsequent five months. Furthermore, the overall relapse rates in the first, second, and third years were, respectively, 26.5%, 61%, and 91% (Table 4). The Kaplan-Meier (KM) curve (Figure 1) demonstrated that there is an increased chance of schizophrenia relapse as follow-up time increases.

In order to compare the likelihood of schizophrenia relapse, we built the KM curve for a few variables. The KM curve for substance abuse showed that patients who used drugs or alcohol had a greater incidence of relapse than patients who did not (log-rank:  $\chi^2(1) = 5.73$ ,  $P$ -value = 0.0167) (Figure 2). The KM curve on treatment adherence status also showed that schizophrenia patients who adhered to their treatment had a considerably lower risk of relapse than those who did not (log-rank:  $\chi^2(1) = 39.44$ ,  $p$  value less than 0.0001) (Figure 3).

**3.5. Predictors of Schizophrenia Relapse.** Age at first hospitalization (continuous), marital status, stressful life events, suicidal attempt, substance misuse, length of first hospitalization (continuous), treatment compliance, history of comorbid

TABLE 3: The number and incidence rate of relapse among patients with schizophrenia divided by selected variables ( $n = 273$ ).

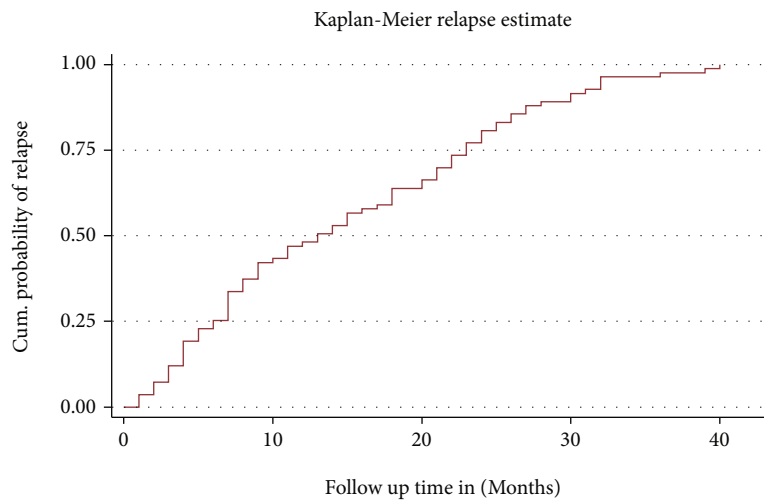
Predictors	Relapse ( $n = 83$ )	Incidence rate [95% CI] per 100 PMs
<i>Sex of the patient</i>		
Female	30	2.9 [2.0-4.1]
Male	53	2.9 [2.2-3.8]
<i>Age of the participants</i>		
15-24	17	2.4 [1.5-3.9]
25-34	40	3.2 [2.3-4.3]
35-44	17	2.5 [1.5-4.0]
≥45	9	4.3 [2.2-8.2]
<i>Marital status</i>		
Single	37	2.5 [1.8-3.4]
Married	23	2.8 [1.8-4.2]
Divorced	21	4.3 [2.8-6.6]
Widowed	2	3.2 [0.8-13.1]
<i>Occupational status</i>		
Employed	15	3.0 [1.8-5.0]
Nonemployed	61	2.9 [2.2-3.7]
Private job	7	2.8 [1.3-6.0]
<i>Living condition</i>		
With family	74	3.0 [2.4-3.8]
Without family(alone)	9	2.2 [1.1-4.3]
<i>Stressful life events</i>		
Yes	40	3.9 [2.8-5.3]
No	43	2.4 [5.0-32.1]
<i>Substance misuse</i>		
Yes	41	4.0 [2.9-5.4]
No	42	2.3 [1.7-3.1]
<i>Duration of first hospitalization</i>		
<2 week	49	3.5 [2.6-4.6]
≥2 weeks	34	2.3 [1.7-33.2]
<i>Treatment adherence</i>		
Adhered	13	0.8 [0.4-1.4]
Not adhered	70	5.4 [4.3-6.9]
<i>History of comorbid depression</i>		
Yes	27	4.9 [3.3-7.1]
No	56	2.4 [1.8-3.1]
<i>Family history of psychiatric illness</i>		
Yes	15	3.3 [2.0-5.5]
No	68	2.8 [2.2-3.6]

depression, and history of discharge with comorbid medical illness were variables chosen from the univariate Cox regression analysis to be included in the final multivariate proportional Cox regression analysis at a  $p$  value of 25%.

Age at first hospitalization (continuous), divorced marital status, substance misuse, duration of first hospitalization, and treatment adherence were statistically significant predictors in the final multivariate Cox model with a  $p$  value of less than 0.05.

TABLE 4: Life table of time to relapse among patients with schizophrenia during the follow-up period 2015-2019 ( $n = 273$ ).

Interval (months)	Beg. total at risk	Average number at risk within interval	Relapse	Censored	Proportion of relapse within interval	Cumulative probability of relapse	[95% CI]
0-5	273	249.5	16	47	0.064	0.064	0.039-0.102
5-10	210	162.5	19	95	0.117	0.174	0.127-0.235
10-15	96	81.5	9	29	0.110	0.265	0.199-0.347
15-20	58	53.5	9	9	0.168	0.388	0.300-0.491
20-25	40	38.5	14	3	0.363	0.610	0.502-0.721
25-30	23	22.5	7	1	0.311	0.732	0.622-0.831
30-35	15	13.5	6	3	0.444	0.851	0.747-0.928
35-40	6	5	2	2	0.40	0.911	0.804-0.972
40-45	2	1.5	1	1	0.667	0.970	0.826-0.999

FIGURE 1: Cumulative probability of relapse among patients with schizophrenia during the follow-up period 2015-2019 ( $n = 273$ ).

The result shows that the incidence of relapse was decreased by 35% as the age of the people with schizophrenia increases (AHR = 0.65; 95% CI: 0.34 to 0.88);  $p$  value = 0.041\*\*). The risk of schizophrenia relapse was 2.5 times greater in divorced schizophrenic patients than in single patients (AHR = 2.5; CI at 95%: 1.18 to 5.28;  $p$  value = 0.016). As the number of days of patients first hospital stay (hospitalization) increases, the incidence of relapse was decreased by 31% (AHR = 0.69; 95% CI: 0.57, 0.86,  $p$  value = 0.011\*\*). Patients who used drugs or alcohol had 1.8 times greater relapse risks for schizophrenia than those who did not (AHR = 1.8; 95% CI: 1.01-3.22;  $p$  value = 0.021). Patients with treatment nonadherence had 5.7-fold higher risk of schizophrenia relapse than those with treatment adherence (AHR = 5.7; CI at 95%: 3.03 to 10.74,  $p$  value < 0.0001) (Table 5).

#### 4. Discussion

Significant therapeutic and socioeconomic implications arise from the early detection and prevention of relapse in schizophrenia patients [38, 39]. This study's goal was to assess the

incidence of relapse, the median time to relapse, and predictors of relapse among patients with schizophrenia.

According to the study's findings, if we follow 100 patients receiving treatment for schizophrenia for a month, three of them will experience a relapse (2.9 per 100 person-months [95% CI: 2.3-3.6]), which is comparable to prior studies carried out in the United States of America (USA), where it was estimated that schizophrenia relapse rates were 3.5% and 3% per month, respectively [16, 40]. This result was lower than that of research conducted in Tanzania, where 10% of schizophrenia patients are readmitted due to relapse per month [16], and for further discussion and comparison, we adjusted the results of the incidence of relapse from being done per 100 persons per month to being done per 100 persons per year. This resulted in the incidence of schizophrenia relapse being 34.8 per 100 persons per year (95% CI: 27.6-43.2). This finding was consistent with a follow-up study done in the Netherlands that discovered 36% of schizophrenia patients had relapses per year [32], a systematic review and meta-analysis of longitudinal studies that found the pooled prevalence of relapse of positive symptoms was 28% [18], a one-year follow-up study done in Turkey that discovered 33% of the schizophrenia

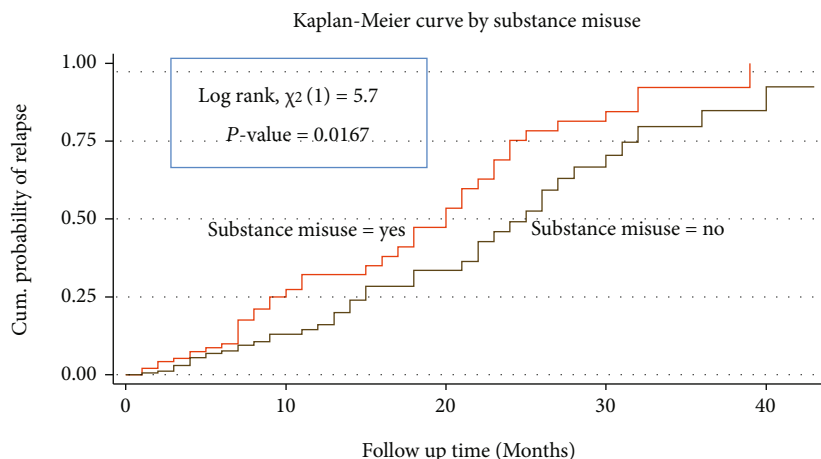


FIGURE 2: Kaplan-Meier curve of schizophrenia relapse divided by substance misuse during the follow-up period 2015-2019 ( $n = 273$ ).

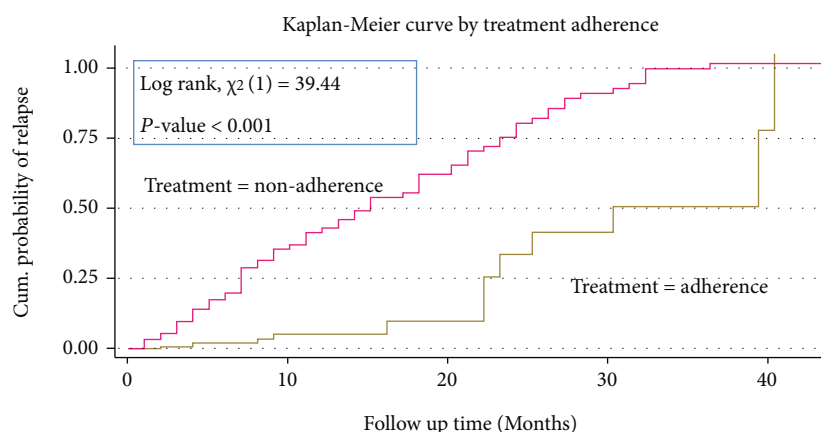


FIGURE 3: Kaplan-Meier curve of schizophrenia relapse divided by treatment adherence during the follow-up period 2015-2019 ( $n = 273$ ).

patients had a relapse during the follow-up period [41], and a study done in Canada that discovered 35.7% [42].

This finding was lower than those of a cohort study conducted in Sweden and a follow-up period study conducted in Birmingham, where the risk of relapse was estimated to be 67% per year and 50% of patients without a prior history of relapse were thought to have experienced their first relapse episode, respectively [43, 44], and a multistate study conducted in the USA found that 54% of schizophrenia patients had at least one episode of relapse [45]. The difference could be the result of different sample sizes, different follow-up periods, and the fact that only the patient's medical records were examined in the current study. All of the studies that were compared were, however, prospective follow-up studies.

In contrast, the results were higher than those of a systematic review and meta-analysis study that determined the pooled incidence of schizophrenia relapse to be 22.97 per 100 participant-years [46]; a retrospective cohort study carried out in China that discovered the incidence of schizophrenia relapse to be 19.3% per year [25]; a three-year follow-up study carried out in Spain that revealed the inci-

dence of schizophrenia relapse to be 18.7% per year [47]; a randomized, double-blind, multicenter, multinational trial that lasted a year and found that 18.3% of patients relapsed during that period [19]; and with another Ethiopian study (24.6%) [29]. This discrepancy may be explained by factors such as the lack of an outreach mental health program in the research area, the preference for nonmedical healers (such as religious and traditional healers) over clinics and hospitals, poor health seeking behavior, and a low degree of community awareness. The inconsistent results regarding relapse rates might also be attributed to the use of various definitions of relapse in various studies, such as a change in consciousness level [21, 48], hospitalization for psychopathology [23, 49], exacerbation of symptoms [23, 26], intentionally harming oneself, engaging in destructive behavior, and/or increasing attempts to kill oneself and/or others [9, 21, 44]. In addition, it may be due to the disparity in population literacy levels and the availability of mental health services in developed nations.

In this study, 13 months (IQR: 6 months to 23 months) was the median time for a schizophrenia relapse, comparable with a cross-sectional study conducted in Germany (7 months) [50]

TABLE 5: Cox regression analysis for predictors of relapse among patients with schizophrenia ( $n = 273$ ).

Predictors	Univariate model CHR [95% CI], $p$ value	Multivariate model AHR [95% CI], $p$ value
Age at first admission (year)	0.69 (0.33-2.83), 0.135*	0.65 (0.34-0.88), 0.041**
<i>Sex of the patients</i>	0.950	
Male	1.00	
Female	0.98 (0.63-1.54)	
<i>Residence</i>	0.406	
Urban	1.00	
Rural	1.20 (0.77-1.88)	
<i>Religion</i>	0.320	
Orthodox	1.00	
Muslim	0.55 (0.28-1.07)	
Others	1.48 (0.46-4.76)	
<i>Marital status</i>	0.009*	
Single	1.00	1
Married	1.20 (0.75-2.14)	1.76 (0.97-3.20), 0.060
Divorced	2.03 (1.18-3.50)	2.50 (1.18-5.28), 0.016**
Widowed	2.33 (0.55-9.91)	2.53 (0.40-16.05), 0.323
<i>Occupational status</i>	0.890	
Employed	1.00	
Nonemployed	1.01 (0.57-1.86)	
Private job	0.91 (0.37-2.24)	
<i>Educational status</i>	0.858	
Unable to read and write	1.00	
Primary	0.98 (0.46-2.11)	
Secondary	0.76 (0.35-1.65)	
College and above	0.99 (0.46-2.15)	
<i>Living conditions</i>	0.438	
With family	1.00	
Living alone	0.76 (0.38-1.52)	
<i>Stressful life events</i>	0.116	
Yes	1.00	
No	0.75 (0.45-1.09)	
<i>Suicidal attempt</i>	0.006*	
Yes	1.00	1
No	0.54 (0.35-0.84)	0.72 (0.44-1.19), 0.202
<i>Substance misuse</i>	0.020*	
Yes	1.67 (1.08-2.63), 1.00	1.8 (1.01-3.22), 0.021
No		1.00
<i>Duration of 1st hospitalization (days)</i>	0.73 (0.23-0.98), 0.046*	0.69 (0.57, 0.86), 0.011**
<i>Treatment adherence</i>	0.001*	
Adhered	1.00	1
Not adhered	5.5 (3.00-9.97)	5.7 (3.03-10.74), 0.001
<i>History of comorbid depression</i>	0.019*	
Yes	1.00	1.00
No	0.57 (0.36-0.91)	0.92 (0.52-1.66), 0.786



TABLE 5: Continued.

Predictors	Univariate model CHR [95% CI], <i>p</i> value	Multivariate model AHR [95% CI], <i>p</i> value
<i>History of discharge with any medical illness</i>	0.045*	
Yes	1	1
No	0.62 (0.41–0.99)	0.77 (0.46–1.30), 0.337
<i>Family history of psychiatric illness</i>	0.595	
Yes	1	
No	0.86 (0.48–1.50)	

Note: AHR: adjusted hazard ratio; CHR: crude hazard ratio; 1.00: reference. \*Predictors with *P* value < 0.25 in univariate analyses were considered for multivariate analysis. \*\*Significant at 5% level of significance in the multivariate model.

and a prospective study conducted in England (8 months) [44]. However, it is lower than the study done in Spain (28 months) [21]. The disparity could be explained by the fact that patients in the study setting received fewer psychosocial rehabilitation or psych educational therapy services and did not seek medical attention as soon as they began to feel sick. Weak familial and social support may also play a role, as shown by earlier research done in Tanzania and Ethiopia [29, 51].

The implications of this study were that early detection and treatment of relapse, as well as the promotion of psychological adjustment to psychotic illness, will all help prevent further harm and deterioration and will serve as a source of data for various stakeholders working on mental health to have vigorous intervention early in the course of illness. Our findings therefore suggest that a sufficient relapse prevention program should be given top priority in mental health services [52]. Moreover, rehabilitation treatments should be established in order to enhance functional outcomes, encourage recovery, and become a significant component of the disease's standard of care.

In this study, younger age predicts higher incidence of schizophrenia relapse. This outcome was comparable to research conducted in the USA [16] and two studies in Asia [10, 25]. The outcome might be due to the nature of the schizophrenia disorder, which manifests in early adulthood [25]. Young people with mental illness had a greater relapse rate, according to a study conducted in Nigeria [53]. A study conducted in Hong Kong [25] indicated that medication discontinuation was more frequent among children, which may make this age group more susceptible to relapse. According to both recent and earlier research, "early intervention," which entails a combination of medical and psychosocial therapy aimed at young people, may aid in preventing schizophrenia relapse.

Being divorced significantly predicts the higher risk of schizophrenia relapse. This result was consistent with a Bangladesh study [54]. However, research conducted in Ethiopia, South Africa, and Korea found no statistically significant association between marital status and schizophrenia relapse [10, 29, 33]. The higher risk of schizophrenia recurrence in divorced individuals may be attributed to psychosocial, financial, and comorbid depressive mood disorders. This argument was supported by a study conducted in Canada, which found that divorced people had the highest prevalence of depression, which could have contributed to the relapse of schizophrenia [55].

Patients who misused substances had higher risk of developing schizophrenia relapse than those who did not.

This outcome was consistent with research from Australia, Kenya, and Ethiopia [18, 30]. However, another Ethiopian study [20] found that substance abuse had a negligible impact on schizophrenia relapse. This might be a result of the patient abusing drugs to get relief from the side effects of antipsychotic medications and psychotic symptoms. The increased psychological problems, infections, sexually risky conduct, and angry and disorderly behavior, as well as the fact that substance addiction by itself prevents patients from taking their prescriptions as prescribed, may all contribute to the likelihood of relapse among substance misusers [33].

Longer initial hospitalization (hospital stay) predicts lower risk of schizophrenia relapse. Our study's findings are consistent with those made by research in China [25]. The finding might be connected to spending more time in the hospital, which could lead to the need for additional tests, therapies, and preparations for home care.

Medication nonadherence had a substantial impact on the risk of schizophrenia relapse, with the risk of relapse were greater in nonadherence patients than in adherent patients with schizophrenia. The results of the current study were consistent with those of studies conducted in Hong Kong, China [25], Korea [10], another Ethiopian study [20, 29], and a Kenyan study [33]. The nonadherence status among patients with schizophrenia in the study setting may be caused by their failure to see the benefits of treatment, underestimating and misinterpreting the risks that clinicians have suggested [22], assuming they are symptom-free, a lack of supervision, forgetfulness due to the disease's impact on cognitive function and medication side effects [33], and the existence of comorbidities [56].

Furthermore, patients with schizophrenia may be at risk for treatment nonadherence due to the presence of comorbid mental illnesses, which results in an enhanced regimen's complexity and possible negative side effects, and nonadherence ultimately causes relapse [57]. This implies that adherence to treatment is essential for the patient to manage symptoms and prevent relapse. As a result, efforts to improve drug adherence at the hospital and community levels ought to be supported, and greater monitoring of patients who stop taking their medicine may lower the chance of relapse. Screening for substance addiction, comorbid psychiatric disorders, and stressful life events is one further step in the prevention and/or reduction of the risk of relapse. Other steps include providing targeted therapy, assisting with coping techniques, and delivering targeted therapy. In addition, caring for these substance users before terminating treatment may help reduce relapse rates.

**4.1. Limitation of the Study.** Since this was a retrospective study, the factors were limited to data from the patients' medical records. Other potential relapse risk factors identified through primary data, such as feelings expressed by family members, the length of untreated psychosis, the participant's monthly income, a lifetime history of substance abuse, social support, the age of disease onset, and the severity of medication side effects, were not fully recorded in the medical records, which could result in an underestimation of the outcome. It was impossible to verify the accuracy of the data that was collected. Ultimately, it was not possible to generalize our findings to other contexts. This study, which focused on a single location in Ethiopia, could not serve as a model for the entire nation or other African nations. Also, one of the limitations of the manuscript may be that we are unable to employ validated scales to measure schizophrenic relapse.

## 5. Conclusion

In this study, out of 100 patients with schizophrenia who were followed up for a month, three of them had a relapse. Treatment nonadherence was the leading risk factor for relapse, followed by being divorced and substance misuse. In contrast, being older and longer hospital stay were protective factors that lowered the risk of schizophrenia relapse. In light of our results, it is advised that all parties involved focus on early detection and taking preventive measures against schizophrenia relapse, as well as providing regular psychoeducation about the significance of treatment adherence and connecting patients with substance misuse to substance rehabilitation centers. We further indicate that "early intervention," which comprises a combination of medical and psychological therapy targeted at young people, may help to prevent schizophrenia relapse. The results of our study also suggest that screening and evaluating patients for cooccurring substance abuse should be given a lot of attention. Moreover, we recommend multicenter research that uses primary data and extensive prospective studies to evaluate additional factors associated with schizophrenia relapse.

## Abbreviations

ACSH:	Ayder Comprehensive Specialized Hospital
AHR:	Adjusted hazard ratio
CHR:	Crude hazard ratio
DALY <sub>s</sub> :	Disability adjusted life years
DSM-IV-TR:	Diagnostic and statistical manual of mental disorders, fourth edition—text revision
FMOH:	Federal Minister of Health
KM:	Kaplan-Meier
NGOs:	Nongovernmental organization
WHO:	World Health Organization
YLD <sub>s</sub> :	Years lived with disability.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

## Ethical Approval

An ethical clearance was issued by the research ethics review committee of the School of Public Health and the College of Health Sciences of Mekelle University, and all methods were carried out in accordance with relevant guidelines and regulations of the university.

## Consent

The informed consent procedure for this study was waived by the College of Health Sciences Institutional Review Board (CHS-IRB) of Mekelle University. Consent to participate was waived since the study was conducted through a review of medical records. Individual patients were not subject to any harm. Other than this study, the data should not be used for other purposes.

## Conflicts of Interest

The authors have declared that no competing interests exist.

## Authors' Contributions

HEH as principal investigator initiated, designed, organized, and analyzed the data, interpretation, and drafting of the manuscript, as well as critical revision for intellectual content. KEG, DSW, and GBG participated in the study's design, data analysis, data interpretation, and manuscript drafting and revision. All authors agree to be accountable for all aspects of the work and have approved the final version of the manuscript to be published.

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## Supplementary Materials

(Supplementary figure). Overall fit of Cox proportional hazard model for schizophrenia patients at ACSH, Mekelle, Ethiopia, 2015-2019 ( $n = 273$ ). (*Supplementary Materials*)

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