

Risk factors for pneumonia in patients with schizophrenia

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Abstract

Aim: Pneumonia is a major cause of death in patients with schizophrenia. Preventive strategies based on identifying the risk factors are needed to reduce pneumonia-related mortality. This study aimed to clarify the risk factors for pneumonia in patients with schizophrenia.

Methods: We retrospectively reviewed the clinical files of consecutive patients with schizophrenia admitted to Tokyo Metropolitan Matsuzawa Hospital during a four-year period from January 2014 to December 2017. We analyzed the clinical differences between patients with and without pneumonia.

Results: Of the 2209 patients enrolled, 101 (4.6%) received the diagnosis of pneumonia at the time of hospital admission while 2108 (95.4%) did not have pneumonia. Multivariable analysis to determine the risk factors related to pneumonia showed that the use of atypical antipsychotics had the highest odds ratio among the predictive factors (2.7; 95% confidence interval [CI] 1.0-17.7; $P = 0.046$), followed by a total chlorpromazine equivalent dose ≥ 600 mg (2.6; 95% CI 1.7-4.0; $P < 0.001$), body mass index < 18.5 kg/m² (2.3; 95% CI 1.6-3.6; $P < 0.001$), smoking history (2.0; 95% CI 1.3-3.1; $P < 0.001$), and age ≥ 50 years (1.7; 95% CI 1.2-2.6; $P = 0.002$).

Conclusions: We found that advanced age, underweight, smoking habit, use of atypical antipsychotics, and large doses of antipsychotics were risk factors for pneumonia in patients with schizophrenia. Among these factors, it was unclear whether the use of antipsychotics was a direct cause of pneumonia due to is uncertain because our retrospective study design. However, our result might be a good basis of further study focused on reducing pneumonia-related fatalities in schizophrenic patients with pneumonia.

KEYWORDS

antipsychotics, atypical antipsychotics, pneumonia, schizophrenia, typical antipsychotics

1 | INTRODUCTION

Schizophrenia is the most common, chronic, and disabling of the major mental illnesses.¹ Patients with schizophrenia have a higher mortality rate than the general population.² Suicide occurs at a

higher frequency in this group. At the same time, they also have a higher risk of physical illness and poorer treatment outcomes.³ Previous studies have reported that the high risk of physical illness and poor treatment outcomes in patients with schizophrenia were associated with specific behaviors and perceptions such as (a) lack of

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proper health care, (b) less access to physical healthcare resources, and (c) increased risk of complications.^{4,5}

One of the major causes of death in patients with schizophrenia is pneumonia.⁶ Pneumonia accounts for about half of all deaths in psychiatric hospitals^{7,8} and has a higher incidence among patients with schizophrenia than the general population. Patients with schizophrenia had a higher incidence of pneumonia (odds ratio = 1.77) in Taiwan.⁹ The risk of pneumococcal disease in patients with schizophrenia was also high in England (odds ratio = 2.3).¹⁰ Preventive strategies based on modifiable risk factors are important to reduce pneumonia-related mortality.

The risk factors for pneumonia in the general population have been well-studied. Koviula et al. reported that advanced age, alcoholism, and comorbidities were independent risk factors for pneumonia.¹¹ Farr et al.¹² added the importance of cigarette smoking. Almirall et al.¹³ found that underweight and previous pneumonia history were significant risk factors. However, to the best of our knowledge, no studies have examined the risk factors for pneumonia among patients with schizophrenia.

Although our hospital is a psychiatric hospital, we have a Medical Comorbidity Ward and have treated patients with both schizophrenia and pneumonia.¹⁴ We therefore performed a retrospective cohort study to elucidate the risk factors for pneumonia in patients with schizophrenia.

2 | METHODS

2.1 | Study population

The clinical files of consecutive patients with schizophrenia who were admitted to Tokyo Metropolitan Matsuzawa Hospital during a four-year period from January 2014 to December 2017 were retrospectively reviewed. If patients were admitted more than once during the study period, the data from their first hospitalization were used. Patients whose period of hospitalization was no more than a couple of days were excluded because their diagnosis of schizophrenia was deemed to be less reliable, and the clinical information regarding the patient was also deemed to be inadequate. The diagnosis of schizophrenia was made by psychiatric physicians in

accordance with the ICD-10 criteria.¹⁵ This study was approved by the institutional review board of Tokyo Metropolitan Matsuzawa Hospital, and written informed consent was waived because of the retrospective design. Patient anonymity was preserved.

We examined each patient's physical characteristics and clinical parameters on admission. The database developed here included the type and dose of the prescribed antipsychotics. For the latter, we used the chlorpromazine equivalent dose table developed by Toru, which is the most commonly used conversion chart in Japan.¹⁶ In addition, the physical characteristics and clinical parameters were compared between the two patient groups with and without pneumonia on admission in order to detect the risk factors for pneumonia. At Tokyo Metropolitan Matsuzawa Hospital, all patients are asked to undergo a chest X-ray on admission. Internal medicine physicians diagnosed pneumonia based on clinical symptoms suggestive of pneumonia (cough, fever, productive sputum, dyspnea, chest pain, or abnormal breath sounds), and pneumonic infiltration detected by chest X-ray. A multivariate analysis determined which risk factors were related to pneumonia.

2.2 | Statistical analyses

Quantitative data are presented as the mean \pm standard deviation. Differences between patients with and without pneumonia were analyzed using the chi-squared test for categorical variables and Student's *t* test for quantitative variables. Multiple logistic regression analysis was used to assess the role of several variables as risk factors related to pneumonia. $P < 0.05$ was considered to be significant. The following variables with $P < 0.05$ in univariate logistic regression were included in multivariate analysis as dependent variables: use of typical and atypical antipsychotics, large dose of antipsychotics, underweight, smoking history, and advanced age. A statistical software package (JMP, version 10.0.2; SAS Institute; Cary, NC, USA) was used for the statistical analysis.

3 | RESULTS

A clinical chart of 4253 admissions and 2974 patients with schizophrenia during the study period was reviewed. Of the 2974 patients, 2209 patients were included in this study (Figure 1).

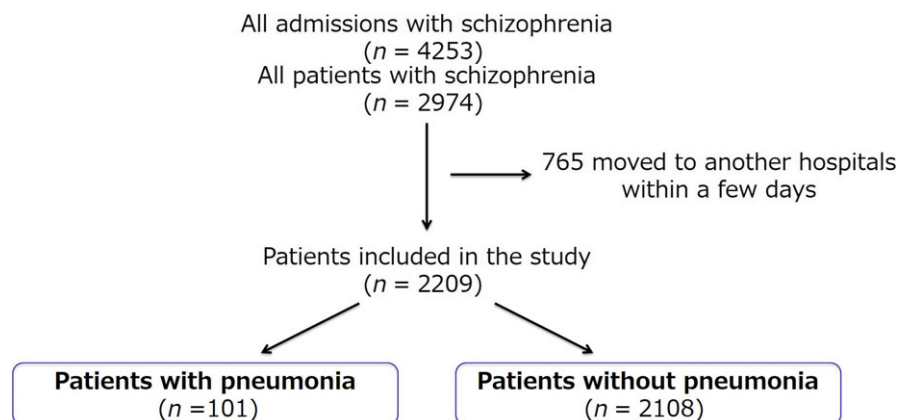


FIGURE 1 Study design



The characteristics of the patients are summarized in Table 1. The characteristics of the patients with pneumonia differed distinctly from those of patients without pneumonia. The pneumonia group tended to be older (52.3 ± 12.0 vs 47.2 ± 12.1 years, $P = 0.002$) and have a smoking history (66.3 vs 49.2% , $P < 0.001$) and lower body mass index (BMI) (19.9 ± 4.1 vs 21.7 ± 4.3 kg/m², $P < 0.001$) than the patients without pneumonia.

TABLE 1 Clinical characteristics of 2209 patients with schizophrenia complicated by pneumonia^a

	With pneumonia (n = 101)	Without pneumonia (n = 2108)	P value
Age, years	52.3 ± 12.0	47.2 ± 12.1	0.002
Males/females, n	55/46	1188/920	0.70
Smoking habit, n (%)			
Current/former smoker	67 (66.3%)	1037 (49.2%)	<0.001
Never smoker	34 (33.7%)	1071 (50.8%)	
Comorbidities, n (%)			
Neoplastic disease	1 (1.0%)	40 (1.9%)	0.50
Cerebrovascular disease	3 (3.0%)	38 (1.8%)	0.40
Congestive heart failure	5 (5.0%)	46 (2.2%)	0.07
Chronic respiratory failure	3 (3.0%)	37 (1.8%)	0.37
Chronic renal disease	5 (5.0%)	77 (3.7%)	0.50
Chronic liver disease	4 (4.0%)	98 (4.6%)	0.75
Diabetes mellitus	9 (8.9%)	198 (9.4%)	0.87
Clinical parameters			
Height, cm	165.5 ± 7.6	165.1 ± 7.6	0.61
Body weight, kg	54.2 ± 10.4	58.8 ± 10.3	<0.001
Body mass index, kg/m ²	19.9 ± 4.1	21.7 ± 4.3	<0.001
Typical antipsychotics, n (%)	10 (9.9%)	507 (24.1%)	0.001
Chlorpromazine	1 (1.0%)	58 (2.8%)	0.28
Levomepromazine	5 (5.0%)	228 (10.8%)	0.06
Haloperidol	5 (5.0%)	223 (10.6%)	0.07
Others	1 (1.0%)	53 (2.5%)	0.33
Atypical antipsychotics, n (%)	97 (96.0%)	1890 (89.7%)	0.04
Risperidone	38 (37.6%)	661 (31.4%)	0.19
Olanzapine	23 (22.8%)	580 (27.5%)	0.30
Quetiapine	18 (17.8%)	425 (20.2%)	0.57
Clozapine	1 (1.0%)	33 (1.6%)	0.65
Aripiprazole	15 (14.9%)	213 (10.1%)	0.13
Others	28 (27.7%)	716 (34.0%)	0.19
Total chlorpromazine equivalent dose, mg	692.0 ± 336.0	517.5 ± 269.2	<0.001

^aData are presented as n (%) or mean ± standard deviation.

The prescribed antipsychotics differed significantly between the patients with and without pneumonia (Table 1). Typical antipsychotics were prescribed less frequently and atypical antipsychotics were prescribed more frequently to patients with pneumonia than to those without pneumonia. The total chlorpromazine equivalent dose was significantly higher for the patients with pneumonia than for those without pneumonia (692.0 ± 336.0 vs 517.5 ± 269.2 mg, $P < 0.001$). Figure 2 shows the distribution of the patients according to the total chlorpromazine equivalent dose. The proportion of patients with pneumonia is shown in Figure 3. The increased risk of pneumonia was dose-dependently observed.

To identify the risk factors related to pneumonia, we performed multivariate analysis (Table 2). Use of atypical antipsychotics had the highest odds ratio among the predictive factors (2.7; 95% confidence interval [CI] 1.0-17.7; $P = 0.046$), followed by large dose of antipsychotics (2.6; 95% CI 1.7-4.0; $P < 0.001$), underweight (2.3; 95% CI 1.6-3.6; $P < 0.001$), smoking history (2.0; 95% CI 1.3-3.1; $P < 0.001$), and advanced age (1.7; 95% CI 1.2-2.6; $P = 0.01$).

4 | DISCUSSION

We identified significant risk factors for pneumonia in patients with schizophrenia, which were advanced age, underweight, smoking habit, and administration of a higher chlorpromazine equivalent dose or atypical antipsychotics. While this study corroborates the findings of previous studies on the risk factors for pneumonia in the general population, it also provides more established evidence of factors associated with the occurrence of pneumonia in patients with schizophrenia. This knowledge will provide the means of identifying groups that are at risk for pneumonia and require preventive intervention.

Advanced age seems to be related to the development of pneumonia. This may be the result of a general weakening of the immune system, efficacy of vaccines, mucosal barrier function, and cough reflex.^{17,18} Our study revealed that advanced age was an independent risk factor for pneumonia. Aged patients with schizophrenia in particular should be carefully observed for the development of pneumonia.

Nutrition has a close relationship with susceptibility to infection. Malnutrition by itself increases the host's susceptibility to infectious diseases, and these infections, in turn, have negative repercussions on the metabolism of the host, worsening the host's nutritional state.¹⁹ BMI is widely used as an index of an individual's nutritional status.²⁰ Several studies have revealed that underweight is associated with the risk of pneumonia.^{13,21} Underweight is prevalent in Japanese patients with schizophrenia. Sugai et al²² reported that Japanese patients with schizophrenia showed a higher prevalence of underweight than the general Japanese population (13.8% vs 7.9%). In the present study, the prevalence of underweight in patients with schizophrenia was consistent with the findings of previous studies (patients with pneumonia: 41.6%; patients without pneumonia: 23%). Because underweight is a potentially treatable condition, nutritional intervention for underweight patients with schizophrenia deserves serious consideration.

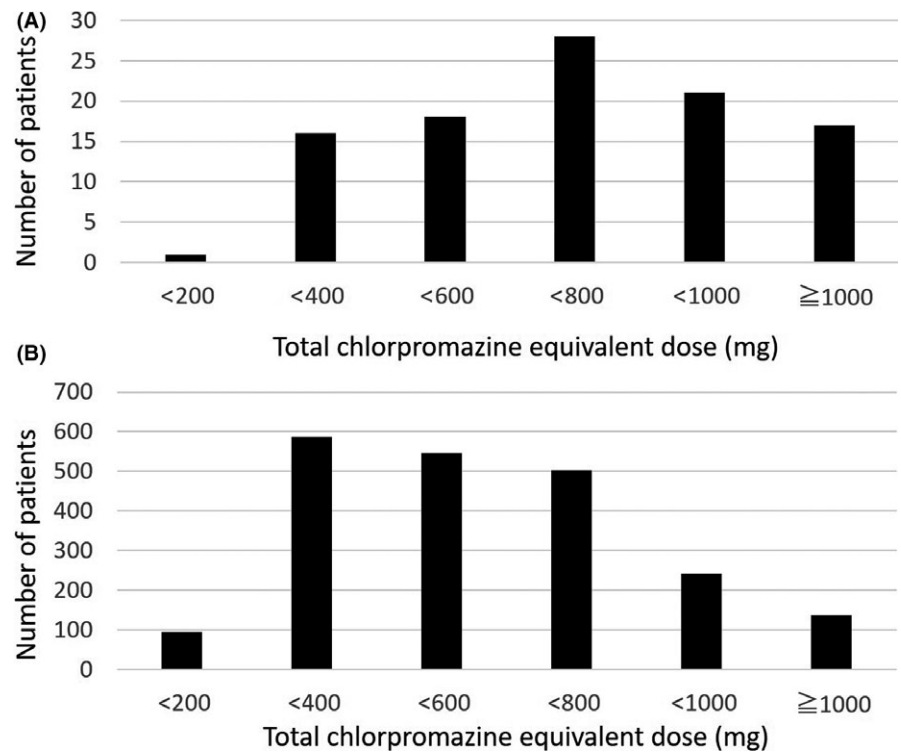


FIGURE 2 Distribution of patients with schizophrenia according to total chlorpromazine equivalent dose. The patients were divided into groups with (A) or without (B) pneumonia

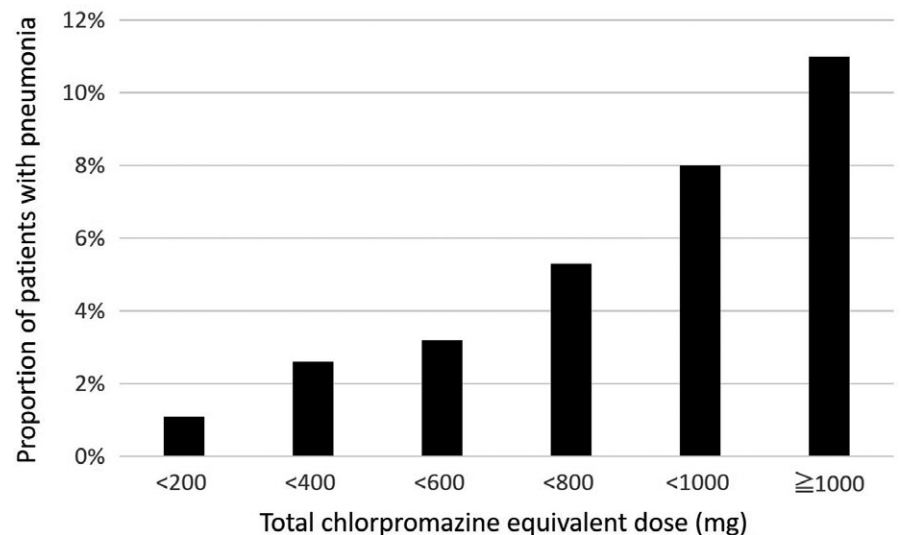


FIGURE 3 Distribution of patients with pneumonia according to total chlorpromazine equivalent dose. The risk of pneumonia increased dose-dependently. The proportion of patients with pneumonia was calculated by dividing the number of patients with pneumonia by the total number of patients

TABLE 2 Risk factors for pneumonia identified by multivariate analysis

Risk factors	Regression coefficient	Odds ratio	95% CI	P value
Body mass index <18.5 kg/m ²	4.165	2.3	1.6-3.6	<0.001
Age ≥ 50 years	2.645	1.7	1.2-2.6	0.01
Smoking history	3.314	2.0	1.3-3.1	0.001
Use of atypical antipsychotics	1.996	2.7	1.0-17.7	0.046
Use of typical antipsychotics	-3.140	0.35	0.18-0.67	0.002
Total chlorpromazine equivalent dose ≥ 600 mg	4.518	2.6	1.7-4.0	<0.001

CI, confidence interval.

An increase in the risk of pneumonia was found to be associated with smoking status in the present study. Smoking is a well-known and important risk factor for pneumonia among the general

population. There is consistent evidence to show that smoking itself increases respiratory infections in smokers. Invasive pneumococcal disease was associated with cigarette smoking (OR = 4.1) in a case-



control study.²³ Smoking is highly prevalent among patients with schizophrenia, but these patients are less likely to be treated than patients without schizophrenia.²⁴ Despite the concern that smoking cessation may exacerbate psychiatric symptoms in patients with schizophrenia, the current evidence does not support this assumption.²⁵ Smoking cessation should be taken into account as a means of preventing pneumonia in patients with schizophrenia.

The use of antipsychotics has been suggested as a possible risk factor for pneumonia. Several observational studies were conducted to explore the association between the use of antipsychotics and pneumonia in a cohort of elderly patients with dementia.²⁶ Blocking dopamine receptors may result in an extrapyramidal effect (dyskinesia, rigidity, and spasm of the oral and pharyngeal muscles), which can result in dysphagia and ultimately in aspiration pneumonia.²⁷ In the present study, the chlorpromazine equivalent dose for antipsychotics was associated with an increase in the risk of pneumonia.

Interestingly, the use of typical antipsychotics was not associated with the development of pneumonia whereas the use of atypical antipsychotics was. Several studies reported similar findings. Knol et al²⁶ reported a higher risk of pneumonia associated with the administration of atypical antipsychotics than of typical antipsychotics in patients with dementia (OR = 3.1 vs 1.5). The risk of extrapyramidal adverse events associated with antipsychotic use was generally lower for atypical than typical antipsychotics.²⁸ Thus, mechanisms other than extrapyramidal adverse events may play a role. The anticholinergic action and blockade of histamine-1 (H1) receptor by atypical antipsychotics have been proposed as an alternative explanation for the development of pneumonia.²⁶ The anticholinergic effect of antipsychotics could be related to contracting pneumonia by inducing dry mouth and impaired oropharyngeal bolus transport. The blockade of H1 receptors may lead to excessive sedation, which can result in a decreased swallowing reflex and thereby conduce to pneumonia.²⁹ For patients with a high risk of pneumonia, physicians should make an effort to reduce the dose of antipsychotics, especially atypical antipsychotics, if the patient's psychotic symptoms can be controlled.

The present study has several limitations. First, we were unable to evaluate the severity of psychiatric conditions on admission due to the retrospective study design. The severity of schizophrenia itself might affect the patient's ability to swallow, which can in turn affect the development of pneumonia.³⁰ In addition, overdose of benzodiazepines, catatonic stupor, and bedridden status is reportedly risk factors for pneumonia.³¹ Further study is needed to determine whether the severity of schizophrenia itself and the use of psychoactive drugs other than antipsychotics are also risk factors for pneumonia. Second, our study demonstrated an association between the use of atypical antipsychotics and pneumonia. However, we were unable to determine how and why atypical antipsychotics were used before the patients were admitted to Tokyo Metropolitan Matsuzawa Hospital. Thus, whether the use of atypical antipsychotics was a direct cause of pneumonia is uncertain. Third, in our study, 765 patients who moved to another hospital after a few days were not

included, possibly influencing our findings. Finally, because this was a retrospective cohort study, a prospective study is needed to validate our results.

In conclusion, we demonstrated that advanced age, underweight, smoking habit, use of atypical antipsychotics, and large doses of antipsychotics were risk factors for pneumonia in patients with schizophrenia. Further study based on our results is needed to establish preventive strategies to reduce pneumonia-related death among schizophrenic patients with pneumonia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest for this article.

AUTHOR CONTRIBUTION

TH conceived and designed the study, acquired the data and subjects, analyzed and interpreted the data, and drafted the manuscript. KI, MO, MI, KS conceived and designed the study, acquired the subjects, and prepared the manuscript. KT conceived and designed the study, analyzed and interpreted the data, and prepared the manuscript. All the authors have read and approved the final manuscript.

DATA REPOSITORY

Supporting information Table S1.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

All study protocols were approved by the institutional review board of Tokyo Metropolitan Matsuzawa Hospital.

INFORMED CONSENT

The approved protocol did not require informed consent from patients, as the protocol was not different from ordinary practice, and as the data remained anonymous and were analyzed in aggregate.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

n/a.

ANIMAL STUDIES

n/a.



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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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