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Early View

Original research article

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Please cite this article as: Takada K, Ogawa K, Miyamoto A, *et al*. Risk factors and interventions for developing recurrent pneumonia in older adults. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00516-2022).

Risk factors and interventions for developing recurrent pneumonia in older adults

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Take-home message

Methods for preventing recurrent pneumonia in older adults are limited. This study shows that avoiding the use of benzodiazepine hypnotics and histamine 1 receptor antagonists could help prevent recurrence of pneumonia in adults aged 75 years or older.

Abstract

Pneumonia is common among older adults and often recurrent. Several studies have been conducted on the risk factors for pneumonia; however, little is known about the risk factors for recurrent pneumonia. This study aimed to identify the risk factors for developing recurrent pneumonia among older adults and to investigate methods of prevention.

We analysed the data of 256 patients aged 75 years or older who were admitted for pneumonia between June 2014 and May 2017. Moreover, we reviewed the medical records for the subsequent 3 years and defined the readmission caused by pneumonia as recurrent pneumonia. Risk factors for recurrent pneumonia were analysed using multivariable logistic regression analysis. Differences in the recurrence rate based on the types and use of hypnotics were also evaluated.

Of the 256 patients, 90 (35.2%) experienced recurrent pneumonia. A low body mass index (odds ratio [OR], 0.91; 95% confidence interval [CI]: 0.83–0.99), history of pneumonia (OR: 2.71; 95% CI: 1.23–6.13), lung disease as a comorbidity (OR: 4.73; 95% CI: 2.13–11.60), taking hypnotics (OR: 2.16; 95% CI: 1.18–4.01), and taking histamine-1 receptor antagonist (H1RA) (OR: 2.38; 95% CI: 1.07–5.39) were risk factors. Patients taking benzodiazepine as hypnotics were more likely to experience recurrent pneumonia than patients not taking hypnotics (OR: 2.29; 95% CI: 1.25–4.18).

We identified several risk factors for recurrent pneumonia. Among them, restricting the use of H1RA and hypnotics, in particular, benzodiazepines may be useful in preventing the recurrence of pneumonia in adults aged 75 years or older.

Introduction

In recent decades, pneumonia has been a major cause of death globally [1]. An increase in the number of patients with pneumonia is a serious issue, especially in super-ageing societies such as Japan, because the morbidity of pneumonia increases with age in adults [2, 3]. Additionally, hospitalisation and treatment for pneumonia lead to a marked decline in physical function, especially in patients aged 75 years or older [4]. Admissions for pneumonia cases also lead to an increase in social welfare costs. Thus, the prevention and treatment of pneumonia in older adults is vital for improving the quality of life of people.

Pneumococcal vaccination and oral care for older adults are effective in preventing pneumonia [5–7]; however, pneumonia is still prevalent, in spite of these preventive measures. Moreover, patients that have previously developed pneumonia are likely to have a recurrence [8, 9], which increases proportionally with age [8, 10]. There have been many studies on the risk factors for the initial episode of pneumonia [10]; however, only a few studies have assessed the risk factors for recurrent pneumonia [9–11]. Moreover, to our knowledge, no reports have been published on the risk factors for recurrent pneumonia using cohorts limited to patients aged 75 years or older, which are critical issue in the clinical practice. Recurrent pneumonia has been defined the pneumonia within a few years of the initial episode of pneumonia in previous studies [10, 12]. Only a few risk factors for developing recurrent pneumonia have been identified. These include chronic lung disease, decreased swallowing function, and the use of inhaled corticosteroids (ICS) [9–11]. Hypnotics and sedatives have also been reported to be associated with aspiration and the development of recurrent pneumonia [9, 11]; however, the results are inconsistent between studies. In addition, the specific types of hypnotics that are associated with recurrent pneumonia are unknown. As medication change is relatively easy for clinicians to implement among the limited preventive measures available for recurrent pneumonia in older patients, it is important to clarify the role of hypnotics in increasing the

risk of recurrent pneumonia among older patients.

We hypothesised that hypnotics and histamine-1 receptor antagonists (H1RA), which also have a sedative effect, are risk factors for developing recurrent pneumonia among patients aged 75 years or older. In this study, we retrospectively reviewed the records of patients aged 75 years or older with recurrent pneumonia, and attempted to determine the risk factors for developing recurrent pneumonia, with a particular focus on these medications.

Material and methods

Study participants

We retrieved the medical records of patients aged 75 years or older who were admitted to the Department of Respiratory Medicine of our hospital (an 819-bed acute care general hospital in Tokyo, Japan) for pneumonia, including aspiration pneumonia, from June 2014 to May 2017. Pneumonia was defined as having relevant clinical and imaging findings on admission, and diagnosis of pneumonia by an attending physician. Medical records were retrospectively reviewed by respiratory physicians, who confirmed that the overall clinical course was consistent with pneumonia. A total of 275 patients were enrolled in the study; however, 19 patients died during their first inpatient stay within this period and were excluded. The remaining 256 patients were included in this study. The study was approved by the local ethics committee of the Toranomon Hospital (approval number: #1960:2020/Feb.) The requirement for informed consent was waived owing to the retrospective nature of the study. This retrospective single-centre study was conducted following the amended Declaration of Helsinki.

Study design

The retrospective single-centre study determined the risk factors for developing recurrent pneumonia in patients aged 75 years or older and the association between the use of hypnotic agents and recurrent pneumonia.

Methods

The “inclusion day” was the day from June 2014 to May 2017 on which the patient was admitted due to the first episode of pneumonia. In addition, we used the records of patient visits to our hospital to follow-up patients for 3 years from the “inclusion day” to determine the incidence of recurrent pneumonia in the cohort, defined as readmission due to a new episode on pneumonia after a previous admission for pneumonia. We evaluated the risk factors for

developing recurrent pneumonia.

We collected data on physical measurements, comorbidities, medical history, and blood test results on the "inclusion day". The patients who were admitted to our hospital owing to pneumonia within the 3 years prior to the "inclusion day" were defined as having a history of pneumonia. Bacterial pathogens were identified by sputum culture or a urinary antigen test. We used the A-DROP scoring system to assess the severity of pneumonia, as recommended by the Japanese Respiratory Society (JRS). A-DROP is a simple modified version of the CURB-65 scoring system, which is advocated by the British Thoracic Society (BTS) [13], and these two systems are considered to correlate with 30-day mortality in patients with community-acquired pneumonia (CAP) [14]. A-DROP is a 6-point (0–5) scoring system that assesses the following parameters: age (male ≥ 70 years, female ≥ 75 years), dehydration (blood urea nitrogen ≥ 210 mg/L), respiratory failure ($SpO_2 \leq 90\%$ or $PaO_2 \leq 60$ mmHg), orientation disturbance, and low blood pressure (systolic blood pressure ≤ 90 mmHg). The number of fulfilled items was scored, and patients with scores over 3 points were considered to have severe disease.

We classified pneumonia as CAP or nursing and healthcare-associated pneumonia (NHCAP). NHCAP is a concept established by the JRS conforming to the Japanese healthcare insurance system, including the nursing-care insurance system, and the Japanese population, which has many older adults who require nursing care or suffer from many complications [15]. Patients categorised as having NHCAP include not only patients who stay at care facilities or nursing homes and immunocompromised patients, but also older or disabled adults who live at home but need nursing care.

As a primary analysis, we examined the risk factors for recurrent pneumonia using data from the inclusion day. We divided the patients into two groups: with or without readmission due to recurrent pneumonia within the subsequent 3 years, and then compared

patient characteristics, blood test results, severity, causative pathogens, and comorbidities among the recurrent pneumonia and non-recurrent pneumonia groups. In addition, as further exploratory analysis, we examined the differences in risks according to the type of hypnotic agent used. We categorised the patients into four groups based on the type and uses of hypnotics and compared their readmission rates and times. Group 1: patients who did not take hypnotics; Group 2: patients who took a benzodiazepine as a hypnotic; Group 3: patients who took Z-drugs (zopiclone, eszopiclone, zaleplon, and zolpidem) as a hypnotic but did not take a benzodiazepine as a hypnotic; and Group 4: patients who took hypnotics other than benzodiazepines or Z-drugs.

Statistical analysis

Categorical variables were compared between the two groups using the χ^2 test, and continuous variables were compared using the Wilcoxon rank-sum test. Multivariable logistic regression analysis was conducted as a primary analysis to identify risk factors for recurrent pneumonia. In addition to the risk factors reported in previous studies [9–11], the use of medications which we hypothesized to be a risk factor for recurrent pneumonia was included in this analysis. The risk factors used in this analysis were predefined before statistic comparison of these two groups according to the results of previous studies and our hypothesis that hypnotics may be a risk factor for recurrent pneumonia. The following factors were considered: age, sex, body mass index (BMI), history of pneumonia, presence or absence of complications of lung disease, administration of H1RA, hypnotics, ICS, and NHCAP. As a further exploratory analysis for evaluating the types of hypnotics used, the readmission rates and readmission times for pneumonia in each group were assessed. Subsequently, univariate logistic regression analyses were conducted to determine the risk of recurrent pneumonia according to type of hypnotics used. In addition, the survival time was analysed using the Kaplan-Meier method, and the risk of recurrent pneumonia according to the use of each

candidate risk medication was assessed by comparing patients who did and did not use the medication, using the log-rank test. We reported a two-tailed *p*-value, and *p*-values <0.05were considered to be statistically significant. All statistical analyses were performed using the R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and the JMP Pro software version 16 (SAS Institute Japan, Tokyo, Japan).

Results

Of the 256 patients, 90 (35.2%) were readmitted to our hospital in the 3 years following the "inclusion day" because of recurrent pneumonia (recurrent group) and 166 were not (non-recurrent group). The median follow-up period from the "inclusion day" was 29 months (893 days; range, 4–1096 days). Of all the patients, 112 (43.8%) had visited our outpatient clinic for more than 3 years, of whom 44 belonged to the recurrent group. Fifty-five patients (28 [21.5%] in the recurrent group) died within 3 years. Patient characteristics on the day of inclusion are summarised according to group in Table 1. The values of BMI and serum C-reactive protein (CRP) on the inclusion day were lower in the recurrent group than in the non-recurrent group. The prevalence of patients with a history of pneumonia prior to the inclusion day was higher in the recurrent group than in the non-recurrent group (p=0.001). With regard to the age, sex, category, and severity of pneumonia, there were no significant differences between the groups.

Complications and medications used in these patients are presented in Table 2. A higher percentage of patients in the recurrent group had lung disease as a comorbidity (90.0%) compared to the non-recurrent group (64.5%) (p<0.001), although lung disease was common among both groups. Regarding medication use, the number of patients who took hypnotics was higher in the recurrent group (38.9% vs. 21.7%; p=0.005). Most patients (95.8%) who used hypnotics took either a benzodiazepine or a Z-drug. The incidence of H1RA use was also higher in the recurrent group (20.0% vs. 10.2%; p=0.048). There was no significant difference in the bacterial pathogens between groups (Supplementary Table S1).

The multivariable analysis for evaluating the risk of recurrent pneumonia showed that low BMI (OR: 0.91; 95% CI: 0.83–0.99), history of pneumonia prior to the inclusion day (OR: 2.71; 95% CI: 1.23–6.13), lung disease as a comorbidity (OR: 4.73; 95% CI: 2.13–11.60), use of H1RA (OR, 2.38; 95% CI: 1.07–5.39), and hypnotics (OR, 2.16; 95% CI: 1.18–4.01) were

independent risk factors for recurrent pneumonia (Table 3).

A stratified analysis according to the type of hypnotic used revealed a difference in the risk of recurrence pneumonia according to the type of hypnotic used (Table 4). Of the 256 patients analysed, 185 (72.3%) did not use any hypnotics. Of the remaining 71 patients, 59 (23.0%) took a benzodiazepine as a hypnotic (Table 4a). Clinical characteristics and the rate of pneumonia recurrence in each group are summarised in Tables 4b and 4c. The risk of recurrent pneumonia was evaluated using group 1 (non-users) as the reference group. Patients in Group 2 (benzodiazepine users) were more likely to experience recurrent pneumonia (OR: 2.29; 95% CI: 1.25–4.18). However, the risk of recurrent pneumonia in Group 3 (Z-drug users) (OR: 2.96; 95% CI: 0.76–12.33) and Group 4 (other hypnotic users) (OR: 1.18; 95% CI: 0.054–12.58) did not differ significantly from non-hypnotic users (Table 4d). There was no significant difference in survival time with or without use of each medication, including H1RA, H2RA, benzodiazepines, and Z-drugs (Supplementary Figure S1).

Discussion

In this study, 35.2% (90 patients) of the 256 patients had recurrent pneumonia within 3 years after the inclusion day. In recent studies, the rates of recurrent pneumonia among patients with CAP within 3–5 years have been estimated to be 9–12% [10]. In a previous study of the Japanese population, 16% of patients had a pneumonia recurrence within 1–2 years [9]. In contrast to these other studies, this study was specific to older adults that were admitted to the respiratory department of our hospital. A cohort selection restricted to older patients might be representative of the real-world clinical setting in a super-ageing society, and might show a higher recurrence rate of pneumonia than previous reports.

Low BMI was an independent risk factor for recurrent pneumonia in our study. Low BMI is associated with the development of pneumonia, recurrence of pneumonia, prolonged hospital stay, and mortality in patients with pneumonia [9, 16–18]. Low BMI is also associated with undernutrition, frailty, and sarcopenia; therefore, it is important to pay attention not only to treating pneumonia, but also to improving nutritional status and increasing respiratory and swallowing muscle mass, especially among older patients.

Furthermore, lung disease was a risk factor in our study. Previous studies have reported that chronic lung disease is a risk factor for pneumonia [19–21], which is consistent with this study. Some patients in the recurrent group might have been hospitalised due to mild pneumonia owing to a decline in their general status, because this group had a significant higher prevalence of underlying lung disease. Therefore, this might explain the lower CRP level in the recurrent group than in the non-recurrent group.

Older adults often have comorbidities and tend to use many medications. Moreover, adverse drug events are common in older adults because of their decreased physiological function [22]. Medications therefore should be kept minimum as necessary. Benzodiazepines are considered potentially inappropriate medications (PIMs) for older people in many studies

based on criteria of PIMs [23]. According to the American Geriatrics Society Beers Criteria 2019, benzodiazepines are identified as PIMs because of the increasing risk of adverse effects such as cognitive impairment, delirium, fall, and fractures [24]. In addition, benzodiazepines reduce muscle tone during sleep. The criteria also state that Z-drugs should be avoided in older adults with delirium. In this study, we examined the relationship between the use of these medications and recurrent pneumonia among older adults. Our findings revealed that use of benzodiazepines as hypnotics were associated with a significantly greater risk of pneumonia recurrence. Insomnia is common in older people. Benzodiazepines, which produce a hypnotic effect by binding to the γ-aminobutyric acid (GABA) type A receptor, have been commonly prescribed for patients with insomnia; however, there are many concerns about some of their side effects such as cognitive decline, dependence, withdrawal symptoms, and falls [25–27]. Z-drugs (zopiclone, eszopiclone, zaleplon, and zolpidem) that bind to GABA type A receptors but are non-benzodiazepines, were launched into the market in the 1990s and are considered safer than benzodiazepines. Since then, the use of Z-drugs has rapidly increased compared to the use of benzodiazepines in patients with insomnia in the United States [28, 29]. In Japan, the use of hypnotics, including Z-drugs, is very high, especially in older adults [30, 31].

Most studies reported that the use of benzodiazepines is a risk factor for pneumonia [32–35]. Z-drugs have also been reported to be a risk factor for pneumonia, especially among older adults [34, 35]; however, some studies have not found an association between Z-drug use and pneumonia [33, 36]. Differences in the study design, inclusion criteria (such as only patients with Alzheimer's disease) [33] and Z-drugs studies (some studies have included only zopiclone as a Z-drug) [36], may have resulted in the disparity between results. A study that showed Z-drugs to be a significant risk factor for pneumonia also showed that the risk of pneumonia is lower with Z-drugs than with benzodiazepines [35]. Our study showed that benzodiazepine use is an important risk factor for of recurrent pneumonia, but survival after

pneumonia did not differ significantly between patients who used benzodiazepine and those who did not. Further studies are needed to examine the differences in the effects of the benzodiazepines and Z-drugs on pneumonia and recurrent pneumonia. New types of hypnotics, including melatonin receptor agonists and orexin receptor antagonists have recently been launched to the market. The use of these drugs is increasing, and the possibility of them being a risk factor for developing pneumonia is unknown. In this study, only a few patients used melatonin receptor agonists or orexin receptor antagonists. Thus, we were unable to evaluate the risk of recurrent pneumonia associated with this type of medication.

In many studies, antihistamines are considered PIMs [23]. In this study, only H1RA were related to recurrent pneumonia. H2RA is used to suppress gastric juice development. Previous studies have shown that proton pump inhibitors are associated with pneumonia due to alterations in the gut flora; however, H2RA do not significantly increase the risk of pneumonia [37, 38]. H1RA are used for their anti-allergic effects; however, it has not been established whether H1RA use is associated with an increased risk of pneumonia. H1RA causes drowsiness by influencing the central histamine neurons and causes dryness of the oral cavity [39, 40], which may lead to pneumonia, especially in older adults.

Our study had some limitations. First, this study was a retrospective, single-centre study. Hence, patients with pneumonia who were treated in an outpatient setting or at other facilities were not included in the analysis. Second, since many of patients who were admitted to our department had underlying lung diseases as comorbidities, so these results may not be representative of pneumonia patients in adults aged 75 years or older the general population. Due to retrospective nature of this study, it was not possible to obtain information regarding vaccination status, swallowing function, dysphagia, or the frailty index on the “inclusion day”. However, as mentioned in method section, the cases with NHCAP contained the frail individuals with declined physical status receiving home-based care. Further investigations are

required to address these limitations.

In conclusion, this study is valuable in that it evaluated the risks of developing recurrent pneumonia in adults aged 75 years or older. Whilst there are limited ways to prevent recurrent pneumonia in older patients, our study suggests that restricting the use of medications such as hypnotics, particularly benzodiazepines, and H1RA, in addition to interventions for undernutrition and low body weight, may help to reduce the risk of recurrent pneumonia.

Conflict of interest statement

All authors have no conflict of interest to declare.

Acknowledgements: None.

Table 1. Patient characteristics on admission

Characteristics	All patients n = 256	Recurrent pneumonia group n = 90	Non- recurrent pneumonia group n = 166	P-value
Age (years), median (IQR)	82.0 (78.0–86.0)	82.0 (78.0–84.8)	82.0 (78.0–86.0)	0.988
Male, n (%)	160 (62.5)	57 (63.3)	103 (62.0)	0.946
BMI, median (IQR)	20.6 (17.9–22.9)	19.6 (17.4–22.0)	21.0 (18.2–23.5)	0.009
Pneumonia type				0.998
CAP, n (%)	155 (60.5)	55 (61.1)	100 (60.2)	
NHCAP, n (%)	101 (39.5)	35 (38.9)	66 (39.8)	
A-DROP (score)				0.146
1, n (%)	94 (36.7)	40 (44.4)	54 (32.5)	
2, n (%)	111 (43.4)	35 (38.9)	76 (45.8)	
3, n (%)	39 (15.2)	14 (15.6)	25 (15.1)	
4, n (%)	9 (3.5)	1 (1.1)	8 (4.8)	
5, n (%)	3 (1.2)	0 (0.0)	3 (1.8)	
History of pneumonia, n (%)	36 (14.1)	22 (24.4)	14 (8.4)	0.001
Smoking history, n (%)	124 (51.7)	47 (53.4)	77 (50.7)	0.782
Blood test				
Alb (g/dL), median (IQR)	3.40 (3.08–3.70)	3.45 (3.10–3.70)	3.40 (3.00–3.70)	0.341
WBC (/μL), median (IQR)	9200 (6975–11725)	9250 (7000–11675)	9150 (6925–11725)	0.746
CRP (mg/dL), median (IQR)	6.10 (1.85–11.50)	4.55 (1.12–9.25)	6.70 (3.00–13.40)	0.003

Alb, albumin; BMI, body mass index; CAP, community-acquired pneumonia; CRP, C-reactive protein; IQR, interquartile range; NHCAP, nursing and healthcare-associated pneumonia; WBC, white blood cell

Table 2. Comorbidities and medication use in patients with recurrent and non-recurrent pneumonia

Characteristics	All patients n = 256 n (%)	Recurrent group n = 90 n (%)	Non- recurrent group n = 166 n (%)	P-value
Comorbidity				
Lung disease	188 (73.4)	81 (90.0)	107 (64.5)	<0.001
Surgical history	42 (16.4)	17 (18.9)	25 (15.1)	0.54
Interstitial pneumonia	54 (21.1)	23 (25.6)	31 (18.7)	0.259
COPD or emphysema	54 (21.1)	23 (25.6)	31 (18.7)	0.259
Lung cancer	36 (14.1)	16 (17.8)	20 (12.0)	0.284
Bronchial asthma	34 (13.3)	15 (16.7)	19 (11.4)	0.326
NTM	23 (9.0)	13 (14.4)	10 (6.0)	0.043
Tuberculosis	26 (10.2)	15 (16.7)	11 (6.6)	0.02
Pulmonary aspergillosis	4 (1.6)	2 (2.2)	2 (1.2)	0.921
Bronchiectasis	19 (7.4)	10 (11.1)	9 (5.4)	0.159
Other than lung disease				
Parkinson's syndrome	5 (2.0)	3 (3.3)	2 (1.2)	0.483
Dementia	27 (10.5)	10 (11.1)	17 (10.2)	0.997
Cerebrovascular disease	26 (10.2)	9 (10.0)	17 (10.2)	>0.999
Gastrointestinal surgery	48 (18.8)	23 (25.6)	25 (15.1)	0.059
Diabetes	55 (21.5)	14 (15.6)	41 (24.7)	0.123
Dialysis	3 (1.2)	1 (1.1)	2 (1.2)	>0.999
Viral hepatitis	16 (6.3)	7 (7.8)	9 (5.4)	0.636
Medication				
Six or more medications	162 (63.3)	63 (70.0)	99 (59.6)	0.132
Inhaled steroids	53 (20.7)	25 (27.8)	28 (16.9)	0.058
Antihistamine	58 (22.7)	29 (32.2)	29 (17.5)	0.011
H1 receptor antagonist	35 (13.7)	18 (20.0)	17 (10.2)	0.048
H2 receptor antagonist	26 (10.2)	13 (14.4)	13 (7.8)	0.145
Hypnotic	71 (27.7)	35 (38.9)	36 (21.7)	0.005
Benzodiazepines	59 (23.0)	29 (32.2)	30 (18.1)	0.016
Z-drugs	15 (5.9)	6 (6.7)	9 (5.4)	0.9
Benzodiazepines or Z-drugs*	68 (26.6)	34 (37.8)	34 (20.5)	0.004

*Six patients used both benzodiazepine and Z-drug.

COPD, chronic obstructive pulmonary disease; H1, histamine 1; H2, histamine 2; NTM: nontuberculous mycobacteria

Table 3. Multivariable logistic regression analysis of risk factors for recurrent pneumonia

Variables	Adjusted odds ratio	95% CI	P-value
Age	1.02	0.96–1.08	0.473
Male	1.05	0.58–1.92	0.874
BMI	0.91	0.83–0.99	0.025
History of pneumonia	2.71	1.23–6.13	0.014
Lung disease	4.73	2.13–11.60	<0.001
H1RA	2.38	1.07–5.39	0.034
Hypnotic	2.16	1.18–4.01	0.013
ICS	1.31	0.66–2.61	0.437
NHCAP	0.87	0.47–1.61	0.658

BMI, body mass index; CI, confidence interval; H1RA, histamine 1 receptor antagonist; ICS, inhaled corticosteroid; NHCAP, nursing and healthcare-associated pneumonia

Table 4. Classification by type of hypnotics

(a) Details of hypnotics of each group

	Benzodiazepines (n=59)	Z-drug (n=15)	Others		N
			Ramelteon (n=4)	Suvorexant (n=1)	
Group 2	+	+	−	−	6
Group 2	+	−	+	−	1
Group 2	+	−	−	−	52
Group 3	−	+	−	+	1
Group 3	−	+	−	−	8
Group 4	−	−	+	−	3

Group 1: patients not taking any hypnotics; Group 2: patients taking benzodiazepines as hypnotics; Group 3: patients taking Z-drugs as hypnotics but not benzodiazepines; Group 4: patients taking other types of hypnotics.

(b) Background

	Group			
	1 n=185	2 n=59	3 n=9	4 n=3
Age (years), median (IQR)	82.0 (78.0–85.0)	82.0 (78.0, 85.5)	87.0 (79.0, 88.0)	88.0 (82.0, 90.0)
Male, n (%)	119 (64.3)	35 (59.3)	4 (44.4)	2 (66.7)
BMI, median (IQR)	20.7 (17.9–23.0)	20.0 (17.7, 23.0)	18.8 (18.4, 21.5)	18.7 (18.6, 20.3)
CAP, n (%)	112 (60.5)	38 (64.4)	5 (55.6)	0 (0.0)
NHCAP, n (%)	73 (39.5)	21 (35.6)	4 (44.4)	3 (100.0)
Comorbidity				
Lung disease	130 (70.3)	49 (83.1)	7 (77.8)	2 (66.7)
Parkinson's syndrome	2 (1.1)	3 (5.1)	0 (0.0)	0 (0.0)
Dementia	21 (11.4)	3 (5.1)	1 (11.1)	2 (66.7)
Cerebrovascular disease	18 (9.7)	7 (11.9)	1 (11.1)	0 (0.0)
Gastrointestinal surgery	35 (18.9)	11 (18.6)	1 (11.1)	1 (33.3)
Diabetes	40 (21.6)	12 (20.3)	2 (22.2)	1 (33.3)
Dialysis	2 (1.1)	1 (1.7)	0 (0.0)	0 (0.0)
Viral hepatitis	13 (7.0)	3 (5.1)	0 (0.0)	0 (0.0)
Blood test				
Alb (g/dL), median (IQR)	3.40 (3.10–3.70)	3.60 (3.15–3.80)	3.20 (3.10–3.80)	2.80 (2.75–2.90)
WBC (/μL), median (IQR)	9300 (6900–11600)	8700 (6850–11700)	8800(8100–14700)	7700 (6800–13600)
CRP (mg/dL), median (IQR)	6.30 (1.80–12.65)	4.50 (1.85–10.30)	2.60 (1.90–6.20)	5.70 (5.35–8.75)

Group 1: patients not taking any hypnotics; Group 2: patients taking benzodiazepines as hypnotics; Group 3: patients taking Z-drugs as hypnotics but not benzodiazepines; Group 4: patients taking other types of hypnotics.

Alb, albumin; BMI, body mass index; CAP, community-acquired pneumonia; CRP, C-reactive protein; IQR, interquartile range; NHCAP, nursing and healthcare-associated pneumonia; WBC, white blood cell.

(c) Number of pneumonia admissions during the 3-year follow-up period

	Group			
	1	2	3	4
	n=185	n=59	n=9	n=3
Recurrent, n (%)	55 (29.7)	29 (49.2)	5 (55.5)	1 (33.3)
Number of pneumonia admissions, n (%)				
1	130 (70.3)	30 (50.8)	4 (44.4)	2 (66.7)
2	36 (19.5)	16 (27.1)	3 (33.3)	1 (33.3)
3	9 (4.9)	5 (8.5)	1 (11.1)	0 (0.0)
4	5 (2.7)	3 (5.1)	1 (11.1)	0 (0.0)
5	1 (0.5)	2 (3.4)	0 (0.0)	0 (0.0)
6	2 (1.1)	1 (1.7)	0 (0.0)	0 (0.0)
7	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
9	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
10	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
14	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Group 1: patients not taking any hypnotics; Group 2: patients taking benzodiazepines as hypnotics; Group 3: patients taking Z-drugs as hypnotics but not benzodiazepines; Group 4: patients taking other types of hypnotics.

(d) Odds ratio of recurrent pneumonia of each group

Group	Odds ratio	95% CI	P-value
Group 1	ref		
Group 2	2.29	1.25–4.18	0.007
Group 3	2.96	0.76–12.33	0.116
Group 4	1.18	0.054–12.58	0.892

Group 1: patients not taking any hypnotics; Group 2: patients taking benzodiazepines as hypnotics; Group 3: patients taking Z-drugs as hypnotics but not benzodiazepines; Group 4: patients taking other types of hypnotics.
CI, confidence interval.

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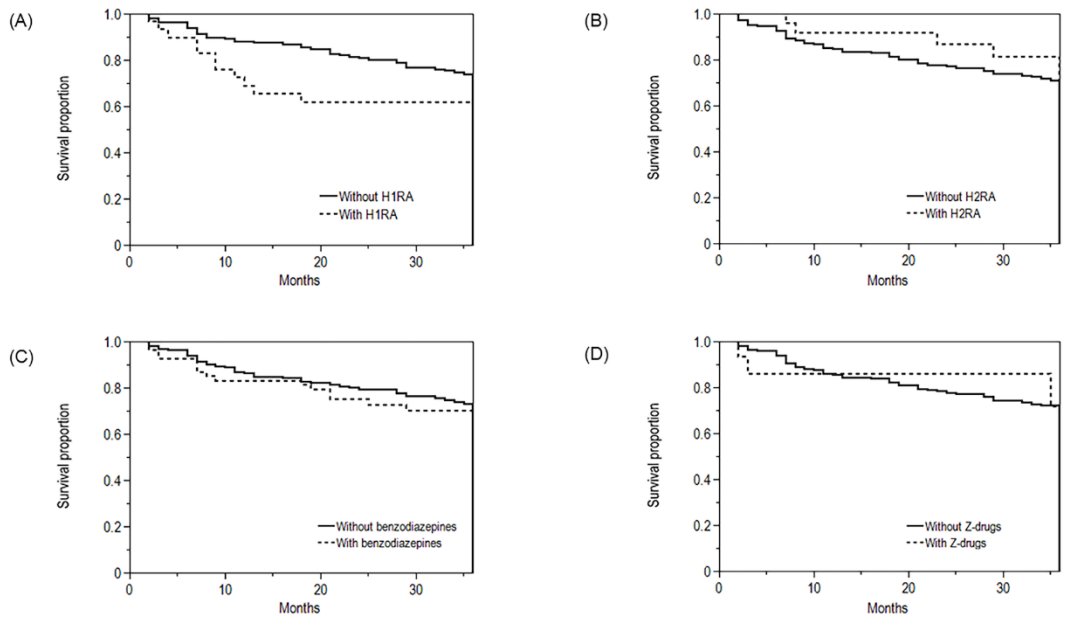
Supplementary Table S1: Bacterial pathogens associated with recurrent and non-recurrent pneumonia

	All patients n = 256 n (%)	Recurrent group n = 90 n (%)	Non- recurrent group n = 166 n (%)	P-value
Streptococcus pneumoniae	15 (5.9)	6 (6.7)	9 (5.4)	0.9
Klebsiella pneumoniae	6 (2.3)	2 (2.2)	4 (2.4)	>0.999
Moraxella catarrhalis	6 (2.3)	3 (3.3)	3 (1.8)	0.735
Haemophilus influenzae	18 (7.0)	5 (5.6)	13 (7.8)	0.672
Pseudomonas aeruginosa	9 (3.5)	4 (4.4)	5 (3.0)	0.811
Escherichia coli	2 (0.8)	1 (1.1)	1 (0.6)	>0.999
Legionella spp.	3 (1.2)	1 (1.1)	2 (1.2)	>0.999



Supplementary Figure 1. Survival curve according to the presence or absence of hypnotic medication use There was no significant difference between patients with and without H1RA use (p = 0.059) (A); patients with and without H2RA use (p = 0.265) (B); patients with and without benzodiazepine use (p = 0.604) (C); or patients with and without Z-drug use (p = 0.877) (D). H1RA: Histamine 1 receptor antagonist, H2RA: Histamine 2 receptor antagonist