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Improving Physical Activity Ensures the Long-Term Survival of Pneumonia Patients in a Super-Aged Society: A Retrospective Study in an Acute-Care Hospital in Japan

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Pneumonia is the third largest cause of death in Japan. Chest physicians have been struggling to improve the outcome of pneumonia treatment in acute care settings. However, a poor long-term prognosis after pneumonia has not been well recognized. Furthermore, the factors related to the poor prognosis, especially the possible involvement of senescence-related disability, have not been identified. In this study, long-term outcomes after discharge from hospital were retrospectively analyzed to identify factors related to the poor long-term prognosis. Outcomes of 958 pneumonia patients who were discharged from South Miyagi Medical Center (Miyagi, Japan) from June 1, 2008 to March 31, 2014 were determined through patient surveys or medical record reviews on September 26, 2014. Survival curves were constructed and compared according to various factors. Multivariate analysis revealed that all levels of decrease in physical activity, an age of 80 years old or more, the most severe status in Japanese Respiratory Society pneumonia severity grading system, the presence of antibiotic-resistant bacteria, and comorbid malignancy significantly reduced long-term survival. The effects of dementia, neuromuscular disease, heart disease, and nursing care residency on long-term survival were detected only with univariate analysis. Physical activity influenced the acute-phase and the long-term prognosis of pneumonia. This report provides information to assist physicians in giving better suggestions to disabled older patients when choosing pneumonia treatment options. In conclusion, we propose that death related to pneumonia can be prevented in the same way as non-communicable diseases by improving physical activity.

Keywords: aging; aspiration pneumonia; community-acquired pneumonia; healthcare-associated pneumonia; quality of life
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Introduction

Japan is one of the most aged societies in the world, and is classified as a "super-aged society", a society in which individuals aged 65 years or older account for more than 21% of the total population. It has been reported that the prevalence and mortality rate of pneumonia drastically increases in persons aged 65 years or older (Kohno et al. 2013). Actually, in 2011 in Japan, pneumonia replaced cerebrovascular disease as the third largest cause of death, despite this being the era of antibiotics (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare 2014). There have been continuous attempts to improve the outcome of pneumonia treatment (Miyashita et al. 2006). However, most of the pneumonia-related deaths that appear in vital statistics and that chest physicians are aiming to improve occur during the acute phase of pneumonia treatment. Some surviving patients are subsequently transferred to other hospitals or health-care facilities from acute care hospitals after completing treatment for pneumonia, usually because they can no longer live independently. A good prognosis for these patients cannot be expected after discharge from an acute care hospital, despite the treatment in acute care hospital occasionally being uncomfortable especially for older patients. We are suspicious of the idea that improving short-term survival during hospitalization sufficiently qualifies as successful pneumonia treatment for these patients.

There are a few reports detailing a poor long-term prognosis for pneumonia patients. Long-term prognoses after hospitalization due to pneumonia are worse than those

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of hospitalization because of other causes (Koivula et al. 1999; Yende et al. 2007; Bordon et al. 2010). Further, factors such as age, pneumonia severity, combinations of comorbidities, nursing home residency, and poor nutrition have been shown as risk factors for a poor long-term prognosis after pneumonia treatment (Hedlund et al. 1993; Mortensen et al. 2003; Johnstone et al. 2008). However, most of these previous reports studied patients of a younger age group than that of much the current Japanese population, and because of this, lack the discussion of patients' senescence-related disability statuses in their analyses.

The Japanese Respiratory Society (JRS) has been releasing guidelines for the treatment of pneumonia in different situations; community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and nursing and healthcare-associated pneumonia (NHCAP). JRS's newest guidelines addressing the treatment of pneumonia in aged and disabled patients requiring nursing care (NHCAP) differ from previous JRS guidelines on CAP or HAP, and suggest that patients, as well as their physicians and family members providing their nursing care, should decide where and how treatment is administered both before and after hospitalization for pneumonia depending on the patient's condition (Miyashita et al. 2006; Japanese Respiratory Society 2008; Kohno et al. 2013). Although each of the guidelines is from a different perspective, all of them were made for the common purpose of improving outcome within acute care settings, but not for longer periods after the development of pneumonia. Further, although the new guidelines for NHCAP suggest attenuating the aggressiveness of treatment based on a patient-surrogate joint decision, the guidelines do not recommend clinical indicators for deciding the appropriate treatment, nor guidance on how to improve long-term survival after pneumonia.

In the present study, we sought to clarify the predicting factors that affect the long-term survival of patients hospitalized for pneumonia in the Japanese population using the parameters employed in the Japanese pneumonia guidelines, including disability status, with the goal of addressing the viewpoint of long-term survival in the current Japanese guidelines on NHCAP. This would improve clinical recommendations for a large amount of the population to increase survival after pneumonia and for elderly pneumonia patients and their families to receive better information and advice on treatment options.

Materials and Methods

This is a retrospective cohort study, evaluating patients who were diagnosed as having pneumonia by chest physicians and were hospitalized and discharged from the South Miyagi Medical Center after completing antibiotic therapy from June 1, 2008 to March 31, 2014. A survey was sent to surviving patients and their families to assess the patients' long-term outcomes. For patients who failed to respond, clinical records were evaluated to determine whether the patient had died. If the patient's fate could not be determined, even after a clinical record review, then the last known hospital visit was recorded as the date of censor. The clinical records of the included patients were examined by one experienced chest physician to determine the manner of hospitalization, the severity of pneumonia, pre-existing comorbidities at the time of hospitalization, and the degree of disability before the development of pneumonia. The A-DROP score established in JRS guidelines to grade CAP severity (which assesses a person for age (A), dehydration (D), respiratory failure (R), orientation disturbance (O), and low blood pressure (P)) was used to grade pneumonia severity (Miyashita et al. 2006). In this JRS-CAP severity grading system, each of A-DROP factors is given one point, and the pneumonia severity was expressed as the number of the matched factors of each patient, as most moderate severity score 0 to most severe score 5. The performance status (PS), as described by the Eastern Cooperative Oncology Group (ECOG) (Oken et al. 1982), was used to grade the degree of disability in accordance with the JRS guidelines on NHCAP (Kohno et al. 2013).

The prognostic data and patient characteristics were combined into one data sheet and subjected to statistical analysis. Long-term survival was compared after stratifying patients in accordance with the following clinical factors: age, pneumonia severity, ECOG PS, location of care, pre-existing comorbidities, and the presence of antibiotic-resistant pathogens. The following comorbidities were evaluated: dementia, including Alzheimer's disease, vascular dementia, and dementia with Lewy bodies; neuromuscular disease, including cerebrovascular disease, Parkinson's disease, and myopathy; cardiovascular disease, including ischemic heart disease, valvular disease, atrial fibrillation, and chronic heart failure; chronic kidney disease, including glomerulonephritis and chronic renal failure; chronic liver disease, including chronic hepatitis and liver cirrhosis; diabetes mellitus; rheumatoid arthritis and other vascular collagen diseases; bone fracture within the previous month; malignancies, irrespective of surgical resection; and chronic respiratory diseases, including chronic obstructive pulmonary disease, bronchial asthma, bronchiectasis, interstitial lung disease, and chronic respiratory failure due to other causes. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Serratia marcescens* were defined as antibiotic-resistant pathogens in this study.

Patients who died while hospitalized during the study period were separately analyzed for the same parameters for comparison with the long-term survival of discharged patients. This study was approved by the Ethics Committee of South Miyagi Medical Center on July 30, 2014.

Statistical analysis

Data pertaining to the first hospitalization of all patients were used for comparisons of the long-term prognosis. Data pertaining to all hospitalizations of all patients, including multiple hospitalizations of the same patient, were used for comparisons of the acute phase prognosis during hospitalization. Fisher's exact test was used for comparison in various patient groups. Survival curves were constructed using the Kaplan-Meier method and compared using a log-rank test. Furthermore, factors relating to long-term survival after hospitalization for pneumonia were analyzed using the multivariate Cox proportional hazards model. For analysis of the effect of various factors on acute phase death during hospitalization, binominal logistic regression analysis was performed. The Student *t*-test was used for

all other comparisons. Missing values were manipulated to blank in the statistical analysis in this study. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Excel Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan), except for the Cox model analysis, and were supported, in part, by Medical Toukei Corporation (Tokyo, Japan).

Results

Patient characteristics

During the study period, 1,093 patients were hospitalized 1,359 times for pneumonia, which was diagnosed by chest physicians at the South Miyagi Medical Center. Among these patients, 82.4% hospitalizations involved patients aged ≥ 70 years. The mean patient age at hospitalization was 78.2 years, and the median age was 82 years. Patients were treated using the strategy in JRS's CAP guidelines. A total of 157 patients (representing 11.5% of all hospitalizations) died during hospitalization (Table 1); among these patients, 136 patients died during the first hospitalization. 161 patients were receiving care at the outpatient care clinic of the hospital. The survey was administered to 807 patients and their families, and there were 454 responses (259 patients were alive; 141 patients had died, and the status of 54 patients was unknown). A total of 56 questionnaires were returned because of an incorrect address. The prognosis of the nonrespondents (n = 353) was determined by examining their medical records. The number of patients bearing each prognostic factor in the patients discharged from hospital after completing antibiotic treatment is shown in Table 2.

Acute phase morbidity

Patients who died during the acute phase treatment had a significantly higher A-DROP score ($p < 0.001$) and higher PS ($p < 0.01$) than patients who were discharged from hospital alive (Table 1). Age, although it is included in the A-DROP score, and rate of nursing care facility residency did not affect acute phase mortality. Concerning comorbidities, only malignancy ($p < 0.05$) was associated with decreased short-term survival during hospitalization (Table 1). Among the patients who died during hospitalization, 21 tested positive for antibiotic-resistant bacteria, and 11 were treated with antibiotics specified for the treatment of these bacteria, such as vancomycin for MRSA. Among the patients discharged from hospital after completing antibiotic therapy, 62 had antibiotic-resistant bacteria, and 29 were treated with specified antibiotics. There was no significant difference in the mortality and the rate of specific antibiotic usage in the patients carrying antibiotic-resistant bacteria between the patients who died during acute-phase treatment and those who survived ($p = 0.156$ and 0.801, respectively).

Table 1. Short-term outcomes of hospitalization for pneumonia.

	Death during hospitalization	Discharge	
Number of patients	157	1,202	
Age (mean ± SD)	83.0 ± 10.1	78.0 ± 14.7	
Sex (male)	101	790	
Number of patients, based on the A-DROP score[a]			
0/1/2/3/4/5	3/6/37/52/35/22	125/228/289/189/63/16	***
Number of patients, based on the performance status			
0/1/2/3/4	1/9/28/22/95	118/140/220/121/312	**
Resistant bacteria/others	21/77	62/546	
Route of hospitalization			
Home/hospital/nursing care	98/11/47	745/34/153	
Comorbidities			
Respiratory disease	39	376	
Neuromuscular disease	50	342	
Dementia	34	229	
Heart disease	47	301	
Renal disease	8	28	
Liver disease	4	22	
Diabetes mellitus	19	149	
Bone fracture	3	9	
Malignancy	48	243	*
Collagen disease	6	36	

[a]The A-DROP scoring system assesses the following parameters: (1) age (men ≥ 70 years, women ≥ 75 years); (2) dehydration (i.e., blood urea nitrogen level ≥ 210 mg/L); (3) respiratory failure ($SaO_2 \leq 90\%$ or $PaO_2 \leq 60$ mmHg); (4) orientation disturbance (i.e., confusion); and (5) low blood pressure (systolic blood pressure ≤ 90 mm Hg). The data are presented as the mean ± the standard deviation or as the number.
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

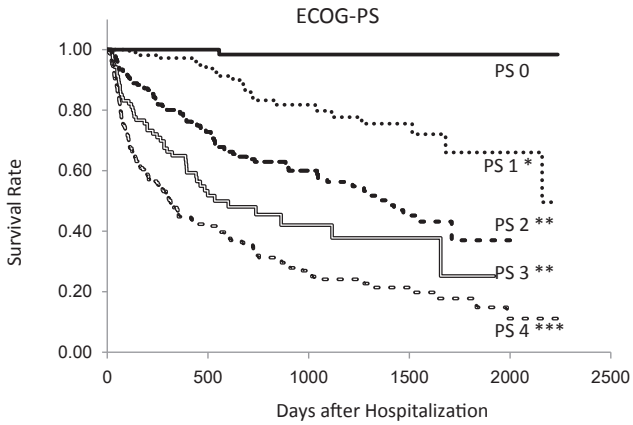

Fig. 1. Effect of disability on long-term survival after pneumonia.
The effect of each grade of disability at hospitalization on long-term survival after hospitalization in pneumonia patients, who completed antibiotic-treatment and were discharged, was studied. Eastern Cooperative Oncology Group (ECOG)-performance status (PS) was used to classify the grade of disability following JRS guideline for NHCAP. Compared to patients with PS 0, a significant decrease in long-term survival was detected in all other PS with multivariate analysis. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Each grade of ECOG-PS was determined as follows; PS 0: Fully active, able to carry on all pre-disease performance without restriction. PS 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. PS 2: Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours. PS 3: Capable of only limited self care, confined to a bed or chair more than 50% of waking hours. PS 4: Completely disabled. Cannot carry on any self care. Totally confined to a bed or chair.

Disease severity, PS, manner of hospitalization, and resistant pathogens

For patients discharged from the hospital after completing antibiotic therapy, long-term survival decreased with the advance in degree of PS (Fig. 1). Compared to the patients with a fully active state; PS 0, long-term survival was significantly reduced in all other PS levels, including the very slightly disabled status; PS 1, when compared with multivariate analysis. Long-term survival also decreased with increasing age, severity of pneumonia, but a significant decrease in long-term survival was observed only in the patients aged 80 or older, or with the most severe pneumonia; A-DROP score 5, with multivariate analysis (Fig. 2, Table 2).

Long-term survival was significantly lower for patients carrying antibiotic-resistant bacteria, although a significant difference was not observed in the acute-phase ($p < 0.001$; Fig. 3 left panel, Table 2). Among the patients with antibiotic-resistant bacteria, treatment with antibiotics specified to antibiotic-resistant bacteria did not alter the prognosis ($p = 0.640$; Fig. 3 right panel).

Univariate analysis, but not multivariate analysis revealed that nursing care facility residency significantly influenced long-term survival ($p < 0.001$; Fig. 2, Table 2).

Comorbidities

For patients discharged from the hospital after completing antibiotic therapy, decreased long-term survival was associated with malignancy ($p < 0.001$), dementia ($p < 0.001$), chronic heart disease ($p < 0.05$), and neuromuscular disease ($p < 0.01$), based on the univariate model (Fig. 4, Table 2). Multivariate analysis revealed that only malignancy ($p < 0.001$) was an independent factor for decreased long-term survival after hospitalization for pneumonia (Table 2). The survival curves for patients with and without chronic respiratory disease intersected but there

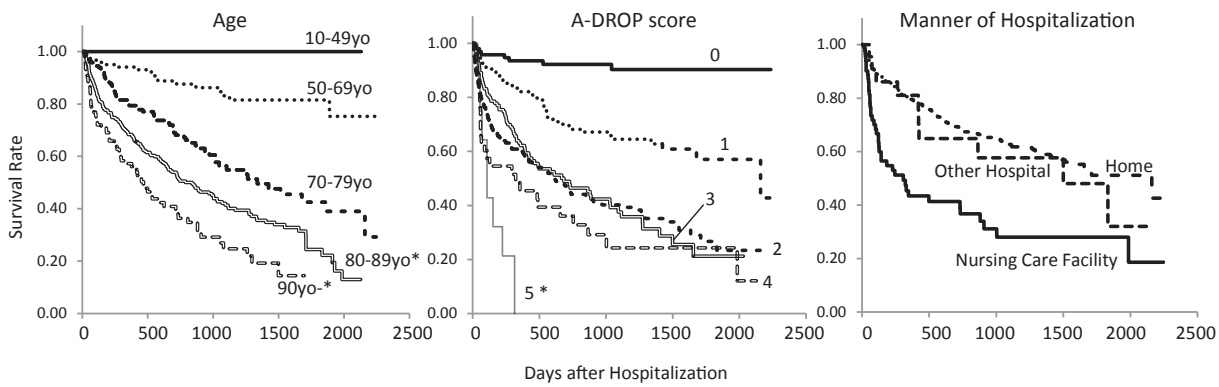

Fig. 2. Effect of age, pneumonia severity, and nursing home residency on long-term survival after pneumonia.
The effect of age, pneumonia severity (A-DROP score), and the manner of hospitalization on long-term survival after hospitalization in pneumonia patients, who completed antibiotic-treatment and were discharged, was studied. Survival decreases with increasing age and with increasing pneumonia severity. A significant decrease in long-term survival was observed in the patients aged 80 years or older compared to patients aged 10~49 years old ($p < 0.05$), and in those with an A-DROP score of 5 compared to those with a score of 0 ($p < 0.05$) with multivariate analysis. Patients transferred from nursing facilities also exhibit decreased long-term survival compared to those who came from their own home, but it was significant only with univariate analysis, not with multivariate analysis.

Table 2. Multivariate Cox proportional hazard model for survival time of the pneumonia patients discharged from hospital.

Prognostic factors		Number of patients	Number of dead patients	1,000 days survival % Kaplan-Meier estimate	Univariate model			Multivariate initial model			Multivariate final model Backward elimination with P < 0.05		
					HR	95% C.I.	P value [for varialble] for category	HR	95% C.I.	P value [for varialble] for category	HR	95% C.I.	P value [for varialble] for category
Total		958	324	55.9%	–	–	–	–	–	–	–	–	–
Age	10-49	53	1	96.8%	Reference	–	[< 0.001***]	Reference	–	[< 0.001***]	Reference	–	[< 0.001***]
	50-69	159	21	85.0%	6.0	(0.8, 44.1)	0.081	5.0	(0.67, 37.7)	0.116	4.7	(0.63, 35.4)	0.131
	70-79	231	76	58.6%	19.1	(2.6, 137.2)	0.003**	6.1	(0.84, 45.2)	0.075	5.6	(0.76, 41.0)	0.092
	80-89	381	162	45.1%	30.3	(4.2, 216.0)	< 0.001***	8.9	(1.22, 65.1)	0.031*	8.5	(1.17, 62.5)	0.035*
	> 90	134	64	26.4%	49.1	(6.8, 353.6)	< 0.001***	12.0	(1.62, 89.1)	0.015*	10.9	(1.48, 80.9)	0.019*
A-DROP score	0	119	6	94.2%	Reference	–	[< 0.001***]	Reference	–	[0.010*]	Reference	–	[0.011*]
	1	196	36	73.5%	4.3	(1.8, 10.3)	< 0.001***	0.86	(0.32, 2.27)	0.754	0.82	(0.32, 2.15)	0.693
	2	239	83	51.4%	9.9	(4.3, 22.7)	< 0.001***	1.46	(0.56, 3.80)	0.443	1.42	(0.55, 3.66)	0.468
	3	163	64	44.7%	13.0	(5.6, 30.2)	< 0.001***	1.50	(0.56, 4.01)	0.42	1.40	(0.53, 3.67)	0.498
	4	55	21	36.8%	18.3	(7.4, 45.5)	< 0.001***	1.89	(0.66, 5.39)	0.232	1.80	(0.64, 5.02)	0.265
	5	12	5	–	40.9	(12.3, 135.6)	< 0.001***	4.71	(1.25, 17.71)	0.022*	4.39	(1.19, 16.2)	0.027*
PS	0	116	1	98.4%	Reference	–	[< 0.001***]	Reference	–	[< 0.001***]	Reference	–	[< 0.001***]
	1	134	20	82.1%	17.2	(2.3, 128.0)	0.005**	9.1	(1.16, 71.5)	0.036*	8.9	(1.13, 69.6)	0.038*
	2	194	58	65.4%	41.3	(5.7, 298.4)	< 0.001***	17.2	(2.2, 134.2)	0.007**	16.3	(2.09, 126.5)	0.008**
	3	95	33	46.1%	75.0	(10.3, 548.8)	< 0.001***	29.5	(3.7, 234.2)	0.001**	28.0	(3.55, 220.6)	0.002**
	4	246	103	29.0%	114.9	(16.0, 823.3)	< 0.001***	43.3	(5.5, 341.9)	< 0.001***	41.8	(5.37, 324.6)	< 0.001***
Manner of Hospitalization	Home	623	162	65.8%	Reference	–	[< 0.001***]	Reference	–	[0.139]			
	Nursing	132	42	31.8%	2.95	(2.10, 4.15)	< 0.001***	1.17	(0.78, 1.74)	0.445			
	Hospital	32	10	57.6%	1.27	(0.67, 2.40)	0.471	0.75	(0.38, 1.49)	0.416			
Resistant Bacteria	no	546	162	59.6%	Reference	–	[0.004**]	Reference	–	[0.024*]	Reference	–	[0.030*]
	yes	62	32	23.1%	2.17	(1.25, 3.78)	0.006**	2.03	(1.15, 3.59)	0.014*	1.94	(1.11, 3.38)	0.020*
Malignancy	no	762	242	58.4%	Reference	–	[0.002**]	Reference	–	[< 0.001***]	Reference	–	[< 0.001***]
	yes	195	82	45.2%	1.58	(1.23, 2.02)	< 0.001***	1.67	(1.28, 2.18)	< 0.001***	1.64	(1.27, 2.13)	< 0.001***
Demenitia	no	756	239	59.5%	Reference	–	[< 0.001***]	Reference	–	[0.899]			
	yes	200	85	38.9%	1.92	(1.50, 2.46)	< 0.001***	1.07	(0.80, 1.43)	0.646			
Lung disease	no	689	218	54.4%	Reference	–	[0.984]	Reference	–	[0.679]			
	yes	268	106	59.0%	0.98	(0.78, 1.24)	0.862	0.89	(0.70, 1.15)	0.379			
Neuromuscular disease	no	693	225	58.6%	Reference	–	[0.035*]	Reference	–	[0.542]			
	yes	264	99	48.1%	1.37	(1.08, 1.73)	0.010**	0.92	(0.71, 1.20)	0.542			
Heart disease	no	715	228	58.4%	Reference	–	[0.117]	Reference	–	[0.442]			
	yes	221	89	46.7%	1.30	(1.01, 1.66)	0.039*	0.87	(0.67, 1.13)	0.301			
Renal disease	no	928	309	56.1%	Reference	–	[0.609]	Reference	–	[0.037*]			
	yes	28	15	47.1%	1.30	(0.78, 2.19)	0.319	1.77	(1.04, 3.01)	0.037*			
Diabetes	no	827	287	54.1%	Reference	–	[0.176]	Reference	–	[0.145]			
	yes	130	37	66.3%	0.72	(0.51, 1.02)	0.062	0.76	(0.53, 1.10)	0.145			
Collagen disease	no	925	313	55.6%	Reference	–	[0.813]	Reference	–	[0.685]			
	yes	32	11	59.7%	0.82	(0.45, 1.50)	0.520	0.87	(0.45, 1.68)	0.685			

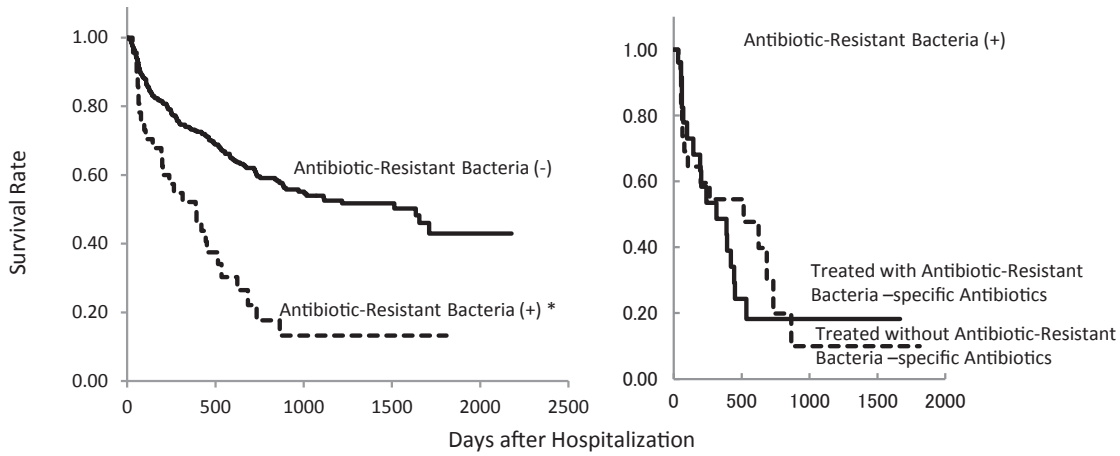

Fig. 3. Effect of antibiotic-resistant bacteria burden on long-term survival after pneumonia.
The effect of carrying antibiotic-resistant bacteria on long-term survival after hospitalization in pneumonia patients, who completed antibiotic-treatment and were discharged, was studied. A significant decrease in long-term survival was observed in patients carrying antibiotic-resistant bacteria (n = 62) compared to those without antibiotic-resistant bacteria (n = 546) (left panel, p = 0.02). However, in the patients carrying antibiotic-resistant bacteria, treatment with antibiotics specified for the treatment of antibiotic-resistant bacteria (n = 29) did not improve the long-term survival (patients carrying antibiotic-resistant bacteria treated without antibiotic-resistant-bacteria specific antibiotics: n = 33) (right panel, p = 0.603).

was no significant difference between the two curves (p = 0.86; Fig. 4). Diabetes mellitus tended to improve the survival curve, although this trend was not significant (p = 0.06; Fig. 4). Rheumatoid arthritis and other vascular collagen diseases showed no impact on long-term survival (p = 0.51). The populations of patients with chronic liver disease or bone fractures were too small; therefore, their survival curves were not assessed.

Discussion

The present results reveal detailed risk factors for poor long-term prognosis; impaired physical activity, an age of over 80 years, very severe pneumonia status at admission; an A-DROP score of 5, the carrying of antibiotic-resistant bacteria, and comorbid malignancy. Among them, physical activity (ECOG PS) was the most prominent factor for poor long-term prognosis after pneumonia. This tendency is different from that of the acute phase mortality; in which pneumonia severity (A-DROP score) was the most prominent factor (Table 2). There was a graded association between the long-term survival and ECOG PS, and in all levels of disability; PS 1 to PS 4, a significant decrease in long-term survival was observed. Furthermore, approximately 40% of patients with PS 1 at hospitalization, and 90% of those with PS 4 die within 5 years of hospitalization. The data shows the possibility that improving and maintaining physical activity to a better degree is important for increasing survival long-term after pneumonia, and this strategy is consistent with that of non-communicable diseases, such as cardiovascular disease, diabetes and chronic respiratory diseases (WHO, World Health Organization 2014). Age, under 80, and nursing care facility residency, which are the indicators of CAP and NHCAP in JRS guidelines, respectively, were not risk factors for both acute phase and long-term mortality in this study. If patients were treated following the JRS's CAP guidelines, these factors are not as important as the patient's disability status.

In the JRS guidelines for NHCAP, pneumonia in disabled patients with an ECOG PS of ≥ 3 is of special concern (Kohno et al. 2013). However, in this study, long-term survival was decreased in patients with less severe disability; PS 1, and long-term survival gradually decreased as the severity of disability increased. It may be difficult to differentiate between NHCAP and CAP by PS if the JRS guidelines aim to improve long-term survival after pneumonia. Teramoto et al. (2008) observed aspiration pneumonia, which is a result of senile deterioration and consists mostly of NHCAP, in patients as young as 50 years of age. They also found that the prevalence of aspiration pneumonia increases with age, accounting for more than 60% of CAP cases. Their results indicate that adult pneumonia develops as a component of senile deterioration in a large proportion of patients from a very young age. Both from the view of disability status and pathogenesis, the boundary between CAP and NHCAP seems indistinct.

Carrying antibiotic-resistant bacteria was an independent risk factor of long-term mortality of pneumonia in this study. However, these antibiotic-resistant bacteria seem to colonize patients' airways rather than pathogenic bacteria for the development of pneumonia, because both acute phase and long-term mortality were not improved by the use of antibiotics specified for the treatment of antibiotic-resistant bacteria. The first guidelines on healthcare-associated pneumonia (HCAP) released by the American Thoracic Society were a treatment strategy for the

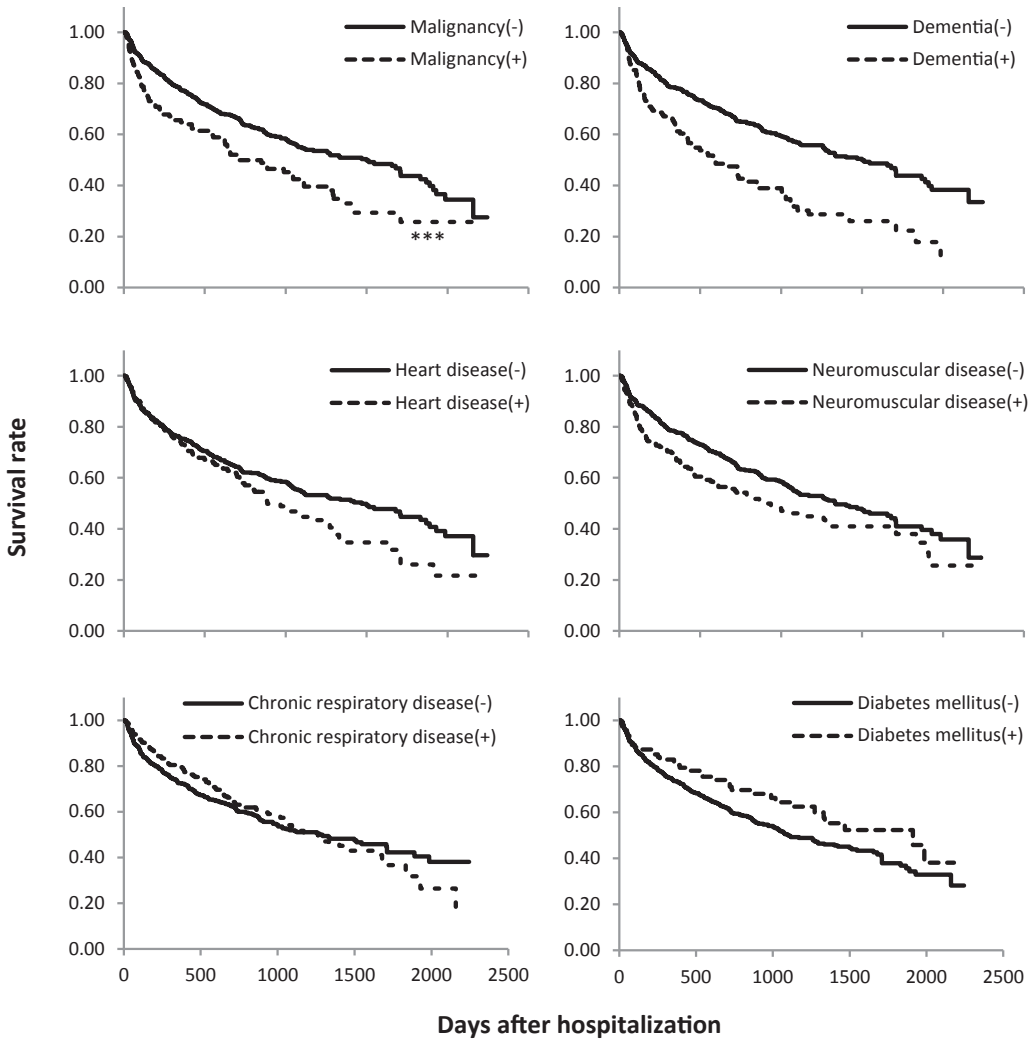

Fig. 4. Effect of comorbidities on long-term survival after pneumonia.
The survival curves illustrate the effect of various chronic comorbidities on long-term survival after pneumonia in hospital-discharged patients. Among the comorbidities, malignancy was the only independent risk factor of long-term survival after pneumonia when compared with multivariate analysis ($p < 0.001$). The effects of dementia ($p < 0.001$), heart disease ($p < 0.05$), and neuromuscular disease ($p < 0.01$) on long-term survival were observed only with univariate analysis. The presence of respiratory disease or diabetes mellitus does not appear to affect long-term survival after pneumonia.

pneumonia patient group with a high prevalence of antibiotic-resistant bacteria aiming at the use of specified antibiotics for these bacteria for a better outcome (American Thoracic Society 2005). However, recent studies indicated the presence of these antibiotic-resistant bacteria is not related to the decreased mortality in HCAP and NHCAP patients (Polverino et al. 2013; Fukuyama et al. 2013). Our results support these reports that antibiotic-resistant bacteria are not pathogenic factors for the development of pneumonia but are reflecting patients' background conditions. In this study, we could not come to specify the background factor(s) influencing the decreased mortality related to the presence of antibiotic-resistant bacteria; it may be different from the factors analyzed in this study.

Among the comorbidities studied in this report, malignancy was the only independent risk factor for long-term survival after pneumonia. The effects of other comorbidities such as dementia, neuromuscular disease, and chronic heart disease on long-term survival were only detected by univariate analysis. Most chronic diseases develop slowly and progressively as a manifestation of senescence in the presence of multiple risk factors, such as raised blood pressure, obesity, hyperglycemia, and smoking; and then, cause various levels of disability (WHO 2014). Thus, it may be difficult to differentiate them as independent risk factors in multivariate analyses in the presence of age and disability as factors. In other words, in combination with patient age and the degree of disability, these factors are important predictors of long-term mortality.

Among chronic diseases, dementia is the most prominent risk factor of long-term pneumonia prognosis in this study, although it was not an independent factor of

long-term survival. Dementia is the most common cause of disability (Agüero-Torres et al. 1998; Yoshida et al. 2012). Further, it is an age-related chronic disease, and the number of patients with dementia is expected to increase with the age of the worldwide population (Alzheimer's Disease International 2009). Therefore, the prevention and treatment of dementia are important for improving survival after pneumonia. Several factors, including poor childhood education, hypertension, smoking, and diabetes mellitus, are known risk factors for developing dementia in old age. It may be difficult to prevent the development of dementia, as sometimes, a change in lifestyle from childhood is required to prevent the development of dementia (Prince et al. 2014). Cholinesterase inhibitors and other dementia medications may also be candidates for relatively short-term improvement of survival after pneumonia or prevention of pneumonia, although the long-term effects of these medications for dementia treatment have not been definitively proven (Hansen et al. 2008).

Even after controlling for the aforementioned chronic comorbidities, pneumonia can occur in older individuals and lead to mortality, despite treatment with appropriate medications. As explained in the NHCAP guidelines, it is important to determine whether the patient has end-of-life pneumonia because treatment in an acute care hospital is often painful, particularly for older patients. Further, even if they could survive the end-of-life pneumonia, their quality of life would be largely deteriorated in most cases. However, in the present study, it was difficult to discern whether the patients had end-of-life pneumonia because the survival curves gradually decreased with increasing disability and age. The presence of comorbidities and confinement to bed before pneumonia develops may help families and attending physicians, who know the patient well, in deciding whether the pneumonia is occurring at the end of life. Notably, several family physicians cite "death from senile deterioration" as the reason for death in older patients who succumb to aspiration pneumonia (Komiya et al. 2013). However, this diagnosis is difficult to determine in acute care settings because a patient's condition on initial presentation to an acute care hospital is usually deteriorated and does not represent the patient's long-term daily condition. Several biomarkers have been proposed as prognostic indicators for the general population, although they are unrelated to pneumonia (Fischer et al. 2014). If these biomarkers are proven as good prognostic predictors of pneumonia, then they may help in deciding the treatment for such patients. Until then, we should persistently ask patients and their families about their disability status before the development of pneumonia for the assessment of patients' long-term prognoses and to be able to provide better advice.

Although this was a retrospective study including one hospital in a rural area of Japan, which is a super-aged society, it has some strength. First, the treatment plan for pneumonia was not affected by the retrospective study design. Second, patients were treated and cared for in the same manner in a single hospital. However, lifestyles can differ substantially among patients, even within a single country. Medical and nursing care also affects the prognosis after hospital discharge, and the density of available care can differ among various populations such as rural or urban populations, or according to geographical location. A comprehensive prospective study with a larger patient population is required to confirm our results.

In conclusion, we have identified several predictors of decreased long-term survival after hospitalization for pneumonia in a super-aged society. These data suggest the targets for improving long-term survival after hospitalization for pneumonia, and may assist in making decisions regarding the treatment of patients in nursing or long-term care facilities during or before they develop pneumonia. This was a retrospective study that involved a single hospital in a rural area of northern Japan. Therefore, additional prospective studies with larger patient samples are required to confirm the results.

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Conflict of Interest

The authors declare no conflict of interest.

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