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ORIGINAL ARTICLE

Disease Burden and Risk Factors of Hospital-acquired Pneumonia Requiring Mechanical Ventilation in Japan：A Retrospective Claims Database Study

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Abstract

Background：Hospital-acquired pneumonia（HAP）includes two subgroups：HAP-with-ventilation（patients with mechanical ventilation）and HAP-without-ventilation（patients without mechanical ventilation）. This study analyzed demographic characteristics, comorbidities, mortality rates, and risk factors between these groups in Japan.

Methods：A retrospective study using Japan's Medical Data Vision database analyzed data between April 2015 and May 2018. Patients were categorized into HAP-with-ventilation and HAP-without-ventilation groups, with a subgroup of HAP-with-ventilation with intubation patients also analyzed. Descriptive statistics examined baseline, demographic, and clinical characteristics, while the Cox proportional hazard model assessed risk factors and clinical outcomes.

Results：Among 2,061 HAP patients, 1,339 were HAP-with-ventilation and 722 were HAP-without-ventilation. Within the HAP-with-ventilation group, 148（11.1%）were intubated. Most HAP（both HAP-without-ventilation and HAP-with-ventilation）patients（>80%）were aged >65 years and predominantly male（65.2% to 74.3%）. The 30-

Key words：pneumonia, nosocomial infection, hospital-acquired pneumonia, hospital-acquired pneumonia patients with ventilation, hospital-acquired pneumonia patients without ventilation

day post-discharge mortality rates were highest in the HAP-with-ventilation with intubation group（17.6%）, followed by the HAP-with-ventilation（10.7%）and HAP-without-ventilation groups（2.9%）. The HAP-without-ventilation group（26.5%）had higher rehospitalization rates（within 30 days）compared to the HAP-with-ventilation（16.4%）and HAP-with-ventilation with intubation groups（14.9%）. Independent risk factors included older age（>85 years）for HAP-with-ventilation（hazards ratio［HR：1.24］, p＝0.040）and a history of hospitalization in the 90-day pre-index period for in-hospital mortality in HAP-with-ventilation patients（HR：1.91, p＜0.001）.

Conclusions：HAP-with-ventilation is a significant health concern in Japan. However, more epidemiological data are required for its inclusion in Japanese Respiratory Society guidelines. Clinicians must carefully consider the concept of HAP-with-ventilation in their daily practice while treating HAP patients.

Introduction

In Japan, pneumonia had a high mortality rate of 77.7 per 100,000 people in 2017[1)2)]. It is the most prevalent nosocomial infection in Japanese hospitals, accounting for over 50% of nosocomial infections[3)]. Globally, nosocomial pneumonia, including hospital-acquired pneumonia（HAP）and ventilator-associated pneumonia（VAP）, is the second most common nosocomial infection after urinary tract infections, with a mortality rate of 30-70% across all age groups[4)5)]. HAP refers to pneumonia after 48 hours of hospital admission, which may be independent of HAP patients without mechanical ventilation and is classified as HAP-without-ventilation[6)]. However, if HAP-without-ventilation patients need mechanical ventilation as a result of increased clinical severity and respiratory failure, it is then further classified as hospital-acquired pneumonia with ventilation（HAP-with-ventilation）[7)8)].

Risk factors for HAP or VAP include serious comorbidities, older age, chronic obstructive pulmonary disease, hospitalization for ≥5 days, and recent surgery[9)]. Continuous mechanical ventilation increases the risk of HAP 6-21 times compared to non-use[10)].

Japan's nationwide representative antimicrobial resistance（AMR）surveillance data informs evidence-based interventions[11)]. Specific AMR bacteria, including methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *Pseudomonas aeruginosa*, vancomycin-resistant *enterococci*, multidrug-resistant *Acinetobacter* sp., and carbapenem-resistant *Enterobacterales*, impact intervention strategies[11)]. The surge in AMR infections complicates nosocomial pneumonia management[12)]. The Japanese Association for Infectious Diseases and the Japanese Society of Chemotherapy diagnose nosocomial pneumonia based on fever, abnormal leukocyte count, purulent secretions, and new pulmonary infiltrate on chest radiography[13)]. Initiation of empirical antimicrobial therapy promptly upon HAP diagnosis or suspicion is recommended[13)].

The incidence of HAP/VAP varies based on the study population, location, and diagnostic criteria[8)]. A multistate point-

prevalence survey using National Healthcare Safety Network criteria found that HAP-without-ventilation and VAP accounted for 21.8% of all hospital-acquired infections (HAIs) in 2011, equivalent to 157,000 infections, with 60.9% classified as HAP-without-ventilation[14)15)]. In Japan, the HAP incidence was estimated to be 6.5 cases per 1,000 patient-days[3)]. In Asia, HAP incidence varies from 1 to 21 per 1,000 hospital admissions[16)]. Globally, HAP incidence ranges from 5 to 20 cases per 1,000 hospital admissions and 2.5 to 6.1 cases per 1,000 non-ICU patients[17)18)].

HAP, as per Japanese Respiratory Society (JRS) guidelines, can range from mild to severe pneumonia cases during hospitalization in Japan, including acute care, general care, and long-term care units[19)20)]. In countries outside Japan, where US clinical practice guidelines (Infectious Disease Society of America [IDSA], American Thoracic Society [ATS]) are followed, hospitalization occurs only in acute care units. Consequently, patients are often admitted in a more critical condition, resulting in a higher incidence of VAP compared to Japan[5)21)].

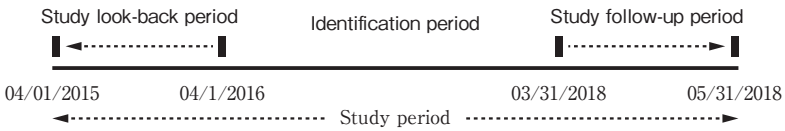
Recent studies categorizing HAP into HAP-without-ventilation and HAP-with-ventilation groups are scarce. These studies show higher 28-day all-cause mortality in the HAP-with-ventilation group, followed by the VAP and HAP-without-ventilation groups[8)22)23)]. In Japan, a few epidemiological studies of HAP have been conducted, including a multicenter clinical surveillance study of 1,356 patients[24)], a post-marketing surveillance study of meropenem with 1,400 patients[25)], and a study that investigated patients who developed HAP during hospitalization[26)]. However, none of these studies included HAP patients with mechanical ventilation (HAP-with-ventilation). Our previous study found that 9.1% of HAP patients required mechanical ventilation, with an overall mortality rate of 23.0%[27)]. The choice to ventilate and intubate a HAP patient varies based on clinical judgement and healthcare settings across different countries[28)]. Identifying HAP-with-ventilation patients is crucial for disease monitoring, investigation, and addressing nosocomial pneumonia challenges[8)].

The definition, categorization, prognosis, and treatment of the HAP-with-ventilation group need thorough validation in Japanese clinical settings due to a paucity of studies. This study evaluated patient characteristics and clinical outcomes, including mortality and rehospitalization and their risk factors, in the HAP-with-ventilation versus the non-VAP group in Japan using large-scale patient medical data. Since our focus is on HAP-with-ventilation, VAP patients are not included in this study.

I Methods

1. Study design, period, and data sources

This retrospective observational cohort study of HAP was conducted using data collected from the Medical Data Vision (MDV) database of Japan[29)], between 01 April 2015 and 31 May 2018 (**Figure 1**). The MDV database contains anonymized claims data from approximately 359 acute care hospitals. Until May 2018, the MDV database covered approximately 23.5 million patients, including patient demographics, clinical characteristics, and diagnoses (International Classification of Diseases, 10th revision [ICD-10] codes), treatment procedures, drugs prescribed,



Study design. Briefly, this retrospective observational cohort study of HAP was conducted using data collected from the MDV database of Japan, between 01 April 2015 and 31 May 2018. All patients included in this study were continuously enrolled for at least one year before the index period and one month following the index date. Further, this study included a 12-month look-back period and a follow-up period of at least two months.

Abbreviations：HAP, hospital-acquired pneumonia；MDV, Medical Data Vision

Figure 1 Study design

prescription dates, dosages, supply duration, hospital stay duration, admission reasons, the most resource-consuming diagnosis during hospitalization, and inpatient complications.

2. Inclusion criteria

The patients included in this study either had a confirmed pneumonia diagnosis (ICD-10 J13.x to J18.x) during the study period or experienced one HAP episode during identification. The patients included in this study were enrolled continuously for at least one year before the index period and one month following the index date, regardless of whether they died within one month following the index date. Further, this study included a 12-month look-back period and a follow-up period of at least two months.

3. Exclusion criteria

Patients without reported HAP episodes at age of ≥18 years during identification or those not meeting inclusion criteria were excluded from this study.

4. Definitions of HAP groups in this study

1) Hospital-acquired pneumonia (HAP)

The HAP definition relied on ICD codes[27], as the MDV database lacked images, lab results, or narrative descriptions of diagnoses or patient issues. The criteria for HAP included：1) hospitalizations with at least one diagnosis record of ICD-10 code pneumonia (J13.x to J18.x)；2) the reason for hospitalization was not ICD-10 codes J13.x to J18.x and J95；3) exclusion of hospitalizations in long-term care units (to Nursing and Healthcare Associated Pneumonia：NHCAP)；4) identification of the most resource-consuming disease or complication as pneumonia；5) no prescription record of injection antibiotics during the first three days of admission；and 6) at least one prescription record of injection antibiotics for five consecutive days, using the same antibiotics for three days. The database lacked essential information for diagnosing HAP, relying solely on ICD codes due to the absence of images and lab results.

2) Ventilated hospital-acquired pneumonia (HAP-with-ventilation)

HAP-with-ventilation patients were identified as HAP patients with at least one record of injection antibiotic prescriptions 1 day before to 2 days after mechanical ventilation (including nasal mask ventilation,

intubated ventilation, or other mechanical ventilation）during hospitalization. In claims data, VAP cannot be clinically adjudicated or confirmed；therefore, VAP was not identified as a distinct entity in this study. As a result, some misclassification between VAP and HAP-with-ventilation cannot be fully ruled out.

3）Ventilated hospital-acquired pneumonia with intubation（HAP-with-ventilation with intubation）

HAP-with-ventilation patients with intubation were identified as those who were intubated during hospitalization.

4）Non-ventilated hospital-acquired pneumonia（HAP-without-ventilation）

HAP-without-ventilation patients were identified as HAP patients who did not meet the HAP-with-ventilation definition.

5. Ethical approval

The study adhered to the Declaration of Helsinki and received approval by the Institutional Ethical Review Board at Kitamachi Clinic（Institutional Ethics Review Board No. MSD08457）on November 17, 2021. Informed consent was unnecessary, as the study utilized de-identified retrospective data for statistical analyses.

6. Outcome measures, study variables, and covariates

The study assessed in-hospital mortality, 30-day post-discharge mortality, and rehospitalization within 30 days. Baseline characteristics encompassed age, gender, hospitalization history, comorbidities, Charlson Comorbidity Index（CCI）in its Dayo adaptation, and hospital size（small：<199 beds, medium：<499 beds, and large：>500 beds). Additionally, clinical characteristics such as sepsis diagnosis, time to onset of HAP-with-ventilation and HAP-without-ventilation, and covariates like mechanical ventilation induction time were considered.

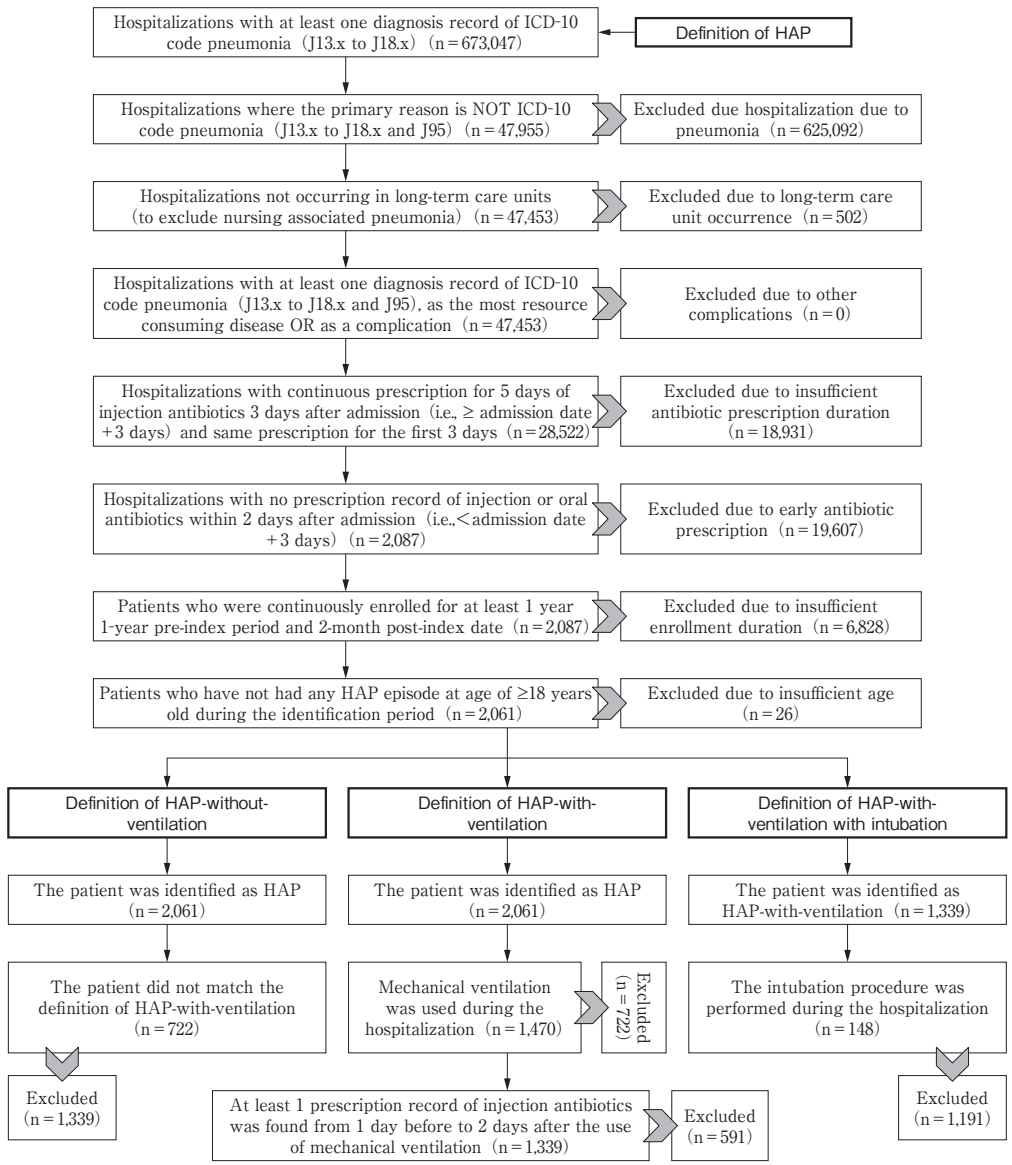
7. Statistical analysis

Baseline, demographic, and clinical characteristics were analyzed using descriptive statistics. Continuous measures were medians（with interquartile ranges［IQRs］), while categorical variables were presented as frequencies and percentages. Cox proportional hazard analysis（models 1, 2, and 3）examined risk factors, clinical outcomes（in-hospital mortality and rehospitalization), and mortality differences between the HAP-with-ventilation and HAP-without-ventilation groups. Cox proportional model 1 was conducted without adjustments, while Cox proportional model 2 considered age, gender, history of pneumonia, history of hospitalization, CCI category, and previous medications. Cox proportional model 3 considered age and gender only. The results of the Cox hazard analyses were presented as hazard ratios（HRs）with 95% confidence intervals（CIs). P-values were reported wherever applicable. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant. The latest version of SAS statistical software（version 9.2）was used for all data analyses.

Ⅱ Results

1. Patient attrition

During the study period of 01 April 2015 to 31 May 2018 in the MVD database, 2,061 patients had HAP；among them：722 were HAP-without-ventilation patients, 1,339 were HAP-with-ventilation patients, and 148 HAP-with-ventilation patients（11.1%）underwent intubation（**Figure 2**）.



Schematic representation of patient attrition. Of the 2,061 patients who had HAP during the study period (01 April 2015 to 31 May 2018) in the MDV database, 722 and 1,339 were identified as HAP-without-ventilation and HAP-with-ventilation patients, respectively. Of the 1,339 HAP-with-ventilation patients, 148 were intubated during hospitalization (HAP-with-ventilation with intubation).

Abbreviations : ICD, International Classification of Diseases ; HAP, hospital-acquired pneumonia ; MDV, Medical Data Vision ; HAP-without-ventilation, non-ventilated hospital-acquired pneumonia ; HAP-with-ventilation, ventilated hospital-acquired pneumonia

Figure 2 Schematic representation of patient attrition

2. Baseline demographics and clinical characteristics

The median (IQR) age of patients in the HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups was 78 (70-85), 79 (72-85), and 75 (66-80) years, respectively. In this study, the male patient population was predominant (494 [68.4%], 873 [65.2%], and 110 [74.3%] in the HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups, respectively). Patients who reported all-cause hospitalization during the 90 days before the index period were 212 (29.4%), 368 (27.5%), and 44 (29.7%) in the HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups, respectively (**Table 1**).

3. Comorbidities

Congestive heart failure was the most common comorbidity in the HAP-with-ventilation and HAP-with-ventilation with intubation groups (669 [50.0%] and 80 [54.1%], respectively). The HAP-without-ventilation group recorded cancer (366 [50.7%]) as the most common comorbidity, followed by congestive heart failure (261 [36.2%]) and cerebrovascular disease (259 [35.9%]). The other most common comorbidities among HAP-with-ventilation patients were cancer and cerebrovascular disease (525 [39.2%] and 485 [36.2%], respectively). In the HAP-with-ventilation with intubation group, cerebrovascular disease (55 [37.2%]) and peptic ulcer disease (44 [29.7%]) were common, besides congestive heart failure (**Table 1**).

4. Charlson Comorbidity Index (CCI)

The mean (S.D.) CCI scores in the HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups were 4.94 (3.18), 4.65 (3.04), and 3.77 (2.68), respectively. CCI scores ≥5 were noted in 333 (46.1%), 579 (43.2%), and 43 (29.1%) patients in the HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups, respectively (**Table 1**).

5. Previous medication use

Regarding previous medications, proton-pump inhibitors (PPIs) were used by a high proportion of the patients in all three groups (377 [52.2%], 798 [59.6%], and 108 [73.0%] in the HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups, respectively). Among the HAP-with-ventilation and HAP-with-ventilation with intubation groups, injection antibiotics were the second most used previous medication (419 [31.3%] and 64 [43.2%], respectively). Steroids were the second most used previous medication in the HAP-without-ventilation group (231 [32.0%]) (**Table 1**).

6. Mortality and rehospitalization events in HAP-with-ventilation vs. HAP-without-ventilation

30-day post-discharge mortality was significantly higher in the HAP-with-ventilation group (n＝143；10.7%) compared with the HAP-without-ventilation group (n＝21；2.9%；$p<0.001$). In the HAP-with-ventilation with intubation group, the mortality rate was 17.6% (n＝26). With regard to risk factor analysis for 30-day post-discharge mortality (HAP-with-ventilation versus HAP-without-ventilation patients), Cox proportional models 1, 2, and 3 had HR (95% CI) values of 3.44 (2.23, 5.59), 3.00 (1.94, 4.88), and 3.51 (2.27, 5.71), respectively, $p<0.001$ for all models

Table 1 Baseline demographic and clinical characteristics of study population

Patient characteristics		HAP-without-ventilation (n = 722)	HAP-with-ventilation (n = 1,339)	HAP-with-ventilation with intubation† (n = 148)
Age	Median age, years (IQR)	78 (70-85)	79 (72-85)	75 (66-80)
	18-64, n (%)	83 (11.5)	140 (10.5)	27 (18.2)
	65-74, n (%)	188 (26.0)	317 (23.7)	46 (31.1)
	75-84, n (%)	255 (35.3)	514 (38.4)	60 (40.5)
	≥85, n (%)	196 (27.2)	368 (27.5)	15 (10.1)
Gender, n (%)	Male	494 (68.4)	873 (65.2)	110 (74.3)
Hospital size, n (%)	Small	60 (8.3)	99 (7.4)	5 (3.4)
	Medium	427 (59.1)	798 (59.6)	84 (56.8)
	Large	235 (32.6)	442 (33.0)	59 (39.9)
History of all-cause hospitalization (90 days pre-index), n (%)	Yes	212 (29.4)	368 (27.5)	44 (29.7)
	No	510 (70.6)	971 (72.5)	104 (70.3)
Comorbidities (12 months pre-index), n (%)	Myocardial infarction	46 (6.4)	134 (10.0)	19 (12.8)
	Congestive heart failure	261 (36.2)	669 (50.0)	80 (54.1)
	Peripheral vascular disease	112 (15.5)	247 (18.5)	34 (23.0)
	Cerebrovascular disease	259 (35.9)	485 (36.2)	55 (37.2)
	Dementia	93 (12.9)	148 (11.1)	7 (4.7)
	Chronic pulmonary disease	235 (32.6)	455 (34.0)	38 (25.7)
	Rheumatic disease	47 (6.5)	73 (5.5)	6 (4.1)
	Peptic ulcer disease	250 (34.6)	437 (32.6)	44 (29.7)
	Mild liver disease	163 (22.6)	239 (17.9)	22 (14.9)
	Diabetes without chronic complication	150 (20.8)	309 (23.1)	33 (22.3)
	Diabetes with chronic complication	71 (9.8)	181 (13.5)	17 (11.5)
	Hemiplegia or paraplegia	34 (4.7)	49 (3.7)	3 (2.0)
	Renal disease	127 (17.6)	301 (22.5)	27 (18.2)
	Any malignancy*1	366 (50.7)	525 (39.2)	39 (26.4)
	Moderate or severe liver disease	14 (1.9)	31 (2.3)	2 (1.4)
	Metastatic solid tumor	117 (16.2)	138 (10.3)	7 (4.7)
	HIV/AIDS	2 (0.3)	0 (0.0)	0 (0.0)

(continued)

(continued)

Patient characteristics		HAP-without-ventilation (n＝722)	HAP-with-ventilation (n＝1,339)	HAP-with-ventilation with intubation† (n＝148)
CCI category (12 months pre-index)	0-4	389 (53.9)	760 (56.8)	105 (71.0)
	≥5	333 (46.1)	579 (43.2)	43 (29.1)
Previous medications (90 days pre-index), n (%)	Injection antibiotics	170 (23.6)	419 (31.3)	64 (43.2)
	PPI	377 (52.2)	798 (59.6)	108 (73.0)
	H2 blocker	139 (19.3)	299 (22.3)	36 (24.3)
	Steroids*	231 (32.0)	354 (26.4)	44 (29.7)

Abbreviations：HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome；CCI, Charlson Comorbidity Index；H2 blocker, histamine type 2 receptor antagonists/blockers；IQR, interquartile range；HAP-without-ventilation, non-ventilated hospital-acquired pneumonia；PPI, proton-pump inhibitor；HAP-with-ventilation, ventilated hospital-acquired pneumonia

† ：Subgroup of HAP-with-ventilation patients who required intubation
* ：Oral and intravenous steroids were included；inhaled, topical, and ophthalmic steroids were not included
*1 ：Including lymphoma and leukemia, except malignant neoplasm of skin

after adjustment（**Table 2**）.

Rehospitalization events（within 30 days）were significantly higher in the HAP-without-ventilation group（n＝191；26.5%）compared with the HAP-with-ventilation group（n＝220；16.4%；p＜0.001, without adjustment）. In the HAP-with-ventilation with intubation group, 22 patients（14.9%）were rehospitalized within 30 days（**Table 2**）. Regarding risk factor analysis for rehospitalization（HAP-with-ventilation vs. HAP-without-ventilation), all three Cox proportional models had HR（95% CI）values＜1, and p＜0.001 for all models after adjustment（**Table 2**）.

7. Assessment of risk factors for HAP-with-ventilation and in-hospital mortality in HAP-with-ventilation

Older age（≥85 years）was a significant risk factor for disease severity, leading to HAP-with-ventilation（n＝564；HR：1.24［95% CI：1.01, 1.51］；p＝0.040]). Although a few other factors（age groups of 65 to 74 and 75 to 84 years, history of hospitalization during the 90-day pre-index period, diagnosis of sepsis, and hospitals with medium and large settings）had HR values ＞1, the association with the risk of HAP-with-ventilation was not statistically significant（**Table 3**）.

The risk factors that were significantly associated with in-hospital mortality in the HAP-with-ventilation group were history of hospitalization in the 90 days before the index period（n＝368；HR：1.91［95% CI：1.33, 2.73］；p＜0.001）and CCI category ≥5（n＝579；HR：1.77［95% CI：1.26, 2.48］；p＝0.001）（**Table 3**）. Interestingly, a history of pneumonia during the 12 months pre-index period reduced the risk of in-hospital mortality in the HAP-with-ventilation group（HR：0.36［95% CI：0.25, 0.51］；p＜0.001）（**Table 3**）.

Table 2 Risk factor analyses for mortality and readmission (HAP-with-ventilation vs. HAP-without-ventilation)

Outcome variable	Cox proportion model adjustment estimation	HAP-without-ventilation (n = 722)	HAP-with-ventilation (n = 1,339)	HAP-with-ventilation with intubation† (n = 148)	HAP-with-ventilation vs. HAP-without-ventilation	
		Number of events, n (%)	Number of events, n (%)	Number of events, n (%)	HR (95% CI)	p-value**
30-day post-discharge mortality‡	without adjustment*	21 (2.9)	143 (10.7)	26 (17.6)	3.44 (2.23-5.59)	<0.001
	with adjustment (Cox proportional model 2)#	NA			3.00 (1.94-4.88)	<0.001
	with adjustment (Cox proportional model 3)$				3.51 (2.27-5.71)	<0.001
Rehospitalization within 30 days	without adjustment**	191 (26.5)	220 (16.4)	22 (14.9)	0.57 (0.47-0.70)	<0.001
	with adjustment (Cox proportional model 2)#	NA			0.58 (0.47-0.70)	<0.001
	with adjustment (Cox proportional model 3)$				0.57 (0.47-0.69)	<0.001

Abbreviations : CCI, Charlson Comorbidity Index ; CI, confidence interval ; HR, hazard ratio ; HAP-without-ventilation, non-ventilated hospital-acquired pneumonia ; HAP-with-ventilation, ventilated hospital-acquired pneumonia

* : No variables were used for this model
\# : Age, gender, history of pneumonia, history of hospitalization, CCI category, and previous medications were used for this model
$: Age and sex were used for this model
** : Statistically significant (p-value <0.05)
† : Subgroup of HAP-with-ventilation patients who required intubation
‡ : 30-day post-discharge mortality was defined as death occurring within 30 days after hospital discharge

Ⅲ Discussion

This retrospective study analyzed Japan MDV database data on HAP patients, exploring patient characteristics, clinical outcomes (mortality and rehospitalization), and risk factors for HAP-with-ventilation versus non-VAP. Most patients were ≥65 years old and male. Patients aged ≥85 years faced a higher risk of HAP-with-ventilation (HR : 1.24, p = 0.040) compared with other age groups. Approximately 11.1% of HAP-with-ventilation patients required intubation. Risk factors for in-hospital mortality in HAP-with-ventilation patients included a history of hospitalization/pneumonia and higher CCI scores.

In this study, 11.1% of HAP-with-ventilation patients required intubation. Most patients (>80%) were above 65 years old, with a

Table 3 Analyses of risk factors for HAP-with-ventilation and in-hospital mortality in HAP-with-ventilation group

Patient characteristics		Risk factors that lead to HAP-with-ventilation			In-hospital mortality in HAP-with-ventilation			
		N	HR (95% CI)	p-value	N	Events number	HR (95% CI)	p-value
Age	18-64	223	ref.	−	140	11	ref.	−
	65-74	505	1.18 (0.97-1.44)	0.106	317	34	1.15 (0.58-2.29)	0.683
	75-84	769	1.16 (0.96-1.40)	0.134	514	56	1.29 (0.67-2.47)	0.451
	≥85	564	1.24 (1.01-1.51)	0.040*	368	42	1.62 (0.83-3.16)	0.159
Gender	Male	1,367	0.97 (0.87-1.09)	0.617	873	105	1.44 (0.99-2.11)	0.056
	Female	694	ref.	−	466	38	ref.	−
History of pneumonia (12 months pre-index)	Yes	NA			1,112	94	0.36 (0.25-0.51)	<0.001*
	No	NA			227	49	ref.	−
History of hospitalization (90 days pre-index)	Yes	580	1.09 (0.96-1.24)	0.189	368	61	1.91 (1.33-2.73)	<0.001*
	No	1,481	ref.	−	971	82	ref.	−
CCI (12 months pre-index)	0-4	1,149	ref.	−	760	58	ref.	−
	≥5	912	0.85 (0.76-0.96)	0.006*	579	85	1.77 (1.26-2.48)	0.001*
Previous medications (3 months pre-index)	Yes	589	0.90 (0.80-1.02)	0.104	498	67	ref.	−
	No	1,472	ref.	−	841	76	0.88 (0.62-1.25)	0.474
Diagnosis of sepsis	Yes	134	1.02 (0.82-1.27)	0.855	NA			
	No	1,927	ref.	−	NA			
Time to onset of HAP-with-ventilation and HAP-without-ventilation (Early onset/Late onset)	Early onset	447	ref.	−	NA			
	Late onset	1,614	0	0.889	NA			
Hospital	Small	159	ref.	−	NA			
	Medium	1,225	1.12 (0.91-1.38)	0.297	NA			
	Large	677	1.16 (0.93-1.46)	0.184	NA			

Abbreviations：CCI, Charlson Comorbidity Index；CI, confidence interval；HR, hazard ratio；NA, not applicable；ref., reference；HAP-with-ventilation, ventilated hospital-acquired pneumonia

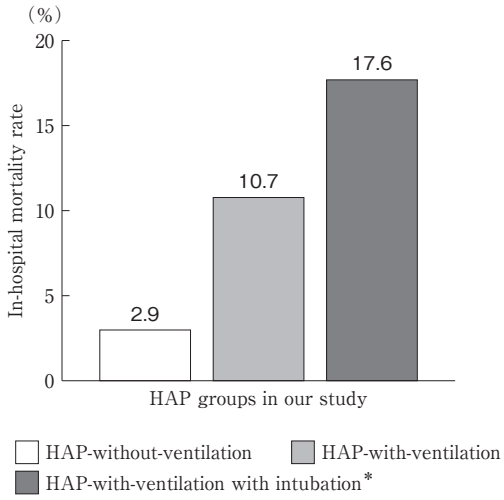
*：Statistically significant（p-value ≤0.05）

median age of 75 (66-80) to 79 (72-85). This aligns with another Japanese study where 81.0% of HAP patients fell into the 65-80 and >80 years age groups[24]. A recent Japanese study on HAP found a mean age of 77 years[27]. Japan's aging population, despite declining birth rates, is rapidly growing[30]. Consequently, the incidence of HAP is expected to increase due to the aging population and higher health care utilization[31]. In both the HAP-without-ventilation and HAP-with-ventilation groups (including HAP-with-ventilation with intubation) in this study, male patients predominated (65.2% to 74.3%), consistent with a recent observational study that found 64.9% of HAP patients were male[27]. A separate Japanese observational study also found that 69.2% of HAP patients were male[24]. This trend may be attributed to men having a higher prevalence of risk factors like smoking, alcoholism, and toxic occupational exposure[9)32)-34)].

PPIs were the most prescribed medication in both HAP-without-ventilation and HAP-with-ventilation groups (including HAP-with-ventilation with intubation) during their 90-day pre-index period (52.2% to 73.0%). Long-term PPI use has been associated with an increased risk of HAP/VAP[35)-37)]. A mechanism likely involving suppressed gastric acid release, pH changes, and bacterial colonization, thereby increasing susceptibility to pneumonia infection[36)38)39)].

The HAP-with-ventilation and HAP-with-ventilation with intubation groups recorded congestive heart failure as the most common comorbidity (50.0% and 54.1%, respectively), compared to the HAP-without-ventilation group (36.2%) in this study. Altered alveolar mechanisms increase pneumonia risk in congestive heart failure patients[40)41)]. Additionally, cancer was the major comorbidity in the HAP-without-ventilation group (50.7%) and the second most common in the HAP-with-ventilation group (39.2%). Cancer patients' susceptibility to pneumonia is associated with immunological dysfunction, neutropenia, lung abnormalities, and malnutrition[42)43)].

In this study, in-hospital mortality varied across the HAP-without-ventilation and HAP-with-ventilation groups (including HAP-with-ventilation with intubation). The highest mortality was in the HAP-with-ventilation with intubation group (17.6%), followed by the HAP-with-ventilation (10.7%) and HAP-without-ventilation groups (2.9%) (**Figure 3**). A separate single-center study and a large retrospective cohort study from Japan reported overall mortality rates of 23.8% and 22.0% in HAP patients, respectively[21)27)]. In an Italian study, HAP-with-ventilation patients had the highest 28-day mortality rate (27.8%), followed by VAP (18.0%) and HAP-without-ventilation (14.5%) patients[8)22)]. The study attributed the varying mortality rates (HAP-without-ventilation <VAP <HAP-with-ventilation) to unknown several patient-related factors, emphasizing the need for further investigation through prospective studies[8)]. In model 3, the Cox proportional analysis revealed a 3.5-fold (HR：3.51) increase in the risk of mortality after adjusting for age and gender；consistent with previous studies linking patient characteristics like age (≥60 years) and male gender as risk factors for ventilation in HAP patients [44)]. Although we adjusted for available baseline covariates in the claims database, important indicators of acute



*: Subgroup of HAP-with-ventilation patients who required intubation

In-hospital mortality rates at the time of discharge in HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups. The highest mortality was observed in the HAP-with-ventilation with intubation group (17.6%), followed by the HAP-with-ventilation (10.7%) and HAP-without-ventilation groups (2.9%).

Abbreviations: HAP-without-ventilation, non-ventilated hospital-acquired pneumonia; HAP-with-ventilation, ventilated hospital-acquired pneumonia

Figure 3 In-hospital mortality rates in HAP-without-ventilation, HAP-with-ventilation, and HAP-with-ventilation with intubation groups

physiologic severity at the time of ventilation initiation were not available. Therefore, the reported HRs should be interpreted as prognostic associations between clinically defined groups in routine practice, and not as evidence that mechanical ventilation itself causes increased mortality. Further investigation is needed to understand how these factors predict ventilation needs and contribute to preventing or reducing HAP-with-ventilation-related morbidity and mortality.

Because initiation of mechanical ventilation is typically driven by clinical deterioration, HAP requiring mechanical ventilation should be interpreted primarily as a marker of greater underlying illness severity rather than as an independent causal exposure. Accordingly, the main contribution of this study is to quantify the real-world burden and to describe the clinical characteristics and outcomes of HAP requiring mechanical ventilation in Japan, including an intubation subgroup as a proxy for more severe respiratory failure.

Consistent with prior research, older age (>85 years) was identified as a risk factor for HAP-with-ventilation[45]. Although the cited study specifically mentions patients aged ≥80 years, the risk increases with age, including those over 85 years. Aging leads to changes in the respiratory tract and decreased immune responses, contributing to higher pneumonia rates in the elderly[46)47)]. Additionally, we found that CCI ≥5 significantly increased in-hospital mortality

risk（HR：1.77, p＝0.001）. This finding corroborates a previous study, highlighting the CCI's potential for identifying high-risk patients[48]. Our findings reaffirm that CCI scores can aid clinicians identify high-risk patients.

There are a few limitations to this study. This study used data collected approximately a decade ago, and it should be noted that critical care management has since evolved, particularly following the COVID-19 pandemic, with the broader adoption of high-flow nasal cannula oxygen therapy and immunomodulatory treatments, among other advances. The potential influence of these changes on the generalizability of the present findings warrants consideration. That said, the underlying pathophysiological mechanisms of pneumonia and the primary outcomes examined in this study are not considered to have changed substantially over this period, and the findings are considered to retain their clinical and scientific relevance. Additionally, the study used a database of reimbursement claims from Diagnosis Procedure Combination hospitals that are not specifically recorded for research purposes and may not accurately represent the general patient population in Japan. The different HAP groups were defined using the ICD-10 codes but couldn't be validated against medical records；therefore, the definition for HAP outlined by MDV did not match our definition. Furthermore, the medical claims database may not capture all patient services due to data gaps from copayment services or referrals to different providers. Residual confounding by indication is likely, because patients who require mechanical ventilation are inherently more severely ill than those who do not. In addition, the MDV claims database does not include laboratory results, vital signs, radiology findings, or validated severity scores, which limits our ability to adjust for acute clinical severity and to validate the timing and clinical certainty of HAP episodes against medical records. As a result, our findings should be interpreted as associations observed in real-world practice rather than causal effects. Because VAP cannot be clinically adjudicated in claims data, we did not identify VAP as a distinct entity in this study；therefore, some misclassification between VAP and HAP-with-ventilation cannot be fully ruled out. Finally, risk analysis for VAP was not possible due to fewer patients being recruited in Japan during the feasibility assessment. Despite the above limitations, the study reflects real-world clinical practice and treatment decisions. Moreover, MDV, the largest retrospective dataset in Japan, ensures national representativeness of the Japanese population.

As a conclusion, the study population was predominantly elderly（≥65 years）and male. Among HAP-with-ventilation patients, around 11.1% required intubation. In-hospital mortality at discharge was highest in the HAP-with-ventilation with intubation group（17.6%）, followed by the HAP-with-ventilation（10.7%）and the HAP-without-ventilation groups（2.9%）.

Older age（≥85 years）correlated with ventilation needs in HAP patients. A history of hospitalization in the 90-day pre-index period and higher CCI scores were associated with in-hospital mortality in the HAP-with-ventilation group. Additional real-world

studies are required to explore factors related to HAP-with-ventilation occurrence and understand in-hospital mortality and rehospitalization rates. Even if poorer outcomes among patients requiring mechanical ventilation are clinically expected, our Japan-specific estimates of mortality, rehospitalization, and risk profiles help quantify the burden of this subgroup and support practical risk stratification. These findings can inform future epidemiologic work and discussions on how HAP requiring mechanical ventilation should be considered in the Japanese clinical context and guideline development. Overall, this study demonstrates a greater disease burden in Japanese hospital settings for patients with HAP-with-ventilation, providing insights for HAP disease management strategies.

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Conflict of interest

Declaration of conflict of interest：Masahiro Kimata, Nobuyuki Oshima, Shohei Shinozaki, and Akiko Harada are current employees of MSD K.K., Tokyo, Japan, and hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Seok-Won Kim and Masafumi Okada declare no conflict of interests.

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原著

日本における人工呼吸管理を要する院内肺炎の疾病負荷および発症リスク因子の検討
──後ろ向き診療報酬データベース研究──

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要　旨

目的：院内肺炎（HAP）を人工呼吸管理の有無（人工呼吸管理あり群/なし群）で比較し，患者背景（併存疾患を含む），転帰およびリスク因子を検討した。

方法：診療報酬請求データベース（Medical Data Vision）を用い，2015年4月～2018年5月までのデータで後ろ向き解析を実施した。人工呼吸管理あり群，なし群，挿管サ

ブ群を設定しCox比例ハザードモデルで評価した。

結果：2,061例のうち1,339例が人工呼吸管理あり群，722例がなし群であり，人工呼吸管理あり群のうち148例（11.1%）が挿管を受けていた。いずれの群でも65歳超が80%以上を占め，男性は65.2～74.3%であった。退院後30日死亡率は挿管サブ群17.6%，人工呼吸管理あり群10.7%，なし群2.9%であり，挿管サブ群で最も高かった。退院後30日以内の再入院率は人工呼吸管理なし群26.5%で，あり群（16.4%）および挿管サブ群（14.9%）より高かった。85歳超は人工呼吸管理あり群のリスク因子であり〔ハザード比（HR）：1.24，p＝0.040〕，直近90日入院歴は人工呼吸管理あり群における入院中死亡（院内死亡）リスクと関連した（HR：1.91，p＜0.001）。

結論：人工呼吸管理を要するHAPは日本において重要な疾病負荷を示した。診療では人工呼吸管理の有無を踏まえた評価が重要であり，日本呼吸器学会（JRS）ガイドラインへの位置付けに向けてさらなる疫学的データの蓄積が望まれる。

キーワード：肺炎，院内感染，院内肺炎，人工呼吸管理下の院内肺炎患者，
非人工呼吸管理下の院内肺炎患者

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