Antimicrobial Resistance and Clinical Outcomes in Nursing Home-Acquired Pneumonia, Compared to Community-Acquired Pneumonia

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Purpose: Patients with nursing home-acquired pneumonia (NHAP) should be treated as hospital-acquired pneumonia (HAP) according to guidelines published in 2005. However, controversy still exists on whether the high mortality of NHAP results from multidrug resistant pathogens or underlying disease. We aimed to outline differences and factors contributing to mortality between NHAP and community-acquired pneumonia (CAP) patients.

Materials and Methods: We retrospectively evaluated patients aged 65 years or older with either CAP or NHAP from 2008 to 2014. Patients with healthcare-associated pneumonia other than NHAP or HAP were excluded.

Results: Among 317 patients, 212 patients had CAP and 105 had NHAP. Patients with NHAP had higher mortality, more frequently used a ventilator, and had disease of higher severity than CAP. The incidences of aspiration, tube feeding, and poor functional status were higher in NHAP. Twenty three out of 54 NHAP patients and three out of 62 CAP patients had multidrug resistant pathogens (p<0.001). Eleven patients with NHAP died at discharge, compared to 7 patients with CAP (p=0.009). However, there was no association between mortality rate and presence of multidrug-resistant pathogens. The number of involved lobes on chest X-ray [odds ratio (OR)=1.708; 95% confidence interval (CI), 1.120 to 2.605] and use of mechanical ventilation (OR=9.537; 95% CI, 1.635 to 55.632) were significantly associated with in-hospital mortality.

Conclusion: Patients with NHAP had higher mortality than patients with CAP. The excess mortality among patients with NHAP and CAP was related to disease severity but not to the presence of multidrug resistant pathogens.

Key Words: Pneumonia, nursing home, antimicrobial resistance, mortality

INTRODUCTION

The growth of older adult populations has led to increases in the number of nursing home residents globally. In 30 years, about 40% of the adults worldwide will be staying in a nursing home or long-term care facility.¹ In Korea, 12.7% of the population was older than 65 years in 2014 and this will reach about 14% in 2017.² In 2009, there were 201226 patients using nursing hospitals and 80025 in nursing homes, and these numbers increased to 296728 and 132235 people, respectively, in 2012.¹ Among the residents in long-term care facilities, the most common cause of hospitalization, morbidity, and mortality was pneumonia.³ Of potentially preventable diseases, pneumonia is the most common.³ Nursing home-acquired pneumonia (NHAP) is one form of healthcare-associated pneumonia (HCAP).⁴ In 2005, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) suggested that HCAP patients, including those with NHAP, should be tr-
evaluated with the same broad-spectrum antibiotics as hospital-
acquired pneumonia to cover multidrug resistant (MDR) pa-
thogens. However, treating NHAP and HCAP has been con-
troversial, although the mortality rate of NHAP is higher than
that of community-acquired pneumonia (CAP). The microbio-
al distributions of NHAP vary among nations, regions, study
designs, and disease severity. The British Thoracic Society gu-
idelines for CAP in 2009 mentioned nursing home residents
as a specific population group of CAP and did not recommend
specific management for NHAP, in contrast to the 2005 ATS/
IDSA guidelines. The nursing home setting has attributes that
differ from those of other health care settings in terms of pa-
tient age, comorbidities, disease severity, functional status, re-
alistic treatment goals, and aggressive disease monitoring. In
addition, it is not clear whether the increased frequency of
MDR pathogens leads to inappropriate antibiotic therapy and
higher mortality. Therefore, we conducted this study to ana-
lyze factors contributing to the mortality rates of NHAP, in
comparison to those for CAP, among elderly patients.

MATERIALS AND METHODS

Study design and patients
We retrospectively analyzed patients older than 65 years old
admitted to a single teaching hospital (600 beds) in South Ko-
rea with either CAP or NHAP from January 2008 to December
2014. Categories of HCAP other than NHAP were excluded:
hospitalization for 2 days or more in the preceding 90 days, long-
term dialysis within 30 days of entering the study, immuno-
compromised status including AIDS, active malignancy receiv-
ing chemotherapy, history of solid-organ transplantation on
immunosuppressive agents, or immunosuppressive therapy
including 10 mg prednisone/day for at least 30 days or equi-

The patients who had do-not-resuscitate (DNR) status
were excluded. We analyzed medical records for baseline char-
acteristics, orientation disturbance, functional status, the de-
gree of aspiration, comorbidities, severity, pathogen, antibiot-
ic, and clinical outcomes. This study was approved by the local
Ethics Committees of the Institutional Review Board of the
Dongguk University Hospital.

Definitions
The diagnosis of pneumonia was based on the following crite-
ia: 1) new or persistent pulmonary infiltrate and 2) two or
more symptoms and signs, including body temperature grea-
ter than 38.5°C or less than 35.5°C, leukocyte count greater
than 12000/mm³ or less than 4000/mm³, and purulent sputum.
NHAP and CAP were divided according to ATS/IDSA guide-
lines. Pneumonia severity was evaluated using CURB-65 score,
which consists of five variables: confusion of new onset, blood
urea nitrogen greater than 7 mmol/L (19 mg/dL), respiratory
rate of 30 breaths per minute or greater, blood pressure less
than 90 mm Hg systolic or diastolic blood pressure 60 mm Hg
or less, and age of 65 years or older. Patients with poor func-
tional status were defined as being bedridden or those who
used a wheelchair. Probable aspiration was defined as any wit-
nessed aspiration before hospital admission or aspiration con-
firmed by video associated swallowing test. Patients with tube
feeding were defined as the administration of liquefied foods
through a nasogastric tube or percutaneous endoscopic gas-
troscopy tube. Initial treatment failure was defined as death
during initial antibiotics treatment or change of antibiotics from
first agents to others after 48 hours due to clinical instability.

Microbiological evaluation
Respiratory samples such as sputum, endotracheal suction and
bronchoalveolar washing, blood cultures, urinary antigen test
for Streptococcus pneumonia and Legionella species, were ob-
tained and investigated. Standard serologic methods were used
to determine antibodies against atypical agents, such as My-
coplasma pneumoniae. MDR pathogens included methicillin-
resistant Staphylococcus aureus (MRSA), Pseudomonas aeru-
ginosa, extended-spectrum beta-lactamase (ESBL)-producing
Enterobacteriaceae, carbapenem resistant Acinetobacter bau-
mannii, and Stenotrophomonas maltophilia. Pseudomonas
species were included as MDR pathogens regardless of the
drug susceptibility test.

Clinical outcomes
The primary outcome was in-hospital mortality. Secondary
outcomes were length of stay and intensive care unit (ICU) stay.

Statistical analysis
All statistical analysis was performed using Statistical Package
for the Social Science ver. 12.0 (SPSS Inc., Chicago, IL, USA).
Shapiro-Wilk’s W test was performed for normality of the data.
For inter-group comparisons, continuous variables were ana-
alyzed using Student’s t-test, and when data were not normally
distributed, the non-parametric Mann-Whitney U test was used.
Descriptive variables were analyzed using chi-squared test or
Fisher’s exact test if more than 20% of the expected cell fre-
cuencies <5. Logistic regression analysis was used to assess the
risk factors of mortality. Further, variables that were associat-
ed with in-hospital mortality at p values less than 0.1 in univar-
iate analysis (age and sex) were included in multivariable lo-
gistic regression analysis. Assessment of the applicability of
multicollinearity indicated no multicollinearity issues (toler-
ance >0.1 and variance inflation factor values <10) between
the chosen independent variables in this study. p values less
than 0.05 were considered statistically significant. The contrib-
ution of each potential risk factor was denoted by the odds
ratio (OR) and associated 95% confidence interval (CI).
# RESULTS

## Patient characteristics

A total of 317 patients with pneumonia aged 65 years or more were analyzed. One hundred five patients had NHAP, and 212 patients had CAP. The baseline characteristics of the patients with NHAP and CAP are presented in Table 1. The median age of the patients with NHAP was 80 years, and that of patients with CAP was 75 years. NHAP patients had a lower body mass index (BMI), compared to CAP patients ($p<0.001$), and fewer current smokers ($p=0.005$). NHAP patients had a higher frequency of poor functional status (66.7% vs. 9.4%; $p<0.001$), confusion rate (68.6% vs. 10.4%; $p<0.001$), use of tube feeding (23.8% vs. 0.5%; $p<0.001$), and probable aspiration (48.6% vs. 13.2%; $p<0.001$) than CAP patients. The incidence of chronic respiratory disease, heart disease, diabetes mellitus, and chronic renal diseases were not different between the two groups. Patients with cerebrovascular disease (50.5% vs. 16.5%; $p<0.001$) and other neurologic disease (54.3% vs. 6.6%; $p<0.001$) were more frequent in NHAP patients than in CAP patients.

## Initial clinical features and severity at presentation

The initial clinical characteristics and severity in the NHAP and CAP groups are shown in Table 2. The time from symptom to admission was shorter in NHAP patients, compared with CAP patients. CURB-65 was higher in NHAP patients than in CAP patients.

### Table 1. Baseline Characteristics and Comorbidity

|                    | NHAP, n=105 | CAP, n=212 | $p$ value |
|--------------------|-------------|------------|-----------|
| Median age, yrs (IQR) | 80 (74–84) | 75 (71–81) | <0.001    |
| Male, n (%)         | 61 (58.1)   | 113 (53.3) | 0.420     |
| BMI, kg/m$^2$       | 19.06±3.52  | 21.88±4.04 | <0.001    |
| Current smoker, n (%) | 4 (3.8)    | 25 (11.8)  | 0.005     |
| Smoking amount (pack yrs) | 12.9±24.0 | 18.3±23.4  | 0.059     |
| Probable aspiration*, n (%) | 51 (48.6) | 28 (13.2)  | <0.001    |
| Tube feeding, n (%) | 25 (23.8)   | 1 (0.5)    | <0.001    |
| Poor functional status†, n (%) | 70 (66.7) | 20 (9.4)   | <0.001    |
| Confusion, n (%)    | 72 (68.6)   | 22 (10.4)  | <0.001    |

**Comorbidities, n (%)**

| Comorbidity                  | NHAP          | CAP           | $p$ value |
|------------------------------|---------------|---------------|-----------|
| Diabetes mellitus            | 24 (22.9)     | 67 (31.6)     | 0.105     |
| Hypertension                 | 58 (55.2)     | 107 (50.5)    | 0.424     |
| Hepatitis                    | 4 (3.8)       | 4 (1.9)       | 0.447     |
| Chronic respiratory disease  | 14 (13.3)     | 45 (21.2)     | 0.089     |
| Heart disease                | 17 (16.2)     | 26 (12.3)     | 0.337     |
| CVD                          | 53 (50.5)     | 35 (16.5)     | <0.001    |
| Other neurologic disease     | 57 (54.3)     | 14 (6.6)      | <0.001    |
| CVD and other neurologic disease | 93 (88.6) | 47 (22.2)    | <0.001    |
| Chronic renal disease        | 5 (4.8)       | 3 (1.4)       | 0.083     |

IQR, interquartile range; NHAP, nursing home-acquired pneumonia; CAP, community-acquired pneumonia; BMI, body mass index; CVD, cerebrovascular disease. Data are presented as mean±standard deviation or n (%), unless otherwise stated.

*Probable aspiration was defined as any witnessed aspiration before hospital admission, †Patients with poor functional status were defined as being bedridden or those who used a wheelchair.

### Table 2. Initial Clinical Features and Severity

|                   | NHAP, n=105 | CAP, n=212 | $p$ value |
|-------------------|-------------|------------|-----------|
| Time from symptom until admission, days | 1 (0–3) | 3 (1–7) | <0.001 |
| Median initial WBC (IQR), count/μL | 10320 (7820–14230) | 9950 (7560–13782) | 0.817 |
| Initial CRP, mg/dL | 11.7±8.2 | 11.9±10.1 | 0.524 |
| CURB-65           | 2.7±1.2    | 1.8±1.0    | <0.001    |
| Chest X-ray, bilateral, n (%) | 58 (55.2) | 75 (35.4) | 0.001 |
| Mechanical ventilation, n (%) | 22 (21.0) | 19 (9.0) | 0.003 |
| ICU admission, n (%) | 50 (47.6) | 39 (18.4) | <0.001 |

NHAP, nursing home-acquired pneumonia; CAP, community-acquired pneumonia; IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; ICU, intensive care unit. Data are presented as mean±standard deviation and/or median (IQR) or n (%), unless otherwise stated.
patients. NHAP patients had higher rates of mechanical ventilation (MV) use (21% vs. 9%; \( p = 0.003 \)) and ICU admission (47.6% vs. 18.4%; \( p<0.001 \)) than CAP patients. Laboratory findings, such as C-reactive protein level or leukocytosis, revealed no differences between two groups, although NHAP patients had more severe pneumonia on chest X-ray, as defined by bilateral involvement of pneumonia, compared with the CAP patients.

**Microbiology and initial antibiotics**

The microbes identified in the NHAP and CAP groups are listed in Table 3. The numbers of both the total population and cases with any pathogen are shown in Table 3. The patients identified with causative pathogens accounted for 51.4% of NHAP and 29.2% of CAP cases. *Streptococcus pneumoniae* was the most frequent pathogen in both groups. MDR pathogens were isolated more frequently in NHAP patients than in CAP patients (21.9% vs. 1.4%; \( p<0.001 \)). MDR pathogens were isolated in 42.6% of NHAP patients with any identified pathogens. In particular, MRSA was a common MDR pathogen in NHAP patients. Pseudomonas species was not frequently identified. Mixed bacteria were detected in 5 patients among NHAPs and 3 patients among CAPs. The antibiotics used initially and fail-

### Table 3. Microbes Identified in NHAP and CAP Patients

| Total population | Case with identified pathogen |
|------------------|-----------------------------|
| Pathogen identified, n (%) | NHAP, n=105 | CAP, n=212 | \( p \) value | NHAP, n=54 | CAP, n=62 | \( p \) value |
| MDR* pathogens identified, n (%) | 23 (21.9) | 3 (1.4) | \( p<0.001 \) | 23 (42.6) | 3 (4.8) | \( p<0.001 \) |
| Gram positive, n (%) |  |  |  |  |  |  |
| *Streptococcus pneumoniae* | 19 (18.1) | 43 (20.3) | 0.644 | 19 (35.2) | 43 (68.4) | \( p<0.001 \) |
| MSSA | 2 (1.9) | 7 (3.3) | 0.723 | 2 (3.7) | 7 (11.3) | 0.172 |
| MRSA | 11 (10.5) | 1 (0.5) | \( p<0.001 \) | 11 (20.4) | 1 (1.6) | 0.001 |
| Gram negative, n (%) |  |  |  |  |  |  |
| *Pseudomonas* species | 7 (6.7) | 2 (0.9) | 0.007 | 7 (13.0) | 2 (3.2) | 0.080 |
| *Klebsiella* species | 6 (7.6) | 3 (1.4) | 0.007 | 6 (14.6) | 3 (4.8) | 0.067 |
| ESBL *Klebsiella* | 4 (3.8) | 0 (0.0) | 0.012 | 4 (7.4) | 0 (0.0) | 0.044 |
| *Escherichia coli* | 5 (4.8) | 0 (0.0) | 0.001 | 5 (9.3) | 0 (0.0) | 0.117 |
| ESBL *Escherichia coli* | 1 (1.0) | 0 (0.0) | 0.331 | 1 (1.9) | 0 (0.0) | 0.466 |
| *Haemophilus influenzae* | 0 (0.0) | 7 (3.3) | 0.100 | 0 (0.0) | 7 (11.3) | 0.014 |
| *Moraxella catarrhalis* | 2 (1.9) | 2 (0.9) | 0.602 | 2 (3.7) | 2 (3.2) | >0.999 |
| CRAB | 2 (1.9) | 0 (0.0) | 0.109 | 2 (3.7) | 0 (0.0) | 0.215 |
| Others | 1 (1.0) | 0 (0.0) | 0.331 | 1 (1.9) | 0 (0.0) | 0.466 |
| Polymicrobial, n (%) | 5 (4.8) | 3 (1.4) | 0.121 | 5 (9.3) | 3 (4.8) | 0.470 |

NHAP, nursing home-acquired pneumonia; CAP, community-acquired pneumonia; MDR, multi-drug resistance; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum beta-lactamase; CRAB, carbapenem resistant *Acinetobacter baumannii*. Data are presented as n (%).

*MRSA, *Pseudomonas* species, CRAB, *Stenotrophomonas maltophilia*, and ESBL-producing *Enterobacteriaceae* were considered as MDR pathogens.

### Table 4. Initial Antibiotics Among Patients with NHAP and CAP

| NHAP, n=105 | CAP, n=212 | \( p \) value |
|-------------|------------|-------------|
| Initial antibiotics treatment, n (%) | 33 | 30 | \( <0.001 \) |
| Monotherapy | 1 (1.0) | 1 (1.0) | 0.331 |
| Quinolone | 2 (1.9) | 7 (3.3) | 0.121 |
| Antipseudomonal penicillin | 30 (28.6) | 27 (12.7) | \( <0.001 \) |
| Carbapenem | 2 (1.9) | 0 (0.0) | 0.001 |
| Combination therapy | 72 | 182 | \( <0.001 \) |
| 3rd cephalosporin and macrolide | 9 (8.6) | 116 (54.7) | 0.001 |
| 3rd cephalosporin and quinolone | 1 (1.0) | 5 (2.4) | 0.001 |
| Antipseudomonal penicillin and macrolide | 9 (8.6) | 20 (9.4) | 0.001 |
| Antipseudomonal penicillin and quinolone | 50 (47.6) | 40 (18.9) | 0.001 |
| Others | 5 (4.8) | 1 (0.5) | 0.001 |
| Failure of initial antibiotics, n (%) | 7 (6.7) | 3 (1.4) | 0.017 |

NHAP: nursing home acquired pneumonia; CAP: community acquired pneumonia. Data are presented as n (%).
ures of initial antibiotics are presented in Table 4. Patients with CAP received more combinations of antipneumococcal β-lactamase and macrolide. However, patients with NHAP received more antipseudomonal penicillin. Failure of initial antibiotics (6.7% vs. 1.4%; \( p=0.017 \)) were more frequent in NHAP patients than in CAP.

Clinical outcomes

The clinical outcomes of patients with NHAP and CAP are shown in Table 5. The proportion of in-hospital mortalities was over two-fold higher in the NHAP group than the CAP group (10.5% vs. 3.3%; \( p=0.009 \)). NHAP patients had a longer duration of hospital stay, ICU stay, and antibiotics use than CAP patients.

Contributing factors to in-hospital mortality

Table 6 lists the risk factors for in-hospital mortality by logistic regression analysis models. According to univariate analysis, mortality was significantly associated with NHAP, CURB-65, confusion, involved lobes in chest X-ray, initial ICU care, MV use, and presence of MDR pathogen. After adjustment for age, sex, and other confounding factors, the number of involved lobes in chest X-ray (OR=1.708; 95% CI, 1.120 to 2.605; \( p=0.013 \)) and MV use (OR=9.537; 95% CI, 1.635 to 55.632; \( p=0.012 \)) were significantly associated with increased in-hospital mortality.

**DISCUSSION**

This study revealed significant differences in mortality and contributing factors between NHAP and CAP, especially in hospitalized elderly patients. The significant findings of this study were that overall in-hospital mortality of NHAP is about twice as high as that of CAP (10.5% vs. 3.3%) and patients with NHAP had more frequent cerebrovascular disease, neurologic disease, poor functional status, aspiration tendency, and tube feeding than those with CAP. In addition, the patients with NHAP had more severe pneumonia in terms of the clinical and radiologic findings, MV use, and ICU admission. NHAP patients had more frequent MDR pathogens, especially MRSA, and higher incidences of initial treatment failure. We treated most patients with NHAP (85%) with antipseudomonal penicillin, with/without fluoroquinolones as recommended in the ATS/IDSA 2005 guidelines, to cover potential MDR pathogens, such as *Pseudomonas* or MRSA. Excess mortality was related to disease severity, such as the MV use and the number of the involved lobes in chest X-ray, but not to the presence of MDR pathogens. To

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**Table 5. Treatment Outcomes of Patients with NHAP and CAP**

|                      | NHAP, n=105 | CAP, n=212 | \( p \) value |
|----------------------|-------------|------------|---------------|
| In-hospital mortality, n (%) | 11 (10.5)   | 7 (3.3)    | 0.009         |
| Hospital stay, days   | 12.3±13.0   | 9.7±7.8    | 0.035         |
| ICU stay, days        | 6.93±11.0   | 1.8±6.2    | <0.001        |
| Duration of antibiotics, days | 18.5±10.5  | 15.7±7.1   | 0.010         |

NHAP: nursing home acquired pneumonia; CAP: community acquired pneumonia; ICU: intensive care unit. Data are presented as mean±standard deviation or n (%), unless otherwise stated.

**Table 6. Factors Contributing to in-Hospital Mortality**

|                                | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | OR (95% CI)         | \( p \) value         | OR (95% CI)         | \( p \) value         |
| Age                            | 1.017 (0.951–1.088) | 0.613                 | 1.005 (0.915–16.230)| 0.914                 |
| Male                           | 2.229 (0.775–6.408) | 0.137                 | 3.854 (0.915–16.230)| 0.066                 |
| BMI                            | 0.961 (0.851–1.085) | 0.519                 |                       |                       |
| Poor functional status         | 2.117 (0.808–5.550) | 0.127                 |                       |                       |
| Confusion                      | 2.518 (0.966–6.559) | 0.059                 | 1.667 (0.390–7.124)  | 0.490                 |
| Neurologic disease             | 2.672 (0.977–7.310) | 0.056                 | 2.425 (0.467–12.586) | 0.292                 |
| CURB–65                        | 2.879 (0.921–4.314) | \(<0.001\)            | 1.326 (0.730–2.408)  | 0.355                 |
| Time from symptom until admission | 0.970 (0.879–1.072) | 0.552                 |                       |                       |
| Mechanical ventilation         | 35.259 (10.84–114.68) | \(<0.001\)          | 9.537 (1.635–55.632) | 0.012                 |
| ICU admission                  | 24.767 (5.563–110.276) | \(<0.001\)        | 1.698 (0.197–14.655) | 0.680                 |
| Involved lobes in chest X–ray  | 2.566 (1.805–3.649) | \(<0.001\)            | 1.708 (1.120–2.605)  | 0.013                 |
| MDR pathogen                   | 3.597 (1.091–11.860) | 0.035                 | 1.232 (0.275–5.516)  | 0.716                 |
| Pathogen identified            | 1.794 (0.691–4.657) | 0.230                 |                       |                       |
| NHAP                           | 3.427 (1.288–9.118) | 0.014                 | 1.412 (0.317–6.297)  | 0.651                 |

BMI: body mass index; ICU: intensive care unit; MDR: multi-drug resistance; NHAP: nursing home acquired pneumonia.

For each variable, the odds ratio (OR) and 95% confidence interval (95% CI) were given. \( p \) values <0.05 were considered statistically significant. Risk factors that were determined as significant by univariate analysis (\( p<0.1 \)) were then subjected to multivariate analysis.
avoids the effect of age, we restricted the analysis to patients aged 65 years or more. Klappdorf et al. showed that NHAP in older adult patients was different from younger patients. CAP in older adults also has different clinical characteristics and outcomes, compared with CAP, in younger patients. Our study is in line with another study of NHAP in terms of mortality. In other studies, the reported 30-day mortality of NHAP ranged from 16.8% to 26.6%, as in our study (19.5%). The higher mortality in NHAP, compared with CAP, is well known, while greater detection of MDR pathogens is controversial. In our study, the prevalence of MDR pathogens was 21.9% (MRSA: 10.5%, Pseudomonas aeruginosa 6.7%, ESBL 4.8%) for the total NHAP population and 1.4% for CAP; the most common pathogen was Strepctococcus pneumonia in both groups. However, the identification of MDR pathogens differs across countries and studies. In the United States, Dhawan et al. reported that the most frequent pathogens of NHAP were gram-negative bacteria (GNB) (up to 55%), Strepctococcus pneumoniae (up to 48%), Staphylococcus aureus (up to 33%), and Pseudomonas aeruginosa (up to 7%). In severe pneumonia, Staphylococcus aureus and GNB were detected more frequently. A prospective German cohort study of 518 NHAP patients aged 65 years and older found that MDR pathogens were very rare (5%), and MRSA was relatively more frequent in the NHAP patients (2.3% of all NHAP). A Spanish study detected potential MDR pathogen in 7%, MRSA in 2%, Pseudomonas in 1%, and GNB in 3%. In a prospective cohort study of 116 NHAP patients aged 65 years and older in Hong Kong, Ma et al. found that the patients with NHAP had more viral infections (55.9%), whereas those with CAP had more bacterial infections (69.9%). MDR pathogens were found only in six patients in the entire study population. In a Japanese study of 138 NHAP aged 65 years or older, MRSA (8.7% vs. 2.3%), Klebsiella pneumoniae (11.6% vs. 3.9%), and Proteus mirabilis (2.9% vs. 0%) were identified more frequently in NHAP than in CAP patients. Our study had similar results for MDR pathogens as Japanese, while the rate was higher in the United States and lower in Europe. There are a few reported Korean studies on NHAP, while there are several studies on HCAP. In a Korean study of 58 NHAP patients, potential drug-resistant pathogens were detected more frequently in the NHAP group (22.4% vs. 9.9%; p=0.018), compared to CAP, and Pseudomonas aeruginosa and MRSA were detected in 8.6% and 10.3%, respectively. In another Korean study of 66 NHAP patients, MDR pathogens were also highly detected in NHAP (39% vs. 10%), compared to CAP. However, the isolation rate of Pseudomonas aeruginosa and MRSA were 3.0% and 4.5%, respectively. These studies showed a similar rate of MDR pathogens in NHAP groups with our study. However, the rate of MDR pathogens in CAP patients was relatively higher than our study. Our study had a greater number of enrolled patients in both groups and included more patients living in the metropolitan area than previous Korean studies. As shown in this and other studies, the mortality in NHAP was higher than in CAP, although the incidence of MDR pathogens varied across the studies. However, there was little evidence that more MDR pathogens caused excess mortality in NHAP. Even for HCAP, including NHAP, the association between high MDR pathogens and high mortality remains controversial. In a meta-analysis, Chalmers et al. showed that HCAP had an increased risk of MRSA, Enterobacteriaceae, and Pseudomonas aeruginosa, although HCAP itself was not associated with a significant increase in mortality after adjusting for age and co-morbid illnesses. In a British study of 437 NHAP patients, atypical pathogen, MRSA, Enterobacteriaceae, and poor functional status were risk factors for mortality. In Spanish study of 150 NHAP patients, neurological disease, septic shock, pleural effusion, GNB, and MRSA accounted for the high mortality in NHAP. In our study, neither MDR pathogens in their entirety nor individual MDR pathogens were associated with mortality, even in the univariate analyses, unlike in some studies. Contrary to other studies that showed HCAP itself was an important risk factor for mortality, significant risk factors for mortality in our study were the extent of pneumonia on chest X-ray and MV use after adjusting for age, sex, and other confounding factors. MDR pathogens, initial ICU admission, CURB-65, and NHAP were not significant after adjusting for other factors. Disease severity in terms of clinical and radiological severity, rather than MDR pathogen and NHAP, resulted in excess mortality in our study. This result was similar to another Korean study in which a higher pneumonia severity index score was significantly associated with mortality. Although we excluded patients who had DNR order, treatment restriction, such as a DNR order, may be more frequent in NHAP patients because NHAP patients are older, disabled, and have a poor functional status, and more neurological and cerebrovascular disease. Thus, NHAP may result in higher mortality in real world situation. Unfortunately, in the present study, almost 85% of NHAP patients were treated with antipseudomonal penicillin without regard to the severity of illness, as recommended by the 2005 ATS/ IDSA guidelines. Pseudomonas species were cultured in only 6.7%, leading them to recommend targeting these pathogens in all of their NHAP patients. Such overtreatment might lead to the development of resistant pathogens and increase costs.

This study has several limitations. First, the data were collected retrospectively from a single institution. Therefore, our results should be interpreted with caution. Second, most of the pathogens were defined based on a positive culture of sputum or endotracheal aspirate, instead of semiquantitative or quantitative cultures. Viral pathogens were not identified. Third, the proportion of patients with the causative pathogens identified was relatively low, especially in CAP (29.2%). Therefore, we could not determine whether the appropriateness of antibiotics was a significant risk factor for mortality or not. Although, more than half of the patients had normal flora in their sputum, we included only patients with positive sputum culture result. Most patients were tested with other microbiologic stud-
ies, such as blood culture and urinary antigen. Despite these limitations, our results include meaningful information about clinical and microbiological features and predictors of mortality in NHAP, compared with CAP, especially for Korean populations.

In conclusion, patients with NHAP had higher mortality rates than patients with CAP. However, the excess mortality was related to disease severity and not to the presence of multidrug-resistant pathogens or NHAP itself. Therefore, not all patients with NHAP may need broad-spectrum antibiotics, and other clinical predictive factors for specific MDR pathogens should be assessed in both CAP and NHAP.

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