Risk Factors for Acquiring Potentially Drug-Resistant Pathogens in Immunocompetent Patients with Pneumonia Developed Out of Hospital

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Key Words

Healthcare-associated pneumonia · Potentially drug-resistant pathogens · Risk stratification model

Abstract

Background: The concept of healthcare-associated pneumonia (HCAP) exists to identify patients infected with highly resistant pathogens who are exposed to the healthcare environment. However, many studies have included immunosuppressed patients who were excluded from the original concept. **Objectives:** The risk factors of potentially drug-resistant (PDR) pathogens in patients with pneumonia developed outside the hospital were reevaluated after excluding the patients who had immunosuppression. **Methods:** This was a retrospective study of prospectively collected data from all consecutive patients with pneumonia who were admitted to hospital via the emergency department between January 2008 and December 2011. **Results:** Pathogens were isolated in a total of 315 patients with pneumonia from our cohort; 33% with PDR pathogens did not meet the criteria for HCAP, but 44% without PDR pathogens did meet the criteria. Variables independently associated with PDR included nursing home residency, hospitalization in the preceding 90 days, antibiotics in the 30 days prior to pneumonia, poor function status and chronic lung disease. The new predictive scoring system based on the logistic regression model had a

higher predictive power for the risk of PDR pathogens than the presence of the risk factors or the HCAP criteria. **Conclusions:** Functional status, pulmonary comorbidity and previous exposure to the healthcare environment were significantly associated with acquiring PDR pathogens in immunocompetent patients with pneumonia that developed out of hospital. However, a risk stratification model was more accurate than the presence of the risk factors or the HCAP criteria for assessing the probability of PDR pathogens.

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Introduction

Traditionally, pneumonia has been classified as a triad: community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) and pneumonia in immunosuppressed patients, depending on the host's immunity and the pneumonia acquisition environment [1]. The distinction is considered relevant because the predictable microbiology and empirical treatment of these types of pneumonia differ. In 2005, the concept of healthcare-associated pneumonia (HCAP) was introduced by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) [2]. HCAP refers to pneumonia that occurs outside the hospital in immunocompetent patients with contact or exposure to the healthcare environ-

ment [2], i.e. patients who were potentially infected with multidrug-resistant bacteria, which is different from CAP but similar to HAP. The purpose of the HCAP concept is to identify patients who may be infected with highly resistant pathogens [2–5], which leads to the use of broad-spectrum empirical antibiotic therapy in all patients meeting the HCAP criteria. These criteria include any patient who: has been hospitalized in an acute-care hospital for ≥ 2 days within 90 days of the infection, has resided in a nursing home or a long-term care facility, has received recent intravenous antibiotic therapy, chemotherapy or wound care within the 30 days prior to the current infection or has attended a hospital or hemodialysis clinic [2].

Several studies have reported conflicting data on the frequency of multidrug-resistant bacteria [6–11]. Although patients who meet the criteria of HCAP are more susceptible to infection by drug-resistant pathogens, the majority of patients diagnosed with HCAP are not truly infected [6–12]. In addition, not all risk factors for HCAP may be equivalent in predicting pneumonia caused by drug-resistant pathogens [12–14]. Risk stratification models to identify patients who are likely to be infected with multidrug-resistant pathogens have therefore been developed [13–17]. All of these studies included patients with immunosuppression as a risk factor for HCAP, but this group was excluded from the ATS/IDSA guidelines because immunosuppression is associated with severe respiratory infection and infection by opportunistic pathogens [2]. In other guidelines, different initial empirical antibiotic therapy has been suggested [18, 19]. This means that the risk factors of drug-resistant pathogens in patients with pneumonia developed outside the hospital need to be reevaluated after excluding the patients with immunosuppression according to the ATS/IDSA.

The objectives of this study were to evaluate the risk factors for acquiring drug-resistant pathogens among immunocompetent patients coming from the community who were hospitalized with pneumonia, and to develop risk stratification models to identify patients with pneumonia caused by drug-resistant pathogens. We also compared the discrimination powers of the risk stratification models to those of the HCAP criteria suggested by the ATS/IDSA.

Patients and Methods

For all consecutive adult patients with pneumonia at the Samsung Medical Center (a 1,961-bed, university-affiliated, tertiary referral hospital in Seoul, South Korea) between January 2008 and December 2011, data were collected and retrospectively analyzed.

Some of the clinical data for patients are included in other articles [8, 20]. The study was approved by the institutional review board of the Center with regard to the review and publishing of information obtained from patient records. Informed consent was waived because of the retrospective nature of the study.

Study Population

Over the study period, all consecutive patients admitted to the hospital via the emergency department with pneumonia were prospectively registered. The patients with HAP that developed after having been hospitalized for >72 h or within 10 days of leaving the hospital were not included [7]. Patients who had been transferred after hospitalization for >48 h in other hospitals were excluded. Immunocompromised patients, such as those with neutropenia (i.e. an absolute neutrophil count of $<1,500/\text{mm}^3$) after chemotherapy or HIV infection and those who had undergone transplantations, were also excluded [2].

During the study period, 2,187 consecutive patients with pneumonia were hospitalized via the emergency department. Of these, we excluded 563 patients with HAP, 315 who were immunocompromised and 95 who had been transferred from other hospitals after hospitalization for >48 h. Thus, in total, 1,214 patients hospitalized with pneumonia were eligible for this study, consisting of 680 (56%) with CAP and 534 (44%) with HCAP. The etiologic pathogen of the pneumonia could be identified in 155 HCAP patients (29%) and 160 CAP patients (24%) ($p = 0.030$). A total of 315 patients were included in the analysis.

Diagnosis of CAP and HCAP

A clinical diagnosis of pneumonia required the presence of new radiographic infiltrates and at least 2 of the following clinical criteria: fever ($>38^\circ\text{C}$) or hypothermia ($\leq 35^\circ\text{C}$), new cough with or without sputum production, pleuritic chest pain, dyspnea and altered breath sounds on auscultation [21]. The patients with pneumonia were classified into the CAP and HCAP groups. HCAP was defined as a diagnosis of pneumonia in patients admitted to the hospital who met at least 1 of the following criteria: (1) a recent history of hospitalization for ≥ 2 days in the preceding 90 days, (2) residence in a nursing home or long-term care facility, (3) recent antibiotic therapy, intravenous chemotherapy or wound care within the 30 days prior to the current infection and (4) attendance at a hospital or hemodialysis clinic [2, 7]. CAP was defined as a diagnosis of pneumonia in patients who did not meet any of the criteria for HCAP.

Data Collection

Based on patient demographics and baseline clinical data that were prospectively registered, pneumonia severity was also evaluated using the Pneumonia Severity Index (PSI) and the CURB-65 (confusion, urea nitrogen, respiratory rate, blood pressure, age ≥ 65 years) [22, 23]. A clinical diagnosis of severe pneumonia was made according to the previous criteria [24]. Functional status was assessed using the system developed by the Eastern Cooperative Oncology Group (ECOG) [25].

Microbiologic Data and Antibiotic Treatment

Microorganisms were identified in a microbiology laboratory. Antimicrobial susceptibility testing was performed by the GNI card in a VITEK II automated system (bioMérieux, Hazelwood, Mo., USA) using the modified-broth microdilution method or the

disk diffusion method, according to the recommendations of the Clinical and Laboratory Standards Institute. Strains showing intermediate antimicrobial susceptibility profiles were considered to be resistant.

An etiologic diagnosis was considered when a respiratory pathogen was isolated from a usually sterile specimen, pneumococcal antigen was detected in urine or a predominant microorganism was isolated from adequate sputum or bronchial washing fluids with compatible Gram-staining, as previously reported [8, 20]. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas* sp., *Acinetobacter* sp., *Stenotrophomonas maltophilia* and extended-spectrum β -lactamase-producing Enterobacteriaceae were considered potentially drug-resistant (PDR) pathogens [5].

Initial antibiotic therapy during the study period recommended a combination of β -lactams plus macrolides for patients with CAP and a combination of antipseudomonal β -lactams plus fluoroquinolones for patients with HCAP or those with a high risk of pseudomonal infection. In our institution, additional vancomycin or linezolid was not recommended for the initial treatment of CAP or HCAP because of the low prevalence of MRSA occurrence in patients with these types of pneumonia.

The appropriateness of antibiotic treatment was analyzed for all cases with an etiologic diagnosis according to susceptibility test criteria for lower respiratory tract pathogens. Antibiotic treatment was classified as inappropriate if the initially prescribed antibiotics were not active against the identified pathogens, based on in vitro susceptibility testing [4].

Statistical Analyses

To identify the risk factors independently associated with PDR pathogen occurrence, we conducted a multivariate analysis using a logistic regression model with backward stepwise selection with $p < 0.05$ for entry of variables and $p > 0.10$ for removal of variables that identified independent predictors of PDR pathogens. Initial candidate variables were those with $p < 0.25$ in the univariate analyses and a priori variables of HCAP criteria suggested by the ATS/IDSA [26]. Variables were assessed for collinearity, and the goodness-of-fit of the model was evaluated with the Hosmer-Lemeshow test.

From the logistic regression findings, a score-based predictive scoring system was developed [27]. To generate a simple integer-based point score for each predictor variable, we assigned scores by dividing the β coefficients by the absolute value of the smallest coefficient in the final model and rounding up to the nearest integer. The total score for each participant was calculated by adding each component together. We then explored the predictive value of the point score for correctly indicating the presence of infection with a PDR pathogen using a receiver operating characteristic (ROC) curve, and validated the prediction rule internally, using the bootstrap method in the original data set by sampling with replacement for 1,000 iterations. The estimated area under the curve (AUC) values for the presence of HCAP criteria, the presence of identified risk factors for PDR pathogens and the new predictive score were compared using the Hanley-McNeil test with the Bonferroni correction [28].

All tests were 2-sided and $p < 0.05$ was considered significant. The data were analyzed using PASW Statistics 18 (SPSS Inc., Chicago, Ill., USA) for descriptive analysis and STATA 11 (STATA Corp, College Station, Tex., USA) for ROC analysis.

Table 1. The baseline characteristics and clinical outcomes of HCAP and CAP patients

Characteristics	HCAP (n = 155)	CAP (n = 160)	p value
Age, years	67 (57–72)	67 (57–74)	0.400
Gender, male	111 (72)	97 (61)	0.040
Functional status, ECOG scores	2 (1–3)	1 (0–2)	<0.001
0	8 (5)	44 (28)	<0.001
1	59 (38)	53 (33)	
2	46 (30)	38 (24)	
3	29 (19)	15 (9)	
4	13 (8)	10 (6)	
ECOG score ≥ 3	42 (27)	25 (16)	0.013
Comorbidities ¹			
Neoplastic disease	95 (61)	33 (21)	<0.001
Chronic lung disease	55 (35)	65 (41)	0.348
Diabetes	27 (17)	36 (23)	0.260
Cerebrovascular disease	22 (14)	31 (19)	0.219
Chronic heart disease	15 (10)	12 (8)	0.490
Chronic kidney disease	16 (10)	10 (6)	0.189
Chronic liver disease	12 (8)	12 (8)	0.936
Rheumatic disease	2 (1)	7 (4)	0.174
Aspiration	14 (9)	7 (4)	0.098
Radiographic findings ¹			
Multiple lung involvement	100 (65)	77 (48)	0.003
Bilateral lung involvement	74 (48)	65 (41)	0.203
Pleural effusion	33 (21)	28 (18)	0.395
Clinical parameters ¹			
Severe pneumonia	69 (45)	46 (29)	0.004
Bacteremia	22 (14)	17 (11)	0.336
Septic shock at presentation	33 (21)	19 (12)	0.024
Need for mechanical ventilation	32 (21)	23 (14)	0.143
ICU admission	45 (29)	33 (21)	0.084
Severity of illness			
CURB-65 score	1 (0–2)	1 (0–2)	0.367
CURB-65 score ≥ 2	64 (41)	59 (37)	0.422
PSI score	113 (89–138)	90 (67–131)	<0.001
PSI high-risk class $\geq IV$	116 (75)	79 (49)	<0.001
Clinical outcomes			
Length of antibiotic treatment, days	14 (11–19)	14 (10–16)	0.018
Inhospital mortality	33 (21)	13 (8)	0.001
Length of hospital stay, days	11 (7–20)	7.5 (5–14)	<0.001

The data are presented as medians (interquartile ranges) or n (%).

¹ Cases are duplicated.

Results

Patient Characteristics

The baseline characteristics of patients with HCAP and CAP are presented in table 1. Patients with HCAP had more comorbidities and a worse functional status than patients with CAP. Septic shock at presentation was higher in HCAP patients than in CAP patients, although the admission rate to the ICU of the 2 groups did not dif-

Table 2. The pathogens identified in HCAP and CAP patients

	HCAP (n = 155)	CAP (n = 160)	p value
Gram-positive pathogens	79 (51)	91 (57)	0.293
<i>S. pneumoniae</i>	45 (29)	63 (39)	0.053
Streptococci other than <i>S. pneumoniae</i>	7 (5)	8 (5)	0.840
<i>S. aureus</i>	25 (16)	22 (14)	0.554
MSSA	10	14	
MRSA	15	8	
Other Gram-positive bacteria	3 (2)	1 (1)	0.365
Gram-negative pathogens	74 (48)	57 (36)	0.029
<i>Pseudomonas aeruginosa</i>	26 (17)	10 (6)	0.003
<i>Haemophilus influenzae</i>	10 (6)	13 (8)	0.568
<i>Klebsiella pneumoniae</i>	23 (15)	20 (13)	0.546
<i>Escherichia coli</i>	6 (4)	1 (1)	0.064
<i>Acinetobacter</i> sp.	4 (3)	2 (1)	0.442
<i>Enterobacter</i> sp.	2 (1)	2 (1)	1.000
Other Gram-negative bacteria	7 (5)	11 (7)	0.367
Polymicrobial	16 (10)	12 (8)	0.379
Anaerobe	3 (2)	7 (4)	0.336
Virus	6 (4)	7 (4)	0.822
Occurrence of PDR pathogens	47 (32)	22 (15)	<0.001
Inappropriate antibiotic treatment	19 (14)	13 (10)	0.328

Data are presented as n (%). PDR pathogens include MRSA, *Pseudomonas* sp., *Acinetobacter* sp., *S. maltophilia* and extended-spectrum β -lactamase-producing Enterobacteriaceae. MSSA = Methicillin-sensitive *S. aureus*.

fer. In addition, the median PSI score was higher in HCAP patients than in CAP patients, in contrast to the median CURB-65 severity score.

The median length of antibiotic treatment and hospital stay were significantly longer in HCAP patients than in CAP patients ($p = 0.018$ and $p < 0.001$, respectively). Hospital mortalities were 21% in HCAP patients and 8% in CAP patients ($p = 0.001$).

Pathogen Distribution

The distributions of pathogens are shown in table 2. Overall, *Streptococcus pneumoniae* was the most frequently isolated pathogen in our patients. PDR pathogen occurrence was significantly higher in HCAP patients than in CAP patients (32 vs. 15%, $p < 0.001$). However, there was no significant difference in inappropriate initial antibiotic treatment between groups (14 vs. 10%, $p = 0.328$).

The baseline characteristics of patients infected or not infected with PDR pathogens are presented in table 3. Patients with PDR pathogens had worse functional status and were more likely to meet at least 1 of the HCAP criteria. Nonetheless, 33% of patients with PDR pathogens did not meet the HCAP criteria, but 44% of patients without PDR pathogens did. Although the HCAP crite-

ria were more prevalent in patients with PDR pathogens, not every HCAP criterion contributed equally to this distribution. The prevalence rates of recent chemotherapy, hemodialysis and wound care were similar between groups.

Logistic regression analysis identified 5 variables that were independently associated with the identification of PDR pathogens (table 4). Residency in a nursing home or long-term care facility [adjusted odds ratio (OR) 4.127 and 95% confidence interval (CI) 1.152–14.781, $p = 0.029$], recent history of hospitalization for ≥ 2 days in the preceding 90 days (adjusted OR 2.324 and 95% CI 1.241–4.352, $p = 0.008$) and recent antibiotic therapy within the past 30 days (adjusted OR 2.699 and 95% CI 1.366–5.334, $p = 0.004$) were independently associated with PDR pathogens (table 4). In addition, poor functional status (ECOG ≥ 3) (adjusted OR 2.904 and 95% CI 1.516–5.564, $p = 0.001$) and chronic lung disease (adjusted OR 1.970 and 95% CI 1.075–3.612, $p = 0.028$) were also independently associated with the recovery of PDR pathogens.

Based on the logistic regression analysis, we created a new predictive scoring system using the β coefficients (table 4). A β coefficient of 0.678 corresponded to approxi-

Table 3. The baseline characteristics and clinical outcomes of patients infected or not infected with PDR pathogens

Characteristics	PDR (n = 73)	Non-PDR (n = 242)	p value
Age, years	69 (59–73)	67 (57–72)	0.331
Gender, male	47 (64)	161 (67)	0.734
Functional status, ECOG scores	2 (1–3)	1 (1–2)	<0.001
0	5 (7)	47 (19)	<0.001
1	20 (27)	92 (38)	
2	20 (27)	64 (26)	
3	19 (26)	25 (10)	
4	9 (12)	14 (6)	
ECOG score ≥ 3	28 (38)	39 (16)	<0.001
HCAP criteria ¹	49 (67)	106 (44)	<0.001
Previous hospitalization	32 (44)	53 (22)	<0.001
Prior antibiotic therapy	27 (37)	33 (14)	<0.001
Recent chemotherapy	10 (14)	44 (18)	0.373
Nursing home residency	7 (10)	6 (2)	0.014
Hemodialysis	3 (4)	7 (3)	0.703
Wound care	1 (1)	1 (0)	0.410
Comorbidities ¹	73 (100)	212 (88)	0.002
Neoplastic disease	29 (40)	99 (41)	0.857
Chronic lung disease	37 (51)	83 (34)	0.012
Diabetes	15 (21)	48 (20)	0.894
Cerebrovascular disease	12 (16)	41 (17)	0.920
Chronic heart disease	8 (11)	19 (8)	0.406
Chronic kidney disease	7 (10)	19 (8)	0.636
Chronic liver disease	2 (3)	22 (9)	0.073
Rheumatic disease	1 (1)	8 (3)	0.690
Aspiration	6 (8)	15 (6)	0.593
Severity of illness			
CURB-65 score	1 (0.5–2)	1 (0–2)	0.431
PSI score	106 (76–139)	105 (77–134)	0.848
Severe pneumonia	35 (48)	80 (33)	0.021
Septic shock at presentation	10 (14)	42 (17)	0.461
Need for mechanical ventilation	15 (21)	40 (17)	0.428
ICU admission	19 (26)	59 (24)	0.775
Clinical outcomes			
Inappropriate antibiotic treatment	27 (37)	10 (4)	<0.001
Length of antibiotic treatment, days	16 (11–23)	14 (10–16)	0.001
Inhospital mortality	13 (18)	33 (14)	0.376
Length of hospital stay, days	14 (7–22)	8 (6–14)	0.001

The data are presented as medians (interquartile ranges) or n (%).

¹ Cases are duplicated.

Table 4. Logistic regression findings for independent variables associated with PDR pathogens

Variables	β coefficient	Adjusted OR (95% CI)	p value	Points assigned
Nursing home residency	1.418	4.127 (1.152–4.781)	0.029	2
ECOG ≥ 3	1.066	2.904 (1.516–5.564)	0.001	2
Previous hospitalization	0.843	2.324 (1.241–4.352)	0.008	1
Prior antibiotic therapy	0.993	2.699 (1.366–5.334)	0.004	1
Chronic lung disease	0.678	1.970 (1.075–3.612)	0.028	1

Goodness-of-fit was measured with the Hosmer-Lemeshow test. $\chi^2 = 7.345$, $p = 0.196$.

Fig. 1. Prevalence of PDR pathogens according to new predictive scores (a) and low-, intermediate- and high-risk stratifications derived from the new predictive scores (b).

Fig. 2. The ROC curves for the presence of PDR pathogen occurrence. Solid black lines with square markers show the ROC curve of the new predictive score. Dashed gray lines show the ROC curve of the presence of 1 risk factor for PDR pathogens in this study. Solid black lines with circle markers show the ROC curve for the presence of 1 of the HCAP criteria. The AUC of the new predictive score (0.756; 95% CI 0.698–0.815) was greater than the AUCs of the presence of risk factors for PDR pathogens (0.670; 95% CI 0.628–0.713, $p < 0.001$) and the presence of the HCAP criteria (0.617; 95% CI 0.554–0.679, $p < 0.001$).

mately 1 point. Points were assigned as follows: 2 points for nursing home residency, 2 points for ECOG ≥ 3 , 1 point for previous hospitalization, 1 point for prior antibiotic therapy and 1 point for chronic lung disease, resulting in a maximum of 7 possible points. Each point increment was associated with a 2.0-fold (OR 1.963 and 95% CI 1.584–2.432, $p < 0.001$) increase in the odds for identification of a PDR pathogen. When patients were grouped into low-, intermediate- and high-risk strata as a function of overall point score, the prevalence of PDR pathogens increased as risk increased (fig. 1). Among patients with <1 point, the prevalence of PDR pathogens was $<5\%$, compared with prevalence rates of 28% in patients with scores ranging from 1 to 3 and $>60\%$ in patients with scores of ≥ 4 ($p < 0.001$ for trend).

The ROC curves for the risk of PDR pathogens for the presence of HCAP criteria, the presence of identified risk factors for PDR pathogens and the new predictive score are shown in figure 2. The new predictive score had good predictive value with an AUC of 0.756 (95% CI 0.698–0.815), which was similar to 0.745 (95% CI 0.678–0.813), the average AUC obtained from internal validation. Moreover, this scoring system had a higher discriminatory power to predict the risk of PDR pathogens than the presence of HCAP criteria (AUC 0.617 and 95% CI 0.554–0.679) and the number of HCAP criteria (AUC 0.670 and 95% CI 0.628–0.713) ($p < 0.001$ for both factors).

Discussion

This study evaluated the risk factors for acquiring PDR pathogens among immunocompetent patients coming from the community who were hospitalized with pneumonia. A risk stratification model to identify patients with pneumonia caused by PDR pathogens was also developed. One third of the patients with pneumonia caused by PDR pathogens did not meet the criteria for HCAP, but the majority of patients who met the criteria – especially those who had recently had chemotherapy, hemodialysis or wound care – had no PDR pathogens. We also found that poor functional status and chronic lung disease were significantly associated with PDR pathogens. However, the risk factors identified were not equivalent in predicting PDR pathogens, and a risk stratification model was more accurate than the presence of the risk factors or the HCAP criteria for assessing the probability of PDR pathogens.

Previous studies have documented the increasing prevalence of drug-resistant pathogens in pneumonia developed in the community. In retrospective microbiological studies from the USA [3, 4], PDR pathogens such as MRSA, *Pseudomonas* sp. and *Acinetobacter* sp. were common in HCAP patients. These results support the ATS/IDSA recommendation for the use of broad-spectrum empirical antibiotic therapy in all patients who meet the HCAP criteria. However, subsequent studies have reported conflicting data on the frequency of multidrug-resistant bacteria [6–11]. Although patients who meet the HCAP criteria have a greater risk for multidrug-resistant bacteria, the majority of patients diagnosed with HCAP are not truly infected with multidrug-resistant pathogens. Consequently, broad-spectrum empirical antibiotic therapy according to the ATS/IDSA may not be adequate and can even constitute overtreatment. In this study, guideline-concordant treatment could not be shown to be associated with improved outcomes [29–31]. Therefore, precise risk stratification rather than HCAP criteria for PDR pathogens would provide better identification of patients infected with these pathogens.

Previous studies evaluated additional risk factors for drug-resistant pathogens in patients with pneumonia [13–17]; however, all of these studies included patients with any type of immunosuppression. They also evaluated the predictive potential of an HCAP definition for the presence of PDR pathogens, but the performance of the HCAP criteria was poor for predicting patients likely to be infected with drug-resistant pathogens [13–15]. Moreover, several HCAP criteria, such as recent chemo-

therapy and wound care, were not associated with drug-resistant pathogens; our results are consistent with this. Subsequent studies also confirmed that not all HCAP criteria are associated with drug-resistant pathogens [16, 17]. However, hospitalization in the preceding 90 days was consistently and independently associated with the identification of drug-resistant pathogens [13–17]. In addition, residents in nursing homes or long-term care facilities and with prior antibiotic exposure were also significantly associated. Consistent with these previous studies, our study found that nursing home residency, previous hospitalization and prior antibiotic therapy were major independent predictors for PDR pathogens.

We also found poor functional status to be an independent risk factor for PDR pathogens in our cohort. This association has been previously demonstrated in patients with nursing home-acquired pneumonia, which is the most important subgroup within the HCAP definition [32]. In other HCAP studies [5, 9], enteral-tube feeding, which indicates increased requirements for patient care, was predictive of infection with drug-resistant pathogens. These associations have been explained by the fact that patients with poor functional status or enteral-tube feeding are more likely to be exposed to the cross-contamination of bacteria due to their increased requirements for care [32]. Therefore, functional status should also be assessed in the evaluation of risk factors for PDR pathogens [1, 33].

Given the limits of the current HCAP criteria, more restrictive risk stratification approaches to improve the risk-benefit balance associated with prescribing broad-spectrum antibiotic therapy have been proposed [13–17]. Until now, the identified risk factors for drug-resistant pathogens were weighted differently, so risk stratification scoring tools showed better predictions of infection by drug-resistant pathogens than the current HCAP criteria [34, 35]. Consistent with previous reports, our risk stratification model based on differently weighted predictors is more accurate than the presence of the identified risk factors or the HCAP criteria for assessing the probability of PDR pathogens. Patients at a low risk for acquiring PDR pathogens who were identified based on our risk stratification model had a low prevalence of PDR pathogen infection, so the adoption of this model could lead to fewer patients unnecessarily receiving broad-spectrum antibiotic therapy. However, our model still needs to be validated, internally and externally [34].

The strength and novelty of our study rely on a specific analysis of all risk factors for acquiring PDR pathogens, including comorbidities and functional status, in a

relatively large population of consecutive immunocompetent patients with pneumonia developed in the community. However, it does have several potential limitations that should be acknowledged. First, given the retrospective nature of the analysis, there is always the possibility that selection bias might have influenced the significance of our findings. However, the data were collected prospectively from all consecutive pneumonia patients admitted to the hospital via the emergency department. Second, we analyzed only patients with culture-positive pneumonia. Therefore, our findings may have been skewed in that many cases of pneumonia may have negative culture results. Nevertheless, because we aimed to evaluate risk factors for predicting PDR pathogens, by necessity we had to rely on the data of patients who had had a respiratory pathogen isolated. Patients with culture-negative pneumonia have a lower severity of illness than those with culture-positive pneumonia [36]. Therefore, our results cannot be generalized to patients who may have had negative culture results. Third, the number of patients residing in a nursing home was relatively small in our cohort. This is

a result of the distinct features of tertiary referral hospitals according to the healthcare system in Korea [9, 37]. Nevertheless, nursing home residency was the main factor leading to PDR pathogen acquisition. Finally, our study was from a single institution with a comprehensive cancer center, so there was a large number of cancer patients on chemotherapy. Although immunosuppressed patients with neutropenia that had developed after chemotherapy were excluded, this situation could limit the generalizability of our findings to other hospitals that have less cancer patients with pneumonia.

In conclusion, functional status, pulmonary comorbidity, nursing home residency, previous hospitalization and prior antibiotic therapy were significantly associated with acquiring PDR pathogens in immunocompetent patients with pneumonia developed outside of the hospital. However, the risk factors identified were not equivalent in predicting PDR pathogens. Therefore, a risk stratification model may be more accurate than the presence of the risk factors or HCAP criteria for assessing the probability of PDR pathogens.

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