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Etiology and epidemiology of community-acquired pneumonia in adults requiring hospital admission: A prospective study in rural Central Philippines

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ABSTRACT

Background: Community-acquired pneumonia (CAP) is a common cause of morbidity and mortality among adults worldwide. However, the distribution of the etiology of CAP varies from one country to another, with limited data from rural areas.
Methods: A prospective hospital-based study on adult CAP was conducted in Leyte, Central Philippines from May 2010 to May 2012. Blood, sputum, and nasopharyngeal samples obtained from patients were used to identify pathogens using standard microbiological culture methods and PCR.
Results: Of the 535 patients enrolled, 38% were younger than 50 years old. More than half of the patients had an underlying disease, including pulmonary tuberculosis (22%). The detection rate was higher for bacteria (40%) than viruses (13%). *Haemophilus influenzae* (12%) was the most commonly detected bacterium and influenza virus (5%) was the most commonly detected virus. The proportion of CAP patients with *Mycobacterium tuberculosis* infection was higher in the younger age group than in the older age group. Among CAP patients, 14% died during hospitalization, and drowsiness on admission and SpO_2 <90% were independent risk factors for mortality.
Conclusions: Bacterial infections contribute substantially to the number of hospitalizations among CAP patients in rural Philippines. This study also highlights the importance of treatment of tuberculosis in reducing the burden of adult CAP in the country.

Introduction

Community-acquired pneumonia (CAP) is one of the most common reasons for hospitalization and mortality among adults (Mandell, 2004; Zar et al., 2013). Despite advances and new interventions in supportive care, the mortality rate among CAP patients has not decreased in the past decades (Restrepo et al., 2013). CAP is treated empirically with antibiotics because the etiological agent is not usually identified upon hospital admission. The etiology of CAP is well documented, and the commonly identified pathogens include *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* (Mandell, 2004; Sicras-Mainar et al., 2012; Jain et al., 2015). However, most studies have been conducted in developed countries and the distribution of these pathogens varies from one country to another (Brown, 2009). As a consequence of these differences, the treatment guidelines based on data from Western countries may not be applicable to developing countries in Asia (Peto et al., 2014). This is a challenge for clinicians in these countries because bacterial culture is not routinely performed. In addition, limited data on the

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viral etiology of CAP in resource-limited settings has compounded the issue of unnecessary antibiotic use in patients with viral infections. This is important due to the global trend of increasing rates of antimicrobial resistance to common treatments for bacterial infections (World Health Organization, 2014).

The particularly high incidence of pulmonary tuberculosis (PTB) among CAP patients in developing countries is one of the important differences when compared to CAP in North America and Europe (Brown, 2009; Zar et al., 2013). In a study performed in Kenya, *Mycobacterium tuberculosis* was the second most commonly identified pathogen among adults with pneumonia (Scott et al., 2000). In studies from China and other Asian countries, *M. pneumoniae* was detected at high rates among adult pneumonia cases (Liu et al., 2009; Cao et al., 2010). In both Asia and Africa, *Klebsiella pneumoniae* has been detected frequently in patients with severe pneumonia, and substantial rates of multidrug resistance have been reported (Feldman et al., 1995; Song et al., 2008; Rammaert et al., 2012). While these studies have increased our understanding of the etiology of CAP in Asian countries, there is still limited information on the bacterial and viral etiologies of CAP in rural areas.

The aim of this study was to determine the clinical profile and the bacterial and viral etiologies of CAP in a tertiary government referral hospital in rural Central Philippines. It was also aimed to evaluate the clinical outcomes and risk factors of CAP among Filipino adults.

Materials and methods

Study design and study site

A prospective observational study of adult patients with a diagnosis of CAP admitted to the Eastern Visayas Regional Medical Center (EVRMC) from May 2010 to May 2012 was conducted. EVRMC is a 250-bed capacity hospital and is the only tertiary care government hospital in the region. The hospital, which has an estimated catchment population of 150 000, serves as the referral center for pediatric and adult patients requiring secondary and tertiary medical care in Tacloban City and other provinces in the region.

Patient enrolment

Patients aged ≥14 years were enrolled in the study based on an initial clinical diagnosis of CAP by the admitting physician, according to the Philippine clinical practice guidelines for the diagnosis, empiric management, and prevention of CAP (Chua et al., 2010). The cut-off age of 14 years and older was based on the EVRMC guidelines: these patients are admitted to the adult ward, while patients <14 years old are admitted to the pediatric ward. The eligibility criteria included acute cough, abnormal vital signs of tachypnea, tachycardia, and fever, with at least one abnormal chest finding of diminished breath sounds, rhonchi, crackles, or wheeze.

Patients were classified as moderate-risk or high-risk CAP cases based on the Philippine guidelines on CAP (Chua et al., 2010). A patient was classified as having moderate-risk CAP if he/she presented to the hospital with any of the following signs and symptoms: respiratory rate ≥30/min, pulse rate ≥125/min, systolic blood pressure <90 mmHg, diastolic blood pressure ≤60 mmHg, temperature ≥40 °C or ≤36 °C, altered mental state of acute onset, suspected aspiration, and unstable/decompensated comorbid condition (including uncontrolled diabetes mellitus, active malignancies, neurological disease in evolution, congestive heart failure, unstable coronary artery disease, renal failure on dialysis, uncompensated chronic obstructive pulmonary disease (COPD), and decompensated liver disease). A patient was classified as having high-risk CAP if he/she presented any of the criteria under the moderate-risk CAP category, plus signs of severe sepsis or septic shock, or the need for mechanical ventilation (Chua et al., 2010). Recommended empiric antibiotics were provided to all enrolled patients in accordance with the Philippine guidelines on CAP (Chua et al., 2010).

Patients were excluded from the study if they were admitted for another illness and developed pneumonia while in the hospital, if they had been admitted to another hospital within the 3 days prior to their admission to EVRMC, or if there was a prior hospital admission without a 1-week symptom-free period when readmitted to EVRMC.

Patient information and sample collection

Patient demographic data and clinical information were collected upon admission using pre-tested questionnaires. For the data analysis, patient outcome was classified as 'survived' if the patient was discharged alive or 'died' if the patient died during hospitalization. Nasopharyngeal swabs, sputum, and blood samples were collected from patients immediately upon admission after obtaining written informed consent. Patients were followed up daily during their entire hospitalization.

Radiological assessment

Chest radiographs were taken upon admission. Interpretation of the results was done by a designated radiologist. Chest X-ray results were assessed using the standardized definition of radiological pneumonia (Jain et al., 2015).

Detection of bacteria

Blood and respiratory cultures for bacteria were performed as described previously (Lupisan et al., 2000). On admission, venous blood was collected aseptically and inoculated into brain–heart infusion broth (1% gelatin, 0.025% sodium polyanethole sulfonate, and 0.1% Bacto agar). Samples were incubated at 36 ± 1 °C for 7 days and subcultures were grown on sheep blood agar, chocolate agar, and MacConkey agar plates. Antimicrobial susceptibility testing was performed by disk diffusion method and resistant isolates were confirmed by gradient diffusion for minimum inhibitory concentration (MIC) determination based on Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2010, 2011, 2012). Of the bacterial pathogens detected in sputum samples, only the following were considered true respiratory pathogens: *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *K. pneumoniae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, and B-hemolytic *Streptococcus* (Winn et al., 2006). Only those with significant growth were reported (Leber, 2016).

A multiplex PCR assay was performed using samples from nasopharyngeal swabs to detect atypical bacteria such as *Bordetella pertussis*, *M. pneumoniae*, *Legionella pneumophila*, and *C. pneumoniae*, as described previously (McDonough et al., 2005). Total DNA in the sample was purified using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany).

Patients collected their sputum for the detection of *M. tuberculosis* under the supervision of the project nurse. All processing of sputum samples was performed in a biosafety cabinet in the Research Project Laboratory at EVMRC. Suitability of each sputum sample was checked by the project medical technologist. Only suitable samples with epithelial cells <25 were processed. If suitable, sputum samples were processed for aerobic culture (blood agar, chocolate agar, MacConkey agar, gentamicin blood agar, bacitracin blood agar) and acid-fast bacillus smear. *M.*

tuberculosis culture was done using the Kudoh modified Ogawa technique and the World Health Organization prescribed procedure for the pre-analytical, analytical, and post-analytical phases at the National Tuberculosis Reference Laboratory, RITM (Fujiki, 2001). Identification of *M. tuberculosis* was done using niacin and capilla tests. If sputum samples were unsuitable, repeat sample collection was performed.

Detection of viruses

Nasopharyngeal swabs were obtained from patients using EX-swab 002 (Denka Seiken, Tokyo, Japan). Swabs were shipped at 4 °C to RITM for virus detection. Total nucleic acid was purified using the QIAamp MinElute Virus Spin Kit (Qiagen, Hilden, Germany). For the detection of RNA viruses, cDNA was synthesized using SuperScript III reverse transcriptase (Invitrogen, CA, USA) and random hexamers. The detection of human influenza virus, respiratory syncytial virus, human metapneumovirus, rhinovirus, enterovirus, adenovirus, and parainfluenza virus was performed by PCR assay, as described previously (Suzuki et al., 2012).

Statistical analysis

The association of clinical characteristics and pathogens with patients who survived and died was evaluated using the Chi-square test or Fisher's exact test. In the logistic regression analysis, continuous variables were converted to categorical variables. Only patients with chest X-ray results were included in the analysis. All variables with p-values <0.05 in the univariate analysis, including clinically relevant variables and potential confounders, were included in the multivariable logistic models to identify factors that were independently associated with fatal CAP. Three models were evaluated according to factors such as patient demographic characteristics and comorbidity information, clinical signs and symptoms. The model with lowest Akaike information criterion (AIC) value was selected as the best-fit model. Estimates and uncertainties were expressed as the odds ratio (OR) and 95% confidence interval (95% CI). All tests were two-tailed and p-values of <0.05 were considered significant. Data were encoded in a FileMaker database (FileMaker, CA, USA) and the statistical analysis was performed using SPSS 18.0J (SPSS Japan, Tokyo, Japan) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The study protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine and the institutional review boards of RITM and EVRMC. Written informed consent was obtained from patients or guardians prior to participation in the study.

Results

Patient characteristics

A total of 549 patients were enrolled during the study period (Figure 1). Of these patients, 14 reported PTB as a concurrent medical condition and were on anti-tuberculosis (TB) medications. These 14 patients were excluded and the remaining 535 were included in the analysis. Half of the patients were male and 38% were under 50 years of age (Table 1). On admission, 57% of the patients had an underlying disease, with PTB (22%) being the most frequently reported comorbidity. About 42% (224/535) were smokers and 9% (47/535) reported daily or weekly alcohol consumption.

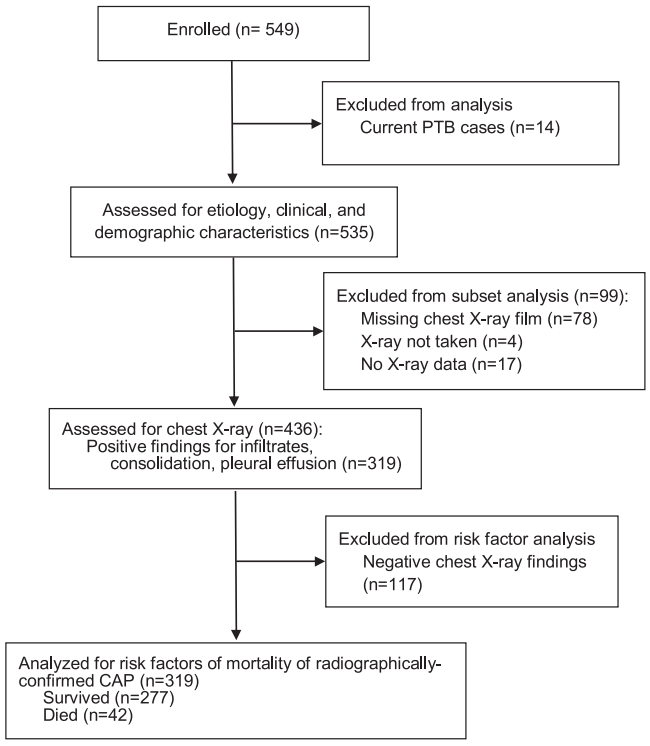

Figure 1. Enrolment and analysis of patients with community-acquired pneumonia requiring hospitalization.

Table 1
Demographic and clinical characteristics of the study patients.

Characteristics	*n* (%)
Total number of patients	535
Sex, male	271 (50.6)
Age group (years)[a]	
14–49	207 (38.7)
50–64	134 (25.0)
≥65	186 (34.8)
Previous history of PTB	110 (20.0)
Comorbid conditions on assessment during admission[b]	
PTB[c]	115 (21.5)
Cardiovascular disease	83 (15.5)
Hypertension	43 (8.0)
COPD	42 (7.8)
Asthma	18 (6.0)
Diabetes mellitus	14 (2.6)
Anemia	11 (2.0)
Renal disease	7 (1.3)
Pregnancy	6 (1.1)
Cancer	5 (1.0)
Number of comorbidities	
0	230 (43.0)
1	205 (38.3)
2	86 (16.1)
3+	14 (2.6)
Smoking	224 (41.9)
Alcohol drinking[d]	47 (8.8)
Use of antibiotics[e]	122 (22.8)
Use of corticosteroids	7 (1.3)

PTB, pulmonary tuberculosis; COPD, chronic obstructive pulmonary disease.
[a] Eight cases with missing age data.
[b] Medical conditions other than pneumonia in physician's assessment.
[c] Including 49 new PTB cases and 35 relapse/default cases.
[d] Daily or weekly consumption.
[e] Ninety-three of 122 were documented/validated.

Clinical manifestations

Cough (99%), rales (99%), and fatigue (97%) were the most common signs and symptoms among patients (Table 2). At the time of enrolment, 90% (481/535) of patients were classified as having moderate-risk pneumonia and 10% (54/535) as having high-risk pneumonia. Chest X-ray data were available for 81% (436/535) of the enrolled patients; infiltrates were seen in 45% (197/436), consolidation in 26% (114/436), pleural effusion in 11% (50/436), and negative findings in 26% (113/436). The average length of hospital stay for the study patients was 6 days.

Bacterial and viral etiologies of CAP

Bacteria were identified in 216 enrolled patients (40%), while viruses were identified in 68 enrolled patients (13%). The distribution of bacterial pathogens according to sample type is shown in the **Supplementary material** (Table S1). The most commonly identified bacteria were *H. influenzae* (64/535; 11.9%), followed by *K. pneumoniae* (62/535; 11.6%), *S. pneumoniae* (56/535; 10.5%), and *M. tuberculosis* (39/399; 9.8%) (Table 3). *S. aureus* were detected in 15 patients; six of these patients had MRSA. The most commonly detected virus among clinical CAP patients was influenza virus (28/535; 5.2%), followed by rhinovirus (17/535; 3.2%), respiratory syncytial virus (11/535; 2.1%), and human metapneumovirus (6/535; 1.1%). Bacterial and viral co-infections were observed in 6.5% (35/535) of the cases, with *H. influenzae* + human metapneumovirus (five cases) being the most frequent combination. Mixed bacterial co-infection was identified in 50 cases (9.3%), with *M. tuberculosis* + *H. influenzae* (five cases) being the most frequent co-infection. Mixed viral co-infections were observed in two cases and included influenza virus + enterovirus and influenza virus + human metapneumovirus.

Table 2
Clinical manifestations and laboratory findings for the study patients.

Findings	*n* (%)
Signs and symptoms	
Cough	534 (99.8)
Difficulty breathing	461 (86.2)
Apnea	71 (13.3)
Rhinorrhea	347 (64.9)
Sore throat	280 (52.3)
Intercostal retraction	379 (70.8)
Decreased breath sounds	78 (14.6)
Wheeze	115 (21.5)
Rales	529 (98.9)
Bronchophony	62 (11.6)
Percussion dullness	68 (12.7)
Myalgia	412 (77.0)
Fatigue	517 (96.6)
Shock	43 (8.0)
Irritability	34 (6.4)
Drowsiness	31 (5.8)
Cyanosis	12 (2.2)
Convulsions	4 (0.7)
Coma	5 (0.9)
Headache	356 (66.5)
Vomiting	121 (22.6)
Diarrhea	43 (8.0)
Vital signs	
Temperature ≥40 °C or ≤36 °C	60 (11.2)
Heart rate ≥125/min	337 (63.0)
Systolic blood pressure <90 mmHg	39 (7.3)
Respiratory rate ≥30/min	477 (89.2)
SpO_2 <90%	100 (18.7)
Chest X-ray findings[a]	
Infiltrate	197 (45.2)
Consolidation	114 (26.1)
Pleural effusion[b]	50 (9.3)
Patient classification	
Moderate-risk pneumonia	481 (89.9)
High-risk pneumonia	54 (10.1)
Length of hospital stay, mean (SD) days	6 (4)
Outcome at discharge	
Survived	459 (85.8)
Died	76 (14.2)

SD, standard deviation.
[a] Chest X-ray results for 436 cases (81.5%).
[b] Pleural effusion with or without infiltrates.

Table 3
Bacterial and viral etiologies in the study patients.

Findings	*n* (%)
Bacterial pathogens[a]	
Streptococcus pneumoniae	56 (10.5)
Haemophilus influenzae	64 (11.9)
Klebsiella pneumoniae	62 (11.6)
Staphylococcus aureus	9 (1.7)
Methicillin-resistant *Staphylococcus aureus*	6 (1.1)
Pseudomonas aeruginosa	22 (4.1)
Escherichia coli	3 (0.6)
Acinetobacter baumannii	1 (0.2)
Moraxella catarrhalis	6 (1.1)
Salmonella serotype Braenderup (group C1)	1 (0.2)
Burkholderia cepacia	1 (0.2)
Mycoplasma pneumoniae	1 (0.2)
Chlamydophila pneumoniae	3 (0.6)
Mycobacterium tuberculosis[b]	39 (9.8)
Viral pathogens[c]	
Influenza virus	28 (5.2)
Rhinovirus	17 (3.2)
Respiratory syncytial virus	11 (2.1)
Human metapneumovirus	6 (1.1)
Parainfluenza virus	4 (0.7)
Adenovirus	3 (0.6)
Enterovirus	1 (0.2)
Mixed pathogens	
Bacteria + virus	35 (6.5)
Bacteria + bacteria	50 (9.3)
Virus + virus	2 (0.4)

[a] Blood, sputum, and nasopharyngeal swab samples from all 535 cases were tested for bacterial identification.
[b] TB culture was done on suitable and adequate sputum samples from 399 cases, while 102 had no samples and 34 had an insufficient quantity of sample; there were no data for one case.
[c] PCR was performed on all 535 nasopharyngeal swab samples for virus identification.

Characteristics of the patients according to age

Patients were categorized into three age groups: 14–49 years, $n = 206$ (38%); 50–64 years, $n = 135$ (25%); and ≥65 years, $n = 186$ (37%) (Table 4). Three patients with missing age data were not included in the analysis. The proportions of patients who had hypertension, COPD, SpO_2 <90%, and *S. pneumoniae* infection were higher in the ≥65 years group than in the younger age groups. In contrast, the proportions of patients who had decreased breathing, vomiting, diarrhea, heart rate ≥125 beats/min, consolidation and pleural effusion on chest X-ray findings, and *M. tuberculosis* infection were highest in the young age group, 14–49 years old (Table 4).

Clinical outcomes of the study patients

Of the 535 patients evaluated for clinical outcome, 86% (459/535) survived while 14% (76/535) died (Table 5). All patients received antibiotic treatment during the study period. None of the patients received pneumococcal vaccination.

In the analysis of a subset of 319 patients with radiographic evidence of pneumonia, 87% (277/319) survived (Table 5). The case fatality rate of patients with radiographically confirmed CAP was 13% (42/319). Of the 319 patients who were evaluated by the CAP

Table 4
Characteristics of patients with community-acquired pneumonia according to age.

Characteristics	Age group (years)			*p*-Value
	14–49 (n = 206)	50–64 (n = 135)	≥65 (n = 186)	
Hypertension	4 (1.9)	14 (10.4)	29 (15.6)	<0.001[a]
COPD	3 (1.5)	12 (8.9)	26 (14.0)	<0.001[b]
Asthma	12 (5.8)	7 (5.2)	0 (0)	<0.001[b]
Smoking	61 (29.6)	64 (47.4)	93 (50.0)	<0.001[a]
Decreased breathing	46 (22.3)	17 (12.6)	14 (7.5)	<0.001[a]
Vomiting	65 (31.6)	25 (18.5)	31 (16.7)	0.002[a]
Diarrhea	26 (12.6)	5 (3.7)	12 (6.4)	0.009[e]
Drowsiness	5 (2.4)	6 (4.4)	18 (9.7)	0.007[d]
Heart rate ≥125 beats/min	139 (67.5)	79 (58.5)	113 (60.8)	<0.001[c]
Respiratory rate ≥30/min	179 (86.9)	120 (88.9)	120 (64.5)	<0.001[b]
SpO_2 <90%	21 (10.2)	30 (22.2)	46 (24.7)	<0.001[a]
Chest X-ray finding				
Consolidation	70 (34.0)	20 (14.8)	25 (13.4)	<0.001[a]
Infiltrate	89 (43.2)	69 (51.0)	106 (57.0)	<0.001[d]
Pleural effusion	33 (16.0)	6 (4.4)	11 (5.9)	<0.001[a]
Streptococcus pneumoniae	20 (9.7)	7 (5.1)	24 (12.9)	0.004[c]
Mycobacterium tuberculosis	22 (16.1)	10 (10.4)	5 (2.5)	<0.001[d]

COPD, chronic obstructive pulmonary disease.
[a] 14–49 years vs. 50–64 years, $p < 0.05$; 14–49 years vs. ≥65 years, $p < 0.05$.
[b] 14–49 years vs. ≥65 years, $p < 0.05$; 50–64 years vs. ≥65 years, $p < 0.05$.
[c] 14–49 years vs. 50–64 years, $p < 0.05$; 50–64 years vs. ≥65 years, $p < 0.05$.
[d] 14–49 years vs. ≥65 years, $p < 0.05$.
[e] 14–49 years vs. 50–64 years, $p < 0.05$.

classification upon initial diagnosis, the case fatality rate was significantly higher in the high-risk group than in the moderate-risk group (40% vs. 10%; $p < 0.01$).

In the univariate analysis of all cases, risk factors associated with mortality included shock, apnea, cyanosis, coma, irritability, drowsiness, SpO_2 <90%, and systolic blood pressure <90 mmHg (all $p < 0.05$) (Table 5). In the univariate analysis of radiographically confirmed CAP, the same factors were associated with mortality except for systolic blood pressure and headache, which was inversely associated with mortality (OR 0.43, 95% CI 0.21–0.88). In the multivariate analysis using logistic regression, model 2 was selected as the best-fit model for risk factors associated with mortality while controlling for sex, age, clinical signs and symptoms, both for all cases (AIC 392.24) and for radiographically confirmed cases (AIC 224.24) (Table 6). Drowsiness (adjusted OR (AOR) 5.95, 95% CI 2.03–17.45) and SpO_2 <90% (AOR 2.65, 95% CI 1.24–5.67) were identified as independent risk factors associated with mortality. Headache (AOR 0.39, 95% CI 0.19–0.79) remained negatively associated with mortality in the multivariate analysis (Table 6).

Discussion

In this study, clinical factors and bacterial and viral pathogens were identified among hospitalized adult patients with CAP in a rural area in Central Philippines. The results showed that the majority of CAP patients were younger than 50 years of age. *H. influenzae*, *K. pneumoniae*, *S. pneumoniae*, and *M. tuberculosis* were the most commonly identified bacteria, while influenza virus, rhinovirus, and respiratory syncytial virus were the most commonly detected viruses. The proportion of clinical CAP patients who died during hospitalization was as high as 13%, which indicates that pneumonia is an important cause of mortality in the country. It was observed that patients who died of pneumonia were most likely drowsy on admission and had an SpO_2 of <90%.

More than 38% of hospitalized CAP patients in this study were young adults who were less than 50 years old. This trend of younger CAP patients is similar to that reported in an earlier study in Vietnam (Takahashi et al., 2013). However, this is in contrast with the age distribution of CAP patients in Western countries, where the majority of patients are elderly (Mandell, 2004). This is the first study on adult pneumonia in this region of the country, and the reasons why CAP patients were mostly young in this study are currently unknown.

PTB was the most common comorbidity, which was observed in 22% of clinical CAP patients. Furthermore, the causative agent, *M. tuberculosis*, was one of the most commonly isolated pathogens and was detected in 10% of clinical CAP cases. This confirms the high prevalence of TB in the country, with the national prevalence rate being 4.7 per 1000 for culture-positive TB in 2007 (Vianzon et al., 2013). This implies that TB patients are more likely to develop CAP. In this study, younger adults aged 14–49 years had a higher proportion of *M. tuberculosis* infection than elderly patients aged ≥65 years (16% vs. 2%, $p < 0.001$). Compared to CAP patients in the USA and Europe, a distinguishing feature of adult pneumonia in low and middle-income countries in Asia is the higher proportion of cases with PTB presenting as CAP requiring hospital admission (Chan et al., 1992; Liam et al., 2006; Garg et al., 2015). *M. tuberculosis* should be considered an important risk factor for CAP in areas where TB is endemic (Luna et al., 2000; Miller et al., 2000).

Pathogens were identified in 53% of clinical CAP cases, with bacteria detected in 40% and viruses detected in 13%. This percentage is within the range of detection (20–76%) in previous studies on adult pneumonia (Song et al., 2008; Brown, 2009; Takahashi et al., 2013; Garg et al., 2015). However, the distribution of bacterial and viral pathogens is in contrast with that found in a previous study on hospitalized children with pneumonia in the Philippines, where respiratory viruses (61%) were more frequently detected than bacteria (4%) (Suzuki et al., 2012). It should be noted that the low frequency of detection of bacteria among children with pneumonia may be due to the low sensitivity of the blood culture method and the difficulty of obtaining appropriate sputum samples from children. Nonetheless, the difference in the distribution of pathogens indicates the importance of identifying bacterial and viral pathogens for guidelines on the management of adult and childhood pneumonia.

Among the pathogens identified, *S. pneumoniae* was one of the most commonly isolated bacteria. This is consistent with previous reports from other Asian countries, the USA, and Europe, which showed *S. pneumoniae* to be the most common pathogen associated with hospitalization among adult CAP patients (Marrie et al., 1989; Mandell, 2004; Song et al., 2008; Takahashi et al., 2013). During the study period, pneumococcal vaccination for adults was not yet included in the national vaccination program. Thus, none of the patients in this study received pneumococcal vaccines. This highlights the need for pneumococcal vaccination among adults who are at risk of CAP in the country.

In the present study, *K. pneumoniae* was isolated in 11% of clinical CAP patients, which is in contrast to studies in the USA and Europe, where *K. pneumoniae* was detected less frequently in CAP patients (Mandell et al., 2007; Brown, 2009; Jain et al., 2015). However, in a study in Taiwan on patients with severe CAP requiring mechanical ventilation, *K. pneumoniae* was the most commonly isolated bacterium and accounted for 38% of mortality among CAP patients (Hu et al., 2005). This highlights the significance of this pathogen in severe CAP cases in the region.

Respiratory viruses were detected in 13% of adult CAP cases, with influenza virus being the most common, followed by rhinovirus and respiratory syncytial virus. While this percentage is within the range of results from previous studies (9–56%), it is lower when compared to temperate countries (Falsey and Walsh, 2006; Lieberman et al., 2010; Ruuskanen et al., 2011; Burk et al., 2016). Concomitant detection of viral and bacterial pathogens among CAP cases has been observed in significant proportions in previous reports and it is more severe than viral infections alone when comparing hospitalization rates (Ruiz et al., 1999a; Falsey and Walsh, 2006; Ruuskanen et al.,

Table 5
Factors associated with mortality among patients with community-acquired pneumonia.

Factors	All cases (n = 535)				Radiographically confirmed CAP (n = 319)			
	Survived n = 459 (%)	Died n = 76 (%)	OR (95% CI)	p-Value	Survived n = 277 (%)	Died n = 42 (%)	OR (95% CI)	p-Value
Sex, male	229 (50)	42 (55)	1.24 (0.74–2.09)	0.458	165 (60)	24 (57)	0.90 (0.45–1.85)	0.866
Age (years)								
14–49	178 (39)	28 (37)	0.76 (0.42–1.36)	0.329	110 (39)	15 (36)	0.74 (0.33–1.67)	0.458
50–64	121 (26)	14 (18)	0.56 (0.26–1.13)	0.106	69 (25)	8 (19)	0.65 (0.23–1.69)	0.393
65–88	154 (34)	32 (42)	Ref.		99 (36)	18 (43)	Ref.	
Underlying conditions[a]								1.000
Cardiovascular disease	48 (10)	8 (10)	0.97 (0.38–2.18)	1.000	30 (11)	2 (5)	0.42 (0.05–1.76)	0.281
Hypertension	40 (9)	7 (9)	1.06 (0.39–2.53)	0.829	19 (7)	1 (2)	0.34 (0.01–2.23)	0.331
COPD	38 (8)	4 (5)	0.62 (0.16–1.79)	0.491	21 (8)	3 (7)	0.95 (0.17–3.41)	1.000
Asthma	18 (4)	1 (1)	0.33 (0.01–2.13)	0.498	4 (1)	1 (2)	1.68 (0.03–17.52)	0.505
Cancer	4 (1)	1 (1)	1.52 (0.03–15.58)	0.537	4 (1)	1 (2)	1.68 (0.03–17.52)	0.505
Smoking	189 (41)	35 (46)	1.22 (0.72–2.04)	0.452	125 (45)	19 (45)	1.02 (0.50–2.07)	1.000
Alcohol drinking	36 (8)	11 (14)	1.99 (0.87–4.24)	0.077	28 (10)	7 (17)	1.80 (0.62–4.63)	0.190
Use of antibiotics	130 (28)	24 (32)	1.17 (0.66–2.02)	0.585	75 (27)	14 (33)	1.36 (0.63–2.85)	0.362
Use of corticosteroids	6 (1)	1 (1)	1.01 (0.02–8.48)	1.000	5 (2)	1 (2)	1.34 (0.03–12.42)	0.571
Cough	458 (100)	76 (100)	–	1.000	277 (100)	42 (100)	–	1.000
Difficulty breathing	390 (85)	71 (93)	2.51 (0.97–8.25)	0.049	241 (87)	39 (93)	2.10 (0.62–11.13)	0.325
Apnea	45 (10)	26 (34)	4.76 (2.59–8.69)	<0.001	32 (11)	13 (31)	3.41 (1.47–7.64)	0.003
Rhinorrhea	300 (65)	47 (62)	0.85 (0.51–1.45)	0.526	175 (63)	26 (62)	0.98 (0.48–2.04)	1.000
Sore throat	240 (52)	40 (53)	1.01 (0.61–1.70)	1.000	132 (48)	22 (52)	1.23 (0.61–2.50)	0.620
Intercostal retraction	320 (70)	59 (78)	1.51 (0.83–2.86)	0.175	198 (71)	35 (84)	2.11 (0.88–5.84)	0.099
Decreased breath sounds	70 (15)	8 (10)	0.65 (0.26–1.44)	0.379	50 (20)	5 (12)	0.55 (0.16–1.49)	0.290
Wheeze	97 (21)	18 (24)	1.16 (0.61–2.10)	0.651	51 (18)	9 (21)	1.21 (0.48–2.79)	0.672
Rales	453 (99)	79 (100)	–	0.601	272 (98)	44 (100)	–	1.000
Bronchophony	55 (12)	7 (9)	0.74 (0.27–1.73)	0.566	44 (16)	5 (12)	0.72 (0.21–1.97)	0.648
Percussion dullness	60 (13)	8 (10)	0.78 (0.31–1.74)	0.710	48 (17)	6 (14)	0.80 (0.26–2.05)	0.796
Myalgia	356 (78)	56 (74)	0.81 (0.45–1.49)	0.463	217 (78)	32 (76)	0.93 (0.42–2.24)	0.845
Fatigue	443 (97)	74 (97)	1.34 (0.30–12.21)	1.000	268 (97)	40 (95)	0.90 (0.19–8.54)	0.702
Shock	25 (5)	18 (24)	5.36 (2.59–10.95)	<0.001	15 (5)	11 (26)	6.14 (2.33–15.82)	<0.001
Irritability	24 (5)	10 (13)	2.74 (1.12–6.27)	0.018	11 (4)	7 (17)	4.80 (1.48–14.63)	0.004
Drowsiness	11 (2)	20 (26)	14.41 (6.21–35.19)	<0.001	9 (3)	11 (26)	10.42 (3.62–30.94)	<0.001
Cyanosis	7 (2)	5 (7)	4.53 (1.10–17.09)	0.018	4 (1)	3 (7)	5.21 (0.87–32.05)	0.051
Convulsions	4 (1)	0 (0)	0.00 (0.00–9.21)	1.000	2 (1)	0 (0)	0.00 (0.00–35.78)	1.000
Coma	2 (0.4)	3 (4)	9.32 (1.05–113.44)	0.022	1 (0.4)	2 (5)	13.59 (0.69–812.14)	0.047
Headache	311 (68)	45 (59)	0.69 (0.41–1.18)	0.150	182 (66)	18 (45)	0.43 (0.21–0.88)	0.017
Vomiting	105 (23)	16 (21)	0.90 (0.46–1.66)	0.882	56 (20)	9 (21)	1.09 (0.43–2.50)	0.838
Diarrhea	34 (7)	9 (12)	1.68 (0.68–3.78)	0.178	22 (8)	3 (7)	0.90 (0.16–3.22)	1.000
Temperature ≥40 °C or <35 °C	50 (11)	10 (13)	1.24 (0.53–2.63)	0.557	28 (10)	6 (14)	1.48 (0.47–3.40)	0.421
Heart rate ≥125/min	285 (62)	52 (68)	1.32 (0.77–2.33)	0.308	170 (61)	32 (76)	2.01 (0.92–4.77)	0.085
Systolic blood pressure <90 mmHg	27 (6)	12 (16)	2.99 (1.31–6.48)	0.006	19 (7)	5 (12)	1.83 (0.50–5.48)	0.223
Respiratory rate >30/min	412 (90)	65 (86)	0.67 (0.32–1.52)	0.317	255 (92)	37 (88)	0.64 (0.22–2.29)	0.375
SpO_2 <90%	53 (11)	21 (28)	2.92 (1.55–5.37)	<0.001	53 (19)	21 (48)	3.82 (1.83–7.95)	<0.001
Chest X-ray findings								
Infiltrate	173 (38)	24 (32)	0.76 (0.43–1.31)	1.000	172 (61)	24 (57)	0.84 (0.41–1.72)	0.614
Consolidation	97 (21)	17 (22)	1.08 (0.56–1.97)	0.880	97 (35)	17 (40)	1.26 (0.61–2.57)	0.494
Pleural effusion	44 (10)	6 (8)	0.81 (0.27–2.00)	0.832	44 (16)	5 (14)	0.88 (0.29–2.29)	1.000
Patient classification								
Moderate-risk pneumonia	429 (94)	52 (68)	Ref.	–	260 (92)	30 (68)	Ref.	–
High-risk pneumonia	30 (6)	24 (32)	6.56 (3.39–12.62)	<0.001	20 (7)	14 (33)	6.36 (2.67–15.00)	<0.001
Length of hospital stay ≥7 days	115 (25)	15 (20)	0.74 (0.37–1.37)	0387	78 (28)	8 (19)	0.60 (0.22–1.40)	0.265
Bacterial pathogens								
Streptococcus pneumoniae	50 (11)	5 (7)	0.58 (0.17–1.51)	0.311	36 (13)	4 (9)	0.70 (0.17–2.14)	0.626
Haemophilus influenzae	58 (13)	6 (8)	0.59 (0.20–1.44)	0.338	32 (12)	4 (9)	0.81 (0.20–2.46)	1.000
Klebsiella pneumoniae	51 (11)	11 (14)	1.35 (0.60–2.80)	0.438	30 (10)	7 (17)	1.64 (0.57–4.21)	0.299
Staphylococcus aureus	11 (2)	4 (5)	2.26 (0.51–7.89)	0.248	6 (2)	3 (7)	3.45 (0.54–16.97)	0.101
Pseudomonas aeruginosa	19 (4)	4 (5)	1.26 (0.31–4.02)	0.553	10 (4)	2 (5)	1.33 (0.14–6.60)	0.663
Mycobacterium tuberculosis	33 (9)	6 (19)	2.41 (0.75–6.60)	0.106	26 (7)	4 (13)	1.93 (0.46–6.12)	0.277
Viral pathogens								
Influenza virus	20 (4)	6 (8)	1.87 (0.60–5.07)	0.242	12 (4)	2 (5)	1.10 (0.12–5.24)	1.000
Rhinovirus	17 (4)	0 (0)	0.00 (0.00–1.44)	0.149	10 (4)	0 (0)	0.00 (0.00–2.63)	0.371
Respiratory syncytial virus	10 (2)	1 (1)	0.60 (0.01–4.32)	1.000	5 (2)	0 (0)	0.00 (0.00–7.30)	1.000
Human metapneumovirus	5 (1)	0 (0)	0.00 (0.00–5.16)	0.601	4 (1)	0 (0)	0.00 (0.00–10.13)	1.000
Parainfluenza virus	4 (1)	0 (0)	0.00 (0.00–9.22)	1.000	2 (1)	0 (0)	0.00 (0.00–35.40)	1.000
Adenovirus	2 (0.4)	1 (1)	3.03 (0.05–59.06)	0.369	1 (0.4)	1 (2)	6.66 (0.08–527.81)	0.246
Mixed pathogens								
Bacteria + virus	33 (7)	3 (4)	0.53 (0.10–1.76)	0.456	10 (7)	1 (4)	0.55 (0.01–4.24)	1.000
Bacteria + bacteria	46 (9)	6 (8)	0.85 (0.28–2.12)	0.831	0 (0)	0 (0)	–	–
Virus + virus	2 (0.4)	0 (0)	0.00 (0.00–14.49)	1.000	1 (0.4)	0 (0)	0.00 (0.00–248.11)	1.000

OR, odds ratio; CI, confidence interval; Ref., reference; COPD, chronic obstructive pulmonary disease.
[a] Multiple conditions in some patients.

Table 6
Independent factors associated with mortality in patients with community-acquired pneumonia.

Factors	All cases AOR (95% CI)	Radiographically confirmed cases AOR (95% CI)
Male sex	1.26 (0.74–2.14)	0.93 (0.45–1.90)
Age ≥65 years	1.11 (0.64–1.92)	1.15 (0.55–2.40)
Drowsiness	9.08 (3.81–21.19)	5.95 (2.03–17.45)
Headache	–	0.39 (0.19–0.79)
SpO_2 <90%	1.98 (1.08–3.62)	2.65 (1.24–5.67)
Systolic blood pressure <90 mmHg	2.13 (0.92–4.96)	–

AOR, adjusted odds ratio; CI, confidence interval.

2011). In the present study, bacterial and viral co-detection was only observed in 6% of clinical CAP cases and there were no significant differences in proportions between patients who survived and those who died. This may be due to the low proportion of viral infections among clinical CAP patients in this study. Since sequential viral and bacterial infections were not investigated, there is a possibility that clinical CAP patients may initially have had a viral infection with milder symptoms that may already have resolved upon hospital admission and then developed more severe symptoms with a subsequent bacterial infection.

In previous reports, risk factors associated with mortality among CAP patients included nursing home residence, mechanical ventilation, malignancy, cardiovascular disease, chronic lung disease, renal disease, immunosuppression, respiratory rate >30/min, hyponatremia, abnormal arterial CO_2 tension, and treatment failure (Ruiz et al., 1999b; Menendez et al., 2004; Roson et al., 2004; Sin et al., 2005; Song et al., 2008). In this study, the proportions of comorbidities, signs and symptoms were similar in patients who survived and those who died except for shock, apnea, cyanosis, coma, irritability, drowsiness, and SpO_2 <90%. After adjusting for sex, age, the presence of underlying conditions, and signs and symptoms, the independent risk factors associated with mortality among radiographically confirmed CAP patients were drowsiness and SpO_2 <90%. The latter emphasizes the importance of SpO_2 monitoring in the management of hospitalized CAP patients, especially in resource-limited settings, where access to pulse oximetry has been associated with improvements in patient outcomes (Kwok et al., 2013).

There are limitations to this study. First, it was not possible to perform a chest X-ray on all enrolled patients and some X-ray results were missing, which may have resulted in underreporting of CAP cases. Second, it was not possible to collect sputum from all patients for TB culture. This may have affected the proportions of pathogens detected between the 'survived' and 'died' groups. Third, the study site is a tertiary hospital in a rural area, where the data obtained might not be representative of the entire adult population in the Philippines.

Despite these limitations, the data generated from this study will add to the CAP data in the Philippines. The usefulness of CAP classification in the management of CAP in the country cannot be overemphasized.

In conclusion, CAP remains a major cause of morbidity and mortality, especially among young adults in the country. Bacterial pathogens, such as *M. tuberculosis*, *H. influenzae*, and *K. pneumoniae*, were detected more frequently than viruses, which indicates the substantial role of bacterial pneumonia in the etiology of CAP in adults. In resource-poor settings, drowsiness and SpO_2 <90% may be predictors of mortality among adult patients with CAP and may serve as indicators for immediate referral.

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Conflict of interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.12.005.

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