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# Relationship Between Clinical Features and Computed Tomographic Findings in Hospitalized Adult Patients With Community-Acquired Pneumonia



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## ABSTRACT

**Background:** Data on the relationship between the clinical and microbiological features of community-acquired pneumonia (CAP) and its computed tomography (CT) findings are limited. The aim of the present study was to investigate the clinic-microbiological features of patients with CAP presenting with ground-glass opacity (GGO) and centrilobular nodules or tree-in-bud pattern on CT images.

**Methods:** Patients with CAP who underwent a CT scan at presentation were retrospectively classified using CT findings into consolidation, GGO and bronchiolitis groups. These 3 groups were compared in terms of clinical parameters and microbiological data.

**Results:** A total of 40 patients (2.4%) were allocated to the bronchiolitis group and 46 (2.8%) to the GGO group. The most common pathogen in the bronchiolitis group was *Mycoplasma pneumoniae*, which was significantly more frequently isolated in this group. The bronchiolitis group was characterized by a higher percentage of cough, a lower percentage of chest pain and lower blood levels of inflammatory markers. Common pathogens in the GGO group were not significantly different from those in the other 2 groups. Unlike that observed in the consolidation group, complicated parapneumonic effusion or empyema was not observed in the bronchiolitis or GGO group. Outcome variables were similar in the 3 groups.

**Conclusions:** The bronchiolitis group was characterized by a higher frequency of *M. pneumoniae* and a less severe form of CAP. The GGO and consolidation groups was similar with respect to causative microorganisms and the clinical features of CAP. No patient in the bronchiolitis or GGO group exhibited complicated parapneumonic effusion or empyema.

**Key Indexing Terms:** Bronchiolitis; Community-acquired pneumonia; Computed tomography; *Mycoplasma pneumoniae*. [Am J Med Sci 2018;356(1):30–38.]

## INTRODUCTION

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality worldwide, despite the use of an antibiotic armamentarium and the availability of vaccines.<sup>1</sup> Therefore, early diagnosis and appropriate antimicrobial treatment are critical steps in the management of CAP. Chest radiography is usually used in combination with a constellation of compatible symptoms or signs, such as cough and sputum production to confirm the diagnosis of pneumonia.<sup>2,3</sup> Computed tomography (CT) is useful when the plain chest radiograph does not reveal findings that explain the patient's clinical presentation.<sup>4</sup> CT images can provide more detailed information

regarding lung parenchyma,<sup>1</sup> suggest specific causative agents,<sup>5</sup> rule out noninfectious pneumonia<sup>5</sup> and detect other underlying conditions.<sup>4</sup> Thus, CT provides additional benefits for the diagnosis of CAP and aids its typing.<sup>2</sup> In particular, when performed early, CT can affect the diagnosis and clinical management of CAP in the emergency department.<sup>4</sup> Accordingly, the use of CT in patients with suspected CAP can be expected to increase in real world practice.

A variety of microbial agents, including typical and atypical pathogens, can cause CAP. A considerable number of studies on the CT findings of CAP triggered by different pathogens, including *Streptococcus pneumoniae*,<sup>6-8</sup> *Klebsiella pneumoniae*,<sup>9,10</sup> *Mycoplasma*

*pneumoniae*,<sup>11-14</sup> *Chlamydia pneumoniae*<sup>14,15</sup> and *Legionella pneumophila*,<sup>16,17</sup> have been published. Patients with CAP attributed to a specific pathogen present with more than 1 CT pattern, although 1 of these patterns predominates.<sup>5</sup> CAP has been classically divided into 3 patterns based on CT findings, that is, consolidation-predominant, peribronchial nodules-predominant and ground-glass opacity (GGO)-predominant.<sup>5</sup> However, data on relationships between the clinical and microbiologic features of CAP and CT findings are scarce. In CAP, pure or nearly pure GGO lesions are uncommon regardless of causative pathogens,<sup>16,18</sup> and a CT finding multiple centrilobular nodules is also rare.<sup>19</sup> We hypothesized that the clinical manifestations of patients with CAP are related to CT findings, and thus, we compared the clinical features and microbiologic data of CAP patients classified based on CT findings.

## MATERIALS AND METHODS

### Study Design

We retrospectively enrolled consecutive patients with CAP admitted to and treated at the Respiratory Department of Kyungpook National University Hospital (KNUH), a tertiary referral center, in Daegu, South Korea between January 2011 and December 2016.<sup>20</sup> Baseline patient characteristics were recorded at admission, although not all patients underwent the same laboratory tests. Pneumonia was diagnosed using the following criteria: (1) a new radiographic infiltrate, (2) 1 or more symptoms or signs consistent with pneumonia (cough, sputum, dyspnea, fever or pleuritic chest pain) and (3) the exclusion of other causes.<sup>21</sup> Patients with hospital-acquired pneumonia,<sup>22</sup> healthcare-associated pneumonia,<sup>22</sup> an active thoracic malignancy or taking immunosuppressants or steroids (>15 mg/day of prednisone for >14 days) were excluded. Patients without an available chest CT scan at presentation were also excluded.

The CT findings of CAP were classified into 3 categories: bronchiolitis, GGO and consolidation. These 3 groups were compared in terms of clinical characteristics and microbiologic data. The study was approved by the Institutional Review Board of KNUH, which waived the requirement for written informed patient consent because of the retrospective nature of the study.

### Radiologic Data

Two chest radiologists (J.K.L. and K.M.S.) reviewed the chest CT scans of patients with CAP and classified them into the 3 groups (Figure). In the bronchiolitis group, chest CT indicated centrilobular nodules or tree-in-bud pattern in most lesions with no or minimal GGO or consolidation (Figure).<sup>23</sup> In the GGO group, chest CT indicated focal or diffuse GGO with no or minimal centrilobular nodules, tree-in-bud pattern or consolidation. In the consolidation group, chest CT

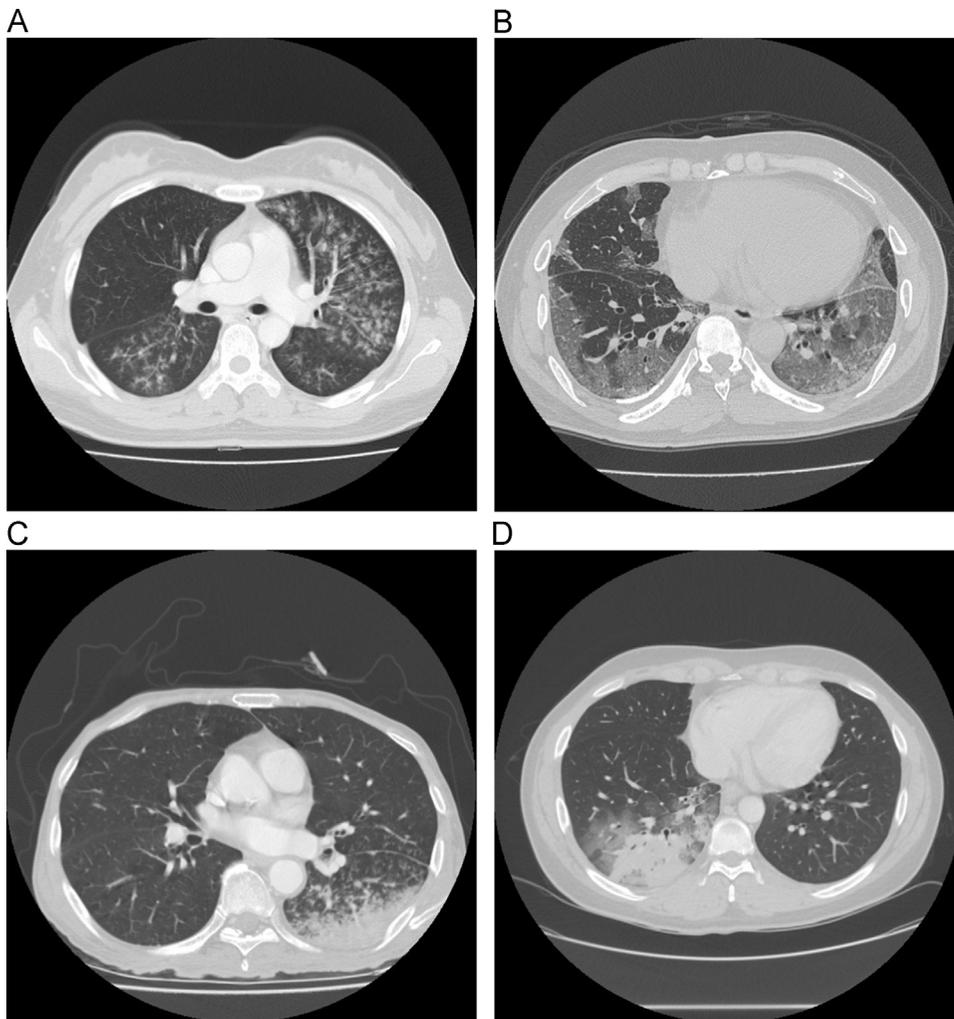
indicated consolidation with or without variable extents of the CT features of bronchiolitis or GGO.

### Data Collection

Two chest physicians (H.S. and S.I.C.) reviewed medical records. Resident physicians initially recorded baseline data, which were confirmed by attending chest physicians. Demographic data included age, sex, smoking history and alcohol consumption. Heavy drinking was defined as the consumption of 7 or more drinks (>60 g of alcohol) on 1 occasion for men, and 5 or more drinks (>40 g of alcohol) on 1 occasion for women at least twice a week. We reviewed symptoms, vital signs, comorbidities, pneumonia severity indices,<sup>24</sup> CURB-65 scores,<sup>25</sup> Eastern Cooperative Oncology Group (ECOG) performance statuses<sup>26</sup> and retrospectively calculated Charlson comorbidity indices.<sup>27</sup> Use of mechanical ventilation, corticosteroid treatment, vasopressor infusion and pleural drainage with percutaneous catheters or chest tubes were checked. Outcome variables included length of hospital stay, 30-day mortality, in-hospital mortality and clinical success. Treatment success was defined as improvements in clinical symptoms or signs and radiologic findings. Laboratory data included complete blood count, erythrocyte sedimentation rate, liver function testing, C-reactive protein (CRP), procalcitonin, N-terminal of prohormone brain natriuretic peptide, blood urea nitrogen, creatinine, sodium, lactate dehydrogenase, lactate and arterial blood gas analysis.

### Microbiological Data

The criteria for a causative pathogen were as follows<sup>21</sup>: a microorganism isolated from blood or pleural fluid; positive urinary antigen test for *S. pneumoniae* or *L. pneumophila* serogroup 1 (BinaxNOW *S. pneumoniae* and *Legionella* urinary antigen cards, Alere, Scarborough, ME); a culture of bacteria from a sputum sample (>25 neutrophils and <10 squamous epithelial cells per low-power field) collected within 24 hours of admission plus a compatible Gram-stain finding; identification of *M. pneumoniae* based on a positive immunoglobulin M (IgM) result or a 4-fold increase in immunoglobulin G (IgG) levels in convalescent versus initial blood samples by chemiluminescence immunoassay (LIAISON, DiaSorin, Saluggia, Italy) or positivity for *M. pneumoniae* in a sputum by polymerase chain reaction (PCR) (AmpliSens *Mycoplasma pneumoniae*-FEP PCR, Central Research Institute for Epidemiology, Moscow, Russia); the presence of *C. pneumoniae* as determined by a positive IgM or a 4-fold increase in IgG levels by micro-immunofluorescence (an in-house method) or by enzyme-linked immunosorbent assay (Diesse Diagnostica Senese, Monteriggioni, Italy); positivity for a respiratory virus (adenovirus, influenza [types A and B], parainfluenza virus [types 1, 2, 3 and 4], rhinovirus, respiratory syncytial virus [types A and B], bocavirus, metapneumovirus, coronavirus [229E, NL63 and OC43]



**FIGURE.** Representative computed tomography images of community-acquired pneumonia. Computed tomography (CT) findings in the bronchiolitis group (A) indicate centrilobular nodules or tree-in-bud pattern in most lesions with no or minimal ground glass opacity (GGO) or consolidation. CT findings in the GGO group (B) indicate focal or diffuse GGO with no or minimal centrilobular nodules, tree-in-bud pattern or consolidation. CT findings in the consolidation group show consolidation with or without variable extents of bronchiolitis or GGO (C-D).

or enterovirus) in a throat or nasopharyngeal swab as determined by multiplex PCR (Anyplex RV16 detection, Seegene, Seoul, Korea) and the identification of influenza A or B antigen in a throat swab by rapid chromatographic immunoassay (SD BIOLINE Influenza Antigen test, Standard Diagnostics, Yongin, Korea or BD Veritor System for Rapid Detection of FluA+B, BD Diagnostics, Sparks, MD).

#### Statistical Analysis

Data were expressed as medians (interquartile ranges) for continuous variables or as numbers and percentages for categorical variables. Continuous variables were compared using the Kruskal-Wallis test, and Dunn's test was used as a *post-hoc* test. Categorical variables were compared using the chi-square test among groups and Bonferroni's correction was

used as a *post-hoc* follow-up test. The kappa statistic was used to measure interinterpreter agreement regarding CT findings. IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY) was used for the statistical analysis.  $P < 0.05$  was considered statistically significant.

## RESULTS

#### Enrolled Patients

Initially, 1,708 patients with CAP were identified. Of these, 12 patients without available CT scans and 31 patients with no identifiable parenchymal lesion due to parapneumonic effusion were excluded. Consequently, 1,665 patients were included in the study. For patients admitted between 2015 and 2016 ( $n = 531$ ), 2 radiologists (K.M.S. and J.K.L.) independently reviewed the

**TABLE 1.** Baseline characteristics of the patients.

Characteristics	Consolidation (n = 1,579)	Bronchiolitis (n = 40)	GGO (n = 46)	P Value
Age, years	69 (56-77)	64 (39-74)	66 (53-76)	0.080
Male	1,053 (66.7)	25 (62.5)	31 (67.4)	0.852
Smoking				
Ever-smoker	896 (56.9)	20 (50.0)	21 (45.7)	0.225
Pack-years	10 (0-33)	2.5 (0-20)	0 (0-30)	0.121
Heavy drinking	282 (17.9)	2 (5.0)	5 (10.9)	0.053
Charlson comorbidity index	0 (0-1)	0 (0-1)	0 (0-1)	0.148
ECOG 3-4	217 (13.7)	6 (15.0)	2 (4.3)	0.178
Systolic blood pressure, mmHg	130 (112-147)	129 (104-142)	128 (102-139)	0.476
Pulse rate/minute	96 (83-109)	92 (82-113)	99 (83-114)	0.652
Respiratory rate/minute	20 (19-22)	19 (18-20)	20 (20-24)	0.004 <sup>a</sup>
Symptoms				
Duration of symptom, days	5 (3-7)	6 (3-7)	5 (2-8)	0.580
Cough	1,368 (86.6)	40 (100.0)	44 (95.7)	0.010 <sup>b</sup>
Sputum production	1,132 (71.7)	35 (87.5)	33 (71.7)	0.089
Dyspnea	884 (56.0)	20 (50.0)	31 (67.4)	0.224
Fever	1,025 (64.9)	23 (57.5)	30 (65.2)	0.624
Altered mental status	84 (5.3)	1 (2.5)	0 (0.0)	0.253
Hemoptysis	130 (8.2)	2 (5.0)	4 (8.7)	0.859
Chest pain	389 (24.6)	0 (0.0)	6 (13.0)	<0.001 <sup>c</sup>
CURB-65	1 (0-2)	1 (0-2)	1 (0-2)	0.182
CURB-65, 3-5	152 (9.6)	1 (2.5)	2 (4.3)	0.199
PSI class	3 (2-4)	2 (1-4)	3 (2-4)	0.099
PSI class 4-5	550 (34.8)	12 (30.0)	13 (28.3)	0.542
Pleural effusion	643 (40.7)	3 (7.5)	10 (21.7)	<0.001 <sup>d,e</sup>
Complicated parapneumonic effusion or empyema	145 (9.2)	0 (0.0)	0 (0.0)	0.006
Pleural drainage	173 (11.0)	0 (0.0)	0 (0.0)	0.001 <sup>f</sup>
Mechanical ventilation	95 (6.0)	0 (0.0)	3 (6.5)	0.300
Corticosteroids	353 (22.4)	6 (15.0)	19 (41.3)	0.005 <sup>g,h</sup>
Vasopressor infusion	142 (9.0)	1 (2.5)	3 (6.5)	0.380
30-day mortality	121 (7.7)	2 (5.0)	4 (8.7)	0.850
In-hospital mortality	105 (6.6)	1 (2.5)	3 (6.5)	0.730
Length of hospital stay, days	9 (6-13)	7 (6-10)	9 (6-14)	0.138
Treatment success	1,428/1,551 (92.1)	36/39 (92.3)	42/45 (93.3)	>0.999

Data are presented as median (interquartile range) or *n* (%).

CURB-65, a 6 point score, 1 point for each of confusion, urea 47 mmol/L, respiratory rate  $\geq 30$ /minute, low systolic (<90 mm Hg) or diastolic ( $\leq 60$  mm Hg) blood pressure, and age  $\geq 65$  years; ECOG, Eastern Cooperative Oncology Group performance status; GGO, ground glass opacity; PSI, pneumonia severity index. *Post-hoc* analysis.

<sup>a</sup> Bronchiolitis vs. GGO,  $P = 0.003$  (Dunn's test).

<sup>b</sup> Bronchiolitis vs. consolidation, Bonferroni's corrected  $P = 0.013$ .

<sup>c</sup> Bronchiolitis vs. consolidation, Bonferroni's corrected  $P < 0.001$ .

<sup>d</sup> Bronchiolitis vs consolidation, Bonferroni's corrected  $P < 0.001$ .

<sup>e</sup> GGO vs. consolidation, Bonferroni's corrected  $P = 0.010$ .

<sup>f</sup> GGO vs. consolidation, Bonferroni's corrected  $P = 0.012$ .

<sup>g</sup> GGO vs. consolidation, Bonferroni's corrected  $P = 0.003$ .

<sup>h</sup> GGO vs. bronchiolitis, Bonferroni's corrected  $P = 0.007$ .

CT findings and classified them as consolidation, bronchiolitis or GGO by consensus (the kappa statistic was 0.943). For the remaining patients, 1 of the 2 radiologists determined CT findings. Of the 1,665 patients, 40 (2.4%) were included in the bronchiolitis group, 46 (2.8%) in the GGO group and 1,579 (94.8%) in the consolidation group. Clinical and microbiologic variables of these 3 groups were compared.

### Clinical Characteristics of the Bronchiolitis, GGO and Consolidation Groups

Clinical parameters are presented in Table 1. The percentage of patients with cough differed significantly among the groups, and the percentage was significantly greater in the bronchiolitis group than in the consolidation group (40 [100.0%] versus 1,368 [86.6%],  $P = 0.013$ ). The frequency of chest pain significantly

**TABLE 2.** Blood laboratory findings of the patients.

Parameters	Consolidation	n	Bronchiolitis	n	GGO	n	P-value
WBC count, / $\mu$ L	10,710 (7,680-15,220)	1,579	10,400 (6,955-13,783)	40	10,385 (7,735-15,350)	46	0.782
ESR, mm/hour	45 (28-64)	1,572	40 (24-61)	40	39 (16-56)	46	0.183
C-reactive protein, mg/dL	12.9 (6.6-21.0)	1,575	9.3 (3.7-14.0)	40	12.0 (6.1-16.9)	46	0.011 <sup>a</sup>
Procalcitonin, ng/mL	0.35 (0.10-1.79)	1,479	0.11 (0.06-0.42)	37	0.21 (0.10-0.90)	40	0.007 <sup>b</sup>
NT-proBNP, pg/mL	432.0 (139.0-1,589.8)	1,480	401.0 (53.0-998.0)	35	365.1 (89.8-1,045.0)	44	0.287
Troponin I, ng/mL	0.015 (0.015-0.030)	1,304	0.015 (0.015-0.050)	28	0.015 (0.015-0.019)	42	0.272
Hemoglobin, g/dL	12.5 (11.2-13.6)	1,579	13.3 (11.0-14.3)	40	13.0 (11.4-14.5)	46	0.067
Platelet, $10^3/\mu$ L	235 (176-318)	1,579	235 (177-294)	40	243 (192-307)	46	0.799
Albumin, g/dL	3.3 (2.9-3.8)	1,579	3.5 (3.4-4.0)	40	3.5 (3.0-3.8)	46	0.002 <sup>c</sup>
Total protein, g/dL	6.4 (5.9-6.9)	1,579	6.8 (6.4-7.4)	40	6.5 (5.9-6.9)	46	< 0.001 <sup>d,e</sup>
Total bilirubin, mg/dL	0.60 (0.39-0.90)	1,578	0.51 (0.37-0.70)	40	0.61 (0.42-0.98)	46	0.169
AST, U/L	25 (18-39)	1,578	24 (16-38)	40	31 (21-50)	46	0.064
ALT, U/L	20 (13-32)	1,578	18 (12-33)	40	23 (17-32)	46	0.215
ALP, U/L	77 (62-105)	1,575	77 (60-93)	40	72 (58-103)	46	0.371
BUN, mg/dL	15.8 (11.1-23.8)	1,579	15.5 (10.7-33.3)	40	15.1 (12.3-20.3)	46	0.969
Creatinine, mg/dL	0.90 (0.70-1.21)	1,579	0.88 (0.69-1.27)	40	0.92 (0.74-1.16)	46	0.899
Sodium, mmol/L	136 (134-139)	1,579	139 (135-141)	40	136 (134-138)	46	0.014 <sup>f</sup>
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	347.1 (282.5-412.4)	1,400	356.7 (304.8-404.1)	36	326.7 (228.0-420.9)	44	0.374
PaCO <sub>2</sub> , mmHg	28.8 (26.0-32.3)	1,400	29.6 (27.5-33.9)	37	28.9 (26.0-33.1)	46	0.485
LDH, U/L	380 (289-479)	1,094	355 (296-416)	27	422 (333-587)	35	0.056
Lactate, mmol/L	2.0 (1.5-2.8)	970	1.8 (1.4-2.7)	21	2.3 (1.6-2.7)	33	0.544

Data are presented as median (interquartile range).

AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; NT-proBNP, N-terminal of prohormone brain natriuretic peptide; LDH, lactate dehydrogenase; WBC, white blood cell.

Post-hoc analysis.

<sup>a</sup> Bronchiolitis vs. consolidation,  $P = 0.009$  (Dunn's test).

<sup>b</sup> Bronchiolitis vs. consolidation,  $P = 0.006$  (Dunn's test).

<sup>c</sup> Bronchiolitis vs. consolidation,  $P = 0.004$  (Dunn's test).

<sup>d</sup> Bronchiolitis vs. consolidation,  $P < 0.001$  (Dunn's test).

<sup>e</sup> Bronchiolitis vs. GGO,  $P = 0.029$  (Dunn's test).

<sup>f</sup> Bronchiolitis vs. consolidation,  $P = 0.010$  (Dunn's test).

differed among groups: none of the 40 patients in the bronchiolitis group presented with chest pain, whereas chest pain was present in a quarter of the 1,579 patients in the consolidation group (Bonferroni's corrected  $P < 0.001$ ). The percentage of pleural effusion was significantly lower in the bronchiolitis (Bonferroni's corrected  $P < 0.001$ ) and GGO (Bonferroni's corrected  $P = 0.001$ ) groups than in the consolidation group. Complicated parapneumonic effusion or empyema was not observed in the bronchiolitis and GGO groups, whereas it was observed in 145 patients (9.2%) in the consolidation group. Along the same lines, no patient in the bronchiolitis and GGO groups underwent pleural drainage, whereas 172 patients (11.0%) in the consolidation group did. Corticosteroids were significantly more frequently administered in the GGO group than in the consolidation group (19 [41.3%] versus 353 [22.4%], Bonferroni's corrected  $P = 0.003$ ) or bronchiolitis group (19 [41.3%] versus 6 [15.0%], Bonferroni's corrected  $P = 0.007$ ). Regarding outcome variables, 30-day mortality, in-hospital mortality, treatment success and length of hospital stay were similar in the 3 groups.

### Laboratory Findings of Patients in the Bronchiolitis, GGO and Consolidation Groups

Blood levels of CRP, procalcitonin, albumin, total protein and sodium were significantly different in the 3 groups (Table 2). CRP (9.3 mg/dL [3.7-14.0 mg/dL] versus 12.9 mg/dL [6.6-21.0 mg/dL],  $P = 0.009$ ) and procalcitonin (0.11 ng/mL [0.06-0.42 ng/mL] versus 0.35 ng/mL [0.10-1.79 ng/mL],  $P = 0.006$ ) were significantly lower in the bronchiolitis group than in the consolidation group, and the bronchiolitis group had significantly higher blood levels of albumin (3.5 g/dL [3.4-4.0 g/dL] versus 3.3 g/dL [2.9-3.8 g/dL],  $P = 0.004$ ) and total protein (6.8 g/dL [6.4-7.4 g/dL] versus 6.4 g/dL [5.9-6.9 g/dL],  $P < 0.001$ ) than the consolidation group.

### Microbiologic Data of Patients in the Bronchiolitis, GGO and Consolidation Groups

Microbiologic data are summarized in Table 3. Eight hundred and fifty-nine potential pathogens were identified in 715 patients (42.9%): 800 pathogens in 670 patients (42.4%) of the consolidation group, 37

**TABLE 3.** Microbiologic diagnosis.

	Consolidation (n = 800)	Bronchiolitis (n = 37)	GGO (n = 22)	P Value
<i>Streptococcus pneumoniae</i>	168 (21.0)	6 (16.2)	4 (18.2)	0.618
Streptococcus milleri group	12 (1.5)	0 (0)	0 (0)	>0.999
<i>S. constellatus</i>	6	0	0	
<i>S. intermedius</i>	5	0	0	
<i>S. anginosus</i>	2	0	0	
Other viridans streptococci	13 (1.6)	0 (0)	0 (0)	>0.999
<i>S. mitis/oralis</i>	7	0	0	
<i>S. sanguis</i>	2	0	0	
<i>S. gordonii</i>	2	0	0	
<i>S. salivarius</i>	2	0	0	
Other streptococci species	5 (0.6)	0	0	>0.999
<i>S. agalactiae</i>	2	0	0	
Not specified	3	0	0	
<i>Staphylococcus aureus</i>	38 (4.8)	1 (2.7)	1 (4.5)	>0.999
Methicillin-susceptible	29	1	1	
Methicillin-resistant	9	0	0	
<i>Klebsiella pneumoniae</i>	106 (13.3)	4 (10.8)	3 (13.6)	0.616
<i>Pseudomonas aeruginosa</i>	23 (2.9)	1 (2.7)	0 (0)	0.526
<i>Acinetobacter baumannii</i>	13 (1.6)	0 (0)	0 (0)	>0.999
<i>Enterococcus faecium</i>	2 (0.3)	0 (0)	0 (0)	>0.999
<i>Enterococcus faecalis</i>	3 (0.4)	0 (0)	0 (0)	>0.999
<i>Escherichia coli</i>	10 (1.2)	1 (2.7)	0 (0)	0.263
<i>Stenotrophomonas maltophilia</i>	4 (0.5)	0 (0)	0 (0)	>0.999
<i>Hemophilus influenzae</i>	8 (1.0)	2 (5.4)	0 (0)	0.029
<i>Serratia marcescens</i>	3 (0.4)	0 (0)	0 (0)	>0.999
<i>Proteus mirabilis</i>	2 (0.3)	0	0	>0.999
<i>Morganella morganii</i>	1 (0.1)	0	0	0.973
<i>Mycoplasma pneumoniae</i>	142 (17.8)	16 (43.2)	7 (31.8)	<0.001 <sup>a,b</sup>
<i>Chlamydia pneumoniae</i>	212 (26.5)	6 (16.2)	6 (27.2)	0.956
<i>Legionella pneumophila</i>	9 (1.1)	0 (0)	0 (0)	>0.999
Virus	26 (3.2)	0 (0)	1 (4.5)	0.764
Influenza A	15	0	1	
Influenza B	2	0	0	
Metapneumovirus	2	0	0	
Rhinovirus	2	0	0	
Adenovirus	2	0	0	
Respiratory syncytial virus-A	2	0	0	
Coronavirus OC43	2	0	0	

Data are presented as n (%).

Post-hoc analysis.

<sup>a</sup> Bronchiolitis vs. consolidation, Bonferroni's corrected  $P < 0.001$ .

<sup>b</sup> Bronchiolitis vs. GGO, Bonferroni's corrected  $P = 0.010$ .

pathogens in 27 patients (67.5%) of the bronchiolitis group and 22 pathogens in 18 patients (39.1%) of the GGO group, respectively. The prevalence of *Hemophilus influenzae* was significantly different among the 3 groups, but not between any 2 groups. The prevalence of *M. pneumoniae* was also significantly different among the 3 groups, the bronchiolitis group had significantly higher prevalence than the consolidation group (16 [43.2%] versus 142 [17.8%], Bonferroni's corrected  $P < 0.001$ ) or GGO group (16 [43.2%] versus 7 [31.8%], Bonferroni's corrected  $P = 0.001$ ). In the bronchiolitis group, the most common pathogen was *M. pneumoniae*

(16 [43.2%]), followed by *S. pneumoniae* (6 [16.2%]), *C. pneumoniae* (6 [16.2%]) and *K. pneumoniae* (4 [10.8%]). The most common pathogens in the GGO group were *M. pneumoniae* (7 [31.8%]) and *C. pneumoniae* (6 [27.2%]), followed by *S. pneumoniae* (4 [18.2%]) and *K. pneumoniae* (3 [13.6%]).

#### Initial Antimicrobial Treatment

Initially used antibiotics are summarized and compared between the groups in Table 4. Third-generation cephalosporin- or ampicillin-sulbactam-based regimen

**TABLE 4.** Initial antibiotic treatment.

Antibiotic regimen	Consolidation (n = 1,579)	Bronchiolitis (n = 40)	GGO (n = 46)	P Value
Third-generation cephalosporin or ampicillin-sulbactam with or without macrolide, fluoroquinolone or clindamycin	1,327 (84.0)	36 (90.0)	39 (84.8)	0.590
Fluoroquinolone with or without aminoglycoside	50 (3.2)	4 (10.0)	3 (6.5)	0.029
Antipseudomonal beta-lactam with or without macrolide, fluoroquinolone or aminoglycoside	138 (8.7)	0 (0.0)	4 (8.7)	0.120
Carbapenem with or without macrolide, fluoroquinolone or aminoglycoside	15 (0.9)	0 (0.0)	0 (0.0)	> 0.999
Antipseudomonal beta-lactam or carbapenem plus glycopeptide with or without macrolide, fluoroquinolone or aminoglycoside	38 (2.4)	0 (0.0)	0 (0.0)	0.711
Others <sup>a</sup>	11 (0.7)	0 (0.0)	0 (0.0)	> 0.999

Data are presented as n (%).

<sup>a</sup> Others include macrolide alone (n = 1), glycopeptide plus clindamycin (n = 1), fluoroquinolone plus clindamycin plus aminoglycoside (n = 1), antipseudomonal beta-lactam plus clindamycin (n = 1), third-generation cephalosporin plus glycopeptide (n = 1), carbapenem plus aminoglycoside plus macrolide (n = 1), fluoroquinolone plus glycopeptide (n = 2), macrolide plus glycopeptide (n = 1) and third-generation cephalosporin plus aminoglycoside (n = 2).

was most commonly used in each group. There were no significant differences in antibiotic regimens between the groups, except fluoroquinolone with or without aminoglycoside. The higher frequency of fluoroquinolone with or without aminoglycoside in the bronchiolitis group was not statistically significant in post-hoc analysis, as compared with the consolidation group (Bonferroni's corrected  $P = 0.042$ ).

## DISCUSSION

This study confirms that predominantly bronchiolitis or GGO pattern on CT images is uncommon in patients with CAP. In the bronchiolitis group, the most common pathogen was *M. pneumoniae*, followed by *S. pneumoniae* and *C. pneumoniae*, and *M. pneumoniae* was significantly more common than in the consolidation group. As compared with the consolidation group, the bronchiolitis group was characterized by a higher percentage of cough, lower rates of chest pain and pleural effusion and the absence of complicated parapneumonic effusion or empyema and pleural drainage. Furthermore, the bronchiolitis group was associated with lower blood levels of inflammatory markers and higher albumin and total protein levels in blood. The common causative pathogens in the GGO group were *M. pneumoniae*, *C. pneumoniae*, *S. pneumoniae* and *K. pneumoniae* and these were not significantly different from those observed in the other 2 groups. As observed for the bronchiolitis group, complicated parapneumonic effusion or empyema was not observed and no patient underwent pleural drainage in the GGO group. Outcome variables, such as 30-day mortality, were not significantly different among the 3 groups.

Centrilobular nodules on CT correspond pathologically to cellular infiltration in bronchioles with exudates or granulation tissue in bronchiolar lumens, whereas consolidation reflects neutrophils and exudates in alveolar lumen.<sup>28</sup> A previous study showed the

microbiological features of CAP patients with a tree-in-bud pattern share similarities with those of pneumonia in the general population.<sup>29</sup> In another study, *M. pneumoniae* infection was frequently associated with a bronchiolitis pattern.<sup>30</sup> *M. pneumoniae* has an affinity for airway cilia and bronchioles and causes peribronchial and perivascular infiltration of mononuclear cells and edematous and ulcerative lesions in bronchial walls.<sup>28</sup> In the present study, more than 40% of cases in the bronchiolitis group were caused by *M. pneumoniae*, which concurs with the findings of a previous study, in which *M. pneumoniae* was determined to be the most common pathogen of diffuse acute infectious bronchiolitis in adults.<sup>19</sup> Interestingly, common CAP pathogens, such as *C. pneumoniae*, *S. pneumoniae* and *K. pneumoniae*, also cause a bronchiolitis pattern. The mechanisms responsible for centrilobular nodules or tree-in-bud pattern in some patients and consolidation or GGO in others can be explained by the up- or down-regulations of host cell-mediated immunity, respectively.<sup>28</sup>

In a previous study, the rate of diffuse bronchiolitis was reported to be 1.2% among community-acquired lower respiratory tract infections.<sup>19</sup> The difference between this rate and the value found in the present study for the bronchiolitis pattern is explained by the different definitions used. In the present study, bronchiolitis was defined as either the presence of centrilobular nodules or a tree-in-bud pattern in most lesions with or without GGO or consolidation in the present study, whereas, in the previous study, diffuse acute infectious bronchiolitis was defined as multiple centrilobular nodules in 4 or more lobes.<sup>19</sup> However, no previous study has addressed the clinical manifestations of the bronchiolitis or bronchiolitis-predominant CAP. As expected based on published findings,<sup>19,30</sup> our bronchiolitis group exhibited a clinically less severe form of CAP characterized by lower levels of inflammatory markers and the absence of complicated parapneumonic effusion or empyema.

Information regarding the incidence of the GGO pattern in CAP patients is lacking. The pathophysiology of GGO includes incomplete alveolar filling by inflammatory cells or exudate, pulmonary edema secondary to infection leaving air in alveoli or interstitial infiltrates of inflammatory cells.<sup>5</sup> The resolving stage of lobar pneumonia can also exhibit a GGO appearance as alveolar aeration is restored. In previous studies, the rate of GGO in CAP was found to depend on the pathogen, that is, 19% for viral infections,<sup>31</sup> 17% for legionella pneumonia<sup>16</sup> and 4% in pneumococcal pneumonia.<sup>8</sup> However, in the present study, the prevalence of causative agents in the GGO and consolidation group were similar. In part, this difference might have arisen only because the CAP patients underwent throat or nasopharyngeal swab testing for respiratory viruses. A GGO pattern on CT is clinically associated with the more frequent use of systemic corticosteroids and the lack of complicated parapneumonic effusion or empyema and pleural drainage. In the present study, the use of corticosteroids was determined by attending physicians, and the reasons why they were administered could not be ascertained. However, we speculate corticosteroids were administered to patients with a GGO pattern because the possibility of a noninfectious condition, such as cryptogenic organizing pneumonia, was not excluded.

As noted earlier, the bronchiolitis and GGO groups had their own clinical features. On the contrary, initial antimicrobial treatment in the bronchiolitis or GGO group was not significantly different from the consolidation group. This discrepancy can be explained by the fact that because this study was retrospective, antibiotic therapy was determined by treating physician's judgement and the CAP guidelines.<sup>3</sup> Consequently, third-generation cephalosporin- or ampicillin-sulbactam-based antibiotic therapy was most commonly used in the present study. Given that *M. pneumoniae* was the most common pathogen in the bronchiolitis group, fluoroquinolone with or without aminoglycoside tended to be more frequently administered in the bronchiolitis group than the consolidation group.

The present study has several limitations. First, it was retrospectively conducted in a single institution, which suggests the possibility of selection bias. As described in a previous study,<sup>21</sup> emergency physicians at our institution that encountered patients with suspected pneumonia tended to confirm the presence of pneumonia and transfer them from the emergency department to the internal medicine department. For this reason, most, though not all, CAP patients underwent a CT scan, although it is usually not necessary for the diagnosis of CAP. Second, some tests for causative pathogens were not performed in all CAP patients, only a proportion of patients underwent evaluation for respiratory viruses. Third, because of the retrospective design of the study, therapeutic decision-making, including the selection of antibiotics, was determined by attending physicians. Finally, the numbers of patients in the

bronchiolitis and GGO groups were too small to allow us to reach definitive conclusions. Thus, we suggest a large-scale prospective study be performed to confirm our findings.

## CONCLUSIONS

In conclusion, the bronchiolitis group was found to be associated with a higher *M. pneumoniae* frequency, a less severe form of CAP, and the absence of complicated parapneumonic effusion or empyema. On the other hand, the GGO group was similar to the consolidation group in terms of causative microorganisms, severity and prognosis, but unlike the consolidation group, was not found to be associated with complicated parapneumonic effusion or empyema. However, bronchiolitis and GGO groups were similar to the consolidation group in terms of 30-day or in-hospital mortality and length of hospital stay.

## AUTHOR CONTRIBUTION

H.S. and S.I.C. conceived and designed the analysis, H.S, S.I.C., K.M.S., J.K.L., S.S.Y., S.Y.L., J.L., C.H.K. and J.Y.P. collected the data, H.S, S.I.C., K.M.S. and J.K.L. contributed data or analysis tools, H.S. and S.I.C. performed the analysis, H.S. and S.I.C. wrote the paper. All authors read and approved the manuscript.

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