Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Clinical relevance of necrotizing change in patients with community-acquired pneumonia

HYEWON SEO,[1] SEUNG-ICK CHA,[1] KYUNG-MIN SHIN,[2] JAE-KWANG LIM,[2] SEUNG-SOO YOO,[1] JAEHEE LEE,[1] SHIN-YUP LEE,[1] CHANG-HO KIM,[1] JAE-YONG PARK[1] AND WON-KEE LEE[3]

[1]*Department of Internal Medicine,* [2]*Department of Radiology, and* [3]*Department of Preventive Medicine, Kyungpook National University School of Medicine, Daegu, Korea*

ABSTRACT

Background and objective: **Few studies have analysed a large number of patients with necrotizing pneumonia (NP) diagnosed based on computed tomography (CT) scans. The aim of the present study was to document the incidence and clinical features of NP in patients with community-acquired pneumonia (CAP).**

Methods: **This retrospective study was conducted on CAP patients who had been admitted to a tertiary referral centre and who had available enhanced CT scan images. Patients were allocated into NP and non-NP groups, and they were compared with respect to various clinical variables.**

Results: **Of the 830 patients included in the present study, necrotizing change was observed in 103 patients (12%). Patients with NP experienced more symptoms of pneumonia, had higher blood levels of inflammatory markers and more often required pleural drainage compared to patients with non-NP. Although the use of mechanical ventilation, vasopressor infusion, 30-day mortality, in-hospital mortality and clinical deterioration did not differ between the NP and non-NP groups, the median length of hospital stay (LOS) was significantly longer in the NP group. Multivariate analysis using Cox proportional hazards model showed that necrotizing change independently predicted LOS in patients with CAP.**

Conclusion: **NP affects approximately one-tenth of hospitalized CAP patients. It may be associated with more severe clinical manifestations and may increase the need for pleural drainage. NP was found to be an independent predictor of LOS, but not of mortality in CAP patients.**

Key words: community-acquired pneumonia, computed tomography, drainage, length of hospital stay, necrotizing.

SUMMARY AT A GLANCE

We investigated the clinical features of community-acquired necrotizing pneumonia. Necrotizing change was noted in approximately 10% of the patients with community-acquired pneumonia (CAP) and was characterized by more severe clinical manifestations and increased need for pleural drainage. Necrotizing change was a predictor of length of hospital stay (LOS) but not of mortality in patients with CAP.

Abbreviations: , ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CAP, community-acquired pneumonia; CCI, Charlson co-morbidity index; CRP, C-reactive protein; CT, computed tomography; CURB-65, a six-point score, one point for each of confusion, urea >7 mmol/L, respiratory rate ≥30/min, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure and age ≥65 years; ECOG, Eastern Cooperative Oncology Group performance status; ESR, erythrocyte sedimentation rate; FiO_2, inspired oxygen fraction; Hb, haemoglobin; HR, hazard ratio; ICU, intensive care unit; Ig, immunoglobulin; IQR, interquartile range; KNUH, Kyungpook National University Hospital; LOS, length of hospital stay; MRSA, methicillin-resistant *Staphylococcus aureus*; NP, necrotizing pneumonia; NT-proBNP, N-terminal of prohormone brain natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PCR, polymerase chain reaction; PSI, pneumonia severity index; WBC, white blood cell.

INTRODUCTION

Necrotizing pneumonia (NP) is characterized by pulmonary inflammation with consolidation, peripheral necrosis and formation of multiple cavitary lesions.[1] Toxins of invasive pathogens, vasculitis and venous thrombosis have been suggested to be involved in the perturbations of bronchial and pulmonary vascular supply, preceding necrotic change of lung parenchyma.[2,3] Tissue necrosis disrupts the delivery of antibiotics to infected lung areas and causes persisting infection and progressive destruction of the pulmonary parenchyma, resulting in bronchopleural fistula, empyema, septic shock and pulmonary gangrene,

Correspondence: Seung-Ick Cha, Department of Internal Medicine, Kyungpook National University School of Medicine, Kyungpook National University Hospital, 130 Dongdeok-ro, Jung-gu, Daegu 700-721, Korea. E-mail: sicha@knu.ac.kr

Received 19 January 2016; invited to revise 9 March and 31 May 2016; revised 27 March and 22 June 2016; accepted 22 August 2016 (Associate Editor: Marcos Restrepo).

which are regarded as markers of the final stage of progressive lung destruction.[1,2] Furthermore, NP was considered as a rare and severe complication of bacterial community-acquired pneumonia (CAP).[1,2,4,5]

On chest radiographs, NP manifests as a rapid progression of airspace disease with development of cavities.[1,6] However, plain chest radiography is an inadequate diagnostic tool because it underestimates parenchymal destruction.[2] Computed tomography (CT) scan with contrast enhancement provides the most sensitive diagnostic modality and is a standard procedure for the diagnosis of NP.[6] On CT scans, NP is characterized by pneumonic consolidation with multiple areas of necrosis of the lung parenchyma.[2,7,8] As described above, the detection of NP in imaging studies might raise concerns of poor prognosis and subsequent treatment failure. However, studies using CT scans for the diagnosis of NP for a large number of patients, especially in adults, are scarce.[5] In addition, data regarding the incidence of NP and the differences between NP and non-NP are limited.[6] The aim of the present study was to determine the incidence of NP among CAP patients and to compare the clinical variables of patients with or without NP, and thereby to elucidate the prognostic role of necrotizing change in these patients.

METHODS

Study design

Consecutive CAP patients admitted to and treated at the Respiratory Department of Kyungpook National University Hospital (KNUH), a tertiary referral centre, in Daegu, Korea, between January 2011 and December 2014, were identified using the CAP patient registry. All patients were enrolled on admission and baseline characteristics were recorded, although not all patients underwent the same laboratory tests. Pneumonia was diagnosed using the following criteria: (i) a new radiographical infiltrate and (ii) one or more compatible symptoms or signs (cough, sputum, dyspnoea, fever and/or pleuritic chest pain). The exclusion criteria for CAP applied were as follows: (i) hospital-acquired pneumonia or healthcare-associated pneumonia,[9] (ii) the presence of an active thoracic malignancy and (iii) immunosuppression or steroid use (>15 mg/day of prednisone for >14 days).

Two chest radiologists (K.-M.S. and J.-K.L) independently reviewed the CT scan images of all patients for the presence of necrotizing changes. NP was defined as consolidation with multiple areas of non-enhancement without rim enhancement on contrast-enhanced CT scan in one or more pulmonary segments or lobes.[10,11] Patients without an available enhanced CT scan at presentation were excluded. Patients were allocated into NP or non-NP group, based on the presence or absence of necrotizing changes. Clinical parameters were compared between the two groups.

The present study was approved by the Institutional Review Board of the KNUH (2015-07-035), which waived the requirement for written informed consent from patients owing to the retrospective nature of the study.

Data collection

Two chest physicians (H.S. and S.-I.C.) analysed the data. Symptoms, vital signs, co-morbid conditions, pneumonia severity indices (PSIs)[12] and CURB-65 scores[13] (a six-point score, one point for each of confusion, urea >7 mmol/L, respiratory rate ≥30/min, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure and age ≥65 years) were reviewed. Baseline data were initially recorded by resident physicians and confirmed by attending chest physicians. Charlson co-morbidity indices (CCIs)[14] were calculated retrospectively. Information about therapeutic interventions, including mechanical ventilation, corticosteroid use, vasopressor infusion and pleural drainage with percutaneous catheters or chest tubes was collected. Length of hospital stay (LOS), admission to an intensive care unit (ICU), 30-day mortality, in-hospital mortality and clinical deterioration were selected as outcome variables. Clinical deterioration was defined as the initiation of mechanical ventilation, vasopressor infusion, ICU admission and 30-day or in-hospital mortality.

Laboratory data, including complete blood cell counts, erythrocyte sedimentation rate (ESR), liver function testing, C-reactive protein (CRP), procalcitonin, N-terminal of prohormone brain natriuretic peptide, blood urea nitrogen, creatinine and arterial blood gas analysis data, were reviewed.

Microbiological data

A causative pathogen was considered if one of the following criteria were met: isolation of a microorganism from blood or pleural fluid; positive urinary antigen test for *Streptococcus pneumoniae* or *Legionella pneumophila* serogroup 1 (Table S1, Supplementary Information); identification of bacteria from a sputum sample (>25 neutrophils and <10 squamous epithelial cells per lower power field) collected within 24 h of admission plus compatible Gram-stain finding; positivity for *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* as determined by a positive IgM result or a fourfold increase in IgG levels between the initial and convalescent samples (Table S1, Supplementary Information); positivity for respiratory viruses in a throat or nasopharyngeal swab by multiplex PCR (Table S1, Supplementary Information); or identification of Influenza A or B antigen or Influenza H1N1 in a throat swab (Table S1, Supplementary Information). The potentially drug-resistant pathogens detected included methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and extended-spectrum β-lactamase-producing Enterobacteriaceae.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). *P*-values <0.05 were considered statistically significant. Data were expressed as means ± SDs or medians (interquartile ranges, IQRs) for non-normally distributed continuous variables and as

numbers and percentages for categorical variables. Continuous variables were compared using the Student's t-test or the Mann–Whitney U-test if non-normally distributed, whereas categorical variables were compared using the chi-square test or Fisher's exact test. LOS was analysed using the Kaplan–Meier method; patients who died were censored from this analysis. Independent prognostic factors of LOS were identified using a stepwise forward Cox regression model.

RESULTS

Baseline characteristics

Initially, 1139 CAP patients were identified, and of these, 309 patients without available enhanced CT scans (10 patients had no CT scan images and 299 had non-enhanced CT scan images only) were excluded. Consequently, 830 patients were included in this study; 103 (12.4%) were allocated to the NP group and 727 (87.6%) to the non-NP group. Patients with NP were demographically characterized by a higher percentage of males, ever-smokers and heavy drinkers compared with the non-NP group (Table 1). Co-morbid conditions (Table S2, Supplementary Information)—

Table 1 Baseline characteristics of the patients

Characteristics	NP (n = 103)	Non-NP (n = 727)	P-value
Age (years)	64 (56–72)	67 (52–76)	0.602
Male	79 (76.7)	448 (61.6)	0.003
BMI (kg/m^2)	21.2 (19.1–24.2)	22.0 (19.7–24.2)	0.257
Smoking			
Ever-smoker	72 (69.9)	366 (50.4)	<0.001
Pack-years	30 (20–50)	30 (20–40)	0.338
Heavy drinking[†]	23 (22.3)	103 (14.2)	0.031
Charlson co-morbidity index	1 (0–1)	0 (0–1)	0.165
ECOG	1 (1–2)	1 (1–1)	<0.001
ECOG (3–4)	13 (12.6)	80 (11.0)	0.626
Systolic blood pressure (mm Hg)	127 (113–142)	128 (112–147)	0.998
Pulse rate (/min)	101 (88–116)	94 (83–107)	0.002
Respiratory rate (/min)	20 (19–22)	20 (18–21)	0.063
Symptoms			
Duration of symptom (days)	7 (5–14)	5 (3–7)	<0.001
Cough	92 (89.3)	626 (86.1)	0.372
Sputum production	67 (65.0)	500 (68.8)	0.372
Dyspnoea	74 (72.5)	383 (52.8)	<0.001
Fever	78 (75.7)	453 (62.3)	0.008
Altered mental status	2 (1.9)	29 (4.0)	0.413
Haemoptysis	16 (15.5)	63 (8.7)	0.027
Chest pain	70 (68.0)	176 (24.2)	<0.001
CURB-65	1 (0–2)	1 (0–2)	0.480
CURB-65 (3–5)	8 (7.8)	36 (5.0)	0.233
PSI class	3 (2–4)	3 (2–3)	0.002
PSI class (4–5)	34 (33)	176 (24.2)	0.055
Complicated parapneumonic effusion or empyema	48 (46.6)	41 (5.6)	<0.001
Pleural drainage	57 (55.3)	53 (7.3)	<0.001
Mechanical ventilation	4 (3.9)	34 (4.7)	>0.999
Vasopressor infusion	8 (7.8)	41 (5.6)	0.391
Corticosteroids	16 (15.5)	148 (20.4)	0.250
Admission to intensive care unit	5 (4.9)	42 (5.8)	0.705
30-day mortality	9 (8.7)	39 (5.4)	0.170
In-hospital mortality	6 (5.8)	35 (4.8)	0.658
Length of hospital stay (days)	14 (11–16)	8 (6–12)	<0.001
Clinical deterioration	14 (13.6)	75 (10.3)	0.315

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

[†]Heavy drinking is defined as the consumption of seven or more drinks (>60 g of alcohol) on one occasion for males, and five or more drinks (>40 g of alcohol) on one occasion for females at least twice a week.

CURB-65, a six-point score, one point for each of confusion, urea >7 mmol/L, respiratory rate ≥30/min, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure and age ≥65 years; ECOG, Eastern Cooperative Oncology Group performance status; NP, necrotizing pneumonia; PSI, pneumonia severity index.

gastrectomy, diabetes and chronic liver disease—were more common in the NP group. However, CCIs did not differ significantly between the two groups.

Patients in the NP group experienced significantly more symptoms, including dyspnoea, fever, haemoptysis and chest pain, than patients in the non-NP group. CURB-65 scores and high CURB-65 (3–5) rates were similar in the two groups, but PSI class was significantly higher (3 (2–4) vs 3 (2–3), $P = 0.002$) and a high PSI class (4–5) tended to be more common (34 (33%) vs 176 (24%), $P = 0.055$) in the NP group. Pleural drainage was performed significantly more often in the NP group (57 (55%) vs 53 (7%), $P < 0.001$). No intergroup differences were noted for the use of mechanical ventilation, vasopressor infusion, ICU admission, 30-day mortality, in-hospital mortality or clinical deterioration. In contrast, median LOS was significantly longer in the NP group (14 days (11–16 days) vs 8 days (6–12 days), $P < 0.001$).

Blood laboratory findings

Inflammatory markers, including white blood cell count, ESR and CRP, were significantly higher and the levels of serum albumin and sodium were significantly lower in the NP group (Table 2).

Microbiological data and antimicrobial treatment

In the NP group, 37 pathogens were identified in 27 patients (26%), and in the non-NP group, 283 pathogens were identified in 218 patients (30%) (Table 3). The most common pathogen in the NP group was *Klebsiella pneumoniae* ($n = 9$), followed by *S. pneumoniae* ($n = 5$) and *S. aureus* ($n = 5$). *Klebsiella pneumoniae* (9 (33%) vs 38 (17%), $P = 0.048$), *S. aureus* (5 (19%) vs 12 (6%), $P = 0.012$) and *Streptococcus milleri* group (4 (15%) vs 3 (1%), $P = 0.003$) were significantly more common in the NP group, whereas *M. pneumoniae* (3 (11%) vs 79 (36%), $P = 0.009$) was significantly less common. On the other hand, the frequencies of potentially drug-resistant pathogens were similar in the two groups.

In the NP group, ampicillin-sulbactam with or without macrolide or fluoroquinolone (50 (49%)) was the most commonly used antibiotic regimen, followed by cefotaxime or ceftriaxone plus clindamycin (21 (20%)) (Table 4). Both regimens were administered significantly more often in the NP group (50 (49%) vs 120 (17%), $P < 0.001$ and 21 (20%) vs. 21 (3%), $P < 0.001$, respectively). Cefotaxime or ceftriaxone with or without macrolide or fluoroquinolone was less frequently administered (19 (18%) vs 490 (67%), $P < 0.001$) in the NP group.

Factors affecting LOS

As mentioned above, LOS was the only outcome variable that differed significantly between the two groups. Kaplan–Meier curve was constructed for the NP and non-NP groups (Fig. 1). Patients with NP were significantly more likely to stay longer in hospital compared to those without NP (log-rank $P < 0.001$ and Breslow $P < 0.001$). Thus, we tried to identify factors associated with LOS. We set up two models based on two clinical prediction scores, that is, PSI and CURB-65 (Table 5). By multivariate analysis using the CURB-65-based Cox proportional hazards model, necrotizing change (hazard ratio (HR): 1.56, 95% CI: 1.24–1.97, $P < 0.001$), CCI of ≥1 (HR: 1.41, 95% CI: 1.22–1.62, $P < 0.001$), high CURB-65 (HR: 2.48, 95% CI: 1.70–3.62, $P < 0.001$) and pleural drainage (HR: 1.63, 95% CI: 1.30–2.05, $P < 0.001$) (Table 5) were found to predict LOS independently. According to the PSI-based model, NP (HR:

Table 2 Blood laboratory findings of the patients

Parameters	NP	*n*	Non-NP	*n*	*P*-value
WBC count (/μL)	14 970 (11 030–18 780)	103	10 130 (7485–13 910)	727	<0.001
ESR (mm/h)	70 (50–92)	103	48 (29–67)	726	<0.001
C-reactive protein (mg/dL)	18.8 (12.0–25.5)	103	11.4 (6.1–18.9)	724	<0.001
NT-proBNP (pg/mL)	249.0 (135.8–812.0)	100	335.0 (119.3–1085.0)	656	0.422
Hb (g/dL)	11.9 ± 1.9	103	12.6 ± 1.7	727	0.001
Platelet (10^3/μL)	340 (263–466)	103	237 (184–313)	727	<0.001
Albumin (g/dL)	2.9 (2.4–3.3)	103	3.4 (3.0–3.8)	727	<0.001
Total protein (g/dL)	6.3 (5.8–6.9)	103	6.5 (6.1–7.0)	727	0.004
Total bilirubin (mg/dL)	0.58 (0.41–0.96)	103	0.60 (0.39–0.88)	726	0.255
AST (U/L)	25 (18–45)	103	25 (18–37)	726	0.533
ALT (U/L)	22 (14–37)	103	20 (13–31)	726	0.173
ALP (U/L)	101 (78–136)	103	77 (62–104)	724	<0.001
BUN (mg/dL)	14.0 (10.3–18.1)	103	14.3 (10.6–19.9)	727	0.612
Creatinine (mg/dL)	0.77 (0.63–0.94)	103	0.83 (0.68–1.03)	727	0.029
Sodium (mmol/L)	135 (132–137)	103	137 (134–139)	727	0.001
PaO_2/FiO_2	345.3 (287.7–394.6)	92	342.1 (286.0–404.3)	613	0.755
$PaCO_2$	27.4 (24.4–31.5)	92	28.9 (26.5–32.6)	613	0.002

Data are presented as mean ± SD, median (interquartile range) or *n* (%).

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; FiO_2, inspired oxygen fraction; LDH, lactate dehydrogenase; NP, necrotizing pneumonia; NT-proBNP, N-terminal of prohormone brain natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; SD, standard deviation; WBC, white blood cell.

Table 3 Microbiological diagnosis

	NP (n = 27)	Non-NP (n = 218)	P-value
Streptococcus pneumoniae	5 (18.5)	75 (34.4)	0.097
Streptococcus milleri group	4 (14.8)	3 (1.4)	0.003
Streptococcus constellatus	2	2	
Streptococcus intermedius	2	1	
Other viridans streptococci	1 (3.7)	5 (2.3)	0.508
Streptococcus mitis/oralis	1	4	
Streptococcus sanguis	0	1	
Other streptococcus species	2 (7.4)	5 (2.3)	0.174
α-Haemolytic	0	2	
Streptococcus agalactiae	1	1	
Not specified	1	2	
Staphylococcus aureus	5 (18.5)	12 (5.5)	0.012
Methicillin-susceptible	5	10	
Methicillin-resistant	0	2	
Klebsiella pneumoniae	9 (33.3)	38 (17.4)	0.048
Pseudomonas aeruginosa	3 (11.1)	14 (6.4)	0.412
Acinetobacter baumannii	1 (3.7)	8 (3.7)	>0.999
Enterobacter cloacae	1 (3.7)	0 (0)	0.110
Escherichia coli	1 (3.7)	3 (1.4)	0.375
Stenotrophomonas maltophilia	1 (3.7)	1 (0.5)	0.209
Proteus mirabilis	0 (0)	1 (0.5)	>0.999
Hemophilus influenzae	0 (0)	4 (1.8)	>0.999
Morganella morgagnii	0 (0)	1 (0.5)	>0.999
Serratia marcescens	0 (0)	1 (0.5)	>0.999
Mycoplasma pneumoniae	3 (11.1)	79 (36.2)	0.009
Chlamydia pneumoniae	1 (3.7)	7 (3.2)	>0.999
Legionella pneumophila	0 (0)	7 (3.2)	>0.999
Virus	0 (0)	19 (8.7)	0.241
Adenovirus	0	2	
Influenza A	0	11	
Metapneumovirus	0	1	
Respiratory syncytial virus-A	0	2	
Respiratory syncytial virus-B	0	1	
Rhinovirus A	0	1	
Coronavirus 229E/NL63	0	1	
Potentially drug-resistant pathogens[†]	5 (18.5)	29 (13.3)	0.460

Data are presented as n (%).

[†]Potentially drug-resistant pathogens include *A. baumannii*, methicillin-resistant *S. aureus*, extended spectrum beta-lactamase-producing Enterobacteriaceae, *P. aeruginosa* and *S. maltophilia*.

NP, necrotizing pneumonia.

1.52, 95% CI: 1.20–1.92, $P < 0.001$), high PSI (HR: 1.85, 95% CI: 1.56–2.20, $P < 0.001$) and pleural drainage (HR 1.64, 95% CI 1.30–2.06, $P < 0.001$) independently predicted LOS.

DISCUSSION

In the present study, NP accounted for 12% of hospitalized CAP patients and it was characterized by higher frequency of symptoms, higher PSI class, higher levels of inflammatory markers and more frequent need for pleural drainage, which suggested that patients with NP experience a more severe clinical course. The most common pathogen of community-acquired NP was *K. pneumoniae*, followed by *S. aureus*, *S. pneumoniae* and *S. milleri* group. In patients hospitalized with CAP, the development of necrotizing changes influenced LOS, but it did not affect 30-day mortality or in-hospital mortality.

NP is considered a rare complication of bacterial lung infection;[2] however, information regarding the proportion of NP in CAP patients affected is limited. The presence of parenchymal lung lesions, a requisite for the diagnosis of pneumonia, is usually based on new infiltrates on chest radiograph.[15] However, because chest radiograph is often insufficient for detecting pulmonary parenchymal lesions of pneumonia, chest CT scan can improve the diagnosis of CAP.[16,17] At our institution, emergency physicians who saw patients with suspected pneumonia tended to confirm pneumonia to transfer them from the Emergency Department to the Internal Medicine Department. Therefore, although CT scan is usually not necessary for the diagnosis of CAP, it was used in the majority of CAP patients treated at our institution, which allowed us to determine the

Table 4 Antimicrobial treatment

	NP (n = 103)	Non-NP (n = 727)	P-value
Ampicillin-sulbactam with or without macrolide or fluoroquinolone	50 (48.5)	120 (16.5)	<0.001
Cefotaxime or ceftriaxone plus clindamycin	21 (20.4)	21 (2.9)	<0.001
Cefotaxime or ceftriaxone with or without macrolide or fluoroquinolone	19 (18.4)	490 (67.4)	<0.001
Fluoroquinolone with or without aminoglycoside	1 (1.0)	29 (4.0)	0.161
Antipseudomonal beta-lactams plus fluoroquinolone or aminoglycoside	9 (8.7)	53 (7.3)	0.601
Meropenem plus fluoroquinolone or aminoglycoside	1 (1.0)	3 (0.4)	0.412
Meropenem plus vancomycin or teicoplanin	0 (0)	7 (1.0)	>0.999
Others[†]	2 (1.9)	4 (0.6)	0.164

Data are presented as n (%).

[†]Others include antipseudomonal beta-lactam plus fluoroquinolone plus teicoplanin (n = 3), antipseudomonal beta-lactam plus teicoplanin (n = 1), vancomycin plus clindamycin (n = 1) and teicoplanin plus moxifloxacin (n = 1).

NP, necrotizing pneumonia.

proportion of patients with NP. Therefore, these facts are likely to reduce the possibility that patients who underwent CT scan had more severe disease. In the present study, NP was observed in approximately 12% of the hospitalized CAP patients. Similarly, in a previous study, 136 (39%) of 351 patients with pneumococcal pneumonia underwent CT scan of the chest, and necrotizing changes in the lungs were observed in 11% (n = 15).[6]

The reasons behind a microbial agent causing necrotizing changes in the lung parenchyma of one patient but not in another remain to be elucidated.[1] One possible explanation could be the differences in the general condition or immune status of the patients. In the present study, NP was demographically characterized by a higher number of males, ever-smokers and heavy drinkers, and was more commonly associated with postgastrectomy status, chronic liver disease and diabetes. This is consistent with a previous review that reported alcoholism and diabetes as common co-morbid conditions commonly accompanying NP.[2] The duration of symptoms in the NP group was significantly longer than that in the non-NP group, suggesting that delayed treatment could facilitate necrotizing changes.

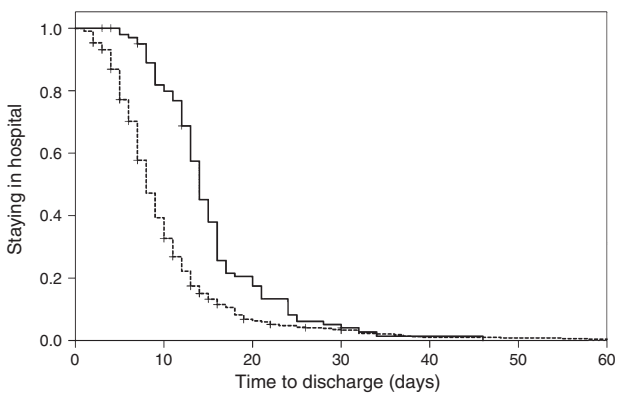

Figure 1 Kaplan–Meier curves showing time to discharge in patients with necrotizing pneumonia (NP, solid line) or non-NP (dashed line; log-rank P < 0.001 and Breslow P < 0.001). + denotes censored data.

As noted in a previous review,[2] NP was associated with more symptoms of pneumonia and unfavourable laboratory data, including higher levels of inflammatory markers. However, in the present study, these clinical features of NP were not associated with 30-day or in-hospital mortality, which suggests that NP severity *perse* does not increase the risk of mortality. In the same context, mechanical ventilation, vasopressor therapy and clinical deterioration rates were similar in the two groups. Interestingly, the two clinical prediction scoring systems showed conflicting results; median PSI class was higher in the NP group but median CURB-65 scores were similar in both groups. In fact, LOS was the only clinical endpoint that allowed to differentiate the two groups. Multivariate analysis showed that necrotizing changes independently predicted LOS. The longer LOS observed in the NP group could be explained as follows: (i) more severe inflammation, reflected by higher blood levels of inflammatory markers; (ii) impaired blood supply to the pulmonary parenchyma, leading to impediment of antibiotic delivery;[2,18,19] and (3) more frequent association with complicated parapneumonic effusion or empyema requiring pleural drainage.

The aetiology of NP has not been previously studied in a large patient cohort. Classically, anaerobes were considered to be among the more important pathogens, and were believed to cause a spectrum of aspiration syndromes, including aspiration pneumonia, lung abscess and empyema.[10,20,21] Pleural fluid and transthoracic needle aspirates are the only sources of specimens currently available for obtaining meaningful anaerobic cultures from patients with NP.[22] In the present study, no anaerobes were cultured from blood and pleural fluid of NP patients. The most common microbe was *K. pneumoniae*, followed by *S. aureus*, *S. pneumoniae* and *S. milleri* group. These findings corresponds with those of other studies, in which *S. pneumoniae*, *S. aureus* and *K. pneumoniae* were common in

Table 5 Variables influencing the length of hospital stay

	Univariate analysis			Multivariate analysis		
	P-value	HR	95% CI	*P*-value	HR	95% CI
CURB-65-based model						
Female	0.002	0.80	0.69–0.92	0.386	0.91	0.74–1.13
Ever-smoker	0.005	1.23	1.06–1.41	0.503	0.93	0.76–1.15
Heavy drinking	0.010	1.29	1.06–1.57	0.312	1.11	0.90–1.37
CCI ≥ 1	<0.001	1.34	1.17–1.55	<0.001	1.41	1.22–1.62
CURB-65 (3–5)	<0.001	2.48	1.71–3.61	<0.001	2.48	1.70–3.62
Pleural drainage	<0.001	1.93	1.57–2.38	<0.001	1.63	1.30–2.05
NP	<0.001	1.88	1.52–2.33	<0.001	1.56	1.24–1.97
PSI-based model						
Ever-smoker	0.005	1.23	1.06–1.41	0.953	0.99	0.86–1.16
Heavy drinking	0.010	1.29	1.06–1.57	0.383	1.10	0.89–1.35
PSI (4–5)	<0.001	1.82	1.54–2.16	<0.001	1.85	1.56–2.20
Pleural drainage	<0.001	1.93	1.57–2.38	<0.001	1.64	1.30–2.06
NP	<0.001	1.88	1.52–2.33	<0.001	1.52	1.20–1.92

CCI, Charlson co-morbidity index; CI, confidence interval; CURB-65, a six-point score, one point for each of confusion, urea >7 mmol/L, respiratory rate ≥30/min, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure and age ≥65 years; HR, hazard ratio; NP, necrotizing pneumonia; PSI, pneumonia severity index.

patients with severe NP requiring surgical intervention.[1,4,23,24] The rates of potentially drug-resistant pathogens were similar in our NP and non-NP groups in the present study.

Several limitations of the present study should be noted. First, it is limited by its retrospective design and because it was conducted in a single institution, the possibility of selection bias has to be considered. Furthermore, because some CAP patients were treated at other departments in our institution, not all CAP patients were enrolled in the present study, and not all CAP patients underwent enhanced CT scan, although many (74%) did. Second, no microbiological study was performed on anaerobes from lung tissues or aspirates, and thus, the possibility that anaerobes were not identified as causative agents should be considered. Moreover, due to the retrospective nature of this study, all patients did not undergo the same tests for the aetiological agents, including atypical pathogens. Finally, decisions regarding treatment including antibiotics depended on attending physicians. For these reasons, we acknowledge that a larger prospective study should be undertaken to confirm our findings.

In conclusion, NP, which affected 12% of the CAP patients in the present study, was associated with more severe clinical manifestations and more frequent need to perform pleural drainage. NP differed microbiologically from non-NP. Interestingly, necrotizing change on CT scan images was associated with longer LOS, but not with mortality in our patient cohort.

REFERENCES

1 Chatha N, Fortin D, Bosma KJ. Management of necrotizing pneumonia and pulmonary gangrene: a case series and review of the literature. *Can. Respir. J.* 2014; **21**: 239–45.

2 Tsai YF, Ku YH. Necrotizing pneumonia: a rare complication of pneumonia requiring special consideration. *Curr. Opin. Pulm. Med.* 2012; **18**: 246–52.

3 Hammond JM, Lyddell C, Potgieter PD, Odell J. Severe pneumococcal pneumonia complicated by massive pulmonary gangrene. *Chest* 1993; **104**: 1610–2.

4 Tsai YF, Tsai YT, Ku YH. Surgical treatment of 26 patients with necrotizing pneumonia. *Eur. Surg. Res.* 2011; **47**: 13–8.

5 Sawicki GS, Lu FL, Valim C, Cleveland RH, Colin AA. Necrotising pneumonia is an increasingly detected complication of pneumonia in children. *Eur. Respir. J.* 2008; **31**: 1285–91.

6 Pande A, Nasir S, Rueda AM, Matejowsky R, Ramos J, Doshi S, Kulkarni P, Musher DM. The prevalence of necrotizing changes in adults with pneumococcal pneumonia. *Clin. Infect. Dis.* 2013; **54**: 10–6.

7 Hodina M, Hanquinet S, Cotting J, Schnyder P, Gudinchet F. Imaging of cavitary necrosis in complicated childhood pneumonia. *Eur. Radiol.* 2002; **12**: 391–6.

8 Moon WK, Im JG, Yeon KM, Han MC. Complications of *Klebsiella pneumonia*: CT evaluation. *J. Comput. Assist. Tomogr.* 1995; **19**: 176–81.

9 Niderman MS, Craven DE, Bonten MJ, Chastre J, Craig WA, Fagon JY, Hall J, Jacoby GA, Kollef MH, Luna CM, *et al.* Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 2005; **171**: 388–416.

10 Hill MK, Sanders CV. Anaerobic disease of the lung. *Infect. Dis. Clin. North Am.* 1991; **5**: 453–66.

11 Hoffer FA, Bloom DA, Colin AA, Fishman SJ. Lung abscess versus necrotizing pneumonia: implications for interventional therapy. *Pediatr. Radiol.* 1999; **29**: 87–91.

12 Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N. Engl. J. Med.* 1997; **336**: 243–50.

13 Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; **58**: 377–82.

14 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 1987; **40**: 373–83.

15 Lim WS, Baudouin SV, Macfarlane JT; British Thoracic Society Community Acquired Pneumonia Guidelines Committee. Community acquired pneumonia. Management in primary care. *BMJ* 2010; **341**: c4469.

16 Syrjälä H, Broas M, Suramo I, Ojala A, Lähde S. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clin. Infect. Dis.* 1998; **27**: 358–63.

17 Claessens YE, Debray MP, Tubach F, Brun AL, Rammaert B, Hausfater P, Naccache JM, Ray P, Choquet C, Carette MF *et al.* Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. *Am. J. Respir. Crit. Care Med.* 2015; **192**: 974–82.
18 Chen CH, Huang WC, Chen TY, Hung TT, Liu HC, Chen CH. Massive necrotizing pneumonia with pulmonary gangrene. *Ann. Thorac. Surg.* 2009; **87**: 310–1.
19 Curry CA, Fishman EK, Buckley JA. Pulmonary gangrene: radiologic and pathologic correlation. *South. Med. J.* 1998; **91**: 957–60.
20 Pennza PT. Aspiration pneumonia, necrotizing pneumonia, and lung abscess. *Emerg. Med. Clin. North Am.* 1989; **7**: 279–307.
21 Fernandez-Sabe N, Carratala J, Dorca J, Roson B, Tubau F, Manresa F, Gudiol F. Efficacy and safety of sequential amoxicillin-clavulanate in the treatment of anaerobic lung infections. *Eur. J. Clin. Microbiol. Infect. Dis.* 2003; **22**: 185–7.
22 Bartlett JG. Anaerobic bacterial infection of the lung. *Anaerobe* 2012; **18**: 235–9.
23 Krishnadasan B, Sherbin VL, Vallieres E, Karmy-Jones R. Surgical management of lung gangrene. *Can. Respir. J.* 2000; **7**: 401–4.
24 Reimel BA, Krishnadasen B, Cuschieri J, Klein MB, Gross J, Karmy-Jones R. Surgical management of acute necrotizing lung infections. *Can. Respir. J.* 2006; **13**: 369–73.

Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Table S1 Methods of microbiological diagnosis.
Table S2 Co-morbidities of the patients.