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ARTICLE

Clinical and microbiological characteristics of community-acquired thoracic empyema or complicated parapneumonic effusion caused by *Klebsiella pneumoniae* in Taiwan

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Abstract *Klebsiella pneumoniae* is the major cause of community-acquired pyogenic infections in Taiwan and is becoming an increasing problem in acute thoracic empyema. This study evaluated the clinical and microbiological characteristics of community-acquired thoracic empyema or complicated parapneumonic effusion caused by *K. pneumoniae* in Taiwanese adults treated during the period 2001–2008 at a tertiary medical center. All clinical isolates were examined for capsular serotypes K1/K2, and pulsed-field gel electrophoresis (PFGE) was performed on strains of the same serotype. *K. pneumoniae* was the most frequent cause of community-acquired thoracic empyema or complicated parapneumonic effusion. It was associated with high mortality (32.4%) and was an independent risk factor for fatal outcome. Diabetes mellitus, liver cirrhosis, and bronchogenic carcinoma were independent risk factors for *K. pneumoniae* infection. Serotypes K1 (9/37, 24.3%) and K2 (13/37, 35.1%) were the prevalent strains but did not predispose patients to poor outcome compared with other non-K1/K2 serotypes. There was no major cluster of isolates found among serotype K1/K2 strains. In summary, physicians should be aware of the risk factors for thoracic empyema or complicated parapneumonic effusion caused by *K. pneumoniae* and the associated high mortality, and monitor these patients more closely.

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Introduction

Thoracic empyema and complicated parapneumonic effusion are serious complications of thoracic infection that are associated with significant morbidity and mortality [1]. It is estimated that in the United States alone, pleural infections affect 60,000 individuals per year with a 15% mortality rate [2]. The reported bacteriology of thoracic empyema varies significantly between community-acquired and nosocomial infections [3]; however, few studies have been reported on the clinical and microbiological characteristics of community-acquired thoracic empyema or complicated parapneumonic effusion in adults.

In Taiwan, *K. pneumoniae* is the major cause of abscesses of the liver, brain, lung, psoas muscle, and prostate; deep neck infection; mycotic aneurysm; complicated skin and soft tissue infections; and Gram-negative bacillary meningitis [4], and is becoming an increasing problem in acute thoracic empyema [5].

In this study, we investigated the clinical characteristics of community-acquired thoracic empyema or complicated parapneumonic effusion caused by *K pneumoniae*, and the virulence characteristics among invasive clinical isolates in a tertiary medical center over an 8-year period in Taiwan.

Materials and methods

Patient selection

In this retrospective study, medical records of patients with community-acquired thoracic empyema or complicated parapneumonic effusion treated at Taipei Veterans General Hospital, a 2,900-bed tertiary medical center in northern Taiwan, from January 2001 to December 2008, were analyzed. Case records were selected through a computerized search of diagnoses codified upon hospital discharge. Those patients having aspirated pleural fluid that was an empyema (frank pus) or a complicated parapneumonic effusion (pH <7.2, glucose <40 mg/dl, or LDH>1,000 U/L) were enrolled [6].

Patients were excluded if they had any of the following three characteristics: (1) surgery or any invasive procedure involving the pleural cavity prior to development of pleural effusion; (2) pleural infection due to a nonbacterial pathogen (i.e., a parasite, fungus, or mycobacterium); (3) pleural infection as a complication of hospital-acquired pneumonia. Patients younger than 18 years old were also excluded. For patients with recurrent thoracic empyema or complicated parapneumonic effusion, only the first episode during the study period was analyzed.

Data collection

The following data were collected for each patient: age, sex, underlying diseases or risk factors, clinical symptoms, interval from the onset of symptoms to presentation, initial haemogram and biochemistry values, antibiotics used, bacteria yielded by culture of sterile specimens, and clinical outcome.

Microbiological laboratory procedures

Pleural fluid specimens obtained by thoracocentesis or during tube thoracotomy were processed according to standard procedures, and cultured for aerobic and anaerobic pathogens. The specimens were collected in airtight, oxygen-free syringes, and were immediately sent to the laboratory for aerobic and anaerobic microbial cultures. Culture isolates were identified by standard aerobic and anaerobic microbial identification methods. Specimens from most pleural fluids were also sent for mycobacterial, fungal, and cytological determinations. All culture isolates of *K. pneumoniae* were stored at−70°C. The VITEK 2 system (bioMérieux, Marcy l'Etoile, France) with the VITEK 2 GN card was used to confirm bacterial identifications. The antimicrobial susceptibility of *K. pneumoniae* was tested by the standard disk diffusion method and interpretations were performed according to the guidelines of the Clinical and Laboratory Standards Institute [7].

Determination of capsular serotypes and polymerase chain reaction (PCR)

All isolates of *K. pneumoniae* causing monobacteric thoracic empyema or complicated parapneumonic effusion were tested for K1 and K2 serotypes by a countercurrent immunoelectrophoresis method as described elsewhere [8]. Antisera were provided by the Gram Negative Serotyping Unit, Laboratory of Healthcare Associated Infection, Health Protection Agency (London, UK). *K. pneumoniae* ATCC9997 (K2) was used as a control strain. All isolates with K1 and K2 serotypes were confirmed by PCR for serotype-specific targets within the K1 and K2 *cps* clusters as described previously [9]. PCR was also used to determine the prevalence of the *rmpA* gene (rmp=regulator of the mucoid phenotype) as described previously [10].

Pulsed-field gel electrophoresis (PFGE)

Total DNA was prepared, and PFGE was performed as described previously [10]. Dendrograms showing percentage similarity were prepared by the Molecular Analyst Fingerprinting Software (Bio-Rad Laboratories, Hercules, CA, USA) and compared using the UPGMA clustering method. A similarity coefficient above 80% was selected to define a major cluster.

Statistical analyses

Contingency data were analyzed by two-tailed chi-square test or Fisher's exact test, and continuous data were analyzed by Student's *t*-test or Mann-Whitney U test. A p-value<0.05 was considered to be statistically significant, and all probabilities were two-tailed. Variables with p values of <0.10 in univariate analyses subsequently entered in the multivariate analysis. The multivariate logistic regression model was used to evaluate the risk factors for mortality in community-acquired thoracic empyema or complicated parapneumonic effusion and the causative aetiology of *K. pneumonia.* All statistical analyses were performed with SPSS, version 15.0 for Windows (SPSS, Chicago, IL, USA).

Results

Bacteriological characteristics and assessment of microbial aetiology as a mortality factor

The medical records of 166 patients with community-acquired thoracic empyema or complicated parapneumonic effusion within the 8-year period were retrieved for this study. Overall, culture results were positive in 150 patients (90%) and 169

microorganisms were identified. *K. pneumoniae* was the most commonly isolated pathogen (40/169, 23.6%), followed by viridans streptococci (including the *Streptococcus milleri* group, 30/169, 17.8%). The isolates from the 150 culture-positive cases were categorized into the following groups: pure *K. pneumoniae* (n=37), pure aerobic gram-negative bacilli other than *K. pneumoniae* (n=18), pure aerobic or facultative gram-positive cocci (n=56), pure anaerobes (n=22), and mixed isolates (n=17). Univariate analyses recording variables related to death are listed in Table 1. The statistical significance was observed during the subsequent multifactorial regression analyses. *K. pneumoniae* as aetiology (OR 3.2, 95% CI 1.2–8.4, p=0.017), malignancy (OR 3.56, 95% CI 1.4–9.04, p=0.008), and respiratory failure (OR 5.07, 95% CI 1.84–13.96, p=0.002) were the independent factors associated with fatal outcome.

Clinical characteristics of patients with community-acquired thoracic empyema or complicated parapneumonic effusion caused by *K. pneumoniae*

Excluding three patients whose infections were determined to be caused by polymicrobial pathogens mixed with *K. pneumoniae*, the remaining 147 patients were divided into two groups concerning the causative pathogen: *K. pneumoniae* and non-*K. pneumoniae*. The clinical characteristics of the patients with infections from these two categories are compared in Table 2. *K. pneumoniae* infection had a significantly higher mortality rate than non-*K. pneumoniae* infection (32.4% vs. 12.7%, respectively, p = 0.007), higher prevalence of progression to shock within 2 days (13.5% vs. 3.6%, respectively, p=0.03), higher prevalence of concurrent bacteraemia (13.5% vs. 3.6%, respectively, p= 0.03), and greater likelihood of acute presentation with a shorter duration of symptoms before diagnosis (8 vs. 14 days, respectively, p=0.011). None of the 37 cases of *K. pneumoniae* pleural infection had concurrent liver abscesses and only one patient with thoracic empyema had concurrent meningitis (0.3%). Patients with thoracic empyema or complicated parapneumonic effusion underwent standard tube thoracotomy or continuous closed drainage with an indwelling pigtail catheter. Some patients also received intrapleural instillation of streptokinase or urokinase, or underwent surgical intervention if there was radiographic or sonographic evidence of a loculated pleural effusion with poor drainage. All patients received appropriate antibiotic treatment according to the results of susceptibility testing.

Table 1 Risk factors for mortality in community-acquired thoracic empyema or complicated parapneumonic effusion

Characteristic	Survivors (N=123)	Nonsurvivors (N=27)	p-value
Age>65 years	78 (63.4)	20 (74.1)	0.292
Male	107 (87)	20 (74.1)	0.092
Aetiology			
K. pneumoniae	25 (20.3)	12 (44.4)	0.008
Aerobic Gram negative bacteria other than *K. pneumoniae*	13 (10.6)	5 (13.5)	0.25
Aerobic Gram positive cocci	51 (41.5)	5 (18.5)	0.026
Anaerobes	21 (17.1)	1 (3.7)	0.075
Mixed pathogens	13 (10.6)	4 (14.8)	0.529
Duration of symptom(s) before diagnosis (days)	13±12	7±6	0.008
Right side empyema	71 (57.7)	19 (70.4)	0.224
Concurrent bacteraemia	5 (4.1)	2 (7.4)	0.456
Concurrent lung abscess	9 (7.3)	2 (7.4)	0.987
Progression to shock within 2 days	5 (4.1)	4 (14.8)	0.033
Respiratory failure	16 (13)	11 (40.7)	0.001
Malignancy	28 (22.8)	14 (51.9)	0.002
Diabetes mellitus	33 (26.8)	8 (29.6)	0.912
Chronic renal failure	10 (8.1)	1 (3.7)	0.419
Chronic lung disease	22 (17.9)	3 (11.1)	0.392
Central nervous system disease	27 (22)	5 (18.5)	0.693
Hypertensive cardiovascular disease	56 (45.5)	9 (33.3)	0.247
C-reactive protein, mg/dL	18.9±9.3	21.4±9	0.262
Serum creatinine, mg/dL	1.3±0.8	1.2±0.5	0.856

Values given as mean±standard deviation (SD) or n patients (%)

Table 2 Comparison of clinical characteristics between patients with *K. pneumoniae* versus non-*K. pneumoniae* pleural infection

Characteristic	*Klebsiella pneumoniae* (*N*=37)	Non-*Klebsiella pneumoniae* (*N*=110)	*p*-value
Age	67±14	66±17	0.785
Male	30 (81.1)	95 (86.4)	0.435
Manifestations			
Fever	17 (45.9)	38 (34.5)	0.215
Chest pain	20 (54.1)	47 (42.7)	0.231
Cough	22 (59.5)	73 (66.4)	0.447
Dyspnea	27 (73)	78 (70.9)	0.81
Expectoration	19 (51.4)	64 (58.2)	0.469
Duration of symptom(s) before diagnosis (days)	8±6	14±13	0.011
Right side empyema	24 (64.9)	63 (57.3)	0.416
Concurrent bacteraemia	4 (10.8)	3 (2.7)	0.046
Concurrent lung abscess	4 (10.8)	7 (6.4)	0.374
Progression to shock within 2 days	5 (13.5)	4 (3.6)	0.03
Respiratory failure	7 (18.9)	19 (17.3)	0.82
Days of hospitalization	31±23	46±88	0.556
Surgical intervention	6 (16.2)	17 (15.5)	0.912
Repetitive infection	2 (5.4)	1 (0.9)	0.156
In-hospital death	12 (32.4)	14 (12.7)	0.007

Values given as mean±standard deviation (SD) or *n* patients (%)

Risk factors and initial laboratory findings for *K. pneumoniae* thoracic empyema or complicated parapneumonic effusion

Table 3 compares the risk factors and laboratory findings of patients with *K. pneumoniae* and non-*K. pneumoniae* thoracic empyema or complicated parapneumonic effusion. Univariate analysis of patients with *K. pneumoniae* and non-*K. pneumoniae* pleural effusion revealed that the former had a higher prevalence of diabetes mellitus (51.4% vs. 20%, respectively, $p<0.001$), liver cirrhosis (21.6% vs. 0.9%, respectively, $p<0.001$), alcoholism (13.5% vs.0.9%, respectively, $p<0.004$), and bronchogenic carcinoma (27% vs. 10.9%, respectively, $p=0.017$). Non-*K. pneumoniae* related infection was associated only with a higher prevalence of chronic renal failure as compared to *K. pneumoniae* infection (10.1% vs. 0%, respectively, $p=0.044$). The statistical significance was observed during the subsequent multifactorial regression analyses. Diabetes mellitus (OR 5.1, 95% CI 2.1–12.4, $p<0.001$), liver cirrhosis (OR 48.9, 95% CI 5.4–442, $p=0.001$) and bronchogenic carcinoma (OR 3.8, 95% CI 1.3–11, $p=0.02$) were the independent risk factors for *K. pneumoniae* infection. Patients with *K. pneumoniae* thoracic empyema or complicated parapneumonic effusion had significantly higher levels of serum total bilirubin ($p=0.012$) and glucose ($p=0.004$).

Susceptibility testing

Antibiograms of *K. pneumoniae* isolates were identical in all patients. All isolates showed uniform resistance to ampicillin and susceptibility to all cephalosporins, aminoglycosides, and fluoroquinolones.

PFGE

Pulsed-field gel electrophoresis (PFGE) was performed on strains of the same serotype. Dendrograms of organisms of serotypes K1 and K2 are shown in Fig. 1. There was no major cluster of isolates found among those isolates with the same serotype.

Capsular serotypes of K. pneumoniae and presence of rmpA

Serotypes K1 and K2 accounted for 24.3% (9/37) and 35.1% (13/37) of all *K. pneumoniae* isolates, respectively. There were no significant differences in clinical outcome between thoracic empyema or complicated parapneumonic effusion due to K1/K2 and non-K1/K2 isolates (Table 4). All nine isolates of serotype K1, all 13 isolates of serotype K2, and 12 (80%) out of 15 non-K1/K2 isolates carried the *rmpA* gene, which tended to be more prevalent in K1/K2 serotypes (22/22) than in non-K1/K2 serotype isolates (12/15) ($p=0.059$).

Table 3 Comparison of risk factors and laboratory findings between patients with *K. pneumoniae* versus non-*K. pneumoniae* pleural infection

Characteristic	*Klebsiella pneumoniae* (n=37)	Non-*Klebsiella pneumoniae* (n=110)	*p*-value
Predisposing condition or risk factor			
Diabetes mellitus	19 (51.4)	22 (20)	<0.001
Malignancy	13 (35.1)	26 (24.6)	0.171
Bronchogenic carcinoma	10 (27)	12 (10.9)	0.017
Smoking	12 (32.4)	26 (23.6)	0.29
Central nervous system disease	4 (10.8)	27 (24.5)	0.076
Chronic renal failure	0	11 (10)	0.046
Chronic lung disease [a]	6 (16.2)	18 (16.4)	0.983
Liver cirrhosis	8 (21.6)	1 (0.9)	<0.001
Alcoholism	5 (13.5)	1 (0.9)	0.004
Autoimmune disease	0	3 (2.7)	0.572
Initial laboratory value			
Leucocyte count, x $10^3/\mu L$	19.7±17.7	16.6±8.5	0.95
Haemoglobin, g/dL	11.5±2.1	11.2±2.3	0.499
Platelet, x $10^3/\mu L$	305±160	361±154	0.051
Albumin, g/dL	2.7±0.6	2.7±0.5	0.72
C-reactive protein, mg/dL	17.6±9.1	20±9.3	0.203
Serum creatinine, mg/dL	1.3±0.7	1.3±0.8	0.559
Total biliburin, mg/dL	1.8±2.6	0.9±0.8	0.012
Glucose, mg/dL	238±167	169±223	0.004

Values given as mean±standard deviation (SD) or *n* patients (%)

[a] Chronic lung disease was defined as chronic obstructive pulmonary disease, bronchiectasis, and any structural lung diseases except bronchogenic carcinoma

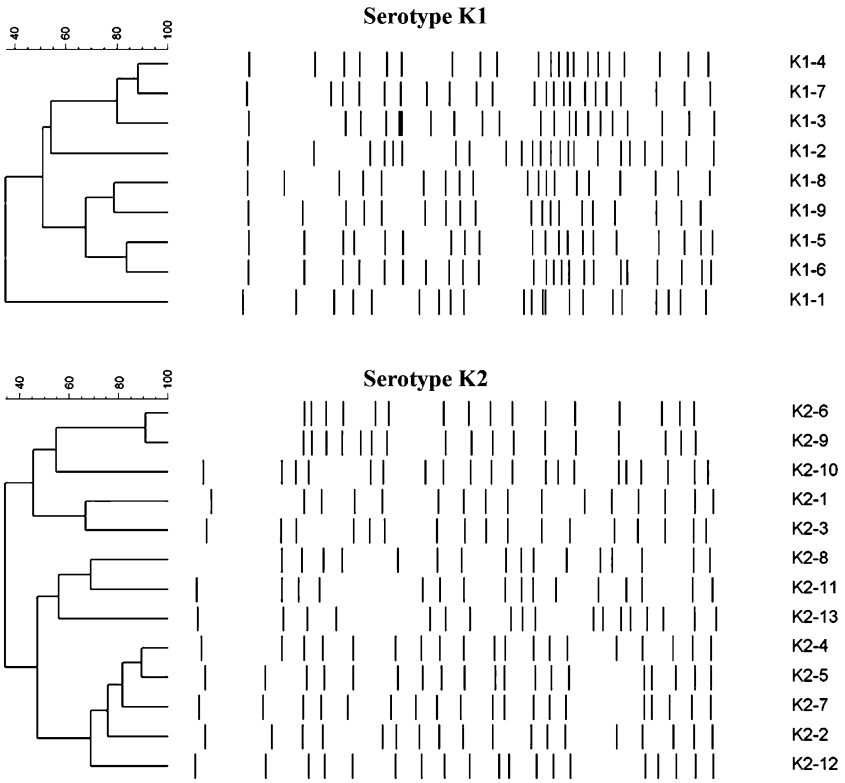

Fig. 1 PFGE of *Klesiella pneumoniae* serotype K1 and K2 isolates. There was no major cluster of isolates found among those isolates with the same serotype

Table 4 Relation of *K. pneumoniae* serotype to clinical outcome

Characteristic	Serotype K1 *N*=9 (24.3 %)	Serotype K2 *N*=13 (35.1 %)	Serotype Non-K1/K2*N*=15 (40.5 %)	*p*-value [a]
Bacteraemia	1 (11.1)	2 (15.4)	1 (6.7)	0.633
Concurrent lung abscess	1 (11.1)	0 (0)	3 (20)	0.283
Duration of hospital stay (days)	33.8±22.1	33.2±27.1	28.1±21.6	0.577
Progression to shock within 2 days	1 (11.1)	2 (15.4)	2 (13.3)	1.000
Respiratory failure	2 (22.2)	2 (15.4)	3 (20)	1.000
Surgical intervention	2 (22.2)	1 (7.7)	3 (20)	0.670
In-hospital death	2 (22.2)	4 (30.8)	6 (40)	0.417

Values given as mean ± standard deviation (SD) or *n* patients (%)

[a] Serotype K1/K2 vs. serotype Non-K1/K2

Discussion

In Taiwan, *K. pneumoniae* is the major cause of pyogenic infections [4]. Our study further highlights the role of *K. pneumoniae* as a dominant pathogen in community-acquired thoracic empyema or complicated parapneumonic effusion in Taiwan. The previous and present findings in Taiwan differ from those of studies done in the United Kingdom. The large prospective MIST 1 trial (Multicenter Intrapleural Sepsis Trial 1), conducted in the United Kingdom in 2005 [11], revealed that most (85%) of those cases were community-acquired infections; Enterobacteriaceae accounted for around 9.3% of all isolates, but no data concerning *K. pneumoniae* was reported. However, an investigation of acute thoracic empyema, conducted in Taiwan from January 1989 to December 1998, first identified *K. pneumoniae* as the most frequently isolated sole pathogen (24.4 %) [5]. Our study demonstrates the continued prevalence of *K. pneumoniae* in clinical isolates obtained from cases of community-acquired thoracic empyema or complicated parapneumonic effusion from a large tertiary-care hospital in Taiwan between 2001 and 2008. The highly endemic nature of *K. pneumoniae* infections in Taiwan [12, 13] are consistent with our findings.

Although *K. pneumoniae* has similarly been reported as a common and important pathogen in thoracic empyema or complicated parapneumonic effusion in Taiwan [3, 5, 14–16], detailed clinical characteristics of community-acquired thoracic empyema or complicated parapneumonic effusion caused by *K. pneumoniae* have not previously been reported in Western studies. Furthermore, the aetiology of community-acquired thoracic empyema or complicated parapneumonic effusion has not been assessed as a risk factor for mortality. In this study, *K. pneumoniae* was shown to be an independent risk factor associated with fatal outcome, and Gram negative bacteria other than *K. pneumonia* failed to demonstrate a significant role in such outcomes. The present isolates of *K. pneumoniae* were uniformly resistant to ampicillin and susceptible to all cephalosporins, consistent with a previous study of *K. pneumoniae* liver abscesses in Taiwan [17]. However, the present mortality rate of patients infected with *K. pneumoniae* (32.4 %) was far higher than that reported for *K. pneumoniae* liver abscess, which is the major cause of pyogenic infections in Taiwan (11.3%) [18]. The likelihood of acute presentation and progression to shock in *K. pneumoniae* thoracic empyema or complicated parapneumonic effusion indicates the need to enhance alertness and monitor patients more closely in addition to appropriate antimicrobial treatment.

A novel finding in this study was the observation that bronchogenic carcinoma, in addition to the classical risk factors, predisposed patients to the development of *K. pneumoniae* thoracic empyema or complicated parapneumonic effusion. The mechanism(s) responsible for this susceptibility is unknown. Further study is also needed to elucidate the role of bronchogenic carcinoma in thoracic empyema or complicated parapneumonic effusion caused by *K. pneumoniae*.

The clonal relationship of *K. pneumoniae*-related thoracic empyema or complicated parapneumonic effusion has not previously been investigated. Studies conducted using ribotyping and PFGE have demonstrated that, in Taiwan, *K. pneumoniae*-related liver abscesses are not caused by a clonally-spread strain [10]. Similar findings have been reported more recently from Taiwan and Singapore [10]. Our study is the first to report no clonal relatedness in *K. pneumoniae* serotype K1/K2 strains causing community-acquired thoracic empyema or complicated parapneumonic effusion.

In this study, capsular serotypes K1 and K2 comprised 24.3% and 35.1%, respectively, of all *K. pneumoniae* isolates. Previous studies have only rarely evaluated the serotype of *K. pneumoniae* isolated from pleural fluid [19]. A previous study in our hospital found that, among 170

respiratory tract isolates, including 17 isolates from pleural fluid, K2 was most common (19%) while K1 accounted for only 9% [19]. Other studies have reported that serotypes K1 and K2 were more common in isolates from community-acquired infections in Taiwan, South Africa, and Singapore than from hospital-acquired isolates in these countries or elsewhere [10, 13]. Metastatic infection is an important complication of *K. pneumoniae* liver abscess in Taiwan [18, 20], and certain capsular serotypes of *K. pneumoniae* including K1 and K2 are thought to play an important role in the development of distal metastatic infections, generally being considered the predominant virulent strains [10, 17, 21, 22]. In our study, patients with K1/K2 serotype *K. pneumoniae* isolates did not have a worse outcome than those with non-K1/K2 serotype of *K. pneumoniae* isolates. Only four cases of *K. pneumoniae* thoracic empyema or complicated parapneumonic effusion were associated with concurrent bacteraemia, and only one of these cases, caused by a non-K1/K2 serotype of *K pneumoniae*, developed metastatic infection (meningitis). This suggests that haematogenous spread of *K. pneumoniae* might only have a minor role in thoracic empyema or complicated parapneumonic effusion, which could also account for the low rate of distant metastasis. Although, we found a high prevalence of the *rmpA* gene (34/37) in *K. pneumoniae* isolates in this study, which was consistent with the notion that the *rmpA* gene was significantly associated with purulent tissue infection [23]. A recent study revealed that not only *rmpA* but also other genetic loci linking to *rmpA* in a virulence plasmid are involved in causing pyogenic infection [24].

In conclusion, during the period 2001–2008, *K. pneumoniae* was the most frequent cause of monomicrobial, community-acquired thoracic empyema or complicated parapneumonic effusion in Taiwanese adults in one tertiary-care hospital in Taiwan. *K. pneumoniae* infection was associated with a high mortality rate and was an independent risk factor for fatal outcome. It should be considered as a possible aetiological agent for acute thoracic empyema or complicated parapneumonic effusion in patients with diabetes mellitus, liver cirrhosis and bronchogenic carcinoma, and with an acute presentation. *K. pneumoniae* serotypes K1 and K2 comprised 24.3% and 35.1% of all isolates, respectively, but they did not predispose patients to a poor clinical outcome compared with other non-K1/K2 serotypes. There were no clonal relatedness in *K. pneumoniae* serotype K1/K2 strains. We suggest that any patient who presents with *K. pneumoniae* community-acquired thoracic empyema or complicated parapneumonic effusion should be monitored more closely due to greater likelihood of rapid progression to shock. Physicians should be aware of the risk factors for thoracic empyaema or complicated parapneumonic effusion caused by *K. pneumoniae* and the associated high mortality.

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Conflict of interest All authors report no conflicts of interest.

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