J Microbiol Immunol Infect
2004;37:176-184

Comparison of pyogenic liver abscess caused by non-*Klebsiella pneumoniae* and *Klebsiella pneumoniae*

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Received: July 28, 2003 Revised: August 28, 2003 Accepted: September 30, 2003

From January 1996 to April 2002, a total of 248 patients with pyogenic liver abscess were enrolled in this study. Abscesses caused by *Klebsiella pneumoniae* accounted for 69% (171) of cases. Abscesses caused by *K. pneumoniae* were more strongly associated with diabetes mellitus or impaired fasting glucose than liver abscesses caused by non-*K. pneumoniae* (70.2% vs 32.5%). Solitary abscess and monomicrobial isolates were more frequent in the *K. pneumoniae* group than that in the non-*K. pneumoniae* group. A total of 42 patients were treated with antibiotics alone. Antibiotics treatment was combined with other procedures, including single aspiration in 23 patients, percutaneous drainage in 176 and surgical drainage in 7. A higher incidence of metastatic infections occurred in the *K. pneumoniae* group than in the non-*K. pneumoniae* group (14.6% vs 3.8%). By contrast, the mortality rate of the *K. pneumoniae* group was lower than that of non-*K. pneumoniae* group (4.1% vs 20.8%). There was no significant difference in the relapse rate between these 2 groups (6.5% vs 6.4%). We also found that the presence of respiratory symptoms (including cough, dyspnea, or chest distress), size of abscess ≥5 cm in diameter and non-*K. pneumoniae* pathogens were significant prognostic factors for mortality.

Key words: *Klebsiella pneumoniae*, liver abscesses, mortality, prognosis, Taiwan

Pyogenic liver abscess was originally a surgical indication, but has been successfully treated with less-invasive managements in the past 2 decades. This transition is mainly attributed to the advent of advanced diagnostic imaging techniques, the development of image-guided techniques for percutaneous aspiration and drainage of abscess, as well as to the availability of more potent antibiotics. However, the overall mortality of pyogenic liver abscess has remained in the range of 5.2 to 18.8% [1-9] despite sustained advancement in knowledge and improvements in management of this disease. The correlation between *Klebsiella pneumoniae* (KP) liver abscess and underlying diabetes mellitus (DM) has been highlighted in Taiwan during the past 20 years [7-16]. Liver abscess due to other microorganisms has the same correlation with DM. This study reviewed the characteristics of patients with KP liver abscess and liver abscess due to other microorganisms from January 1996 to April 2002. Differences in underlying diseases, clinical manifestations, characteristic features of liver abscesses, microorganisms, therapy and outcome were compared between the KP group and non-KP group.

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Materials and Methods

A total of 293 patients (all ethnic Taiwanese) aged 18 years or over with a diagnosis of liver abscess were admitted to our hospital from January 1996 to April 2002. Data were obtained by a review of medical records of patients with pyogenic liver abscess. All patients received either ultrasound (US)-guided needle aspiration, computerized tomography (CT)-guided percutaneous drainage or surgical drainage. The diagnosis of pyogenic liver abscess was based on the following criteria in addition to identification on imaging: (1) pus and/or blood cultures revealed positive findings; (2) lesions subsided after antibiotic treatment despite lack of positive cultures or no performance of the above invasive procedures; and (3) suspected amebic liver abscesses were excluded from this analysis if not yielded from any cultures and no positive identification on wet-mount examination or indirect hemaaglutination antibody titers greater than 1:64.

Data collected included clinical features, underlying diseases, laboratory data, imaging findings, methods of treatment, duration of antibiotics use, results of cultures, and complications. No yield of blood or pus cultures was noted in 45 patients who were therefore excluded from this study. The remaining 248 patients were divided into 2 groups: the KP (only KP isolated or concomitant other microorganisms isolated) group and the non-KP group. Multi-sensitive KP meant that the organism was only resistant to ampicillin.

Underlying diseases and related risk factors were analyzed, including DM, biliary diseases, peptic ulcer diseases, alcoholism, intra-abdominal malignancies (such as hepatoma, carcinoma of biliary tree, pancreatic carcinoma, colon carcinoma, metastasis to intra-abdominal organs), liver cirrhosis, hematological diseases, dental procedure, human immunodifficiency virus (HIV) serostatus, trauma, and cryptogenic origin. DM was defined as follows: symptoms of DM plus random blood glucose concentration ≥200 mg/dL, or fasting plasma glucose ≥126 mg/dL, or 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test (adapted from American Diabetes Association, 2000). Impaired fasting glucose (IFG) was defined as values of glucose between normal and frank diabetes and follow-up values were not frank diabetes during the convalescent period.

When liver abscess was suspected on admission it was confirmed though ultrasonography and/or CT immediately. An 8 Fr pigtail catheter for CT-guided percutaneous drainage was initially placed by a radiologist in cases with high suspicion of liver abscess. The obtained pus was sent for Gram staining and aerobic/anaerobic cultures. At least 2 sets of blood cultures were collected. Microorganisms from blood and/or abscess material cultures were isolated and identified by standard aerobic and anaerobic diagnostic techniques. Susceptibility to antimicrobial agents was determined by using the Bauer-Kirby disk-diffusion method on Mueller-Hinton agar medium (BD BBL™ Sensi-Disc™; Antimicrobial Susceptibility Test Discs, Sparks, MD, USA). The procedure was performed according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) [17]. Afterwards, patients all received parenteral empirical antibiotic(s) initially and a shift to adequate antibiotics was tailored based on their clinical status and/or culture results. The duration of administration of antibiotics was also recorded during admission, including oral antibiotics when the patients were discharged from wards and followed up at outpatient departments. Metastatic (distant) infections were detected sequentially by X-ray, CT and/or gallium inflammation scan if necessary. The pigtail catheter drainage was continued until the convalescent stage. Indications for removal of the catheter were negative culture results, and daily drainage output less than 5 mL. All surviving patients were followed up at our outpatient departments or were interviewed by telephone for at least 5 months after discharge from the hospital.

Statistical analysis was performed using the SPSS statistical software package (SPSS for Windows, version 8.0, Chicago, IL, USA). Descriptive statistics was applied to process the demographic data of the 248 patients. Univariate analysis was performed by Student's *t* test for continuous variables, chi-squared test for categorical variables, and Fisher's exact test for any table with an expected value less than 5. Then multivariate logistic regression analysis was performed on the independently significant variables from the univariate analyses to identify the prognostic factors associated with mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated in the logistic regression model. A value of $p<0.05$ was considered statistically significant in all analyses.

Results

Demographic characteristics and underlying conditions

Of 247,874 hospital admissions in the study period, there were 248 patients discharged from our hospital with a definite diagnosis of pyogenic liver abscess between January 1996 and April 2002. The crude annual incidence of pyogenic liver abscess in this study was 0.1%. The male-to-female ratio was 1.7:1.0 in the study group. Of the 248 patients, 77 (31.0%) had liver abscesses caused by non-KP and 171 (69.0%) had liver abscesses caused by KP. The mean age was 62.3 years (range, 18 to 91 years; median, 64 years) in the non-KP group and 57.0 years (range, 27 to 93 years; median, 57 years) in the KP group (data not shown). There were significant differences in age but not in gender between the 2 groups ($p<0.05$). There were also no significant differences in alcoholism, liver cirrhosis, hematological diseases, uremia, extraction of teeth, and trauma between the 2 groups. Patients with biliary diseases (biliary tree stones and/or biliary tract infection), gastrointestinal (GI) ulcer disorders, and intra-abdominal malignancies were more likely to be infected by non-KP organisms

in comparison with the KP group (57.1% vs 25.1% in biliary diseases, $p<0.001$; 27.3% vs 14.0% in GI ulcer disorders, $p<0.05$; 19.5% vs 7.6% in intra-abdominal malignancies, $p<0.05$). The prevalence rates of DM/IFG and cryptogenic origin in the KP group were higher than in the non-KP group (70.2% vs 32.5%, $p<0.001$; 59.6% vs 18.2%, $p<0.001$, respectively). None of the patients were HIV seropositive. Of the 102 patients with cryptogenic origin in the KP group, 72 had DM, 12 had alcoholism, 4 had GI ulcer disorders, 3 had intra-abdominal malignancies, 3 had uremia, 2 had liver cirrhosis, 1 had thalassemia trait, and 20 had no co-existing medical illness. Of the 14 patients with cryptogenic origin in the non-KP group, 5 had DM, 2 had alcoholism, 1 had intra-abdominal malignancy, 1 had uremia, 1 had liver cirrhosis, 1 had acute myeloblastic leukemia (AML), 1 had thalassemia trait, none had GI ulcer disorders, and 4 had no co-existing medical illness. There were no significant differences in the prevelance of alcoholism, liver cirrhosis, uremia, intra-abdominal malignancies, GI ulcer disorders, hematological disorders, and no co-existing medical illness between patients with cryptogenic origin in the non-KP group and the KP group. The prevalence rate of DM in the patients with cryptogenic origin in the KP group was higher than in the non-KP group (70.6% vs 35.7%; $p<0.05$). The underlying diseases and possible predisposing factors in the KP and non-KP groups are summarized in Table 1.

Table 1. Demographic data, clinical characteristics, and underlying diseases of patients with non-KP and KP liver abscess (n = 248)

	No. (%) of patients		*p*
	Non-KP group (n = 77)	KP group (n = 171)	
Gender			NS[a]
Male	47 (61.0)	109 (63.7)	
Female	30 (39.0)	62 (36.3)	
Age (years) [mean ± SD]	62.3 ± 16.6	57.0 ± 13.7	<0.05[b]
Alcoholism	3 (3.9)	18 (10.5)	NS[a]
Biliary diseases	44 (57.1)	43 (25.1)	<0.001[a]
Liver cirrhosis	3 (3.9)	3 (1.8)	NS[c]
GI ulcer disorders	21 (27.3)	24 (14.0)	<0.05[a]
DM or IFG	25 (32.5)	120 (70.2)	<0.001[a]
Intra-abdominal malignancies	15 (19.5)	13 (7.6)	<0.05[a]
Hematological diseases	2 (2.6)	2 (1.2)	NS[c]
Uremia	2 (2.6)	3 (1.8)	NS[c]
Extraction of teeth	0 (0.0)	1 (0.6)	NS[c]
Trauma	1 (1.3)	1 (0.6)	NS[c]
Cryptogenic origin	14 (18.2)	102 (59.6)	<0.001[a]

Abbreviations: KP = *Klebsiella pneumoniae*; DM = diabetes mellitus; IFG = impaired fasting glucose; GI = gastrointestinal; NS = not significant

[a]Using chi-squared test.

[b]Using Student's *t* test.

[c]Using Fisher's exact test.

Clinical and laboratory features

In the 2 groups, the most common symptoms were fever and/or chills (80.5% in the non-KP group vs 90.6% in the KP group; $p<0.05$), followed by GI upset (79.2% in the non-KP group vs 64.9% in the KP group; $p<0.05$). Other symptoms/signs, such as respiratory symptoms (including cough, dyspnea, or chest distress), weight loss, septic shock and jaundice were not significantly different between the 2 groups. On admission, white blood cell counts, aspartate aminotransferase, alkaline phosphatase, C-reactive protein, and total bilirubin levels were frequently elevated and the albumin levels frequently decreased, but there were no significant differences in these values between the 2 groups. Anemia was common in both groups, and the incidence of anemia (<14 g/dL in men; <12 g/dL in women) in the non-KP group was significantly higher than in the KP group (79.2% vs 63.2%; $p<0.05$). Clinical manifestations and laboratory data of patients with KP and non-KP liver abscesses are shown in Table 2.

Characteristics of liver abscess

The incidence of liver abscess with right lobe involvement was higher than that with left lobe involvement or involvement of both lobes in the 2 groups. The majority of liver abscesses in the 2 groups were not more than 10 cm in diameter. The frequency of gas-forming abscess was low in both groups (5.2% in the non-KP group and 4.1% in the KP group). Of the 11 patients with gas-forming liver abscesses, 7 were in the KP group (all with DM), 4 were in the non-KP group (1 with DM), and 2 died (1 each in both groups). A higher incidence of solitary abscess was observed in the KP group than in the non-KP group (73.1% vs 58.4%; $p<0.05$). Monomicrobial isolates were mostly found in the KP group (87.7% in the KP group vs 49.4% in the non-KP group; $p<0.001$). The characteristics of liver abscess in the KP and the non-KP groups are shown in Table 3.

Microorganisms in non-KP liver abscess

In the non-KP liver abscess group, the causative microorganism was predominantly *Escherichia coli* (*E. coli*) in both monomicrobial and polymicrobial isolates (17/38 and 25/39, respectively), followed by

Table 2. Clinical symptoms/signs and laboratory findings in patients with non-KP and KP liver abscess (n = 248)

	No. (%) of patients		*p*
	Non-KP group (n = 77)	KP group (n = 171)	
Symptom/sign			
Fever or chills	62 (80.5)	155 (90.6)	<0.05[b]
GI upset	61 (79.2)	111 (64.9)	<0.05[b]
Respiratory symptoms[a]	11 (14.3)	23 (13.5)	NS[b]
Weight loss	2 (2.6)	3 (1.8)	NS[c]
Septic shock	1 (1.3)	8 (4.7)	NS[c]
Jaundice	25 (32.5)	39 (22.8)	NS[b]
Laboratory findings			
WBC count (>10^4/mm^3)	58 (75.3)	136 (79.5)	NS[b]
Hb (male <14 g/dL; female <12 g/dL)	61 (79.2)	108 (63.2)	<0.05[b]
AST (>34 IU/L)	55/70 (78.6)	116/152 (76.3)	NS[b]
Alk-P (>126 IU/L)	42 (54.5)	99 (57.9)	NS[b]
Total bilirubin (>1.3 mg/dL)	43 (55.8)	89 (52.0)	NS[b]
CRP (>0.8 mg/dL)	49/49 (100.0)	144/145 (99.3)	NS[c]
Albumin (<3.5 g/dL)	31/36 (86.1)	61/69 (88.4)	NS[c]

Abbreviations: KP = *Klebsiella pneumoniae*; GI = gastrointestinal; NS = not significant; WBC = white blood cell; Hb = hemoglobin; AST = aspartate aminotransferase; Alk-P = alkaline phosphatase; CRP = C-reactive protein

[a]Including cough, dyspnea, or chest distress.

[b]Using chi-squared test.

[c]Using Fisher's exact test.

viridans streptococci in monomicrobial isolates and *Bacteroides fragilis* in polymicrobial isolates, respectively (Table 4). In the non-KP group, the incidence of *B. fragilis* isolation in polymicrobial isolates was higher than in monomicrobial isolates, but this difference was not significant (11.1% vs 5.6%; p=0.681; chi-squared test). *Klebsiella oxytoca* was also cultivated in each subgroup (1 in monomirobial isolates and 3 in polymicrobial isolates). In addition, *Candida albicans* and *Candida tropicalis* were found in 1 case each with monomicrobial isolates. The former was isolated in a patient with gouty arthritis under long-term steroid treatment and the latter in a patient with AML during an episode of neutropenic fever.

Microorganisms in KP liver abscess

In the KP group, there were 150 patients in the monomicrobial subgroup and 21 patients in the polymicrobial subgroup. In the monomicrobial subgroup, blood culture was positive in 99 patients (99/150, 66.0%) and abscess culture was positive in 127 patients (127/150, 84.7%). Of them, KP was isolated from abscess cultures and blood cultures simultaneously in 80 patients (53.3%). In the polymicrobial subgroup, blood culture was positive in 9 patients (9/21, 42.9%) with 14 isolates, and abscess culture was positive in 20 patients (20/21, 95.2%) with 46 isolates. *E. coli* was the most common pathogen after KP in the polymicrobial subgroup (7 isolates from abscess material cultures and 2 from blood cultures). *C. albicans* was isolated in 1 patient who had concomitant KP (extended spectrum β-lactamases strain) and enterococci infections as well as DM, peptic ulcer disease, and chronic obstructive pulmonary disease.

Table 3. Characteristics of liver abscess in the 248 patients

	No. (%) of patients		*p*
	Non-KP group (n = 77)	KP group (n = 171)	
Location of abscess			NS[a]
Left lobe	19 (24.7)	34 (19.9)	
Right lobe	52 (67.5)	128 (74.9)	
Both lobes	6 (7.8)	9 (5.2)	
Abscess size (diameter in cm)			NS[a]
<5	36 (46.8)	72 (42.1)	
5–10	37 (48.1)	87 (50.9)	
>10	4 (5.1)	12 (7.0)	
Gas-forming abscess	4 (5.2)	7 (4.1)	NS[b]
Abscess number			<0.05[a]
Solitary	45 (58.4)	125 (73.1)	
Multiple	32 (41.6)	46 (26.9)	
Type of infection			<0.001[a]
Monomicrobial	38 (49.4)	150 (87.7)	
Polymicrobial	39 (50.6)	21 (12.3)	

Abbreviation: KP = *Klebsiella pneumoniae*

[a]Using chi-squared test.

[b]Using Fisher's exact test.

Treatment and outcome

There were no significant differences in the duration of symptoms prior to hospitalization and the length of treatment between the non-KP and KP groups. In the non-KP group, 15 patients (19.5%) were treated with antibiotics alone and 62 (80.5%) with antibiotics plus invasive approaches (such as needle aspiration, percutaneous drainage or surgery). In the KP group, 27 patients (15.8%) were treated with antibiotics alone and 144 (84.2%) with antibiotics plus invasive approaches. A total of 42 patients (16.9%) were treated with antibiotics alone, 23 (9.3%) with needle aspiration, 176 (71.0%) with percutaneous drainage, and 7 (2.8%) with surgical drainage. Metastatic infection was more frequent in the KP group than in the non-KP group

Table 4. Microbiological isolates found in pus and/or blood cultures of patients with non-*Klebsiella pneumoniae* liver abscess (n = 77)

Monomicrobial (n = 38)			Polymicrobial (n = 39)		
Microorganism	Abscess n = 30 (%)	Blood n = 29 (%)	Microorganism	Abscess n = 28 (%)	Blood n = 9
Escherichia coli	11 (47.8)	8 (44.4)	*Escherichia coli*	21 (29.2)	8
Viridans streptococci	3 (13.0)	4 (22.2)	*Bacteroides fragilis*	8 (11.1)	4
Streptococcus constellatus	1 (4.3)	0	Enterococci	8 (11.1)	0
Klebsiella oxytoca	1 (4.3)	0	Viridans streptococci	7 (9.7)	0
Salmonella enteritidis	1 (4.3)	0	*Morganella morganii*	3 (4.2)	3
Morganella morganii	1 (4.3)	0	GDS	3 (4.2)	1
Serratia marcescens	0	1 (5.6)	ORSA	3 (4.2)	0
Citrobacter freundii	1 (4.3)	0	*Klebsiella oxytoca*	3 (4.2)	0
Pseudomonas aeruginosa	1 (4.3)	0	*Proteus vulgaris*	3 (4.2)	0
Proteus mirabilis	1 (4.3)	0	*Proteus mirabilis*	2 (2.8)	2
Enterococci	0	1 (5.6)	Other anaerobes[a]	2 (2.8)	2
OSSA	1 (4.3)	0	GFS	2 (2.8)	0
CoNS	0	1 (5.6)	*Enterobacter cloacae*	1 (1.4)	1
Bacteroides fragilis	0	1 (5.6)	*Stenotrophomonas maltophilia*	1 (1.4)	1
Candida albicans	1 (4.3)	1 (5.6)	CoNS	1 (1.4)	1
Candida tropicalis	0	1 (5.6)	*Pseudomonas aeruginosa*	1 (1.4)	0
			Serratia marcescens	1 (1.4)	0
			Klebsiella ozanae	1 (1.4)	0
			Pasteurella multocida	1 (1.4)	0
			Haemophilus parainfluenzae	0	1
			Aeromonas hydrophila	0	1
Total	23 (100.0)	18 (100.0)	Total	72 (100.0)	25

Abbreviations: OSSA = oxacillin-sensitive *Staphylococcus aureus*; CoNS = coagulase-negative *Staphylococcus aureus*; GDS = group D streptococci; ORSA = oxacillin-resistant *Staphylococcus aureus*; GFS = group F streptococci

[a]Other anaerobes include *Bacteroides thetaiotamicron*, *Bifidobacterium*, *Eubacterium*, and *Peptostreptococcus micros.*

(14.6% vs 3.9%; $p<0.05$). Of the 25 patients with metastatic infections in the KP group, 7 had only endogenous endophthalmitis (6 were diabetic patients), 1 had concomitant endophthalmitis and pulmonary septic emboli, 5 had meningitis (all were diabetic patients), 1 had concomitant pulmonary septic emboli and prostatic abscess, 1 had only pulmonary septic emboli, 3 had only pleural empyema, 1 had concomitant pleural empyema and peritonitis, 2 had subcutaneous abscess (1 each in the occipital area and in the chest wall), 1 had deep neck infection involving the mediastinum, 1 had pneumonia, 1 had splenic abscess, and 1 had epidural abscess (L1-L2). Of the 3 patients with metastatic infection in the non-KP group, 1 had endophthalmitis caused by *C. albicans*, 1 had empyema caused by *Proteus mirabilis*, and 1 had infective endocarditis caused by viridans streptococci. Pleural effusion was found on imaging (including chest X-ray, US, or CT) in 17 patients (22.1%) of the non-KP group and 38 patients (22.2%) of the KP group. Although rupture of abscess was more frequently noted in the non-KP than that in the KP group, this difference was not significant. There was also no significant difference in relapse between the 2 groups. The overall mortality rate of patients with pyogenic liver abscess was 9.3% (23/248). The mortality rate in the non-KP group was higher than in the KP group (20.8% vs 4.1%; $p<0.001$). Of the 23 patients who died, 5 had received antibiotic alone and 18 had received percutaneous drainage. However, none of the patients treated with needle aspiration or surgical drainage died. The treatment and outcome in the KP and the non-KP groups are shown in Table 5.

Prognostic factors for mortality

The relationships of clinical factors and laboratory variables to mortality were analyzed by univariate analyses. There was no difference in any of the laboratory variables between patients who died and patients who survived (data not shown). The results revealed that age ≥60 years, intra-abdominal malignancy, cryptogenic origin, respiratory symptoms,

Table 5. Therapy and outcome in the 248 patients

	No. (%) of patients		*p*
	Non-KP group (n = 77)	KP group (n = 171)	
Duration of symptoms (days) [mean ± SD]	7.4 ± 8.1	5.8 ± 5.3	NS[a]
Treatment length (days) [mean ± SD]	34.3 ± 28.7	38.5 ± 21.6	NS[a]
Treatment method			NS[b]
Antibiotics alone	15 (19.5)	27 (15.8)	
Antibiotics + invasive procedures	62 (80.5)	144 (84.2)	
Metastatic infections	3 (3.9)	25 (14.6)	<0.05[b]
Pleural effusion	17 (22.1)	38 (22.2)	NS[b]
Abscess rupture	5 (6.5)	7 (4.1)	NS[c]
Relapse	5 (6.5)	11 (6.4)	NS[c]
Death	16 20.8)	7 (4.1)	<0.001[b]

Abbreviation: KP = *Klebsiella pneumoniae*

[a]Using Student's *t*-test.

[b]Using chi-squared test.

[c]Using Fisher's exact test.

multiple liver abscesses, abscess ≥5 cm in diameter, rupture of abscess, polymicrobial infection, and non-KP pathogens were significant prognostic factors for mortality (Table 6). These significant prognostic factors were included in the multivariate logistic regression analysis. The presence of respiratory symptoms (OR, 3.81; 95% CI, 1.22 to 11.96; p=0.022), abscess ≥5 cm in diameter (OR, 3.63; 95% CI, 1.09 to 12.17; p=0.036), and non-KP pathogens (OR, 5.50; 95% CI, 1.67 to 18.10; p=0.005) were found to be significant independent risk factors for mortality.

Table 6. Significant prognostic factors related to mortality in univariate analysis

Variable	Categories	Mortality rate (%)	*p*
Age (years)	<60	6/122 (4.9)	0.020[a]
	≥60	17/126 (13.5)	
Intra-abdominal	Yes	6/28 (21.4)	0.031[b]
malignancies	No	17/220 (7.7)	
Cryptogenic	Yes	6/116 (5.2)	0.037[a]
origin	No	17/132 (12.9)	
Respiratory	Yes	8/34 (23.5)	0.060[b]
symptoms	No	15/214 (7.0)	
Abscess number	Solitary	11/170 (6.5)	0.025[a]
	Multiple	12/78 (15.4)	
Abscess size (cm)	<5	4/108 (3.7)	0.008[a]
	≥5	19/140 (13.6)	
Abscess rupture	Yes	4/12 (33.3)	0.017[b]
	No	19/236 (8.1)	
Type of infection	Monomicrobial	12/188 (6.4)	0.005[a]
	Polymicrobial	11/60 (18.3)	
Pathogen group	KP	7/171 (4.1)	<0.001[a]
	Non-KP	16/77 (20.8)	

Abbreviation: KP = *Klebsiella pneumoniae*

[a]Using chi-squared test.

[b]Using Fisher's exact test.

Discussion

KP liver abscess is rare and usually ranks second to *E. coli* as a cause of liver abscess in western populations [18-23]. By contrast, the prevalence of KP liver abscess remains high (30% in 1980s, increasing to 82.1% in 1990s) [14], and this condition has become endemic in Taiwan. The number of cases of KP liver abscess was twice as high as that of non-KP liver abscess in this study. These 2 groups each had specific characteristic features and different outcomes.

In this study, males outnumbered females in both groups, as in most previous reports [1,3-8,10-12,15,16, 19-28], although these differences were not significant. Middle- to older-aged patients were at higher risk of developing liver abscesses. The median age of the non-KP group was higher than that of the KP group. Patients in the KP group were more likely to have polymicrobial etiology, multiple abscesses, and infection sources from biliary diseases, GI ulcer disorders and intra-abdominal malignancies. Patients in the non-KP group were more likely to have monomicrobial etiology, solitary abscess, DM or IFG and no attributable infection sources. In this study, DM or IFG was found in 70.2% of patients. These findings indicate that DM or IFG may be an important predisposing factor for KP liver abscess. Some diabetic patients have neutrophil phagocytic and/or intracellular killing defects [29] and the capsule of KP may impair these mechanisms [30]. However, the predilection for

KP abscess in diabetic patients in Taiwan remains unclear.

The clinical manifestations of both groups in the present study were similar to those reported elsewhere [10,15,16]. The incidence of anemia was higher in the non-KP group, which may have been because of the greater number of debilitated, elderly patients and/or long-term impairment of GI absorption. Elevated alkaline phosphate level could be seen in almost all patients with biliary tract obstruction in this study, although this study was not as specific as in Western countries [31], where the biliary diseases are a major cause of pyogenic liver abscess.

The right lobe was most commonly involved due to its size and propensity to receive most of the portal blood flow. Abscess sizes larger than 10 cm were rarely observed in the 2 groups. A close correlation with diabetes mellitus and a higher mortality rate have been found in patients with gas-forming liver abscess caused by KP [3], although the gas-forming liver abscess was not obviously predominant in the KP and non-KP groups of this study.

As in most previous reports from western countries [18-23], *E. coli* was predominant in the non-KP group. The anaerobes (*B. fragilis*, predominantly), ranked second, and were commonly isolated with aerobes in mixed infections. Anaerobes were more common in the non-KP group, but this difference was not significant. With the advent of improved techniques of anaerobic culture, these organisms have been recognized and emphasized gradually. In this study, they were usually associated with biliary tract disease, inflammatory bowel disease, intra-abdominal malignancy, or surgery of the gastrointestinal tract. On the other hand, the high frequencies of long-term indwelling catheters and broad-spectrum antibiotics use in this study were associated with increased prevalence of hospital-acquired or water-borne microorganisms (such as *Pseudomonas, Morganella, Stenotrophomonas, Enterobacter, Citrobacter, Acinetobacter*, etc), enterococcal, staphylococcal, streptococcal, and fungal species.

Multi-sensitive KP (149/150) was most common among single isolates of the KP group, whereas *E. coli* and enterococci were usually isolated from KP-including mixed flora in the KP group. Multi-sensitive KP liver abscess accounted for 98% (168/171) of KP isolates. These results are consistent with the findings of Wang et al [10]. The respiratory, urinary and GI tracts are well-known predominant routes of entry for *Klebsiella* bacteremia. These patients did not suffer from concomitant primary respiratory or urinary tract infection. Thus, it was estimated that the most probable source in KP liver abscess was the gastrointestinal tract. In addition, a higher percentage (53.3%, 80/150) of septicemia also occurred in patients with a single KP isolate. This indicated the need for alertness to the possibility of KP liver abscess if blood culture yields KP, particularly a multi-sensitive strain.

The relative of KP, *K. oxytoca*, was classified as being in the non-KP group in this study, despite the lack of difference in clinical features and antimicrobial susceptibilities of isolates between *K. oxytoca* and KP [32]. *K. oxytoca* bacteremia originated predominantly from the hepatobiliary tract, was less associated with DM than KP bacteremia, and had a lower mortality rate [32]. There were 5 patients with a *K. oxytoca* isolate, all of which originated from the biliary tract. The overall mortality rate for these patients was 20% (1 patient, who belonged to the KP group died) in this study.

More than 80% of patients in the 2 groups received antibiotics plus invasive procedures; and the remaining patients received only antibiotics because of either small abscess size or refusal to undergo invasive procedures.

Metastatic infections played an important role in complications of liver abscess, especially in the KP group. Chang et al found that the metastatic infection rate of patients with KP liver abscess was higher than that of non-KP, but this difference did not reach significance [16]. This may have been due to their small sample size. In this study, the incidence of metastatic infections in the KP group was markedly higher than in the non-KP group (14.6% vs 3.8%). In the KP group, endogenous endophthalmitis was predominant in metastatic infections, and most patients were diabetics (6/8). All of the isolates in the KP group were multi-sensitive KP. Cheng et al hypothesized that intimal vascular defect in diabetic patients may predispose to hematogenous seeding of KP and cause liver abscess and metastatic infections [33]. The late onset of metastatic infections in KP liver abscess could occur accidentally after discharge from the hospital. For example, a prostatic abscess in 1 patient of the KP group was found through abdominal CT 2 months after the completion of treatment.

Endogenous endophthalmitis is commonly caused by Gram-positive cocci (*Staphylococcus aureus*, streptococci) in western populations [34]. In contrast, the incidence of endogenous endophthalmitis caused by Gram-negative bacilli (especially caused by KP liver

abscess, first reported in Taiwan in 1981 [33]), ranges from 0.8 to 5.6% [8,13,15,35,36]. In this study, this condition developed in 1.3% (1/77) of patients in the non-KP group and 4.7% (8/171) in the KP group (overall incidence, 3.6%; 9/248). None of these patients died but two-thirds had permanent vision loss, and 1 of them received enucleation of the left eye. However, blurred vision and/or swelling, or erythematous eyeballs were complained of on initial admission by only 3 of the patients who developed endogenous endophthalmitis. The poor visual outcome may be attributable to delayed diagnosis and/or lack of effective antibiotics. These findings suggest the need for suspicion of septic metastatic endophthalmitis in an ophthalmologic emergency. Patients with KP liver abscess should be examined by an ophthalmologist routinely and rapidly. Treatment with the third-generation cephalosporin ceftriaxone (Rocephin), the first antibiotic that has been shown to penetrate the vitreous in therapeutic concentration after intravenous administration, should be started once the condition is diagnosed [37]. Cheng et al also found that the use of an extended-spectrum cephalosporin instead of cefazolin might optimize the outcome of liver abscess caused by KP, especially in patients with metastatic infections [38].

In the non-KP group, 1 patient with metastatic endophthalmitis caused by *C. albicans* had underlying gouty arthritis and received long-term steroid therapy. *C. albicans* probably colonized in the mucosa of the GI tract of this patient initially, and then transmitted through a gut barrier leak in the mucosa, via hepatic portal circulation to the liver, and then seeded to the left eye via the bloodstream. The process of disease translocation is clinically relevant in severely ill patients with immunocompromised status, and is primarily due to host defense rather than infection. Metastatic meningitis also only occurred in the KP group, and was thus only related to multi-sensitive KP. The meningitis caused by KP only occurred in diabetic patients. When metastatic meningitis is highly suspected, lumbar puncture for CSF (cerebrospinal fluid) studies must be performed at once, and then parenteral antibiotics (e.g., treatment with a third-generation cephalosporin, due to its better ability to penetrate the brain-blood barrier) should be started [16].

The overall mortality rate in this study was 9.3% (23/248; 20.8% in the non-KP and 4.1% in the KP group) and those of previous studies in the past 2 decades ranged from 5.2% to 18.8% [1-9]. Wang et al found that KP liver abscess is a relatively benign disease that is associated with a low mortality rate, good clinical response, and low relapse rate [10]. In the present study, there was a significantly lower mortality in the KP group, but no difference in the relapse rate between the non-KP and KP groups (6.5% vs 6.4%). The most important determinants of mortality were the presence of respiratory symptoms (including cough, dyspnea, or chest distress), size of abscess ≥5 cm in diameter and non-KP pathogen infections. No general consensus has been achieved regarding prognostic factors, and this discrepancy may be due to differences in subject populations.

In conclusion, Taiwan has a high prevalence of KP liver abscess and a high index of clinical suspicion is needed, especially when patients with fever of unknown origin are encountered. Once liver abscess is confirmed, possible extrahepatic metastatic infections should be kept in mind. Adequate parenteral antibiotics plus timely drainage is the gold standard of therapy for KP or non-KP liver abscess.

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