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Risk factors for developing metastatic infection from pyogenic liver abscesses

Shiuan-Chih Chen[a,b,c], *Yuan-Ti Lee*[a,d], *Kuang-Chi Lai*[a,e], *Ken-Sheng Cheng*[f], *Long-Bin Jeng*[e], *Wei-Ya Wu*[a,c], *Chun-Chieh Chen*[a,b,c], *Meng-Chih Lee*[a,c]

[a] Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
[b] School of Medicine, Chung Shan Medical University, Taichung, Taiwan
[c] Department of Family Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan
[d] Division of Infectious Diseases, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan
[e] Department of Surgery, China Medical University Hospital, Taichung, Taiwan
[f] Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan

Summary

Objectives: The aim of this study was to identify the risk factors for developing extra-hepatic metastases from pyogenic liver abscesses.

Methods: We conducted a retrospective study and reviewed 225 patients (age, 19–93 years) with a discharge diagnosis of pyogenic liver abscess from a large medical centre in Taiwan, between January 1995 and June 2000. Clinical data were collected from medical records. Of the 225 patients with a pyogenic liver abscess, 24 had extra-hepatic metastases and were classified into the metastatic infection group; the remaining 201 were classified into the non-metastatic infection group and served as the control group. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by exact logistic regression.

Results: After adjustment for age, sex, and the duration of symptoms before admission, diabetes mellitus (adjusted OR, 12; 95% CI, 3.3–67), alcoholism (adjusted OR, 5.2; 95% CI, 1.4–20), the time interval >7 days from the onset of symptoms to the time appropriate antibiotics were administered (adjusted OR, 3.9; 95% CI, 1.2–13), bacteraemia (adjusted OR, 5.4; 95% CI, 1.4–30), and *Klebsiella pneumoniae* infection (adjusted OR, 5.0; 95% CI, 1.1–47) were associated with the development of extra-hepatic metastases from pyogenic liver abscesses. On the other hand, fever (adjusted OR, 0.28; 95% CI, 0.089–0.92) and right upper quadrant pain/tenderness (adjusted OR, 0.091; 95% CI, 0.0020–0.50) were associated with the non-metastatic abscesses. We performed a multivariate analysis and found that diabetes mellitus (multivariate OR, 7.7; 95% CI, 2.1–29) and alcoholism (multivariate OR, 8.9; 95% CI, 2.6–30) were the independent risk factors for developing metastatic infections; yet right upper quadrant pain/tenderness (multivariate OR, 0.11; 95% CI, 0.014–0.87) was the predictor of no metastatic abscesses.

Conclusions: Our data suggest that diabetes mellitus and alcoholism are significant risk factors for developing metastatic infections from pyogenic liver abscesses. These findings seem to imply that underlying conditions of the host influence the development of extra-hepatic metastases from pyogenic liver abscesses.

Key words: risk factors; diabetes mellitus; alcoholism, metastatic infection; pyogenic liver abscess

Introduction

The incidence of extra-hepatic metastases from pyogenic liver abscess increased over the last two decades. Before 1980, few reports were published on metastatic infections in patients with pyogenic liver abscess [1, 2]. The incidence of metastatic infections ranged from 3% to 12% of patients with pyogenic liver abscesses [3–11]. Extra-hepatic metastases from pyogenic liver abscesses were found in eyes [4–9, 12–14], lungs [4, 6–9, 15–17], pleura [5, 18], brain/meninges [4–9, 14, 17, 19], prostate [6, 9, 14, 16], kidney [6, 9], epidural space [9], bone/joints [2, 4, 19], skin/soft tissue [3, 4, 6, 7, 9, 19, 20], and spleen [7]. Such metastatic complications, especially involving ocular, central nervous system (CNS), and pulmonary lesions, could lead to a devastating outcome without a prompt and appropriate management [6, 7, 10]. Awareness of the clinical presenta-

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tion and risk factors of septic metastases from pyogenic liver abscesses is very important. So far, only one study attempted to identify the risk factors for developing septic metastatic infections from pyogenic liver abscesses. In that study, bivariate analysis identified *Klebsiella pneumoniae* liver abscess, bacteraemia, and underlying diabetes mellitus as risk factors [4]. However, the previous study did not adjust for covariates to determine the independent risk factors for developing extra-hepatic metastatic sites from pyogenic liver abscesses. Furthermore, the majority of the septic metastatic lesions in that study were located in ocular/CNS sites. In addition, the risk factors for the development of different extra-hepatic metastatic sites from pyogenic liver abscesses were not addressed. Hence, we conducted a retrospective case-control study to identify risk factors for the development of extra-hepatic metastases, and also to delineate the clinical features of these extra-hepatic metastases from pyogenic liver abscesses.

Methods

Study patients

We reviewed the medical records of consecutive patients aged 19 years and older (range, 19–93 years), who had been diagnosed with pyogenic liver abscess at the China Medical University Hospital, Taichung, Taiwan, from January 1, 1995 to June 30, 2000. During the five and a half year period, 258 patients were enrolled by a systematic search. Patients were included when one or more discrete abscess cavities of the liver had been confirmed by abdominal ultrasonography (US) and/or computerised axial tomography (CT) scans with contrast enhancement, and when a bacterial blood or abscess culture was positive. A total of 33 patients were excluded because of the following conditions: infected bilomas (n = 2), incomplete medical records (n = 2), parasitic liver abscess (n = 2), fungal liver abscess (n = 3), amoebic liver abscess (n = 5), no organism identified in both blood and abscess cultures (n = 16), and simultanous abscesses of the liver and an extra-hepatic site at admission (concomitant liver and splenic abscesses [n = 2]; concomitant liver and renal abscesses [n = 1]). A total of 225 patients with pyogenic liver abscesses were eligible for the analysis. This study was approved by the ethical committee of the hospital.

Data collection

We collected the demographic information, clinical features, underlying medical conditions, laboratory data, microbiological and roentgenographic findings, type of therapeutic modalities, outcome, and subsequent follow-up information for these patients. The clinical features included presenting symptoms and signs at admission. The medical conditions studied included underlying diabetes mellitus, alcoholism (alcohol abuse or dependence), malignancy, uraemia, and liver cirrhosis. Clinical data of the first episode were collected of patients with recurrent liver abscesses. However, if patients had septic metastasis during a recurrent liver abscess, clinical data of that episode would be collected. Abscess material was obtained by image (CT or US)-guided percutaneous needle aspiration (diagnostic or therapeutic), image-guided percutaneous catheter drainage, or direct surgical intervention.

Microorganisms from blood and abscess material cultures were isolated and identified by standard aerobic and anaerobic diagnostic techniques and then tested for antibiotic susceptibility. Susceptibility to antimicrobial agents was tested by the Bauer-Kirby disc diffusion method on Mueller-Hinton agar medium (BD BBL™ Sensi-Disc™ Antimicrobial Susceptibility Test Discs, Sparks, Maryland, USA) according to the guidelines of the National Committee for Clinical Laboratory Standards [21, 22]. After the initial microbiological work-up from blood and/or liver abscess material was completed, broad-spectrum antibiotic agents were administered intravenously. Subsequent antibiotics administered to patients were modified according to the results of the microbiologic cultures and antibiotic susceptibility tests.

The origins of the abscesses were determined from images (including US, CT scan with contrast enhancement, and/or endoscopic retrograde cholangiopancreatography), and clinical, pathological and/or surgical information available in each patient's medical record by a modified version of the classification developed by Frey et al. [23]. Biliary-related origin of liver abscess was defined if clinical features of cholecystitis/cholangitis or extrahepatic biliary ductal abnormalities were identified on radiographic images. Cryptogenic origin of liver abscess was defined as those in which no obvious extra-hepatic source of infection could be identified. Drinkers who met DSM-IV criteria for alcohol dependence or abuse were considered having alcoholism. Drinkers were defined as individuals who drank more than 14 drinks per week the preceding 12 months. The amount of alcohol in one drink was defined as 12 gm ethanol, which is equivalent to that found in a 12 ounce bottle of regular strength beer, a 5 ounce glass of wine, or a 1.5 ounce glass of 80-proof distilled spirits. Metastatic infection was defined when extra-hepatic infectious foci were found in patients who had undergone treatment for liver abscess and when bacterial strains isolated from the extra-hepatic foci were the same as those that had been isolated from the abscess/blood culture. Mortality was defined as death resulting directly from the abscess or the death from a treatment complication. The follow-up of patients in the outpatient clinic after discharge from the hospital ranged from 3 to 13 months (median, 6 months).

Statistical analyses

All statistical analyses were performed using a statistical software package (SAS version 8.2, SAS Institute Inc., Cary, NC, USA). Descriptive data were presented as median with interquartile ranges (IQRs) for continuous data and percentages for categorical data. On the basis of the clinical findings concerning occurrence of extra-hepatic metastases, all eligible patients with pyogenic liver abscess were divided into two groups, a metastatic infection group and a non-metastatic infection group. Because of the imbalanced data set in our study, we performed exact methods for logistic regression instead of conventional logistic regression procedures [24]. We constructed an exact logistic regression model with covariate adjustment to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between dependent and independent variables. For all OR estimates, we considered possible confounding by sex, age, and duration of symptoms prior to

admission. With regard to the specific location of extra-hepatic metastases from pyogenic liver abscesses, patients with metastatic infection of the pleural/pulmonary and those with ocular/CNS lesions were classified into the pleuropulmonary metastatic and ocular/CNS metastatic infection groups, respectively. Patients in the non-metastatic infection group served as the control group. All tests were two-tailed. P <0.05 was considered statistically significant in all analyses.

Results

Of the 225 patients with a pyogenic liver abscess, 24 were classified into the metastatic infection group and 201 were classified into the non-metastatic infection group. Demograhics and clinical characteristics of each patient with metastatic infection are shown in table 1. The median age at the time of admission was 55 years (IQR, 45–67 years) in the metastatic infection group and 61 years (IQR, 47–70 years) in the non-metastatic infection group, respectively. There was a male predominance in the metastatic infection (male/female: 19/5) and non-metastatic infection (male/female: 124/77) groups. The median duration of prodromal symptoms before admission was 3 days (IQR, 1–7 days) in the metastatic infection group and 5 days (IQR, 2–8 days) in the non-metastatic infection group, respectively. There was a higher frequency of diabetes mellitus (adjusted OR, 12; 95% CI, 3.3–67) and alcoholism (adjusted OR, 5.2; 95% CI, 1.4–20) in the metastatic infection group than in the non-metastatic infection group after adjustment for age, sex, and the duration of prodromal symptoms before admission. At admission, fever (adjusted OR, 0.28; 95% CI, 0.089–0.92) and right upper quadrant pain/tenderness (adjusted OR, 0.091; 95% CI, 0.0020–0.50) were less frequently present in patients of the metastatic infection group than in patients of the non-metastatic infection group. There were no differences in demographic data and origin of liver abscess between the metastatic and non-metastatic infection groups. The underlying diseases, origin of abscess, and presenting symptoms/signs at admission of these patients are summarised in table 2.

The recovery rate of blood cultures in the metastatic infection group was higher than that in the non-metastatic infection group after adjustment for confounders (adjusted OR, 5.4; 95% CI, 1.4–30). With respect to specific pathogens, *K. pneumoniae* were more frequently cultured in patients of the metastatic infection group than in patients of the non-metastatic infection group after adjusting covariates (adjusted OR, 5.0; 95% CI, 1.1–47) (table 3). The median duration from the time symptoms developed to the time appropriate antibiotics were administered (on the basis of the results of the antibiotic susceptibility profiles) was 8 days (IQR, 5–12 days) in the metastatic infection group and 7 days (IQR, 4–10 days) in the non-metastatic infection group. After adjusting for covariates, patients in the metastatic infection group had a longer duration from the time symptoms had developed to the time appropriate antibiotics had been administered compared those in the non-metastatic infection group (adjusted OR, 3.9; 95% CI, 1.2–13) (table 3). No differences in the imaging and laboratory findings at admission, and initial therapeutic modality were observed between the two groups. Recurrence of liver abscess was observed in 12 patients (2 patients in the metastatic infection group and 10 patients in the non-metastatic infection group). The 2 septic metastases in the metastatic infection group occurred in the first episode of pyogenic liver abscess. The median length of hospital stay was 29 days (IQR, 22–36 days) in the metastatic infection group and 18 days (IQR, 13–26 days) in the non-metastatic infection group. After adjusting for covariates, patients in the metastatic infection group had a higher frequency of hospital stay >3 weeks than those in the non-metastatic infection group (metastatic vs non-metastatic, 20/24 [83%] vs 72/201 [36%]; adjusted OR, 10; 95% CI, 3.2–31). There was no difference in mortality between the two groups after adjustment for confounders (metastatic vs non-metastatic, 3/24 [13%] vs 19/201 [10%]; adjusted OR, 2.0; 95% CI, 0.33–8.8).

We also looked at risk factors associated with the development of the different extra-hepatic metastatic infections from pyogenic liver abscesses. With respect to the specific location of extra-hepatic metastases, 10 patients were classified into the pleuropulmonary metastatic infection group and 12 patients were classified into the ocular/CNS metastatic infection group. Differences in the estimated risk of the development of pleuropulmonary metatases were more pronounced in patients with diabetes mellitus (adjusted OR, 13; 95% CI, 1.6–580), alcoholism (adjusted OR, 12; 95% CI, 1.6–105), those with chest symptoms (including cough, chest pain, and/or short of breath) (adjusted OR, 9.3; 95% CI, 2.1–47), and patients with pleural effusion at admission (adjusted OR, 9.3; 95% CI, 1.9–60) after adjustment for age, sex, and the duration of prodromal symptoms before admission. Differences in the estimated risk of developing ocular/CNS metatases were significant in patients with diabetes mellitus (adjusted OR, 26; 95% CI, 3.2–1233), those with right upper quadrant pain/tenderness (adjusted OR, 0.12; 95% CI, 0–0.76), patients with mental confusion at admission (adjusted OR, 6.9; 95% CI, 1.3–37), and those with *K. pneumoniae* infection (adjusted OR, 7.1; 95% CI, 1.1–∞) after adjusting covariates.

The significant variables in relation to metastatic infection obtained from the above

Table 1

Pyogenic liver abscess cases with extra-hepatic metastases.

Case No.	Age (y)	Sex	Underlying medical condition	Liver abscess culture	Blood culture	Extra-hepatic metastatic infection	Initial medical therapy	Procedure	Outcome
1	72	F	DM	*K. pneumoniae*	No growth	Endophthalmitis (left eye)	Cefixime	PNA	Survived, decreased vision (left eye)
2	62	M	DM, cholelithiasis, HTN	*K. pneumoniae*	*K. pneumoniae*	Occipital subcutaneous abscess	Cefotaxime sodium	PCD	Survived
3	61	F	DM	*K. pneumoniae*	No growth	Pleural empyema, septic pulmonary embolism	Cephradine + gentamicin sulfate	PCD	Survived
4	55	M	DM	ND	*K. pneumoniae*	Meningitis	Cefotaxime sodium	Antibiotics alone	Survived
5	57	M	DM	*K. pneumoniae*	*K. pneumoniae*	Meningitis	Cephradine + gentamicin sulfate	PCD	Survived
6	65	M	DM, prior stroke	*K. pneumoniae*	*K. pneumoniae*, *S. maltophilia*	Septic pulmonary embolism	Cefoxitin sodium	Antibiotics alone	Survived
7	50	M	DM	*K. pneumoniae*	*K. pneumoniae*	Meningitis	Cefotaxime sodium	PCD	Died
8	67	M	DM, chronic cholecystitis	*K. pneumoniae*	*K. pneumoniae*	Endophthalmitis (right eye), pneumonia	Cephradine + gentamicin sulfate	Antibiotics alone	Survived, blindness (right eye)
9	45	M	DM, alcoholism, ischaemic heart disease, cholelithiasis, dyslipidaemia	*K. pneumoniae*	*K. pneumoniae*	Septic pulmonary embolism	Cephradine + gentamicin sulfate	PCD	Survived
10	45	M	DM, chronic hepatitis B	*K. pneumoniae*	No growth	Pleural empyema, septic pulmonary embolism	Cephradine + gentamicin sulfate	PCD	Survived
11	68	F	DM, HTN	*K. pneumoniae*	*K. pneumoniae*	Pleural empyema, septic pulmonary embolism	Cephradine + gentamicin sulfate	PCD	Survived
12	53	M	DM, alcoholism, HTN, gouty arthritis, liver cirrhosis	*K. pneumoniae*	*K. pneumoniae*	Endophthalmitis (left eye), septic pulmonary embolism	Cephradine + gentamicin sulfate	PCD	Survived, decreased vision (left eye)
13	37	M	DM, alcoholism, chronic hepatitis C	*K. pneumoniae*, Viridans streptococci	*K. pneumoniae*, Viridans streptococci	Splenic abscess	Cefoxitin sodium	PCD	Survived
14	76	F	DM	*K. pneumoniae*	*K. pneumoniae*	Pulmonary abscess	Penicillin G sodium + gentamicin sulfate	PCD	Died
15	62	M	DM, HTN, chronic renal insufficiency	*K. pneumoniae*	*K. pneumoniae*	Endophthalmitis (both eyes)	Cephradine + gentamicin sulfate	PCD	Survived, decreased vision (both eyes)
16	46	M	DM, alcoholism	*K. pneumoniae*	*K. pneumoniae*	Meningitis	Cefotaxime sodium	PCD	Survived
17	52	F	DM	*K. pneumoniae*	*K. pneumoniae*	Psoas abscess	Cephradine + gentamicin sulfate	PCD	Survived
18	55	M	HTN, cholelithiasis	*K. pneumoniae*	No growth	Endophthalmitis (left eye)	Cefazolin sodium	PCD	Survived, blindness (left eye)
19	53	M	DM	*K. pneumoniae*	*K. pneumoniae*	Meningitis	Cephradine + gentamicin sulfate	PCD	Survived
20	37	M	DM, alcoholism, chronic pancreatitis	ND	*K. pneumoniae*	Epidural spinal abscess	Cephradine + gentamicin sulfate	Antibiotics alone	Survived
21	31	M	DM, alcoholism	*K. pneumoniae*	*K. pneumoniae*	Endophthalmitis (left eye)	Cefotaxime sodium	PCD	Survived, blindness (left eye)
22	34	M	DM, alcoholism	*K. pneumoniae*	*K. pneumoniae*	Septic pulmonary embolism	Cefotaxime sodium	PCD	Survived
23	69	M	Pancreatic carcinoma, peptic ulcer disorder	ND	Viridans streptococci	Infectious endocarditis	Cephradine + gentamicin sulfate	Antibiotics alone	Survived
24	69	M	Alcoholism, gastric carcinoma	*E. coli*, *P. mirabilis*	*E. coli*, *P. mirabilis*	Septic pulmonary embolism	Cefoxitin sodium + metronidazole	PCD	Died

DM: diabetes mellitus; *E. coli: Escherichia coli;* ND: not done; HTN: hypertension; *K. pneumoniae*: *Klebsiella pneumoniae*; PCD: percutaneous catheter drainage; *P. mirabilis: Proteus mirabilis;* PNA: percutaneous needle aspiration; *S. maltophilia: Stenotrophomonas maltophilia*.

Table 2

Underlying diseases, origin of abscess, and clinical features at admission in the metastatic and non-metastatic infection groups.

Variable	Metastatic group	Non-metastatic group	Metastatic vs non-metastatic adjusted OR (95% CI)[d]
Underlying condition, No. (%)			
Diabetes mellitus	21/24 (88)	89/201 (44)	12 (3.3–67) *
Alcoholism	8/24 (33)	14/201 (7)	5.2 (1.4–20) *
Malignancy	2/24 (8)	25/201 (12)	0.70 (0.071–3.4)
Uraemia	0/24	5/201 (3)	1.4 (0–11)
Liver cirrhosis	0/24	3/201 (2)	2.2 (0–22)
Origin of abscess, No. (%)			
Biliary-related origin[a]	4/24 (17)	81/201 (40)	0.34 (0.08–1.1)
Cryptogenic origin	17/24 (71)	105/201 (52)	2.2 (0.79–6.6)
Other origin[b]	3/24 (13)	15/201 (8)	1.2 (0.30–4.6)
Symptoms/signs, No. (%)			
Fever	16/24 (67)	169/201 (84)	0.28 (0.089–0.92) *
Chills	12/24 (50)	130/201 (65)	0.50 (0.19–1.3)
RUQ pain/tenderness	1/24 (4)	69/201 (34)	0.091 (0.0020–0.50) *
Chest symptoms[c]	7/24 (29)	27/201 (13)	2.8 (0.88–8.2)
Mental confusion	6/24 (25)	18/201 (9)	3.5 (0.98–12)
Shock	2/24 (8)	6/201 (3)	2.1 (0.19–13)
Visual impairment	1/24 (4)	0/201	6.1 (0.16-∞)

CI: confidence interval; OR: odds ratio; RUQ: right upper quadrant; ∞, infinity

[a] Biliary-related origin included cholecystitis, cholangitis or documented extrahepatic biliary ductal abnormalities.

[b] Other origin of abscesses in the metastatic infection group was acute pancreatitis (n = 3); other origin of abscesses in non-metastatic infection group included acute pancreatitis (n = 2), acute pyelonephritis (n = 2), recent liver trauma (n = 2), colonic carcinoma with metastases (n = 2), ulcerative colitis (n = 1), transcatheter arterial embolisation for hepatocellular carcinoma (n = 1), acute myeloid leukaemia (n = 1), appendicitis (n = 1), recent hepato-biliary surgery (n = 1), recent anal surgery (n = 1), and recent dental retraction (n = 1).

[c] Chest symptoms included cough, chest pain, and/or short of breath.

[d] The exact logistic regression model included adjustment for age, sex, and duration of symptoms before admission.

* $p < 0.05$

analysis, including diabetes mellitus, alcoholism, fever, RUQ pain/tenderness, bacteraemia, *K. pneumoniae* infection, and the time interval >7 days from the onset of symptoms to the time of appropriate antibiotic treatment were entered into multivariate analysis with a stepwise method. Only diabetes mellitus, alcoholism, and RUQ pain/tenderness were significantly associated with the development of metastatic infection (table 4).

Discussion

In the present study, multivariate analysis revealed that diabetes mellitus was one of the independent risk factors for developing extra-hepatic metastases from pyogenic liver abscesses, a result consistent with previous studies [4, 6]. In addition to diabetes mellitus, our study suggests alcoholism to be another independent risk factor for the development of septic metastases from pyogenic liver abscesses. This finding has not been mentioned previously. Human and animal studies have shown that chronic ethanol intake can suppress the systemic immune defense, impair epithelial barrier function, inactivate Kupffer cells, increase bacterial growth, and to cause susceptibility to various infections [26–30]. Furthermore, chronic ingestion of ethanol can decrease the pulmonary glutathione concentration, increase alveolar barrier permeability, and the risk of acute lung injury in animal models [31–34]. The findings of the human and animal studies above might explain, at least in part, why alcoholism tended to develop pleuropulmonary metastases from pyogenic liver abscesses in the present study. However, the exact pathophysiology of developing extra-hepatic metastases from pyogenic liver abscess in alcoholic patients is yet to be elucidated. Although the actual mechanism of metastatic infection from pyogenic liver abscesses has not been shown, diabetes mellitus or alcoholism might affect the patients' host-defense mechanisms that favours the development of extra-hepatic metastases from pyogenic liver abscesses.

K. pneumoniae infection was not an independent risk factor according to the multivariate analysis in our study; this finding is in contrast with results published by a few investigators [4, 7, 35]. The conflicting results might be attributed to the lack of multivariate analyses performed in the

previous studies. Studies in which the prevalence of diabetes mellitus ranged from 10% to 15% reported that no metastatic infection was noted among patients with *K. pneumoniae* liver abscesses [36–39]. This phenomenon seems to imply that some kind of underlying medical condition, such as diabetes mellitus or alcoholism is required for *K. pneumoniae* to result in metastasis of pyogenic liver abscesses.

Haematogenous seeding has been considered as a possible route of septic metastases from pyogenic liver abscesses [4, 6]; however, some investigators have hypothesised that pyogenic liver abscesses could spread to the pleuropulmonary space through direct rupture or hepatobronchial fistula [40, 41]. Although pleuropulmonary metastases were significantly associated with pleural effusion in our study, a causal relationship was not clear; further studies are required to validate the hypothesis.

The occurrence of metastatic endophthalmitis in our patients was not fatal, as there were no deaths in our series; however, it could lead to visual disability. Among the 6 patients with metastatic endophthalmitis in the present study, only one (case 12) patient retained his vision and recovered,

Table 3

Imaging, microbiologic, and laboratory findings at admission, and initial treatment in the metastatic and non-metastatic infection groups.

Variable	Metastatic group	Non-metastatic group	Metastatic vs non-metastatic adjusted OR (95% CI)[f]
Imaging finding, No. (%)			
Pleural effusion	9/24 (38)	39/201 (19)	2.3 (0.82–6.5)
Unilobar abscess	22/24 (92)	190/201 (95)	0.72 (0.13–7.3)
Right-lobe abscess	16/24 (67)	146/201 (73)	0.72 (0.26–2.1)
Solitary abscess	19/24 (79)	160/201 (80)	1.0 (0.33–3.8)
Size of abscess >5 cm (in diameter)	15/24 (63)	111/201 (55)	1.4 (0.55–3.9)
Gas-forming abscess	2/24 (8)	8/201 (4)	1.9 (0.18–13)
Rupture of abscess	1/24 (4)	9/201 (5)	0.92 (0.021–8.4)
Microbiologic finding, No. (%)			
Bacteraemia	20/24 (83)	113/194 (58)	5.4 (1.4–30) *
K. pneumoniae infection[a]	22/24 (92)	132/201 (66)	5.0 (1.1–47) *
E. coli infection[b]	1/24 (4)	40/201 (20)	0.22 (0.0050–1.5)
Polymicrobial infection[c]	3/24 (13)	52/201 (26)	0.46 (0.079–1.7)
Anaerobic infection[d]	0/24	16/201 (8)	0.35 (0–2.7)
Laboratory tests, No. (%)			
WBC count (>10×10^9 L^{-1})	21/24 (88)	155/201 (78)	2.3 (0.61–13)
Hb (<140 g L^{-1} in male; <120 g L^{-1} in female)	15/24 (63)	138/201 (69)	0.72 (0.27–2.1)
Serum albumin (<35 g L^{-1})	10/10 (100)	67/74 (91)	1.3 (0.16–∞)
Serum AST (>40 UL^{-1})	13/21 (62)	127/182 (70)	0.55 (0.20–1.7)
Serum ALP (>126 UL^{-1})	13/16 (81)	82/122 (67)	5.2 (0.59–250)
Total bilirubin (>22.2 μmol L^{-1})	9/14 (64)	89/131 (68)	0.73 (0.19–3.0)
Duration from the beginning of symptoms to the time of appropriate antibiotics administered >7 days, No. (%)	10/24 (42)	74/201 (37)	3.9 (1.2–13)*
Therapeutic modality, No. (%)			
Antibiotics alone	5/24 (21)	30/201 (15)	1.4 (0.47–4.1)
Invasive procedure[e] plus antibiotics	19/24 (79)	171/201 (85)	0.55 (0.24–2.1)

ALP: alkaline phosphatase; AST: aspartate aminotransferase; CI: confidence interval; *E. coli: Escherichia coli*; Hb: haemoglobin; *K. pneumoniae: Klebsiella pneumoniae;* OR: odds ratio; WBC: white blood cell; ∞, infinity.

[a] *K. pneumoniae* was cultured in blood or abscess cultures.

[b] *E. coli* was cultured in blood or abscess cultures.

[c] Mixed bacterial florae were cultured in blood or abscess cultures.

[d] Anaerobic isolates were cultured in blood and/or abscess cultures.

[e] Invasive procedure: percutaneous needle aspiration, percutaneous catheter drainage, or surgical intervention

[f] The exact logistic regression model included adjustment for age, sex, and duration of symptoms before admission.

* p <0.05

Table 4

Multivariate analysis of risk factors in relation to development of metastatic infection from pyogenic liver abscesses (n = 225).

Variable	Multivariate OR (95% CI)[a]
Diabetes mellitus (present vs absent)	7.7 (2.1–29) *
Alcoholism (present vs absent)	8.9 (2.6–30) *
RUQ pain/tenderness (present vs absent)	0.11 (0.014–0.87) *

CI: confidence interval; OR: odds ratio; RUQ: right upper quadrant

[a] Using stepwise logistic regression analysis

* p <0.05

whereas 2 patients (cases 1 and 21) initially treated intravenously with a third-generation cephalosporin, eventually lost or developed limited vision. Our data suggest that the ophthalmic complication of pyogenic liver abscess has an extremely poor prognosis, and blindness or decreased vision of the affected eye is a common result. It is advocated that the recommended intravenous antibiotics, including ceftrioxone, ceftazidine, or ciprofloxacin for those with penicillin allergy, as well as the subconjunctival/intravitreal injections of amikacin and ceftazidime within 48 hours after infection of the eye are warranted if evidence for metastatic endophthalmitis exists [6, 8, 10, 13, 35, 42, 43].

Laboratory parameters did not help clinicians to increase the index of suspicion for metastatic infection from pyogenic liver abscess. Similarly, physical examination data did not offer the physicians a clue in most of the pyogenic liver abscess cases with extra-hepatic metastases. In this regard, patients with pyogenic liver abscesses in the metastatic infection group had a lower frequency of fever and right upper quadrant pain/tenderness in comparison with the non-metastatic infection group. This finding seems to reveal a weak immunological response in the metastatic infection group, which probably contributed to the higher prevalence of underlying immunocompromised diseases, such as diabetes mellitus and alcoholism, in this group. It also reflects how difficult it is to make an early diagnosis of metastatic infection from pyogenic liver abscesses. Nevertheless, different metastatic locations seem to have their own unique presenting symptoms/signs. We found that chest symptoms, including cough, chest pain and short of breath, were associated with the development of pleuropulmonary metastases. On the other hand, mental confusion was associated with the development of ocular/CNS metastases. This also suggests that a high index of suspicion is critical for early detection of different extra-hepatic metastases in patients with pyogenic liver abscesses who present with the above signs/symptoms at admission.

There were some limitations in the present study. Our study was retrospective and data were limited to what had been recorded in the medical records. However, there was no significant difference in missing laboratory measurements at admission between the metastatic and non-metastatic infection groups. The possible influence of this non-random effect of missing data on the study results was minimised. We are aware that our sample size is small; however, the fact that pyogenic liver abscess is relatively rare and metastatic infection is an uncommon complication of pyogenic liver abscess, makes collecting a large sample size during a limited study period difficult. Hence, we performed the exact method instead of the usual asymptotic method for logistic regression modelling, whose inference is more reliable and valid in such a situation [25]. However, we must draw the readers' attention to the wide confidence intervals for many of the variables and remind that such intervals do not rule out important differences between the two groups. Furthermore, the number of patients with septic metastases in our study is comparable with patient numbers in previously published reports for a study period ranging from 5 to 13 years [3–5, 7, 9, 11].

In conclusion, our data suggest that diabetes mellitus and alcoholism are significant risk factors for developing extra-hepatic metastases from pyogenic liver abscesses. This finding implies that the underlying condition of the host would play an important role in development of septic metastases from pyogenic liver abscesses.

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Correspondence:
Chun-Chieh Chen, MD, MS
Department of Family Medicine,
Chung Shan Medical University Hospital,
No. 110, Section 1, Chien Kuo N. Road,
Taichung 402, Taiwan
E-Mail: sccy399@yahoo.com.tw

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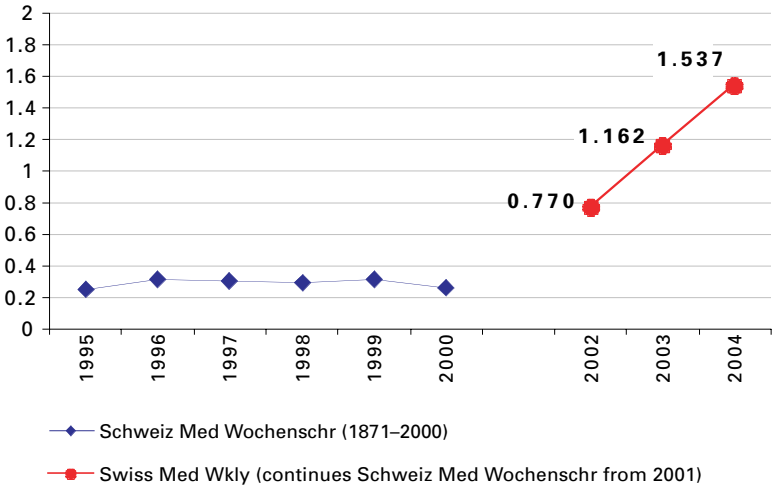

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