Journal of the Formosan Medical Association (2015) 114, 916–922

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Risk factors for in-hospital mortality in patients with type 2 diabetes complicated by community-acquired *Klebsiella pneumoniae* bacteremia

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Received 12 May 2015; received in revised form 7 July 2015; accepted 8 July 2015

KEYWORDS
albumin;
community-acquired bacteremia;
Klebsiella pneumonia;
sites of infection;
type 2 diabetes mellitus

Background/Purpose: Patients with diabetes are at a high risk of infection-related morbidity and mortality. *Klebsiella pneumoniae* bacilli are prevalent among diabetic patients, especially in Asian populations. The present study aimed to identify risk factors for in-hospital mortality among diabetic patients complicated by community-acquired *K. pneumoniae* bacteremia.
Methods: We evaluated the clinical characteristics of 341 Taiwanese type 2 diabetic patients who were treated for community-acquired *K. pneumoniae* bacteremia. We then analyzed outcome predictors, and in particular comorbidities and the site of infection.
Results: The overall in-hospital mortality rate was 14.1%. Comorbid cancer was the leading factor, accounting for 32.1% of all cases of mortality. Pulmonary infection, primary bacteremia, afebrile or shock presentation and low serum albumin level were risk factors for in-hospital mortality. Regardless of comorbidities, pulmonary infection [odds ratio (OR) 10.74, 95% confidence interval (CI) 2.02–57.09] and albumin level (OR 0.15, 95% CI 0.03–0.76) were the main risk predictors. The receiver operating characteristic curve indicated that a serum albumin level lower than 2.4 g/dL (71.1% sensitivity and 77.4% specificity) suggested a poor prognosis in the diabetic patients with *K. pneumoniae* bacteremia. In patients with pulmonary infection, the capsular serotypes of *K. pneumoniae* were not related to poor outcomes, and an initial presentation of blunted fever or shock were independent factors for mortality.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2015.07.011

Conclusion: Cancer, pulmonary infection, and low serum albumin levels were independent indicators of in-hospital mortality in the diabetic patients complicated by *K. pneumoniae* bacteremia. The sites of infection and host characteristics should always elicit medical attention when treating these patients.

Introduction

Infectious diseases are known to cause complications in patients with diabetes,[1] and diabetic patients have been reported to have a 4.4-fold higher risk of bacteremia compared to patients without diabetes.[2] In addition to a higher risk of morbidities,[1,3] patients with diabetes have also been reported to be at a higher risk of death from infectious diseases.[4] The hazard ratio for death due to infections is as high as that for vascular diseases in patients with diabetes (2.39 vs. 2.32, respectively).[4] Nevertheless, few reports have investigated the outcome predictors for mortality in patients with diabetes complicated by severe infections.

K. pneumoniae, a Gram-negative bacillus, causes infection with a high mortality rate.[5,6] Many reports have suggested that patients with diabetes are at a high risk of *K. pneumoniae* infections,[2,7–10] possibly because of impairment of bacterial phagocytosis in patients with diabetes.[11] The incidence of *K. pneumoniae* infection has been reported to be higher in Taiwan, other Asian countries, and South Africa, especially as a unique presentation of liver abscess.[7]

In this study, we aimed to investigate the clinical features affecting in-hospital mortality in patients with type 2 diabetes complicated by community-acquired *K. pneumoniae* bacteremia.

Patients and methods

In this retrospective study, we reviewed and analyzed 341 consecutive patients with type 2 diabetes who were admitted to Chang Gung Memorial Hospital, Taoyuan, Taiwan (a 3,700-bed medical center) between January 2005 and December 2008 and who were diagnosed with community-acquired *K. pneumoniae* bacteremia. The Institutional Review Board of Chang Gung Memorial Hospital approved this study (No. 100-0417B).

K. pneumoniae bacteremia was defined as the isolation of *K. pneumoniae* in one or more blood cultures in association with the clinical features of bacteremia and/or sepsis. Community-acquired bacteremia was defined as a positive blood culture taken on admission or within 48 hours of admission. The blood cultures of all 341 patients were collected within 48 hours of admission and documented as *K. pneumoniae*.

The diagnosis of diabetes mellitus and major comorbidities were made by thoroughly reviewing medical records. The patients with a tympanic temperature lower than 38°C at admission were considered to have a blunted fever response. Meanwhile, the patients with an initial systolic blood pressure lower than 90 mmHg or requiring an inotropic agent within the first 2 days of admission were defined as having septic shock.

We thoroughly investigated the primary site of the *K. pneumoniae* infection during the hospital stay. Imaging studies, based on a *K. pneumoniae*-positive local tissue or fluid culture, clinically confirmed the site of infection. We defined patients without a detectable primary site of infection as having *K. pneumoniae* primary bacteremia, and multifocal infection as the presence of more than one primary site of infection.

In the bacteremic pneumonia group, available bacterial isolates from 24 patients were further examined microbiologically. To analyze the impact of capsule serotypes on the clinical outcomes in this specific high-mortality group of patients, we performed polymerase chain reaction for capsular K serotyping.[12]

We analyzed the correlation between serum albumin level and mortality using a receiver operating characteristic (ROC) curve, and we calculated the best cutoff point based on the Youden index. We used SPSS software version 16.0 (IBM SPSS Inc., Chicago, IL, USA) for all statistical analyses. We used independent sample *t* test and Chi-square test as appropriate to compare variables in the patients who died and those who survived. Multivariate analysis with binary logistic regression was applied to identify the independent factors for in-hospital mortality. We used one-way analysis of variance and Chi-square test as appropriate to compare variables in the patients with the three major sites of infection. All statistical tests were performed at a two-tailed significance level of 0.05.

Results

Patients' demographic characteristics, diabetes status, and in-hospital mortality

The mean age of the 341 patients was 63.0 ± 13.2 years, and the male-to-female ratio was 55.1%. The mean duration of diabetes was 7.9 ± 7.2 years, with a mean serum glycated hemoglobin level of 9.3 ± 2.7% at admission. Among the 341 patients, 6.5% had coronary artery disease, 16.7% had a history of stroke, and 6.2% had end-stage renal disease and were on maintenance hemodialysis (Table 1).

K. pneumoniae bacteremia primarily caused the death of 48 of the 341 patients during the study period. The overall in-hospital mortality rate was 14.1% (Tables 1 and 2). The three leading comorbidities in this studies participants were cancer (15.5%), cirrhosis (11.1%), and chronic

Table 1 Factors associated with in-hospital mortality in diabetic patients with community-acquired *Klebsiella pneumoniae* bacteremia.

		All cases (n = 341)	Mortality (n = 48)	Survival (n = 293)	p
Demographic data and diabetic vascular complications	Age (y)	63.0 ± 13.2	64.7 ± 12.7	62.8 ± 13.4	0.338
	Male	188 (55.1)	29 (60.4)	159 (54.1)	0.413
	Duration of diabetes (y)	7.9 ± 7.2	8.2 ± 7.0	7.9 ± 7.5	0.879
	Glycated hemoglobin levels (%)	9.3 ± 2.7	8.6 ± 2.8	9.4 ± 2.7	0.254
	History of stroke	57 (16.7)	11 (22.9)	46 (15.6)	0.267
	History of CAD	22 (6.5)	4 (8.3)	18 (6.1)	0.563
	Hemodialysis	21 (6.2)	4 (8.3)	17 (5.8)	0.507
Major comorbidities	Cancer	53 (15.5)	17 (35.4)	36 (12.2)	< 0.001
	Liver cirrhosis	38 (11.1)	8 (16.7)	30 (10.2)	0.042
	Chronic steroid use	8 (2.3)	3 (6.2)	5 (1.7)	0.073
Site of primary infection	Pneumonia	42 (12.3)	16 (33.3)	26 (8.9)	< 0.005
	Primary bacteremia	48 (14.1)	12 (25)	36 (12.3)	0.019
	Soft-tissue infection	20 (5.9)	5 (10.4)	15 (5.1)	0.148
	Liver abscess	81 (23.8)	2 (2.5)	79 (97.5)	0.001
Clinical manifestations and laboratory findings	Afebrile state	97 (28.4)	26 (54.2)	71 (24.5)	< 0.005
	Initial presentation of shock	64 (18.8)	31 (64.6)	33 (11.2)	< 0.005
	Polymicrobial bacteremia	61 (17.9)	13 (27.1)	48 (16.3)	0.071
	C-reactive protein levels (mg/L)	190.3 ± 126.3	213.2 ± 127.2	186.9 ± 126.1	0.282
	White blood cell count ($\times 10^3/\mu L$)	12.9 ± 7.5	13.2 ± 9.6	12.9 ± 7.2	0.817
	Albumin (g/dL)	2.6 ± 0.6	2.2 ± 0.6	2.7 ± 0.5	< 0.005
	eGFR (mL/min/1.73 m^2)	55.1 ± 32.9	44.5 ± 31.4	56.7 ± 32.8	0.018

Data presented as n (%) or mean ± standard deviation for continuous variables.
CAD = coronary artery disease; eGFR = estimated glomerular filtration rate.

steroid usage for various diseases (2.3%; Table 1). Twenty-eight of 99 patients with major comorbidities died (mortality rate, 28.3%). Twenty of the 242 patients who did not have comorbidities died (mortality rate, 8.3%). The mortality rates between these two groups were significantly different ($p < 0.001$).

Risk factors for in-hospital mortality among the diabetic patients with *K. pneumoniae* bacteremia

Based on multivariate analysis using binary logistic regression analysis, comorbid cancer appeared to be an independent factor for a poor outcome. The cause-specific in-hospital mortality rate in diabetic patients with cancer comorbidity was 32.1% [17/53; odds ratio (OR) 3.55, 95% confidence interval (CI) 1.06–11.85].

The other indicators for mortality were pulmonary infection (OR 6.16, 95% CI 1.67–22.72), primary bacteremia (OR 3.92, 95% CI 1.04–14.72), being clinically afebrile (OR 3.35, 95% CI 1.20–9.40), shock (OR 5.74, 95% CI 2.09–15.77), and serum albumin level (OR 0.18, 95% CI 0.06–0.52). For the patients with diabetes who had no comorbidities, the indicators were pulmonary infection (OR 10.74, 95% CI 2.02–57.09) and serum albumin level (OR 0.15, 95% CI 0.03-0.76; Table 2).

Table 2 Independent factors associated with in-hospital mortality in diabetic patients with community-acquired *K. pneumoniae* bacteremia.

Variables	All patients (n = 341; mortality 14.1%)			Patients without major comorbidities (n = 242; mortality 8.3%)		
	Adjusted OR	95% CI	p	Adjusted OR	95% CI	p
Cancer	3.545	1.060–11.853	0.040	—	—	—
Pneumonia	6.158	1.669–22.724	0.006	10.743	2.022–57.085	0.005
Afebrile state	3.352	1.195–9.398	0.021	4.563	0.924–22.538	0.062
Initial shock	5.739	2.088–15.770	0.001	3.670	0.778–17.305	0.100
Albumin level	0.182	0.064–0.518	0.001	0.154	0.031–0.755	0.021
Primary bacteremia	3.918	1.043–14.715	0.043	—	—	—

Factors for this multivariate logistic regression were determined by significant factors in univariate analysis. For all patients, the included factors were cancer, cirrhosis, chronic steroid use, pneumonia, primary bacteremia, liver abscess, afebrile state, initial shock, albumin level, and estimated glomerular filtration rate. For patients without major comorbidities, the included factors were pneumonia, liver abscess, afebrile state, initial shock, and albumin level. The survival group was used as the baseline in both regression models.
CI = confidence interval; OR = odds ratio.

The duration of diabetes and serum glycated hemoglobin level did not seem to have direct impacts on in-hospital mortality. Complications related to diabetes such as stroke and coronary artery disease, and those under maintenance hemodialysis were not associated with poor outcomes.

The prognosis of the patients with hypoalbuminemia, with or without major comorbidities, was poor (Table 2). Analysis of the ROC curve revealed that a serum albumin level of 2.4 g/dL was a cutoff value with 71.1% sensitivity and 77.4% specificity. The risk of mortality for the patients with a serum albumin level below 2.4 g/dL was 9.38 times higher (adjusted OR 9.38, 95% CI 3.15—27.94) than for the patients with a serum albumin level higher than 2.4 g/dL. For the 242 patients with no comorbidities, the cutoff value of serum albumin level was also 2.4 g/dL (adjusted OR 7.95, 95% CI 1.62—39.08).

Sites of infection and mortality rates

As shown in Figure 1, the bacteremic liver abscess was the most common focal infection (23.7%), followed by urinary tract infection (18.5%) and primary bacteremia (14.1%). The group with bacteremic pneumonia had the highest mortality rate (38%), followed by the groups with primary bacteremia (25%), soft tissue infection (25%), and central nervous system infection (25%). The group with a bacteremic liver abscess had a mortality rate of only 2.5%. Approximately 5% of the patients had multifocal organ infections, with a mortality rate of 17.6%.

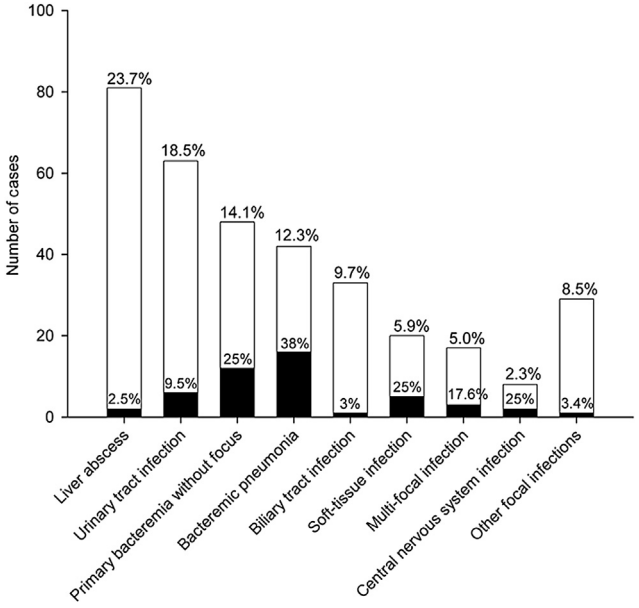

Figure 1 Sites of infection and site-specific mortality in the patients with diabetes complicated by *Klebsiella pneumoniae* bacteremia. The subgroups were sorted by prevalence and are presented in descending order. The stacked vertical bars represent survival (white) and in-hospital mortality (black) of the patients with diabetes complicated by *K. pneumoniae* bacteremia, grouped according to the site of infection. The label above each white bar indicates the prevalence in that subgroup. The label above each black bar indicates the in-hospital mortality rate in that subgroup. "Other focal infections" includes seven patients with spontaneous peritonitis, six patients with prostatic abscess, five cases with anal abscess, four cases with acute pancreatitis, three patients with acute appendicitis, three patients with endophthalmitis, and one case with splenic abscess.

Comparison of the indicators between major sites of infection

Table 3 demonstrates comparisons of clinical characteristics between the three different major sites of infection: bacteremic liver abscess (the most common site of infection with the lowest mortality rate), bacteremic pneumonia, and primary bacteremia. The patients with a *K. pneumoniae* liver abscess were more likely to be young, have a normal body mass index (BMI), and present with fewer comorbidities. By contrast, the patients with bacteremic pneumonia and primary bacteremia were more likely to be older, have a lower BMI, higher rate of comorbidities and shock, or to be afebrile.

Analysis of the risk factors for mortality in the bacteremic pneumonia group

Since bacteremic pneumonia was the site of infection most related to a high mortality rate, we studied capsular serotyping in this specific group. The capsular serotyping of the available 24 isolates of *K. pneumoniae* identified the following serotypes: four K1, four K2, and 16 non-K1/K2 serotypes. Thus, the K1 and K2 serotypes accounted for only one third of the isolates. Six of the 24 patients died, and the capsular serotyping of these six patients showed that one had the K1 serotype and five had the non-K1/K2 serotype. The serotype distribution was diverse and was not associated with in-hospital mortality. We therefore analyzed the clinical factors in this bacteremic pneumonia group (Table 4), and found that initial shock (adjusted OR 16.99, 95% CI 2.69—107.14) and a blunted fever response (adjusted OR 15.99, 95% CI 1.91—133.55) were predictors of in-hospital mortality.

Discussion

Community-acquired infection is a serious complication for diabetic patients. This study examined the in-hospital risk factors for mortality in a large group of diabetic patients with community-acquired *K. pneumoniae* bacteremia. We identified comorbid cancer, pulmonary infection, primary bacteremia, being afebrile or in shock, and lower serum albumin level as indicators of mortality. Patients with type 2 diabetes mellitus more commonly have comorbid systemic disorders and cancer compared to patients without diabetes,[13,14] and we found that the in-hospital mortality rate was different between those with (28.3%) and without (8.3%) comorbid diseases. For the patients with comorbid cancer, the mortality rate increased to 35.4%. Notably, indicators other than comorbid diseases such as pulmonary infection and low serum albumin level were noted in the patients either with or without comorbidities.

Table 3 Comparison of parameters between the three major sites of infection.

	Bacteremic liver abscesses	Bacteremic pneumonia	Primary bacteremia	*p*
n	81	42	48	
Mortality rate	2 (2.5)	16 (38.1)	12 (25)	< 0.005
Age (y)	58.9 ± 12.2	65.9 ± 14.6	69.4 ± 11.2	< 0.005
Male	51 (63.0)	31 (73.8)	24 (50)	0.066
Body mass index (kg/m^2)	24.5 ± 2.7	21.9 ± 4.5	23.3 ± 2.9	0.003
Duration of diabetes (y)	6.0 ± 6.1	9.3 ± 7.4	9.0 ± 7.2	0.047
Glycated hemoglobin (%)	10.3 ± 2.9	8.9 ± 2.8	9.4 ± 2.8	0.107
Hemodialysis	2 (2.5)	4 (9.5)	3 (6.2)	0.233
History of stroke	9 (11.1)	15 (35.7)	8 (16.7)	0.012
History of CAD	3 (3.7)	6 (14.3)	1 (2.1)	0.025
Cancer	3 (3.7)	15 (35.7)	12 (25.0)	<0.005
Cirrhosis	6 (7.4)	5 (11.9)	11 (22.9)	0.039
Chronic steroid usage	0	2 (4.8)	4 (8.3)	0.040
C-reactive protein (mg/L)	211.6 ± 115.4	210.6 ± 111.0	152.1 ± 112.7	0.056
White blood cell count (× 10^3/μL)	12.2 ± 6.7	12.5 ± 9.1	11.8 ± 8.1	0.920
eGFR (mL/min/1.73 m^2)	58.7 ± 28.7	54.8 ± 32.3	44.5 ± 23.7	0.032
Albumin (g/dL)	2.7 ± 0.5	2.5 ± 0.5	2.6 ± 0.7	0.157
Afebrile state	6 (7.4)	7 (16.7)	11 (22.9)	0.010
Initial presentation of shock	12 (14.8)	16 (38.1)	9 (18.8)	0.001
Polymicrobial bacteremia	7 (8.6)	9 (21.4)	17 (35.4)	0.001

Data presented as *n* (%) or mean ± standard deviation for continuous variables.
CAD = coronary artery disease; eGFR = estimated glomerular filtration rate.

As previously reported,[15] a blunted fever response to a serious bacterial, viral, or fungal infection suggests a poorer prognosis than a robust fever response.[16] The lack of a robust febrile response may be associated with a greater risk of mortality in patients with hospital-acquired bacteremia, and a blunted fever response may reflect a failure of the host to respond to the infection.

A low albumin level was a predictor of the outcome of *K. pneumoniae* bacteremia in the diabetic patient with or without comorbidities. A previous study reported similar observations of a low albumin level and higher mortality rate in other bloodstream infections.[17] Although serum albumin levels usually reflect the nutritional status of a patient, the low serum albumin levels in patients with sepsis may be due to catabolism exacerbated by septicemia.[18] Our results further revealed that a serum albumin level lower than 2.4 g/dL led to a 9.38-fold higher risk of in-hospital mortality in the patients with community-acquired *K. pneumoniae* bacteremia. Whether albumin supplementation should be recommended to patients with acute illnesses remains controversial.[19]

The in-hospital mortality rates varied according to the site of infection, from 2.5% in patients with liver abscesses to 38.1% in those with pulmonary infections. Medical attention on the site of infection should be provided while treating for *K. pneumoniae* bacteremia. A multi-center study in Taiwan reported that *Klebsiella* spp. were common pathogens in patients with community-acquired pneumonia.[20] Similarly, Meatherall et al[6] reported that diabetic patients with pneumonia had a high mortality rate of 42%, compared to 25% in patients with primary bacteremia and 7% in patients with liver abscesses in both community-acquired and nosocomial *K. pneumoniae* bacteremia. Wu et al[21] reported a similar trend of mortality for pneumonia, primary bacteremia, and liver abscesses in Taiwanese patients with *K. pneumoniae* bacteremia. When the liver is the site of *K. pneumoniae* infection, the bacteria seem to be restricted in the solid organ, thus forming abscesses. Therapeutic drainage and removal of the bacteria from the abscesses may have been another contributing factor to the good outcomes in our study. When the lung is the site of infection, the pulmonary tissue seems to be more vulnerable to the bacteria. In addition, we found that the characteristics of the host also explained this finding. Based on our analysis, the patients with liver abscesses were younger, had a lower incidence of associated comorbidities, and were relatively healthy as indicated by their BMIs compared with the patients with lung infections or primary bacteremia.

The K1 and K2 bacterial capsular serotypes have been demonstrated to cause virulent and invasive syndromes in patients with liver abscesses.[12,22,23] However, the mortality rate of the liver abscess group was not significantly worse in this study. Yu at al[24] reported a strong association between the K1/K2 serotypes and pneumonia. Of note, the K1/K2 serotypes were not correlated with in-hospital mortality in our pneumonia group, and the independent risk factors in this specific group were the clinical manifestations of a blunted fever or septic shock, suggesting that a fulminant infection at admission determined the outcome of the patients with diabetes who had *K. pneumoniae* bacteremic pneumonia. Lin et al[25] also reported that the K1/K2 serotypes did not predispose patients to a poor clinical outcome from community-acquired *K. pneumoniae* among the general population.

High blood sugar levels have been shown to impair the phagocytic defense against *K. pneumoniae* in patients with diabetes.[11] Moreover, acute metabolic decompensation

Table 4 Factors associated with in-hospital mortality in the patients with bacteremic pneumonia.

	Bacteremic pneumonia ($n = 42$)		
	Mortality ($n = 16$)	Survival ($n = 26$)	p
Age (y)	61.5 ± 12.9	68.5 ± 15.2	0.118
Male	12 (75)	19 (73.1)	> 0.99
Body mass index (kg/m^2)	20.5 ± 4.7	22.5 ± 4.3	0.291
Duration of diabetes (y)	7.1 ± 5.6	10.9 ± 8.3	0.157
Glycated hemoglobin (%)	11.5 ± 3.0	8.4 ± 2.6	0.121
Hemodialysis	1 (6.3)	3 (11.5)	> 0.99
History of stroke	5 (31.3)	10 (38.5)	0.740
History of CAD	2 (12.5)	4 (15.4)	> 0.99
Cancer	6 (37.5)	9 (34.6)	> 0.99
Cirrhosis	3 (18.8)	2 (7.7)	0.632
Chronic steroid usage	0	2 (7.7)	0.517
C-reactive protein (mg/L)	229.7 ± 126.8	199.6 ± 104.3	0.579
White blood cell count (× 10^3/μL)	11.5 ± 1.0	13.1 ± 8.5	0.610
eGFR (mL/min/1.73 m^2)	47.4 ± 24.8	59.1 ± 35.7	0.226
Albumin (g/dL)	2.4 ± 0.6	2.6 ± 0.4	0.296
Afebrile state	9 (56.3)	2 (7.7)	0.004[a]
Initial presentation of shock	12 (75)	4 (15.4)	<0.005[a]
Polymicrobial bacteremia	4 (25)	5 (19.2)	0.711

Data presented as n (%) or mean ± standard deviation for continuous variables.
CAD = coronary artery disease; eGFR = estimated glomerular filtration rate.
[a] Independent risk factors after multivariate analysis by logistic regression.

during infection has been reported to negatively affect the outcome in patients with diabetes.[4] Nevertheless, glycated hemoglobin levels did not affect mortality in this study. The high mean glycated hemoglobin level, indicating chronically poor glycemic control among our patients, may have increased the susceptibility to severe infection. A lower BMI and lower serum albumin level may further indicate acute illness. Therefore, our data should be interpreted with caution, taking into account the fact that the glycated hemoglobin level did not affect the mortality rate during treatment for *K. pneumoniae* bacteremia. Yu et al[26] reported that the significant impact of human glycemic change in neutrophil phagocytosis of *K. pneumoniae* does not reflect the seroepidemiology of *K. pneumoniae* between diabetic patients with strict or poor glycemic control. These mechanisms may make it complex and difficult to interpret the outcomes. It has been reported that patients with diabetes do not have poorer outcomes compared to patients without diabetes with regards to bacteremia overall,[2,27] bacteremia caused by enterobacteria,[28,29] and *K. pneumoniae* liver abscess.[30] In contrast to comorbid cancer, the duration of diabetes and severe preexisting chronic complications of diabetes such as stroke, myocardial infarction, and maintenance hemodialysis had little impact on the in-hospital mortality rate of patients with *K. pneumoniae* bacteremia.

The main limitation of this study is its retrospective nature. In addition, given that most of our patients were not admitted to an intensive care unit, we did not apply common mortality risk scores such as the Acute Physiology and Chronic Health Evaluation.

We identified comorbid cancer, pulmonary infection, and low serum albumin level as prognostic indicators of in-hospital mortality in patients with diabetes who had community-acquired *K. pneumoniae* bacteremia. These factors also implied poor host characteristics. Clinicians should be aware of these predictors when treating patients with diabetes complicated by *K. pneumoniae* bacteremia.

Acknowledgments

This research was supported by a grant (CMRPG3D0331) from Chang Gung Memorial Hospital to Y.Y.H.

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