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Original Article

A multicenter study on clinical characteristics of *Acinetobacter* bacteremia in patients with liver cirrhosis

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KEYWORDS
Acinetobacter;
Bacteremia;
Cirrhosis;
Mortality;
Risk

Abstract *Background:* Clinical characteristics and risk factors for mortality of *Acinetobacter* bacteremia in cirrhotic patients have not been investigated.
Methods: Acinetobacter bacteremia cases from four medical centers were collected from 2009 to 2014, to compare between patients with and without liver cirrhosis. Risk factors for mortality of *Acinetobacter* bacteremia among cirrhotic patients were identified using multivariate logistic regression.
Results: Among the patients with *Acinetobacter* bacteremia, 72 had liver cirrhosis and 816 had not. Patients with cirrhosis were younger (57.5 [50—71] vs. 72 [50.25—71], $p < 0.001$), had more solid tumor (51.4% vs. 31.4%, $p = 0.001$), lower Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (17 [12—24] vs. 20 [13—28], $p = 0.012$), less sourced from pneumonia (19.4% vs. 35.8%, $p = 0.008$), and less caused by *Acinetobacter baumannii* (33.3% vs. 50.6%, $p = 0.007$) than those without. After matching for age, sex, and causative pathogens, the 30-day mortality (34.7% vs. 29.2%, $p = 0.592$) and APACHE II scores (17 vs. 17, $p = 0.769$) were not significant. APACHE II score (odds ratio [OR], 1.146; 95% confidence interval [CI], 1.035—1.268; $p = 0.009$), bacteremia caused by *A. baumannii* (OR, 20.501; 95% CI, 2.301—182.649; $p = 0.007$), and solid tumor (OR, 18.073; 95% CI, 1.938—168.504; $p = 0.011$) were independent risk factors for 30-day mortality of cirrhotic patients with *Acinetobacter* bacteremia.
Conclusion: Even though cirrhotic patients with *Acinetobacter* bacteremia were younger and had lower APACHE II scores than non-cirrhotic patients, the mortality rates were insignificantly different between the two groups.

Introduction

Acinetobacter species became an important pathogen causing high mortality in nosocomial and community-acquired infections, especially in immunocompromised hosts.[1—3] Among those infections, bloodstream infections play an important role.[4—6] The three most clinically relevant *Acinetobacter* species are *A. baumannii*, *A. nosocomialis*, and *A. pittii*.[3,7]

Cirrhosis is a locally and systemically immunocompromised state that leads to various infections due to immune system dysfunction.[8—10] Patients who have survived a significant episode of infection are still at high risk for mortality in the first year, as cirrhosis accounts for a fourfold increase in mortality.[9,11] The mortality rate is approximately 30.4—53% in cirrhotic patients with bacteremia.[12,13] In cirrhotic patients with bacteremia, gram-negative bacteria such as *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Aeromonas* spp., and *Vibrio* spp. are commonly involved.[9,14,15] Since *Acinetobacter* bacteremia causes high mortality rates in immunocompromised patients and little knowledge is known about those with liver cirrhosis,[16] we conduct this study to investigate the clinical characteristics and outcome of that.

Methods

Study population

Blood isolates of *Acinetobacter* spp. and patient data were collected from the AntimiCrobial studies in Taiwan Operating Network (ACTION), from January 2009 to December 2014. The ACTION hospitals are Changhua Christian Hospital (CCH, 1676 beds), MacKay Memorial Hospital (MKH, 2055 beds), Tri-Service General Hospital (TSGH, 1712 beds) of National Defense Medical Center, and Taipei Veterans General Hospital (TVGH, 2900 beds). The study protocol was reviewed and approved by the institutional review boards of each hospital with a waiver for informed consent (approval numbers: CCH, 140514; MKH, 14MMHIS125; TSGH, 1-105-5-100; and TVGH, 2015-04-003C).

Patients aged >20 years with at least one positive blood culture yielding *Acinetobacter* spp. and infection-related symptoms and signs were included in this study. In cases with two or more positive blood cultures, only the first one was included. The source of infection was determined as recommended in the Centers for Disease Control guidelines.[17,18] Bacteremia cases without an identified source of infection were defined as primary bacteremia.

Medical records were reviewed to obtain clinical information, such as demographic characteristics, underlying diseases, duration of stay in an intensive care unit (ICU), hospital stay, time of receipt, dose and route of administration of individual antimicrobials, and use of a ventilator, central venous catheters, a nasogastric tube, or a foley catheter at the time of onset of bacteremia. Immunosuppressive therapy was defined as initiation of cytotoxic agents (inhibiting or preventing the function of cells for treating cancers or some autoimmune diseases) within 6 weeks, ≥10 mg of prednisolone daily for more than 5 days within 4 weeks, or other immunosuppressive agents (suppressing or reducing the strength of the body's immune

Table 1 Comparisons of demographic and clinical characteristics between cirrhotic and non-cirrhotic patients with *Acinetobacter* bacteremia.

	n (% or interquartile range)[a]		*p*-value
	With liver cirrhosis (n = 72)	Without liver cirrhosis (n = 816)	
Demographic characteristics			
Age, years	57.5 (50–71)	72 (59–81)	<0.001
Male sex	47 (65.3)	530 (65.0)	1.000
Recent ICU stay	29 (40.3)	358 (43.9)	0.641
Acquired in ICU	24 (33.3)	284 (34.8)	0.903
Days of hospitalization before bacteremia	18 (8.25–33)	15 (6–30)	0.260
Comorbid conditions			
Alcoholism	11 (15.3)	34 (4.2)	<0.001
Peptic ulcer	17 (23.6)	107 (14.8)	0.074
Chronic obstructive pulmonary disease	7 (9.7)	145 (17.8)	0.115
Chronic kidney disease	17 (23.6)	263 (32.2)	0.169
Diabetes mellitus	20 (27.8)	280 (34.3)	0.320
Hypertension	20 (27.8)	355 (43.5)	0.014
Coronary artery disease	3 (4.2)	125 (15.3)	0.016
Congestive heart failure	6 (8.3)	143 (17.5)	0.066
Cerebrovascular accident	7 (9.7)	154 (18.9)	0.076
Collagen vascular disease	3 (4.2)	29 (3.6)	0.739
Immunosuppressive therapy	5 (6.9)	86 (10.5)	0.446
Solid tumor	37 (51.4)	256 (31.4)	0.001
Hematological malignancy	2 (2.8)	48 (5.9)	0.422
Chemotherapy	3 (4.2)	83 (10.2)	0.149
Neutropenia	4 (5.6)	40 (4.9)	0.775
Trauma	3 (4.2)	26 (3.2)	0.724
Burn	0 (0.0)	11 (1.3)	1.000
Recent surgery	14 (19.4)	178 (21.8)	0.750
Disease severity			
APACHE II score	17 (12–24)	20 (13–28)	0.012
Charlson comorbidity index	5.5 (5–7)	3 (2–6)	<0.001
Shock	15 (20.8)	229 (28.1)	0.238
Invasive procedures			
Arterial catheter	21 (29.2)	254 (31.1)	0.832
Central venous catheter	23 (31.9)	333 (40.8)	0.178
Ventilator use	27 (37.5)	391 (47.9)	0.115
Hemodialysis	10 (13.9)	118 (14.5)	1.000
Thoracic drain	5 (6.9)	51 (6.3)	0.799
Abdominal drain	13 (18.1)	77 (9.4)	0.034
Sources of bacteremia			
Pneumonia	14 (19.4)	292 (35.8)	0.008
Primary bacteremia	36 (50.0)	276 (33.8)	0.009
Intra-abdominal infection	13 (18.1)	49 (6.0)	<0.001
Catheter	4 (5.6)	118 (14.5)	0.054
Urinary tract infection	3 (4.2)	41 (5.0)	1.000
Wound	2 (2.8)	37 (4.5)	0.763
Species of causative *Acinetobacter*			
A. baumannii	24 (33.3)	413 (50.6)	0.007
A. nosocomialis	27 (37.5)	261 (32.0)	0.408
A. pittii	10 (13.9)	89 (10.9)	0.565
A. soli	6 (8.3)	26 (3.2)	0.038
Other *Acinetobacter* species	5 (6.9)	27 (3.3)	0.113
Antimicrobial non-susceptibility			
Amikacin	16 (22.2)	236 (28.9)	0.284
Ampicillin/sulbactam	21 (29.2)	326 (40.0)	0.095
Cefepime	33 (45.8)	448 (54.9)	0.175
Ceftazidime	39 (54.2)	505 (61.9)	0.245
Piperacillin/tazobactam	35 (48.6)	459 (56.3)	0.260

Table 1 (*continued*)

	n (% or interquartile range)[a]		*p*-value
	With liver cirrhosis (n = 72)	Without liver cirrhosis (n = 816)	
Imipenem	27 (37.5)	402 (49.2)	0.073
Meropenem	36 (50.0)	518 (63.5)	0.033
Ciprofloxacin	35 (48.6)	475 (58.2)	0.146
Levofloxacin	28 (38.9)	392 (48.0)	0.171
Colistin	2 (2.8)	13 (1.6)	0.347
Tigecycline	9 (12.5)	156 (19.1)	0.220
Appropriate antimicrobial therapy	33 (45.8)	337 (41.3)	0.533
30-day mortality	25 (34.7)	292 (35.8)	0.959

[a] Data are median value (interquartile range) for continuous variables and number of cases (%) for categorical variables. APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

system for patients receiving organ transplantations or with some autoimmune diseases) within 2 weeks prior to the onset of bacteremia. Neutropenia was defined as an absolute neutrophil count of $<0.5 \times 10^9$/L. Recent surgery was defined as operations performed within 4 weeks prior to the onset of bacteremia. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2. Shock was defined as hypotension (systolic blood pressure [SBP] of <90 mmHg, mean arterial pressure of <70 mmHg, or a SBP decrease of >40 mmHg) with evidence of end organ dysfunction.[19] The severity of illness was evaluated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score[20] within 24 h prior to the onset of bacteremia. Appropriate antimicrobial therapy was defined as administration of at least one antimicrobial agent, to which the causative pathogen was susceptible, within 48 h after the onset of bacteremia, with an approved route and dosage for end organ(s) function. Antimicrobial therapy that did not meet this definition was considered inappropriate. Monotherapy using an aminoglycoside was not considered as appropriate therapy.

Liver cirrhosis was diagnosed by the gastroenterologists based on ultrasound, radiological, and pathological evidences. The severity of cirrhosis were classified using the Child-Pugh classification.[21] Cirrhotic patients were compared with those non-cirrhotic for clinical and microbiological characteristics and mortality. Further comparisons were made using patients that matched for age (within 5 years), sex, and causative *Acinetobacter* spp. The outcome measures of this study were all-cause 30-day mortality after the onset of *Acinetobacter* bacteremia.

Microbiological studies

The presumptive identification of the isolates on the *Acinetobacter* spp. level was performed using the Vitek 2 system (bioMérieux, Marcy l'Etoile, France). A multiplex PCR method was used to identify the genomic species level of *A. baumannii*.[22] Isolates identified as non-*baumannii Acinetobacter* species were identified based on the genomic species level of 16S–23S ribosomal DNA intergenic spacer sequence analysis.[23] Antimicrobial susceptibilities were determined using the agar dilution method according to the Clinical Laboratory Standards Institute (CLSI).[24]

Statistical analysis

To assess the differences, the chi-square test with Yate's correction or Fisher's exact test was used to compare the discrete variables, while the Student's t-test or Mann–Whitney rank sum test was used to analyze continuous variables. Logistic regression models were used to explore independent risk factors for 14-day mortality. Univariate analyses were performed separately for each of the risk factor variables to confirm the odds ratio (OR) and 95% confidence interval (CI). All biologically plausible variables with a *p*-value of ≤ 0.10 in the univariate analysis exhibited by at least 10% of the patients were included in the logistic regression model for the multivariate analysis. A backward selection process was utilized. A *p*-value of <0.05 was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software version 18.0 (SPSS, Chicago, IL, USA).

Results

During the 6-year study period, 888 patients had monomicrobial *Acinetobacter* bacteremia; 72 of whom had liver cirrhosis (8.1%). Table 1 shows the clinical features of the 72 cirrhotic and 816 comparative non-cirrhotic patients. In the cirrhotic group, patients were significantly younger (57.5 [50–71] vs. 72 [50.25–71], $p < 0.001$), were more likely alcoholic (15.3% vs. 4.2%, $p < 0.001$), had solid tumor (51.4% vs. 31.4%, $p = 0.001$), had higher Charlson comorbidity indexes (5.5 [5–7] vs. 3 [2–6], $p < 0.001$), and lower APACHE II scores (17 [12–24] vs. 20 [13–28], $p = 0.012$) than the non-cirrhotic group. The sources of bacteremia were significantly different between the two groups. In the cirrhotic group, the most common source of bacteremia was primary bacteremia (50% vs. 33.8%, $p = 0.009$), followed by respiratory tract (19.4% vs. 35.8%, $p = 0.008$) and intra-abdominal infections (18.1 vs. 6%, $p < 0.001$), whereas in the non-cirrhotic group, the most frequent source was respiratory tract infections (35.8%), followed by primary bacteremia (33.8%). The causative *Acinetobacter* spp. were also different between the two groups. In the cirrhotic group, the most frequent pathogens were *A. nosocomialis* (37.5%), followed by *A. baumannii* (33.3%),

Table 2 Comparisons of demographic and clinical characteristics between cirrhotic and non-cirrhotic patients with *Acinetobacter* bacteremia after matching.[a]

	n (% or interquartile range)[b]		*p* value
	Liver cirrhosis ($n = 72$)	No liver cirrhosis ($n = 72$)	
Demographic characteristics			
Age, years	57.5 (50—71)	58 (50.25—71)	0.922
Male sex	47 (65.3)	47 (65.3)	1.000
Recent ICU stay	29 (40.3)	39 (54.2)	0.133
Acquired in ICU	24 (33.3)	21 (29.2)	0.719
Days of hospitalization before bacteremia	18 (8.25—33)	13 (6.25—26)	0.205
Comorbid conditions			
Alcoholism	11 (15.3)	7 (9.7)	0.450
Peptic ulcer	17 (23.6)	7 (11.5)	0.112
Chronic obstructive pulmonary disease	7 (9.7)	8 (11.1)	1.000
Chronic kidney disease	17 (23.6)	21 (29.2)	0.571
Diabetes mellitus	20 (27.8)	22 (30.6)	0.855
Hypertension	20 (27.8)	29 (40.3)	0.159
Coronary artery disease	3 (4.2)	9 (12.5)	0.132
Congestive heart failure	6 (8.3)	9 (12.5)	0.585
Cerebrovascular accident	7 (9.7)	11 (15.3)	0.450
Collagen vascular disease	3 (4.2)	2 (2.8)	1.000
Immunosuppressive therapy	5 (6.9)	12 (16.7)	0.121
Solid tumor	37 (51.4)	20 (27.8)	0.006
Hematological malignancy	2 (2.8)	5 (6.9)	0.441
Chemotherapy	3 (4.2)	9 (12.5)	0.132
Neutropenia	4 (5.6)	2 (2.8)	0.681
Trauma	3 (4.2)	4 (5.6)	1.000
Burn	0 (0.0)	1 (1.4)	1.000
Recent surgery	14 (19.4)	23 (31.9)	0.127
Disease severity			
APACHE II score	17 (12—24)	17 (11—26)	0.769
Charlson comorbidity index	5.5 (5—7)	3 (2—5)	<0.001
Shock	15 (20.8)	21 (29.2)	0.336
Invasive procedures			
Arterial catheter	21 (29.2)	30 (41.7)	0.163
Central venous catheter	23 (31.9)	33 (45.8)	0.124
Ventilator use	27 (37.5)	35 (48.6)	0.239
Hemodialysis	10 (13.9)	11 (15.3)	1.000
Thoracic drain	5 (6.9)	3 (4.2)	0.719
Abdominal drain	13 (18.1)	13 (18.1)	1.000
Sources of bacteremia			
Pneumonia	14 (19.4)	19 (26.4)	0.428
Primary bacteremia	36 (50.0)	30 (41.7)	0.403
Intra-abdominal infection	13 (18.1)	5 (6.9)	0.078
Catheter	4 (5.6)	10 (13.9)	0.160
Urinary tract infection	3 (4.2)	2 (2.8)	1.000
Wound	2 (2.8)	6 (8.3)	0.275
Species of causative *Acinetobacter*			
A. baumannii	24 (33.3)	24 (33.3)	1.000
A. nosocomialis	27 (37.5)	27 (37.5)	1.000
A. pittii	10 (13.9)	10 (13.9)	1.000
A. soli	6 (8.3)	6 (8.3)	1.000
Other *Acinetobacter* species	5 (6.9)	5 (6.9)	1.000
Antimicrobial non-susceptibility			
Amikacin	16 (22.2)	14 (19.4)	0.837
Ampicillin/sulbactam	21 (29.2)	18 (25.0)	0.708
Cefepime	33 (45.8)	35 (48.6)	0.867
Ceftazidime	39 (54.2)	41 (56.9)	0.867
Piperacillin/tazobactam	35 (48.6)	32 (44.4)	0.738

Table 2 (*continued*)

	n (% or interquartile range)[b]		*p* value
	Liver cirrhosis ($n = 72$)	No liver cirrhosis ($n = 72$)	
Imipenem	27 (37.5)	27 (37.5)	1.000
Meropenem	36 (50.0)	36 (50.0)	1.000
Ciprofloxacin	35 (48.6)	37 (51.4)	0.868
Levofloxacin	28 (38.9)	23 (31.9)	0.486
Colistin	2 (2.8)	2 (2.8)	1.000
Tigecycline	9 (12.5)	13 (18.1)	0.487
Appropriate antimicrobial therapy	33 (45.8)	32 (44.4)	1.000
30-day mortality	25 (34.7)	21 (29.2)	0.592

[a] Matching for age (within 5 years), sex, and causative *Acinetobacter* spp.
[b] Data are median value (interquartile range) for continuous variables and number of cases (%) for categorical variables. APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

whereas in the non-cirrhotic group, the most frequent pathogens were *A. baumannii* (50.6%), followed by *A. nosocomialis* (32.0%). The antimicrobial susceptibilities of causative pathogens and suitability of antimicrobial therapy were insignificantly different between the two groups, except that the causative *Acinetobacter* isolates in the cirrhotic group were more susceptible to meropenem than those in the non-cirrhotic group. The 30-day mortality is not different between the two groups (34.7% vs. 35.8%, $p = 0.959$).

Table 2 shows further comparison between the two groups after matching for age (within 5 years), sex, and causative *Acinetobacter* spp. Significant differences between the two groups were not observed, except the Charlson comorbidity indexes (5.5 [5—7] vs. 3 [2—5], $p < 0.001$) and solid tumors (51.4% vs. 27.8%, $p = 0.006$) were higher in the cirrhotic group than that of the comparative group. After matching, the 30-day mortality was similar between cirrhotic and non-cirrhotic groups (34.7% vs. 29.2%, $p = 0.592$).

Table 3 shows the comparisons between 30-day survivors and non-survivors among cirrhotic patients with *Acinetobacter* bacteremia. The non-survivors had higher APACHE II scores than survivors (24 [15—28.5] vs. 16 [11—19], $p < 0.001$). In Child-Pugh cirrhosis classification, most of the patients were in class C (54.2%), followed by classes B and A (26.4% vs. 19.4%, respectively). The Child-Pugh classification between survivors and non-survivors was statistically insignificant.

Table 4 shows the multivariate analyses revealing the APACHE II score (OR, 1.146; 95% CI, 1.035—1.268; $p = 0.009$), bacteremia caused by *A. baumannii* (OR, 20.501; 95% CI, 2.301—182.649; $p = 0.007$), and solid tumor (OR, 18.073; 95% CI, 1.938—168.504; $p = 0.011$) as the independent factors associated with 30-day mortality among cirrhotic patients with *Acinetobacter* bacteremia.

Discussion

This multicenter study was conducted to investigate the clinical characteristics and outcomes of *Acinetobacter* bacteremia in cirrhotic patients. Even though the cirrhotic group were younger, had more solid tumors, higher Charlson comorbidity indexes, and lower APACHE II scores than the non-cirrhotic group, their 30-day mortality rates were similar. After matching, the cirrhotic group still had higher comorbidities and more solid tumor, but the 30-day mortality rate remained similar between the two groups. Higher APACHE II score, bacteremia caused by *A. baumannii*, and solid tumor were independent risk factors for mortality of cirrhotic patients with *Acinetobacter* bacteremia.

Cirrhotic patients were prone to various infections due to immune system dysfunction.[8—10] Even though the 30-day mortality rates were close in the cirrhotic and non-cirrhotic groups, the APHCHE II scores were significantly lower in the cirrhotic group. APACHE II score was considered superior than other scoring systems in predicting hospital mortality in cirrhotic patients.[25—28] However, parameters in the scoring system were closely related to host immune response.[20] Compared to normal individuals, cirrhotic patients were associated with a dysregulated cytokine response and thus hampered the inflammation process.[8,29] Since the initial response to infection or sepsis is hampered, the scoring system might not reflect the actual severity at the initial stage. The results of our study suggest that cirrhotic patients may have lower APACHE II scores at the onset of *Acinetobacter* bacteremia. Nevertheless, APACHE II score is still a good parameter to predict the poor outcome in cirrhotic patients with *Acinetobacter* bacteremia, which was also identified in previous studies.[30—32] In addition, liver diseases and solid tumors were parameters for calculating Charlson comorbidity indexes, explaining that cirrhotic patients would have higher scores than non-cirrhotic patients.

In current study, *A. nosocomialis* was the predominant causative species and primary bacteremia was the most common infectious source in cirrhotic patients. However, those without cirrhosis were mainly caused by *A. baumannii* and the most common source of bacteremia was pneumonia. The prevalence of each *Acinetobacter* spp. can vary in different geographic areas and hospitals. In Taiwan, *A. baumannii* and *A. nosocomialis* accounted for >80% of clinical infections caused by *Acinetobacter* spp.; the ratio differs among centers, ranging from >2:1 to approximately 1:1.[33—38] Primary bacteremia accounted for 22% of nosocomial bacteremia[39] and was even higher in ICUs

Table 3 Comparison between 30-day survivors and non-survivors in cirrhotic patients with *Acinetobacter* bacteremia.

	n (% or interquartile range)[a]			*p*-value
	All (n = 72)	Survivors (n = 47)	Non-survivors (n = 25)	
Demographical characteristics				
Age, years	57.5 (50—71)	57 (50—68)	59 (50—73)	0.445
Male sex	47 (65.3)	29 (61.7)	18 (72.0)	0.539
Recent ICU stay	29 (40.3)	15 (31.9)	14 (56.0)	0.083
Acquired in ICU	24 (33.3)	11 (23.4)	13 (52.0)	0.029
Days of hospitalization before bacteremia	18 (8.25—33)	17 (7—30)	24 (9.5—35.5)	0.500
Comorbid conditions				
Alcoholism	11 (15.3)	6 (12.8)	5 (20.0)	0.497
Peptic ulcer	17 (23.6)	10 (21.3)	7 (28.0)	0.728
Chronic obstructive pulmonary disease	7 (9.7)	4 (8.5)	3 (12.0)	0.688
Chronic kidney disease	17 (23.6)	11 (23.4)	6 (24.0)	1.000
Diabetes mellitus	20 (27.8)	10 (21.3)	10 (40.0)	0.158
Hypertension	20 (27.8)	15 (31.9)	5 (20.0)	0.425
Coronary artery disease	3 (4.2)	1 (2.1)	2 (8.0)	0.275
Congestive heart failure	6 (8.3)	4 (8.5)	2 (8.0)	1.000
Cerebrovascular accident	7 (9.7)	4 (8.5)	3 (12.0)	0.688
Collagen vascular disease	3 (4.2)	3 (6.4)	0 (0.0)	0.547
Immunosuppressive therapy	5 (6.9)	4 (8.5)	1 (4.0)	0.652
Solid tumor	37 (51.4)	20 (42.6)	17 (68.0)	0.070
Hematological malignancy	2 (2.8)	1 (2.1)	1 (4.0)	1.000
Chemotherapy	3 (4.2)	2 (4.3)	1 (4.0)	1.000
Neutropenia	4 (5.6)	1 (2.1)	3 (12.0)	0.117
Trauma	3 (4.2)	2 (4.3)	1 (4.0)	1.000
Recent surgery	14 (19.4)	10 (21.3)	4 (16.0)	0.758
Disease severity				
APACHE II score	17 (12—24)	16 (11—19)	24 (15—28.5)	<0.001
Charlson comorbidity index	5.5 (5—7)	5 (4—6)	6 (5—8.5)	0.031
Shock	15 (20.8)	6 (12.8)	9 (36.0)	0.045
Invasive procedures				
Arterial catheter	21 (29.2)	11 (23.4)	10 (40.0)	0.229
Central venous catheter	23 (31.9)	13 (27.7)	10 (40.0)	0.422
Ventilator use	27 (37.5)	14 (29.8)	13 (52.0)	0.110
Hemodialysis	10 (13.9)	5 (10.6)	5 (20.0)	0.301
Thoracic drain	5 (6.9)	2 (4.3)	3 (12.0)	0.334
Abdominal drain	13 (18.1)	9 (19.1)	4 (16.0)	1.000
Sources of bacteremia				
Pneumonia	14 (19.4)	6 (12.8)	8 (32.0)	0.064
Primary bacteremia	36 (50.0)	24 (51.1)	12 (48.0)	1.000
Intra-abdominal infection	13 (18.1)	10 (21.3)	3 (12.0)	0.521
Catheter	4 (5.6)	4 (8.5)	0 (0.0)	0.291
Urinary tract infection	3 (4.2)	1 (2.1)	2 (8.0)	0.275
Wound	2 (2.8)	2 (4.3)	0 (0.0)	0.540
Child-Pugh class				
A	14 (19.4)	10 (21.3)	4 (16.0)	0.758
B	19 (26.4)	12 (25.5)	7 (28.0)	1.000
C	39 (54.2)	25 (53.2)	14 (56.0)	1.000
Species of causative *Acinetobacter*				
A. baumannii	24 (33.3)	9 (19.1)	15 (6.0)	0.001
A. nosocomialis	27 (37.5)	22 (46.8)	5 (20.0)	0.048
A. pittii	10 (13.9)	9 (19.1)	1 (4.0)	0.149
A. soli	6 (8.3)	4 (8.5)	2 (8.0)	1.000
Other *Acinetobacter* species	5 (6.9)	3 (6.4)	2 (8.0)	0.797
Antimicrobial non-susceptibility				
Amikacin	16 (22.2)	8 (17.0)	8 (32.0)	0.247
Ampicillin/sulbactam	21 (29.2)	11 (23.4)	10 (40.0)	0.229
Cefepime	33 (45.8)	19 (40.4)	14 (56.0)	0.310

Table 3 (*continued*)

	n (% or interquartile range)[a]			*p*-value
	All ($n = 72$)	Survivors ($n = 47$)	Non-survivors ($n = 25$)	
Ceftazidime	39 (54.2)	24 (51.1)	15 (60.0)	0.634
Piperacillin/tazobactam	35 (48.6)	20 (42.5)	15 (60.0)	0.245
Imipenem	27 (37.5)	16 (34.0)	11 (44.0)	0.774
Meropenem	36 (50.0)	24 (51.1)	12 (48.0)	1.000
Ciprofloxacin	35 (48.6)	21 (44.7)	14 (56.0)	0.505
Levofloxacin	28 (38.9)	15 (31.9)	13 (52.0)	0.158
Colistin	2 (2.8)	1 (2.1)	1 (4.0)	1.000
Tigecycline	9 (12.5)	6 (12.8)	3 (12.0)	1.000
Appropriate antimicrobial therapy	33 (45.8)	21 (44.7)	12 (48.0)	0.983

[a] Data are median value (interquartile range) for continuous variables and number of cases (%) for categorical variables. APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

Table 4 Logistic regression analyses of risk factors associated with 30-day mortality in cirrhotic patients with *Acinetobacter* bacteremia.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p value*	OR (95% CI)	*p value*
APACHE II score	1.173 (1.074–1.281)	<0.001	1.146 (1.035–1.268)	0.009
Acquired in ICU	3.545 (1.259–9.982)	0.017		
Bacteremia due to *A. baumannii*	6.333 (2.149–18.665)	0.001	20.501 (2.301–182.649)	0.007
Solid tumor	2.869 (1.034–7.956)	0.043	18.073 (1.938–168.504)	0.011
Shock	3.844 (1.177–12.554)	0.026		
Pneumonia	3.216 (0.969–10.677)	0.056		
Recent ICU stay	2.715 (0.999–7.380)	0.050		

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

(28–29%).[40,41] In immunocompromised patients, such as liver cirrhosis and malignancy, *A. nosocomialis* and primary bacteremia were also predominantly observed.[2,42] In cirrhotic patients, occult infections can be originated from bacterial translocation, which is the migration of bacteria from the gut lumen to the systemic circulation. Bacterial translocation pathologically increased in cirrhotic patients due to a multifactorial immune-deficient condition,[43–47] which increased the risk of spontaneous infections, such as primary bacteremia and peritonitis.[47–49]

Even though some causative *Acinetobacter* spp. were different in the cirrhotic and non-cirrhotic groups, bacteremia caused by *A. baumannii* is still independently associated with a higher 30-day mortality in cirrhotic patients with *Acinetobacter* bacteremia. This condition may be due to higher pathogenicity of *A. baumannii*.[2,34,38] Therefore, genomic species identification is important to better delineate the role of various *Acinetobacter* spp.[23,50]

This study is subject to some limitations regularly found in retrospective studies. Several confounding factors, such as detailed demographic data and treatment course cannot be well controlled under retrospective design, further prospective study may need for better elucidation.

In conclusion, although cirrhotic patients with *Acinetobacter* bacteremia were younger and with lower APACHE II scores than non-cirrhotic patients, their mortality rates were insignificantly different. APACHE II score is a reliable tool for predicting the mortality rate of cirrhotic patients with *Acinetobacter* bacteremia, as well as the other two independent risk factors, solid tumors and bacteremia caused by *A. baumannii*.

Conflicts of interest

All authors declare that they have no relevant conflicts of interest related to this article.

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References

1. Chen CT, Wang YC, Kuo SC, Shih FH, Chen TL, How CK, et al. Community-acquired bloodstream infections caused by *Acinetobacter baumannii*: a matched case-control study. *J Microbiol Immunol Infect* 2018;**51**:629—35.
2. Chuang YC, Sheng WH, Li SY, Lin YC, Wang JT, Chen YC, et al. Influence of genospecies of *Acinetobacter baumannii* complex on clinical outcomes of patients with *acinetobacter* bacteremia. *Clin Infect Dis* 2011;**52**:352—60.
3. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. *Clin Microbiol Rev* 2008; **21**:538—82.
4. Cisneros JM, Reyes MJ, Pachon J, Becerril B, Caballero FJ, Garcia-Garmendia JL, et al. Bacteremia due to *Acinetobacter baumannii*: epidemiology, clinical findings, and prognostic features. *Clin Infect Dis* 1996;**22**:1026—32.
5. Garcia-Garmendia JL, Ortiz-Leyba C, Garnacho-Montero J, Jimenez-Jimenez FJ, Perez-Paredes C, Barrero-Almodovar AE, et al. Risk factors for *Acinetobacter baumannii* nosocomial bacteremia in critically ill patients: a cohort study. *Clin Infect Dis* 2001;**33**:939—46.
6. Seifert H, Strate A, Pulverer G. Nosocomial bacteremia due to *Acinetobacter baumannii*. Clinical features, epidemiology, and predictors of mortality. *Medicine (Baltimore)* 1995;**74**: 340—9.
7. Ahmed SS, Alp E. Genotyping methods for monitoring the epidemic evolution of *A. baumannii* strains. *J Infect Dev Ctries* 2015;**9**:347—54.
8. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011;**9**:727—38.
9. Bunchorntavakul C, Chavalitdhamrong D. Bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. *World J Hepatol* 2012;**4**:158—68.
10. Garcia-Tsao G, Wiest R. Gut microflora in the pathogenesis of the complications of cirrhosis. *Best Pract Res Clin Gastroenterol* 2004;**18**:353—72.
11. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010;**139**:1246—56.
12. Thulstrup AM, Sorensen HT, Schonheyder HC, Moller JK, Tage-Jensen U. Population-based study of the risk and short-term prognosis for bacteremia in patients with liver cirrhosis. *Clin Infect Dis* 2000;**31**:1357—61.
13. Park H, Jang KJ, Jang W, Park SH, Park JY, Jeon TJ, et al. Appropriate empirical antibiotic use and 30-d mortality in cirrhotic patients with bacteremia. *World J Gastroenterol* 2015;**21**:3587—92.
14. Liu BM, Chung KJ, Chen CH, Kung CT, Ko SF, Liu PP, et al. Risk factors for the outcome of cirrhotic patients with soft tissue infections. *J Clin Gastroenterol* 2008;**42**:312—6.
15. Taneja SK, Dhiman RK. Prevention and management of bacterial infections in cirrhosis. *Int J Hepatol* 2011;**2011**: 784540.
16. Shizuma T. Spontaneous bacterial peritonitis and bacteremia in patients with liver cirrhosis. *J Med Microb Diagn* 2014;**3**:142—7.
17. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. *Am J Infect Control* 1988; **16**:128—40.
18. Horan TC, Gaynes RP. Hospital epidemiology and infection control. In: *Surveillance of nosocomial infections*. 3rd ed. Baltimore: MD: Lippincott Williams & Wilkins; 2004.
19. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2008;**36**:296—327.
20. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**:818—29.
21. Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: the model for end-stage liver disease—should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment Pharmacol Ther* 2005;**22**:1079—89.
22. Chen TL, Siu LK, Wu RC, Shaio MF, Huang LY, Fung CP, et al. Comparison of one-tube multiplex PCR, automated ribotyping and intergenic spacer (ITS) sequencing for rapid identification of *Acinetobacter baumannii*. *Clin Microbiol Infect* 2007;**13**: 801—6.
23. Chang HC, Wei YF, Dijkshoorn L, Vaneechoutte M, Tang CT, Chang TC. Species-level identification of isolates of the *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex by sequence analysis of the 16S-23S rRNA gene spacer region. *J Clin Microbiol* 2005;**43**:1632—9.
24. Clinical and Laboratory Standards Institute. *M100-S25. Performance standards of antimicrobial susceptibility testing, 25th informational supplement*. Clinical and Laboratory Standards Institute. Wayne, PA, USA: CLSI; 2015.
25. Chen YC, Tian YC, Liu NJ, Ho YP, Yang C, Chu YY, et al. Prospective cohort study comparing sequential organ failure assessment and acute physiology, age, chronic health evaluation III scoring systems for hospital mortality prediction in critically ill cirrhotic patients. *Int J Clin Pract* 2006;**60**: 160—6.
26. Ho YP, Chen YC, Yang C, Lien JM, Chu YY, Fang JT, et al. Outcome prediction for critically ill cirrhotic patients: a comparison of APACHE II and Child-Pugh scoring systems. *J Intensive Care Med* 2004;**19**:105—10.
27. Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. *Hepatology* 2001;**34**:255—61.
28. Tsai MH, Peng YS, Lien JM, Weng HH, Ho YP, Yang C, et al. Multiple organ system failure in critically ill cirrhotic patients. A comparison of two multiple organ dysfunction/failure scoring systems. *Digestion* 2004;**69**:190—200.
29. Gustot T, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology* 2009;**50**:2022—33.
30. Huang ST, Chiang MC, Kuo SC, Lee YT, Chiang TH, Yang SP, et al. Risk factors and clinical outcomes of patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. *J Microbiol Immunol Infect* 2012;**45**:356—62.
31. Aydemir H, Celebi G, Piskin N, Oztoprak N, Keskin AS, Aktas E, et al. Mortality attributable to carbapenem-resistant nosocomial *Acinetobacter baumannii* infections in a Turkish university hospital. *Jpn J Infect Dis* 2012;**65**:66—71.
32. Choi JY, Park YS, Kim CO, Park YS, Yoon HJ, Shin SY, et al. Mortality risk factors of *Acinetobacter baumannii* bacteraemia. *Intern Med J* 2005;**35**:599—603.
33. Lee NY, Chang TC, Wu CJ, Chang CM, Lee HC, Chen PL, et al. Clinical manifestations, antimicrobial therapy, and prognostic factors of monomicrobial *Acinetobacter baumannii* complex bacteremia. *J Infect* 2010;**61**:219—27.

34. Lee YC, Huang YT, Tan CK, Kuo YW, Liao CH, Lee PI, et al. *Acinetobacter baumannii* and *Acinetobacter* genospecies 13TU and 3 bacteraemia: comparison of clinical features, prognostic factors and outcomes. *J Antimicrob Chemother* 2011;**66**: 1839—46.
35. Lee YT, Kuo SC, Yang SP, Lin YT, Chiang DH, Tseng FC, et al. Bacteremic nosocomial pneumonia caused by *Acinetobacter baumannii* and *Acinetobacter nosocomialis*: a single or two distinct clinical entities? *Clin Microbiol Infect* 2012;**19**:640—5.
36. Liang-Yu C, Kuo SC, Liu CY, Luo BS, Huang LJ, Lee YT, et al. Difference in imipenem, meropenem, sulbactam, and colistin nonsusceptibility trends among three phenotypically undifferentiated *Acinetobacter baumannii* complex in a medical center in Taiwan, 1997—2007. *J Microbiol Immunol Infect* 2011;**44**: 358—63.
37. Schleicher X, Higgins PG, Wisplinghoff H, Korber-Irrgang B, Kresken M, Seifert H. Molecular epidemiology of *Acinetobacter baumannii* and *Acinetobacter nosocomialis* in Germany over a 5-year period. *Clin Microbiol Infect* 2005-2009;**2012**(19):737—42.
38. Yang YS, Lee YT, Tsai WC, Kuo SC, Sun JR, Yang CH, et al. Comparison between bacteremia caused by carbapenem resistant *Acinetobacter baumannii* and *Acinetobacter nosocomialis*. *BMC Infect Dis* 2013;**13**:311.
39. Pittet D, Wenzel RP. Nosocomial bloodstream infections. Secular trends in rates, mortality, and contribution to total hospital deaths. *Arch Intern Med* 1995;**155**:1177—84.
40. Renaud B, Brun-Buisson C, Group IC-BS. Outcomes of primary and catheter-related bacteremia. A cohort and case-control study in critically ill patients. *Am J Respir Crit Care Med* 2001;**163**:1584—90.
41. Valles J, Leon C, Alvarez-Lerma F. Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Espanola de Medicina Intensiva y Unidades Coronarias (SEMIUC). *Clin Infect Dis* 1997; **24**:387—95.
42. Wu HS, Kuo SC, Lee YT, Yang YS, Cheng SS, Chen TL, et al. Clinical characteristics and prognostic factors of *Acinetobacter nosocomialis* bacteraemia in patients with solid tumours. *Clin Microbiol Infect* 2012;**18**:E373—6.
43. Campillo B, Pernet P, Bories PN, Richardet JP, Devanlay M, Aussel C. Intestinal permeability in liver cirrhosis: relationship with severe septic complications. *Eur J Gastroenterol Hepatol* 1999;**11**:755—9.
44. Chang CS, Chen GH, Lien HC, Yeh HZ. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 1998;**28**: 1187—90.
45. Guarner-Argente C, Sanchez E, Vidal S, Roman E, Concepcion M, Poca M, et al. Toll-like receptor 4 D299G polymorphism and the incidence of infections in cirrhotic patients. *Aliment Pharmacol Ther* 2010;**31**:1192—9.
46. Nischalke HD, Berger C, Aldenhoff K, Thyssen L, Gentemann M, Grunhage F, et al. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. *J Hepatol* 2011;**55**:1010—6.
47. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology* 2005;**41**:422—33.
48. Bellot P, Frances R, Such J. Pathological bacterial translocation in cirrhosis: pathophysiology, diagnosis and clinical implications. *Liver Int* 2013;**33**:31—9.
49. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol* 2014;**60**:197—209.
50. Gundi VA, Dijkshoorn L, Burignat S, Raoult D, La Scola B. Validation of partial rpoB gene sequence analysis for the identification of clinically important and emerging Acinetobacter species. *Microbiology* 2009;**155**:2333—41.