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ORIGINAL ARTICLE

Monomicrobial *Aeromonas* and *Vibrio* bacteremia in cirrhotic adults in southern Taiwan: Similarities and differences



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Results: The study population consisted of 77 cirrhotic patients with *Aeromonas* bacteremia and 48 patients with *Vibrio* bacteremia. Both pathogens clustered during the summer season; *Vibrio* bacteremia was more correlated with higher temperatures (*Vibrio*: $r^2 = 0.95$, p < 0.0001; *Aeromonas*: $r^2 = 0.74$, p = 0.006) and was associated with ingestion of undercooked seafood (p = 0.03) or cutaneous exposure (p < 0.001). *Vibrio* bacteremia mainly occurred in mildly or moderately decompensated cirrhosis (Child–Pugh class A and B: 45.8% vs. 20.8%, p = 0.003), and caused more soft-tissue infections (31.3% vs. 5.2%; p < 0.001) and renal dysfunction (1.6 \pm 1.2 mg/dL vs. 1.3 \pm 0.8 mg/dL, p = 0.006). Sepsis-related mortality was similar in the cases of *Vibrio* and *Aeromonas* bacteremia (14.6% vs. 14.3%, p = 0.96), but those with *Vibrio* bacteremia underwent a fulminant course, as evidenced by a shorter time from bacteremia onset to death (3.1 days vs. 8.2 days, p = 0.04).

Conclusion: In cirrhotic patients, bacteremia caused by *Aeromonas* and *Vibrio* species clustered in summer months and caused similar mortality, but *Vibrio* bacteremia led to a more severe and fulminant sepsis.

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Introduction

Bacterial infections remained common and accounted for significant morbidity and mortality in cirrhotic patients. The cumulative mortality rate after infections in cirrhotic patients could be up to 43.5%, four-fold higher than those without infections.¹ Approximately 76% of bacteremia in cirrhotic patients were caused by Gram-negative bacteria, and Escherichia coli and Klebsiella spp. were the most common microorganisms.² Vibrio, Aeromonas, and Campylobacter spp. occasionally caused bacteremia in cirrhotic patients, but these individuals are at great risks for invasive infections caused by these less commonly encountered pathogens.³ Previous studies have described the clinical features, infection foci, and short-term outcome of Aeromonas or Vibrio infections, such as primary bacteremia, spontaneous bacterial peritonitis, or soft tissue infection, especially in patients with hepatic problems. Their occurrence may be related to food or water exposure.⁴⁻⁶ Taiwan, especially its southern region, could be regarded as one of the endemic areas of Aeromonas and Vibrio infections because of their ubiquitous presence in the environment and the high incidence of chronic hepatitis. However, a poor outcome had been prescribed in the cases of Aeromonas or Vibrio infections,⁸ and underlying hepatic cirrhosis is often referred to as a prognostic host factor.^{8,9} Empirical antimicrobial therapy that covers both pathogens among the susceptible population is an important clinical issue in Taiwan.

Recently, among clinical *Aeromonas* isolates β -lactamases conferring cephalosporin resistance, which were absent in clinical *Vibrio* isolates, had been discussed,¹⁰ and such a finding highlighted the importance of the identification of the *Aeromonas* genus. However, infectious diseases caused by *Aeromonas* or *Vibrio* species could not be clinically distinguished. So far, there is no study detailing their similarities and dissimilarities among cirrhotic patients. Therefore, our study was intended to describe and compare the clinical features and outcome of *Aeromonas* and *Vibrio* bacteremia in cirrhotic patients who sought treatment at a medical center in southern Taiwan.

Materials and methods

The cases of Aeromonas and Vibrio bacteremia between January 2003 and September 2013 were identified from the database of the Microbiology Laboratory of National Cheng Kung University Hospital, Tainan, Taiwan. Clinical and laboratory information, including demographic characteristics, underlying disease, clinical presentations and course, laboratory data, antimicrobial agents administered, and clinical outcomes, were collected. The clinical diagnosis of liver cirrhosis was made by sonographic findings in conjunction with the presence of cirrhotic complications, such as ascites, esophageal varices, hepatic encephalopathy, or coagulopathy. Only monomicrobial bacteremia was included. The monthly mean outdoor temperatures (°C) in the Tainan area between 2003 and 2013 were obtained from the Central Weather Bureau, Taiwan, and would be used to correlate with the seasonal distribution of all episodes of monomicrobial Aeromonas and Vibrio bacteremia. Only the first episode of Aeromonas or Vibrio bacteremia was taken into account in other analyses in this study.

The blood culture system used was BACTEC 9240 (Beckon Dickinson, Sparks, MD, USA). Identification of the Aeromonas genus was based on a positive oxidase test, fermentation of D-glucose, the absence of growth in 6.5% sodium chloride, and resistance to the vibriostatic agent, 0/129 (150 µg), as described previously.¹¹ Because recent advances in nomenclature in the genus Aeromonas are based on genetic identification, which led to a reclassification of the Aeromonas species,¹² species identification is beyond the scope of this study, and only the details of Aeromonas bacteremia are discussed. Vibrio isolates identified were oxidase positive, susceptible to 0/129, tolerable to salt solution, and can ferment glucose. Species identification relied on typical biochemistry characteristics as described previously.⁵ Both genera were confirmed using the commercial identification system, API 20E system (BioMérieux, Marcy-l'Étoile, France). Serotyping of Vibrio cholerae was studied by the O1 antiserum. In vitro antimicrobial susceptibilities of all isolates were determined with the disk diffusion method described by the Clinical and Laboratory Standards Institute.¹³

Nosocomial infections were defined as the bacteremic episodes detected at least 72 hours after admission. The severity of liver cirrhosis was assessed by the Pugh scoring system based on serum albumin, total serum bilirubin, prolongation of prothrombin time, amount of ascites, and degree of hepatic encephalopathy.¹⁴ Patients who had antecedent trauma, fish bone injury, or recent contact with freshwater or seawater, were reported as cutaneous exposure. Recent consumption of uncooked seafood was regarded as ingestion exposure. Bacteremia without concomitant attributable infectious focus was considered primary bacteremia, and other infectious foci were determined on the basis of clinical findings or bacterial culture results. Hypotension was defined as a systolic blood pressure <90 mmHg or the need for an inotropic agent support within 24 hours prior to or 48 hours after bacteremia onset. The severity of illness was graded using the Pitt bacteremia score, which was based on the evaluation of body temperature, mental status, blood pressure, need for mechanical ventilation, and presence of cardiac arrest.¹⁵ When the septic process was deemed to be the cause of death, the fatality was regarded as being directly related to the bacteremia. Deaths resulting from any events other than septicemia, such as gastrointestinal bleeding or underlying problem, were defined as not directly related to bacteremia. Initial antimicrobial therapy was the drug prescribed continuously for at least 48 hours after the symptom onset. If it was demonstrated to be in vitro active against the causative pathogen, it was defined as being appropriate.

Statistical analyses were performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA). Pearson's Chi-square test or two-tailed Fisher's exact test was used to examine nominal data and unpaired Student t test was used for continuous data. Mann—Whitney U test was used for outcome analysis, and Kaplan—Meier survival curves were performed for the survival duration of *Aeromonas* and *Vibrio* species. The correlation of monthly episodes of bacteremia and the average outdoor temperature in Tainan City were examined using the Spearman correlation analysis. A p value of ≤ 0.05 was regarded as statistically significant.

Results

Between January 2003 and September 2013, a total 240 Aeromonas isolates obtained from 227 patients and 92 Vibrio isolates from 91 patients were found. Among these patients, 77 (33.9%) patients with 86 episodes of Aeromonas bacteremia and 48 (52.7%) patients with 49 episodes of Vibrio bacteremia had hepatic cirrhosis. Regarding Vibrio bacteremia, 27 episodes were caused by Vibrio vulnificus, 20 by non-O1, non-O139 V. cholera, and two by Vibrio spp. Compared with Aeromonas bacteremia, Vibrio bacteremia was more correlated with warmer temperatures (Aeromonas: $r^2 = 0.74$, p = 0.006; Vibrio: $r^2 = 0.95$, p < 0.0001) (Fig. 1).

The mean age of patients with *Aeromonas* bacteremia was 57.0 years (range, 29–93 years) and that of patients with *Vibrio* bacteremia was 55.4 years (range, 35–84 years) (Table 1). Males predominated in both groups. Diabetes

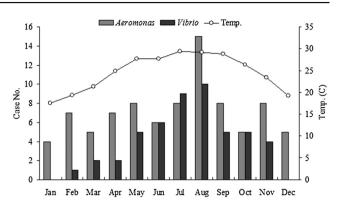


Figure 1. Seasonal distribution of *Aeromonas* and *Vibrio* bacteremia in cirrhotic patients in southern Taiwan. There is a more significant correlation of *Vibrio* bacteremia episodes $(r^2 = 0.95, p < 0.0001)$ with average ambient temperature than those of *Aeromonas* bacteremia $(r^2 = 0.74, p = 0.006, Spearman's correlation)$. P = 0.04.

mellitus and hepatocellular carcinoma, in addition to cirrhosis, were common comorbidities in both groups. Nosocomial acquisition was more common in *Aeromonas* bacteremia than in *Vibrio* bacteremia (23.4% vs. 8.3%, p = 0.03). The interval between the admission and acquisition of *Aeromonas* bacteremia tended to be longer than that of *Vibrio* bacteremia (14.8 days vs. 7.0 days, p = 0.39), although the difference was not statically significant.

Only two (2.6%) patients with *Aeromonas* bacteremia were associated with an exposure history, but for *Vibrio* bacteremia, six (12.5%) patients with seafood exposure (p = 0.03) and 14 (29.2%) patients with cutaneous exposure (p < 0.001) were noted. *Vibrio* bacteremia occurred in cases of mild-to-moderate decompensated cirrhosis (Child–Pugh class A and B: 45.8% vs. 20.8%, p = 0.003), whereas *Aeromonas* bacteremia often occurred in those with severely decompensated cirrhosis.

As for clinical manifestations, the initial presentation of fever was common at arrival. Of note, patients with *Vibrio* bacteremia more often experienced dyspnea (33.3% vs. 15.6%, p = 0.02) and tended to have more severe sepsis, as indicated by more patients with a Pittsburgh bacteremia score \geq 4 (33.3% vs. 19.5%, p = 0.08; Table 1). In terms of leukocytosis, leukopenia, or thrombocytopenia, there were no differences, but serum creatinine levels at initial presentation were higher in the cases of *Vibrio* bacteremia (1.6 \pm 1.2 mg/dL vs. 1.3 \pm 0.8 mg/dL; p = 0.006).

As for the potential source or infectious focus of bloodstream infections, primary bacteremia was most common in both study groups (*Aeromonas*: 43/77, 55.8%; *Vibrio*: 22/48, 45.8%; p = 0.28), followed by spontaneous bacterial peritonitis (*Aeromonas*: 21/77, 27.3%; *Vibrio*: 7/48, 14.6%; p = 0.10). Of note, soft-tissue infections were more common in *Vibrio* bacteremia (15/48, 31.3% vs. 4/77, 5.2%; p < 0.001) (Fig. 2). Four cases of *Aeromonas* bacteremia and soft-tissue infections had necrotizing fasciitis. Of 15 cases of *Vibrio* bacteremia and soft-tissue infections, 86.7% (13) had necrotizing fasciitis requiring emergent fasciotomy. The other infectious foci included intra-abdominal infections (3 cases of *Aeromonas*)

Characteristic Case no. (%) or mean \pm standard deviation p value Aeromonas, n = 77Vibrio, n = 480.28 57.0 ± 13.9 $\textbf{55.4} \pm \textbf{12.6}$ Age, year Male 53 (68.8) 34 (70.8) 0.81 Healthcare-associated bacteremia 18 (23.4) 4 (8.3) 0.03 7 (3-15) 14.8(3-46)0.39 Davs after admission, mean (range)^a Etiology of liver cirrhosis Hepatitis B virus 0.17 45 (58.4) 22 (45.8) Hepatitis C virus 22 (28.6) 15 (31.3) 0.75 Alcoholism 18 (23.4) 13 (27.1) 0.64 Mild-to-moderate cirrhosis^b 16 (20.8) 22 (45.8) 0.003 Comorbid conditions Hepatocellular carcinoma 35 (45.5) 0.27 17 (35.4) **Diabetes mellitus** 17 (22.1) 16 (33.3) 0.17 Malignancy other than hepatoma 5 (6.5) 4 (8.3) 0.70 0.39 Chronic kidney disease 4 (5.2) 1 (2.1) Steroid use 0 0.07 2 (4.2) Exposure history Ingestion exposure 2 (2.6) 6 (12.5) 0.03 Cutaneous exposure to water or trauma 0 14 (29.2) < 0.001 Prior antibiotics within 1 month before onset 18 (23.4) 6 (12.5) 0.13 Clinical presentations Fever 74 (96.1) 43 (89.6) 0.15 Hypotension 29 (37.7) 25 (52.1) 0.11 Altered mental status 24 (31.2) 10 (20.8) 0.21 **Dyspnea** 12 (15.6) 16 (33.3) 0.02 13 (27.1) Abdominal pain 28 (36.4) 0.28 Diarrhea 14 (18.2) 4 (8.3) 0.13 Laboratory data 0.78 Leukocytosis (>12,000/mm³) 16 (20.8) 11 (22.9) Leukopenia (<4000/mm³) 16 (20.8) 13 (27.1) 0.42 Thrombocytopenia (<100,000/mm³) 0.83 63 (81.8) 40 (83.3) Serum creatinine (mg/dL) $\textbf{1.3} \pm \textbf{0.8}$ $\textbf{1.6} \pm \textbf{1.2}$ 0.006 Pittsburgh bacteremia score >4 0.08 15 (19.5) 16 (33.3)

 Table 1
 Clinical characteristics of cirrhotic patients with Aeromonas or Vibrio bacteremia

^a Two cases transferred from other hospitals without complete information were excluded.

^b Child-Pugh class A and B.

infection, 3 cases of *Vibrio* infection), spontaneous bacterial empyema (3 cases of *Aeromonas*, 1 case of *Vibrio*), biliary tract infection (1 case of *Aeromonas*), urinary tract infection (1 case of *Aeromonas*), and pneumonia (1 case of *Aeromonas*). Of the patients with *Vibrio* bacteremia, four (30.8%) of 13 with necrotizing fasciitis and 12 (34.3%) of 35 without necrotizing fasciitis had severe illness (Pitt bacteremia score \geq 4), compared with 15 (19.5%) of 77 with *Aeromonas* bacteremia (p = 0.36 and p = 0.09, respectively).

Of the cases of *Aeromonas* and *Vibrio* bacteremia, there were no differences in crude (20.8% vs. 29.2%, p = 0.29) or sepsis-related mortality rate (14.3% vs. 14.6%, p = 0.96) (Table 2). However, the interval between the bacteremia onset to sepsis-related death was shorter in the cases of *Vibrio* bacteremia than that of *Aeromonas* bacteremia (3.1 days vs. 8.2 days, p = 0.04) (Fig. 3).

Interestingly, three cirrhotic cases of *Aeromonas* bacteremia experienced *Vibrio* bacteremia at 2–12 months after the previous *Aeromonas* episodes. By contrast, four

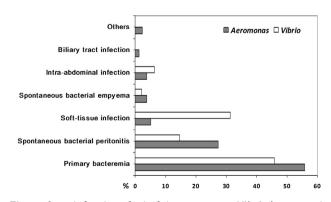


Figure 2. Infectious foci of *Aeromonas* or *Vibrio* bacteremia in cirrhotic patients. *Vibrio* bacteremia more often manifests as soft-tissue infections than *Aeromonas* bacteremia (15/48, 31.3% vs. 4/77, 5.2%; p < 0.001).

Table 2 Clinical outcome of Aeromonas or Vibrio bacteremia in cirrhotic patients

Variables	Case no.	p value	
	Aeromonas, $n = 77$	Vibrio, $n = 48$	
Appropriate antibiotics initially	61 (79.2)	43 (89.6)	0.13
Hospital stay, days			
All cases (mean, range)	16.1 (1-80)	17.4 (1-67)	0.83
Survivors (mean, range)	14.4 (4-80)	19.0 (1-67)	0.56
Intensive care unit admission	9 (11.7)	10 (20.8)	0.17
Mortality			
Sepsis-related	11 (14.3)	7 (14.6)	0.96
At 14 days	10 (13.0)	10 (20.8)	0.25
At 1 month	16 (20.8)	13 (27.1)	0.42
In hospital	16 (20.8)	14 (29.2)	0.29

cirrhotic cases of *Vibrio* bacteremia experienced *Aero-monas* bacteremia at 22–68 months afterward (Table 3).

Discussion

Both *Aeromonas* and *Vibrio* spp. are important pathogens that cause clinical infections, including primary bacteremia, spontaneous bacterial peritonitis, soft-tissue infections, and gastroenteritis, especially in regions with a high prevalence of chronic hepatitis and warm climate, such as Taiwan. The individual characteristics of clinical presentations and outcomes of human infections due to *Aeromonas* and *Vibrio* species, which often were linked to wild water exposure, had been well described.^{5,6,16} However, no report ever compared the clinical characteristics of cirrhotic patients with *Aeromonas* and *Vibrio* infections. To our knowledge, this is the first report to investigate the differences in clinical manifestations.

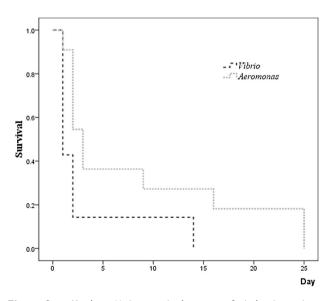


Figure 3. Kaplan-Meier survival curves of cirrhotic patients with sepsis-related mortality due to *Aeromonas* or *Vibrio* bacteremia. The mean duration after bacteremia onset to death was significantly shorter in those with *Vibrio* bacteremia than in those with *Aeromonas* bacteremia (3.1 days vs. 8.2 days, p = 0.04).

As compared with Western countries, the incidence of *Aeromonas* bacteremia in southern Taiwan was 143-, 50-, and 115-fold higher than those in California in 1998, England and Wales in 2004, and France in 2006, respectively, whereas non-*cholerae Vibrio* bacteremia was 50-fold higher than that in Florida, USA.⁷ Prior to 2000, the predominance of underlying cirrhosis in the cases of *Aeromonas* and non-01, non-0139 *V. cholerae* bacteremia has been recognized in Taiwan.^{5,17} In this study, 33.9% of monomicrobial *Aeromonas* bacteremia and 52.7% of *Vibrio* bacteremia were found in cirrhotic patients. These epidemiological figures highlighted the endemicity of *Aeromonas* and *Vibrio* bacteremia in Taiwan.

As compared with other underlying diseases, cirrhosis posed a significant impact on the mortality of patients with community-acquired bacteremia.¹⁸ Although medical care of cirrhotic patients had been improved in the past decades and prophylactic antibiotics had been utilized under certain conditions, including gastrointestinal bleeding or while undergoing invasive procedures,¹⁹ bacterial infections cause substantial morbidity and mortality among cirrhotic patients.²⁰ Those with decompensated hepatic function are in a multifactorial state of local and systemic immune dysfunction,²¹ including portosystemic shunting allowing more endotoxins in the portal circulation to bypass the liver,²² impaired phagocyte activity and opsonic activity,²³ and bacterial translocation.²⁴ Moreover, as hepatic decompensation progressed, it is often associated with bloodstream infections and a worse outcome.²⁵ The exact mechanism may be, at least partially, related to bacterial translocation.²⁶

Specific virulence-associated genes and markers of *Aeromonas* and *Vibrio* species had been studied,²⁷ but the reasons why invasive infections attributed to both pathogens dominated in cirrhotic patients remain unsettled.²⁸ However, previous studies have been addressed wherein cases of *Aeromonas* and *Vibrio* infections were more common in the Child–Pugh class C of decompensation,^{5,17} and the average Child–Pugh score was higher in cirrhotic patients with *Aeromonas* infections than those with infections due to other bacterial species.²⁹

In this study, seven patients had sequential *Aeromonas* and *Vibrio* bacteremia at different intervals (2–64 months). Those with initial *Vibrio* bacteremia tended to have mild-to-moderate cirrhosis and developed *Aeromonas*

Case no.	Age/sex	Comorbidities	Pugh class ^a	Date/Pathogen/Clinical diagnosis		Outcome of 2 nd	
				1 st episode	2 nd episode	Interval	episode
1	44/M	Hepatoma, diabetes mellitus	C→C	2003.05/ <i>Aeromonas/</i> primary bacteremia	2003.07/V. <i>cholerae/</i> primary bacteremia	2 months	Survived
2	69/F	Hepatoma	C→C	2008.04/Aeromonas/ SBP	2008.07/V. cholerae ^b / SBE	3 months	Died
3	55/F	No	C→C	2010.02/ <i>Aeromonas/</i> primary bacteremia	2011.02/V. vulnificus/ primary bacteremia	12 months	Survived
4	41/M	Diabetes mellitus	A→C	2003.10/V. vulnificus/ primary bacteremia	2009.06/ <i>Aeromonas/</i> primary bacteremia	68 months	Survived
5	57/F	Hepatoma	C→C	2004.09/V. vulnificus/ primary bacteremia	2006.07/ <i>Aeromonas^b/</i> primary bacteremia	22 months	Died
6	39/M	Squamous cell carcinoma	$B \rightarrow C$	2007.08/V. cholerae/ SBP	2009.10/Aeromonas/ SBP	26 months	Survived
7	68/F	Diabetes mellitus	$B \rightarrow C$	2010.08/V. cholerae/ enteritis	2012.08/ <i>Aeromonas/</i> pneumonia	24 months	Survived

 Table 3
 Clinical characteristics of seven cirrhotic patients with sequential Aeromonas and Vibrio vulnificus or non-O1, non-O139 V. cholerae bacteremia

^a Pugh class of 1^{st} episode $\rightarrow 2^{nd}$ episode.

^b Hospital-associated infections.

SBP = spontaneous bacterial peritonitis; SBE = spontaneous bacterial empyema.

bacteremia later, while liver function deteriorated. As compared with those with *Aeromonas* infections, *Vibrio* infections developed in individuals with less severe hepatic dysfunction, suggestive of a higher virulence of *Vibrio* isolates. Moreover, we found that patients with *Vibrio* bacteremia experienced more hypotension, renal function deterioration, and a high disease severity than those with *Aeromonas* bacteremia. Furthermore, *Vibrio* sepsis runs a fulminant clinical course, that is, a shorter interval between disease onset to death. The above facts indicate that *Vibrio* spp. is more virulent than *Aeromonas* spp. in cirrhotic patients.

Both pathogens are environmental pathogens in Taiwan, related to exposure to wild water or marine creatures, and often cause diseases among humans during warm seasons as community-acquired infections. *Vibrio* infection was often linked to warmer seasons in previous studies.^{4,5} However, there were inconsistent opinions about the seasonal variation of *Aeromonas* bacteremia, because some studies reported that it correlated with warmer seasons¹⁷ whereas others did not.³⁰ In this study, the seasonal variation was relevant to warmer seasons, and is more evident in *Vibrio* bacteremia ($r^2 = 0.95$, p < 0.0001) than in *Aeromonas* bacteremia ($r^2 = 0.74$, p = 0.006).

Furthermore, 23.4% (18 cases) of *Aeromonas* bacteremia and 8.3% (4) of *Vibrio* bacteremia were nosocomial infections, developing late during hospitalization, approximately 2 weeks after admission in *Aeromonas* bacteremia but 1 week after admission in *Vibrio* bacteremia. Only one patient with *Vibrio* bacteremia recalled recent seafood ingestion. Because their portals of entry were not clear, physicians should keep in mind the scenario that Aeromonas or Vibrio sepsis can develop even during hospitalization and cause mortality. For cirrhotic patients, food safety, including avoidance of raw or undercooked food consumption, should be emphasized.

Most patients received appropriate empirical antibiotics, but the mortality remained high in this study. Although no prospective, controlled clinical trial can conclude optimal therapeutic regimens for *Vibrio* infections, a combination regimen with cefotaxime plus minocycline showed *in vitro* synergistic antibacterial effects for *Vibrio* infections^{31,32} and was supported by a case series.³³ However, *Aeromonas* species possessed various β -lactamases, which can confer resistance to a broad spectrum of antibiotics.¹⁰ For optimal antibiotics against *Aeromonas* infections, species identification and *in vitro* susceptibility are essential to guide antimicrobial therapy.³⁴

With the nature of a retrospective study, the exposure history would not be retrieved with precision, which underestimated the relevance of contact history in the cases of *Aeromonas* bacteremia. In addition, polymicrobial *Aeromonas* or *Vibrio* bacteremia was excluded, which may influence the likelihood of environmental exposure. Because other studies involving cases of polymicrobial bacteremia reported the predominance of cancer patients, ^{35,36} the study result of monomicrobial bacteremia in cirrhotic individuals that the portals of entry in the cases of *Aeromonas* infections are not always evident clinically, remain valid.

In conclusion, in cirrhotic patients bacteremia caused by *Aeromonas* and *Vibrio* species clustered during summer and caused similar mortality, but *Vibrio* bacteremia led to a more severe and fulminant sepsis.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

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