The risk for bacterial endocarditis in cirrhotic patients: a population-based 3-year follow-up study

Tsung-Hsing Hung [a,b], Yu-Hsi Hsieh [a,b], Kuo-Chih Tseng [a,b], Chih-Chun Tsai [c], Chen-Chi Tsai [b,d,*]

[a] Division of Gastroenterology, Department of Medicine, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan
[b] School of Medicine, Tzu Chi University, Hualien, Taiwan
[c] Institute of Statistics, National Tsing-Hua University, Hsinchu, Taiwan
[d] Division of Infectious Diseases, Department of Medicine, Buddhist Dalin Tzu Chi General Hospital, No. 2, Minsheng Rd, Dalin Township, Chiayi County 62247, Taiwan

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SUMMARY

Background: We noted only rare reports of cirrhotic patients with bacterial endocarditis (BE). There is insufficient data on the risk of BE in liver cirrhosis. This is the first national population-based study evaluating the risk of BE in cirrhotic patients.
Methods: We used the National Health Insurance Database, which is derived from the Taiwan National Health Insurance Program. The study cohort comprised 40 803 patients with cirrhosis and the comparison cohort consisted of 40 841 randomly selected subjects with a similar age and sex distribution.
Results: Of the total 81 644 patients, 192 (0.24%) experienced BE during the 3-year follow-up period, 121 patients from the study cohort (0.30% of the cirrhotic patients) and 71 patients from the comparison group (0.17% of non-cirrhotic patients) ($p < 0.001$). After adjusting for patient age, sex, and comorbid disorders, the Cox regression analysis showed that cirrhotic patients had a high risk of BE compared to non-cirrhotic patients during the 3-year follow-up period (hazard ratio 2.04, 95% confidence interval 1.61–2.44, $p < 0.001$).
Conclusion: We conclude that liver cirrhosis is a risk factor for the occurrence of BE.

1. Introduction

Because of the immune-compromised status, cirrhotic patients are prone to infectious diseases. The most well-studied infectious diseases in cirrhotic patients are spontaneous bacterial peritonitis, pneumonia, and urinary tract infection.[1,2] Reports of bacterial endocarditis (BE) in cirrhotic patients are rare.[3–7] In one study, cirrhosis was observed in about 10% of the patients with BE.[3] However, it is still not known if cirrhosis is associated with the occurrence of BE. In order to identify any relationships, we used a nationwide population-based database to examine the occurrence of BE among cirrhotic patients during a 3-year follow-up period and compared this to the general hospitalized population during the same period.

2. Patients and methods

2.1. Database

We used the Taiwan National Health Insurance Research Database for this study. Approval for the analysis of this database

in the present study was obtained from the National Health Research Institute with application and agreement number 100101. The Taiwan National Health Insurance Bureau and the National Health Research Institute established and maintain this database. This database was used to identify all discharges in Taiwan. The National Health Insurance Program in Taiwan was established in 1995 for all citizens who live in Taiwan. The National Health Insurance Program covered more than 98% of Taiwan's population in 2004. All researchers were evaluated by the National Health Research Institute prior to using the National Health Insurance Research Database and were required to sign a permit to protect the privacy of patients, the hospital, and health care providers.

2.2. Study sample

The study was designed as a retrospective study. Patients discharged with a diagnosis of cirrhosis (International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM) code 571.5 or 571.2) from January 1, 2004 to December 31, 2004 were identified from the database. We excluded patients who were aged <30 years in order to rule out congenital anomaly-related cirrhosis. In this cohort study, a total of 40 803 cirrhotic patients without baseline BE were enrolled. The comparison group comprised other hospitalized patients without cirrhosis in the

* Corresponding author. Tel.: +886 5 2648000; fax: +886 5 2648999.
  E-mail address: antibody_1@msn.com (C.-C. Tsai).

same database. We randomly selected 40 841 patients with a similar sex and age distribution. The diagnosis of BE was based on the modified Duke criteria in our country. Each patient (*n* = 81 644) was individually followed for a 3-year period starting from their enrolled hospitalization until BE (ICD-9-CM codes 421).[8,9]

BE-associated factors were selected as comorbid disorders, including alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03, 571.0–571.3), drug abuse (ICD-9-CM code 304), diabetes mellitus (DM) (ICD-9-CM code 250.00), chronic renal failure (CRF) (ICD-9-CM code 585), and congenital or acquired cardiac defects. As in a previous study, congenital and acquired cardiac defects included congenital heart disease (ICD-9-CM code 745.xx–747.xx), chronic rheumatic heart disease (ICD-9-CM code 393.xx–398.xx), cardiac device (ICD-9-CM code V45.0x), heart replaced (ICD-9-CM code V42.1, V43.2), and heart valve replaced (ICD-9-CM code V42.2, V43.3).[10] Comorbid disorders were identified at the enrolled hospitalization.

2.3. Statistical analyses

The SPSS statistical package (SPSS System for Windows, version 13.0) was used to perform the analyses in this study. Cox proportional hazard regressions were performed to evaluate the association between BE and cirrhosis. Finally, we present hazard ratios (HR) along with the 95% confidence intervals (CI) using a significance level of 0.05 for this study.

3. Results

Table 1 presents the distribution of demographic characteristics and selected comorbid disorders at baseline for the sampled patients according to the presence or absence of cirrhosis. Of the 40 803 sampled patients, the mean age was 59.3 years (standard deviation 13.9 years). In the total 81 644 patients, 192 (0.24%) experienced BE during the 3-year follow-up period, 121 from the study cohort (0.30% of the cirrhotic patients) and 71 from the comparison group (0.17% of the non-cirrhotic patients) ($p < 0.001$).

Table 2 presents the results of the Cox regression analysis with the forward stepwise selection procedure based on the likelihood ratio. After adjustment for patient gender, age, and underlying comorbid disorders, the hazard of BE in a 3-year period was 2.04 (95% CI 1.61–2.44, $p < 0.001$) times greater for cirrhotic patients than for non-cirrhotic patients. Furthermore, the patients with congenital or acquired cardiac defects (HR 7.22, 95% CI 3.69–14.13, $p < 0.001$), DM (HR 1.59, 95% CI 1.16–2.19, $p < 0.001$), drug abuse (HR 27.77, 95% CI 6.88–112.15, $p < 0.001$), and CRF (HR 2.86, 95% CI 1.66–4.95, $p < 0.001$) had a greater likelihood of BE after adjustment by other factors.

4. Discussion

Cirrhotic patients, particularly those with advanced disease, have leukocyte dysfunction and phagocytic defects that make them prone to focal and systemic bacterial infections. In the study of Fernández Guerrero et al., cirrhosis was observed in almost 10% of BE, and 45% of BE in cirrhotic patients was hospital-acquired, which was significantly higher than that found in the endocarditis patients who did not have cirrhosis.[3] A poor prognosis is noted in cirrhotic patients with bacterial endocarditis, but whether cirrhosis is a risk factor for BE is still unknown due to limited case numbers and the lack of an appropriate control group. In the study of Snyder et al., the frequency of BE at autopsy was higher in

Table 1
Demographic characteristics and comorbid medical disorders for cirrhotic patients and reference group (*n* = 81 736)

Characteristics	Liver cirrhosis, *n* = 40 852		Reference group, *n* = 40 884		*p*-Value
	Total *n*	%	Total *n*	%	
Gender					0.982
Male	29 013	71.1	29 043	71.1	
Female	11 790	28.9	11 798	28.9	
Age, years					0.596
30–44	7071	17.3	7092	17.4	
45–59	13 066	32.0	13 096	32.1	
60–74	14 159	34.7	14 157	34.7	
>75	6507	15.9	6496	15.9	
Drug abuse	10	0.0	28	0.1	0.004
Heart disease[a]	206	0.5	417	1.0	<0.001
Diabetes	8031	19.7	7179	17.6	<0.001
CRF	1242	3.0	1147	2.8	0.046
Alcoholism	7960	19.5	683	1.7	<0.001

CRF, chronic renal failure.
[a] Heart disease: congenital heart disease, chronic rheumatic heart disease, cardiac device, heart replaced, or heart valve replaced.

Table 2
Unadjusted and adjusted hazard ratios for bacterial endocarditis during the 3-year follow-up period following first hospitalization

Variables	Unadjusted analysis		Adjusted analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	1.00 (0.99–1.00)	0.593	–	–
Male	1.13 (0.82–1.56)	0.445	–	–
Drug abuse	21.92 (5.44–88.27)	<0.001	27.77 (6.88–112.15)	<0.001
Heart disease[a]	6.18 (3.17–12.08)	<0.001	7.22 (3.69–14.13)	<0.001
Diabetes	1.67 (1.22–2.29)	0.002	1.59 (1.16–2.19)	0.004
CRF	3.02 (1.75–5.20)	<0.001	2.86 (1.66–4.95)	<0.001
Alcoholism	1.50 (1.01–2.24)	0.047	1.20 (0.79–1.82)	0.397
Cirrhosis	2.07 (1.54–2.77)	<0.001	2.04 (1.61–2.44)	<0.001

HR, hazard ratio; CI, confidence interval; CRF, chronic renal failure.
[a] Heart disease: congenital heart disease, chronic rheumatic heart disease, cardiac device, heart replaced, or heart valve replaced.

cirrhotic patients (1.8%) than in non-cirrhotic patients (0.9%).[7] However, there was no statistically significant difference in the frequency of BE at autopsy in cirrhotic patients and non-cirrhotic patients in the study by Denton et al.[6] The case number of cirrhotic patients with BE in previous studies has been very small, so the real association between cirrhosis and BE remains to be identified.

Using the National Health Insurance Research Database, our study aimed to discover whether cirrhosis is a predisposing factor for BE. BE-related comorbid disorders we chose included DM, alcoholism, drug abuse, congenital or acquired cardiac defects, and CRF. These are established factors of BE or are potentially associated.[11–20] Our study also showed congenital or acquired cardiac defects, drug abuse, DM, and CRF to be independent factors for BE, compatible with previous studies.[11–16] As noted in previous studies, BE is related to intravenous (IV) drug abuse.[12–14] In the database we selected, we could not identify the real IV drug users by ICD-9 code. Hence, we could only choose the patients with substance abuse as confounders by ICD-9 coding. We believe that for the patients involved in substance abuse there is a high possibility of IV drug use behavior.

In the present study, the patients with cirrhosis showed an increased risk of BE, with the adjusted HR during a 3-year follow-up period being 2.04 (95% CI 1.61–2.44, $p < 0.001$) compared to the comparison group. Furthermore, the very large sample size provided the statistical power to detect a difference in the risk of BE between the cirrhotic patients and non-cirrhotic patients. Because of the high risk of the occurrence of BE in cirrhotic patients, clinical doctors should pay attention to BE in cirrhotic patients, especially in those who have congenital or acquired cardiac defects, IV drug abuse, DM, and CRF. To our knowledge, our study is the first reported population-based cohort study investigating BE in cirrhotic patients.

There are several limitations to the present study. First, we could not level the risk of BE in all patients according to cardiac procedures, intravenous procedures, dental procedures, surgical procedures, cardiac condition, and use of prophylactic anti-biotics because our database could not provide detailed data for this. However, we enrolled all BE-associated heart diseases, including congenital heart disease, chronic rheumatic heart disease, cardiac device, heart replaced, and heart valve replaced as a comorbid disorder. Secondly, the exact etiology of liver cirrhosis was not identified in this national population-based study. In our study, the etiology of cirrhosis could only be classified into alcohol-related and non-alcohol related. However, the etiology of cirrhosis in Taiwan has already been well established in many previous studies, and is mostly related to hepatitis B virus.[21,22] In our study, about 80% of cirrhotic patients had disease that was non-alcohol related, compatible with the data in Taiwan. Despite these limitations, our study is the first complete nationwide population-based study to identify the risk of BE in cirrhotic patients.

In summary, our analysis demonstrates that patients with cirrhosis are at risk of BE. Clinical doctors should pay attention to BE in cirrhotic patients, especially in those who have congenital or acquired cardiac defects, IV drug abuse, DM, and CRF. Further studies are needed in this area, and also to evaluate the relationship between the severity of cirrhosis and BE.

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References

1. Christou L, Pappas G, Falagas ME. Bacterial infection-related morbidity and mortality in cirrhosis. *Am J Gastroenterol* 2007;**102**:1510–7.
2. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;**35**:140–8.
3. Fernández Guerrero ML, González López J, Górgolas M. Infectious endocarditis in patients with cirrhosis of the liver: a model of infection in the frail patient. *Eur J Clin Microbiol Infect Dis* 2010;**29**:1271–5.
4. Hsu RB, Chen RJ, Chu SH. Bacterial endocarditis in patients with liver cirrhosis. *J Formos Med Assoc* 2004;**103**:355–8.
5. McCashland TM, Sorrell MF, Zetterman RK. Bacterial endocarditis in patients with chronic liver disease. *Am J Gastroenterol* 1994;**89**:924–7.
6. Denton JH, Rubio C, Velázquez J, de Arellano GR. Bacterial endocarditis in cirrhosis. *Dig Dis Sci* 1981;**26**:935–7.
7. Snyder N, Atterbury CE, Pinto Correia J, Conn HO. Increased concurrence of cirrhosis and bacterial endocarditis. A clinical and postmortem study. *Gastroenterology* 1977;**73**:1107–13.
8. Abbott KC, Duran M, Hypolite I, Ko CW, Jones CA, Agodoa LY. Hospitalizations for bacterial endocarditis after renal transplantation in the United States. *J Nephrol* 2001;**14**:353–60.
9. Abbott KC, Agodoa LY. Hospitalizations for bacterial endocarditis after initiation of chronic dialysis in the United States. *Nephron* 2002;**91**:203–9.
10. Day MD, Gauvreau K, Shulman S, Newburger JW. Characteristics of children hospitalized with bacterial endocarditis. *Circulation* 2009;**119**:865–70.
11. Moreillon P, Que YA. Infective endocarditis. *Lancet* 2004;**363**:139–49.
12. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in the Netherlands: I. Patient characteristics. *Arch Intern Med* 1992;**152**:1863–8.
13. Hogevik H, Olaison L, Andersson R, Lindberg J, Alestig K. Epidemiologic aspects of infective endocarditis in an urban population: a 5-year prospective study. *Medicine (Baltimore)* 1995;**74**:324–39.
14. Tleyjeh IM, Abdel-Latif A, Rahbi H, Scott CG, Bailey KR, Steckelberg JM, et al. A systematic review of population-based studies of bacterial endocarditis. *Chest* 2007;**132**:1025–35.
15. Hoen B. Infective endocarditis: a frequent disease in dialysis patients. *Nephrol Dial Transplant* 2004;**19**:1360–2.
16. Nucifora G, Badano LP, Viale P, Gianfagna P, Allocca G, Montanaro D, et al. Bacterial endocarditis in chronic haemodialysis patients: an increasing clinical challenge. *Eur Heart J* 2007;**28**:2307–12.
17. Movahed MR, Hashemzadeh M, Jamal MM. Increased prevalence of infectious endocarditis in patients with type II diabetes mellitus. *J Diabetes Complications* 2007;**21**:403–6.
18. Miller CS, Egan RM, Falace DA, Rayens MK, Moore CR. Prevalence of infective endocarditis in patients with systemic lupus erythematosus. *J Am Dent Assoc* 1999;**130**:387–92.
19. Fariñas MC, Pérez-Vázquez A, Fariñas-Alvarez C, García-Palomo JD, Bernal JM, Revuelta JM, et al. Risk factors of prosthetic valve endocarditis: a case–control study. *Ann Thorac Surg* 2006;**81**:1284–90.
20. Wilson LE, Thomas DL, Astemborski J, Freedman TL, Vlahov D. Prospective study of infective endocarditis among injection drug users. *J Infect Dis* 2002;**185**:1761–6.
21. Hsu HC, Lin WS, Tsai MJ. Hepatitis B surface antigen and hepatocellular carcinoma in Taiwan. With special reference to types and localization of HBsAg in the tumor cells. *Cancer* 1983;**52**:1825–32.
22. Tsai JF, Chang WY, Jeng JE, Ho MS, Wang LY, Hsieh MY, et al. Hepatitis C virus infection as a risk factor for non-alcoholic liver cirrhosis in Taiwan. *J Med Virol* 1993;**41**:296–300.