Tzu Chi Medical Journal 2020; 32(1): 47–52

Original Article

Effects of poor hepatic reserve in cirrhotic patients with bacterial infections: A population-based study

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Submission : 09-Aug-2018
Revision : 18-Sep-2018
Acceptance : 03-Oct-2018
Web Publication : 18-Feb-2019

Abstract

Objective: Ascites, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, and esophageal variceal bleeding are major complications associated with cirrhosis. The presence of these complications indicates poor hepatic reserve. This study aimed to identify the effects of poor hepatic reserve on mortality in cirrhotic patients with bacterial infections. **Patients and Methods:** The Taiwan National Health Insurance Database was used to identify 43,042 cirrhotic patients with bacterial infections hospitalized between January 1, 2010, and December 31, 2013, after propensity score matching analysis. Of these, 21,521 cirrhotic patients had major cirrhotic-related complications and were considered to have poor hepatic reserve. **Results:** Mortality rates at 30 and 90 days were 24.2% and 39.5% in the poor hepatic reserve group and 12.8% and 21.7% in the good hepatic reserve group, respectively ($P < 0.001$ for each group). The cirrhotic patients with poor hepatic reserve (hazard ratio [HR], 2.10; 95% confidence interval [CI] = 2.03–2.18; $P < 0.001$) had significantly increased mortality at 90 days. The mortality HRs in patients with one, two, and three or more complications compared to patients without complications were 1.92 (95% CI = 1.85–1.99, $P < 0.001$), 2.61 (95% CI = 2.47–2.77, $P < 0.001$), and 3.81 (95% CI = 3.18–4.57, $P < 0.001$), respectively. **Conclusion:** In cirrhotic patients with bacterial infections, poor hepatic reserve is associated with a poor prognosis. The presence of three or more cirrhotic-related complications increases mortality almost four folds.

Keywords: *Bacterial infections, Complications, Liver cirrhosis*

Introduction

Ascites, hepatic encephalopathy (HE), hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), and esophageal variceal bleeding (EVB) are major complications associated with cirrhosis. The presence of these complications may correlate with poor hepatic reserve. Patients diagnosed with liver cirrhosis are prone to infectious diseases due to their underlying immunocompromised status [1-3]. However, evaluating immune status in clinical practice can be difficult.

Very few studies have been conducted to evaluate the prognosis of cirrhotic patients with complications and bacterial infections. The associations between the number of complications and the short-term survival of patients with liver cirrhosis and bacterial infections remain unclear. The purpose of this study was to determine the role of hepatic reserve in mortality in cirrhotic patients with bacterial infections and to identify the risk of mortality with cirrhotic-related complications.

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_142_18

Patients and methods

Database

A nationwide population-based dataset from the Taiwan National Health Insurance Administration was used in the current study. This study was approved by the National Health Research Institute in Taiwan (application and agreement number 104359) and the Institutional Review Board of Buddhist Dalin Tzu Chi Hospital, Chiayi, Taiwan (IRB number B10403026). Considering that this database does not include all identifying personal information (e.g., name, address, and identification number), the review board waived the requirement for written informed consent for this secondary de-identified study. This database has been used for many studies [4-6]. The Taiwan National Health Insurance program was developed

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How to cite this article: Hung TH, Tsai CC, Lee HF. Effects of poor hepatic reserve in cirrhotic patients with bacterial infections: A population-based study. Tzu Chi Med J 2020;32(1):47-52.

in 1995 which includes all citizens who live in Taiwan. This program covers at least 99% of Taiwan's population, and all study protocols need to be evaluated by the National Health Research Institute; otherwise, all information regarding the privacy of the patients and clinicians was protected.

Study sample

This study included patients who were discharged with a diagnosis of liver cirrhosis (International Classification of Diseases, 9th Revision, Clinical Modification code 571.5, or 571.2 in the database) (ICD-9-CM) between January 1, 2010, and December 31, 2013. The dataset we applied enrolled cirrhotic patients hospitalized between January 1, 2010, and December 31, 2013, in Taiwan. Patients were only enrolled if they had bacterial infections, which included pneumonia (ICD-9-CM code 481-487, without 484) [7], liver abscess (ICD-9-CM code 572.0), empyema (ICD-9-CM code 510), cellulitis (ICD-9-CM code 681 or 682), central nerve system infection (including bacterial meningitis or brain abscess: ICD-9-CM code 324 or 320), necrotizing fasciitis (ICD-9-CM code 728.86), infective endocarditis (ICD-9-CM code 421), urinary tract infection (ICD-9-CM code 590.1, 595.0, 595.9 or 599.0) [8], biliary tract infection or acute cholecystitis (ICD-9-CM code 576.1, 575.0, 574.00, 574.01, 574.30, 574.31, 574.60, 574.61, 574.80, 574.81), septic arthritis, (ICD-9-CM code 711), perianal abscess (ICD-9-CM code 566), SBP (ICD-9-CM code 567.2, 567.8, or 567.9) [9-11], and sepsis (ICD-9-CM code 038, 020.2, 790.7, or 112.81) [12]. In cases of multiple hospitalizations, only the first episode was included in this study.

Figure 1 shows the flowchart for this study. A total of 43,042 cirrhotic patients with bacterial infections were enrolled. Complications of liver cirrhosis in the current study were defined as HE (ICD-9-CM code 572.2) [13], EVB (ICD-9-CM code 456.0, 456.20) [14], undergoing an endoscopic procedure to control bleeding (ICD-9 v3 procedure codes 42.33), HRS (ICD-9-CM code 572.4), SBP, and ascites (ICD-9-CM code 789.5, or procedure code 54.91) [15]. Many factors affect mortality in cirrhotic patients with bacterial infections. Therefore, comorbid medical disorders were included as follows: a high Charlson Comorbidity Index (CCI), alcoholic-related disorders (ICD-9-CM codes 291, 303, 305.00–305.03, 571.0–571.3), peptic ulcer bleeding (ICD-9-CM code: 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, and 533.6), renal function impairment (RFI) (ICD-9-CM code 584, 585, 586, 572.4, or other procedure codes that may relate to renal failure), and hepatocellular carcinoma (HCC) (ICD-9-CM code 155.0). In this study, a CCI ≧ 4 was defined as high [16]. Some medications have been associated with the prognosis of patients with chronic liver disease, so we evaluated the usage of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, statins, proton pump inhibitors (PPIs), metformin, antiviral drugs for chronic hepatitis B (lamivudine, adefovir, telbivudine, entecavir, and tenofovir), and beta-blockers. In subgroup analysis, we evaluated the effects of poor hepatic reserve on major types of bacterial infections in cirrhotic patients. We did not analyze the role of poor hepatic reserve in SBP independently because patients with SBP are in a decompensated status by definition.

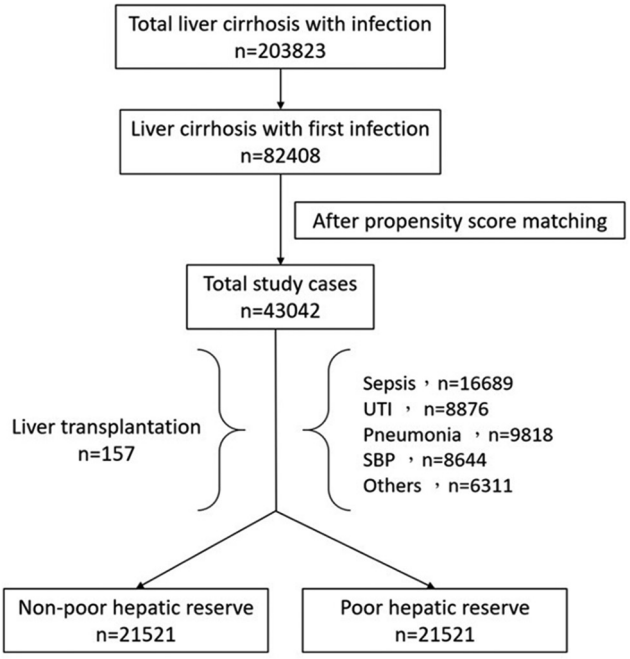

Figure 1: The flowchart for this study. UTI: Urinary tract infection, SBP: Spontaneous bacterial peritonitis

Statistical analysis

The SPSS statistical package (SPSS System for Windows, version 13.0; SPSS Inc, Chicago, IL) was used to perform the analyses in this study. Student's *t*-test and the Chi-square test were used to compare continuous variables and categorical variables, respectively. We performed propensity score matching analysis according to age, gender, underlying comorbidities, and medications to minimize potential confounding effects. The Cox regression model was used to identify risk factors associated with mortality. The Kaplan–Meier method with the log-rank test was used to estimate the survival probabilities with different numbers of complications (from 0 to 3 or more) in cirrhotic patients with bacterial infections. Hazard ratios (HRs) with 95% confidence intervals (CI) using a significance level of 0.05 were used in this study.

Results

A total of 43,042 cirrhotic patients with bacterial infections were enrolled in this study. A total of 83.8% (n = 36,050) of hospitalizations were from physicians' service. The characteristics of the patients with bacterial infections are listed in Table 1. The overall mortality rates among the enrolled cirrhotic patients with bacterial infections at 30 and 90 days were 18.5% and 30.6%, respectively. The overall 30- and 90-day mortality rates in the poor hepatic reserve group were 24.2% and 39.5% and those in the good hepatic reserve group were 12.8% and 21.7%, respectively (P < 0.001). The mean follow-up durations of the good and poor liver reserve groups were 77 and 66 days, respectively (P < 0.001). Because the 90-day mortality in each group was less than 50%, the median follow-up duration in both groups was 90 days. The results of Cox regression analysis of HRs for predisposing factors of 90-day mortality are provided in Table 2. After

adjusting for gender, age, and underlying comorbidities and medications, the adjusted HR for 90-day overall mortality in the complication group compared with the noncomplication group was 2.10 (95% CI = 2.03–2.18; $P < 0.001$). After adjusting for other factors, patients with HCC (HR, 2.04; 95% CI = 1.96–2.13; $P < 0.001$), older age (HR, 1.01; 95% CI = 1.01–1.02; $P < 0.001$), male gender (HR, 1.24; 95% CI = 1.19–1.29; $P < 0.001$), alcoholic-related disease (HR, 0.95; 95% CI = 0.90–1.00; $P = 0.032$), PUB (HR, 0.98; 95% CI = 0.88–1.08; $P = 0.635$), a high CCI (HR, 1.45; 95% CI = 1.39–1.51; $P < 0.001$), and RFI (HR, 2.17; 95% CI = 2.08–2.27; $P < 0.001$) had statistically significant differences in the 90-day mortality compared with their counterparts without these factors. The other prognostic factors related to medication usage were antiviral drugs for hepatitis B virus (HBV) (HR, 1.21; 95% CI = 1.14–1.29; $P < 0.001$), statins (HR, 0.69; 95% CI = 0.56–0.85; $P < 0.001$), PPIs (HR, 0.84; 95% CI = 0.81–0.88; $P < 0.001$), NSAIDs (HR, 0.90; 95% CI = 0.87–0.94; $P < 0.001$), metformin (HR, 0.64; 95% CI = 0.58–0.69; $P < 0.001$), aspirin (HR, 0.83; 95% CI = 0.74–0.94; $P = 0.002$), and beta-blockers (HR, 0.75; 95% CI = 0.72–0.79; $P < 0.001$).

To calculate the effect of the numbers of complications on patient mortality, patients with complications were compared with those in the good hepatic reserve group [Table 3]. The HRs for mortality in patients with one, two, and three or more complications compared with patients without complications were 1.92 (95% CI = 1.85–1.99, $P < 0.001$), 2.61 (95% CI = 2.47–2.77, $P < 0.001$), and 3.81 (95% CI = 3.18–4.57, $P < 0.001$), respectively. Only 157 patients received liver transplantation during the study follow-up period. Figure 2 shows the Kaplan–Meier overall survival curve and liver transplantation-free survival curve in patients with complications, and the log-rank test revealed statistically significant differences in both ($P < 0.001$). The cumulative survival rate decreased when the number of complications increased. In patients with three or more complications, the 30-day and 90-day mortality rates were 40.8% and 58.0%, respectively.

We also performed subgroup analysis according to different major kinds of infections. The data are provided in Table 4 and Figure 3. The main findings were similar for each kind of bacterial infection, and poor hepatic reserve still correlated with a poor prognosis in each kind of bacterial infection in cirrhotic patients.

Discussion

According to one meta-analysis, infections in cirrhotic patients increase mortality approximately four folds [17]. It is well known that cirrhotic patients are prone to infectious diseases, and the risk of mortality increases in cirrhotic patients with bacterial infections [18,19]. A major strength of the current study is the use of a population-based database that provided a large sample size. With the use of a nationwide population-based database with 4 years of patient data, reliable information regarding the risk of mortality for each complication in cirrhotic patients with bacterial infections could be assessed in this study.

Table 1: Characteristics of cirrhotic patients with bacterial infections

	Good hepatic reserve (*n*=21,521)	Poor hepatic reserve (*n*=21,521)	*P*
Age (years)	60.32±15.2	60.44±14.6	0.393
Male, *n* (%)	14795 (68.7)	14842 (69.0)	0.625
Alcoholic related, *n* (%)	5486 (25.5)	5451 (25.3)	0.698
RFI, *n* (%)	2871 (13.3)	2830 (13.1)	0.560
PUB, *n* (%)	714 (3.3)	712 (3.3)	0.957
HCC, *n* (%)	5367 (24.9)	5462 (25.4)	0.291
Antiviral drugs, *n* (%)	1321 (6.1)	1385 (6.4)	0.204
Statins, *n* (%)	211 (1.0)	212 (1.0)	0.961
PPIs,*n* (%)	16922 (78.6)	16855 (78.3)	0.432
NSAIDs, *n* (%)	4747 (22.1)	4721 (21.9)	0.762
Metformin, *n* (%)	1308 (6.1)	1272 (5.9)	0.465
Aspirin, *n* (%)	534 (2.5)	517 (2.4)	0.595
Beta-blockers, *n* (%)	4449 (20.7)	4340 (20.2)	0.192
High CCI (≥4), *n* (%)	3426 (15.9)	3503 (16.3)	0.313

PUB: Peptic ulcer bleeding, HCC: Hepatocellular carcinoma, RFI: Renal function impairment, PPIs: Proton pump inhibitors, CCI: Charlson Comorbidity Index, NSAIDs: Nonsteroidal anti-inflammatory drugs

Table 2: Adjusted hazard ratios for mortality in cirrhotic patients with bacterial infections during the 90-day follow-up

Variable	HR	95% CI	*P*
Age	1.01	1.01-1.02	<0.001
Male	1.24	1.19-1.29	<0.001
Poor hepatic reserve	2.10	2.03-2.18	<0.001
Alcoholic related	0.95	0.90-1.00	0.032
RFI	2.17	2.08-2.27	<0.001
PUB	0.98	0.88-1.08	0.635
HCC	2.04	1.96-2.13	<0.001
Antiviral drugs, *n* (%)	1.21	1.14-1.29	<0.001
Statins, *n* (%)	0.69	0.56-0.85	<0.001
PPIs, *n* (%)	0.84	0.81-0.88	<0.001
NSAIDs, *n* (%)	0.90	0.87-0.94	<0.001
Metformin, *n* (%)	0.64	0.58-0.69	<0.001
Aspirin, *n* (%)	0.83	0.74-0.94	0.002
Beta-blockers, *n* (%)	0.75	0.72-0.79	<0.001
High CCI (≥4), *n* (%)	1.45	1.39-1.51	<0.001

PUB: Peptic ulcer bleeding; HCC: Hepatocellular carcinoma; RFI: Renal function impairment, PPI: Proton pump inhibitors; CCI: Charlson Comorbidity Index, NSAIDs: Nonsteroidal anti-inflammatory drugs, HR: Hazard ratio, CI: Confidence interval

Table 3: Adjusted hazard ratios for the effect of the number of complications on mortality in cirrhotic patients with bacterial infections during the 90-day follow-up

	HR	95% CI	*P*
Complications	2.10	2.03-2.18	<0.001
No complications	Reference		
One complication	1.92	1.85-1.99	<0.001
Two complications	2.61	2.47-2.77	<0.001
Three or more complications	3.81	3.18-4.57	<0.001

HR: Hazard ratio, CI: Confidence interval

It has been established that the increased mortality observed in cirrhotic patients with bacterial infections is due to an immunocompromised state. However, it remains difficult to

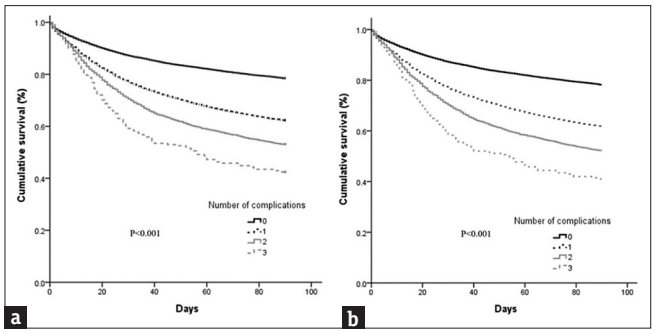

Figure 2: Kaplan–Meier survival analysis for overall survival (a) and liver transplantation-free survival (b) in cirrhotic patients with different numbers of complications during the 90-day follow-up

Table 4: Adjusted hazard ratios for the effect of poor hepatic reserve on mortality in cirrhotic patients with different major bacterial infections during the 90-day follow-up

Variable	HR	95% CI	*P*
Sepsis	1.73	1.64-1.81	<0.001
Pneumonia	2.04	1.90-2.18	<0.001
Urinary tract infection	2.76	2.51-3.03	<0.001
Other bacterial infections	3.31	2.98-3.68	<0.001

HR: Hazard ratio, CI: Confidence interval

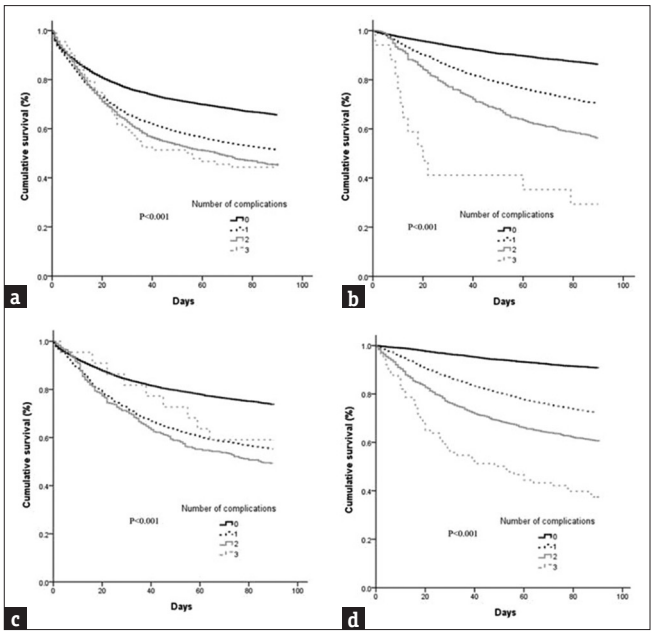

Figure 3: Kaplan–Meier survival analysis for 90-day overall survival in cirrhotic patients with different numbers of complications for different major bacterial infections. (a: Sepsis; b: Urinary tract infection; c: Pneumonia; d: Other bacterial infections)

quantify immune status in clinical practice. Our study provides a simple and useful dataset for evaluating mortality in cirrhotic patients with bacterial infections. We reported that cirrhotic patients with complications who had bacterial infections had a two-fold higher mortality than those without complications. In this study, cirrhotic patients with ascites, SBP, HE, variceal bleeding, or HRS were classified into the poor hepatic reserve group. Patients with poor hepatic reserve are actually in a decompensated status. The high mortality of complicated liver cirrhosis is well documented. Patients with poor liver reserve have a poor immune status, and the mortality related to bacterial infections is usually high [1,20]. The homeostatic role of the liver in the immune response is usually impaired in advanced cirrhosis [21]. Impairment of the immune response is usually correlated with other systemic organ dysfunction, which may increase the risk of mortality in cirrhotic patients with bacterial infections. This can also explain the correlation of poor liver reserve and high morality in cirrhotic patients with bacterial infections. In previous studies, renal function was the most important prognostic factor in patients with and without SBP [22,23]. This is not surprising considering RFI as an important marker for the severity of disease and is associated with sepsis-related mortality. Our study also demonstrated that the risk of mortality increased with the number of complications. In cirrhotic patients with three or more complications, the risk of mortality increased almost four folds compared with those without complications. In the current study, 40.8% of these patients died within 30 days, with a 90-day mortality of about 58%. Physicians should be aware of the high mortality in these patients and try to avoid cirrhotic-related complications during hospitalization. In our subgroup analysis, the effects of poor hepatic reserve were similar with different major kinds of bacterial infections.

Some medications have been associated with the prognosis of patients with liver cirrhosis. In this study, usage of antiviral drugs for HBV, statins, PPI, NSAIDs, metformin, aspirin, and beta-blockers was a prognostic factor related to cirrhosis with bacterial infections. However, some special conditions should be mentioned because sometimes the usage of medication is related to selection bias. In our study, use of antiviral drugs for HBV was a poor prognostic factor in cirrhotic patients with bacterial infections. We do not think that these drugs are harmful for these patients. This is because in Taiwan, antiviral drugs for HBV-related cirrhosis are provided to patients with a high viral load (HBV DNA more than 2000 IU) or those who have jaundice. Antiviral drug users actually have more severe liver cirrhosis. We believe that the effect of anti-viral drugs for HBV-related cirrhosis could not be observed in this short-term follow-up study.

The usage of statins, aspirin, metformin, and beta-blockers had a protective role in liver cirrhosis. This is compatible with previous studies [24-28]. Although there are potential risks of NSAIDs related to renal function impairment and gastrointestinal tract bleeding, some studies have mentioned that they have benefits in decreasing the degree of liver fibrosis and improving hyposensitivity to vasopressin [29,30]. However, we believe that there may have been some selection bias related to NSAID usage in this study. About 83.8% of patients were admitted from physicians' service. Because the risks of renal toxicity and gastrointestinal tract bleeding are well known among physicians in Taiwan, NSAIDs may only be prescribed in less severe liver disease or for relief of fever related to bacterial infections. Both of these descriptions may explain our results in patients with NSAID usage. Similar findings can also be observed in users of beta-blockers. Although beta-blockers are well known for preventing variceal bleeding in liver

cirrhosis, patients with profound septic shock usually do not take them. Even though we performed propensity score matching and regression analysis, some initial selection bias could not be avoided. This is a limitation of these kinds of retrospective population-based studies.

To the best of our knowledge, the current study is the first population-based study to identify the effect of the numbers of cirrhotic-related complications on mortality in cirrhotic patients with different bacterial infections. Nonetheless, there were several limitations in our study. First, it was not possible to identify laboratory data by ICD-9 codes in the database. However, the use of liver cirrhosis stage and the presence of ascites, HE, SBP, HRS, and variceal bleeding were identified in many studies, and the presence of these complications consistently correlates with poor hepatic reserve [31-33]. Second, about 25.4% of cirrhosis in our study was a result of alcohol intake. The etiology of nonalcoholic cirrhosis was not well evaluated in this study due to underestimated coding for chronic hepatitis B and C. However, we evaluated antiviral drugs for HBV which can somewhat correlate with advanced chronic hepatitis B-related liver cirrhosis, and direct antiviral agents for hepatitis C virus were not available in Taiwan during the study period. Finally, the coding accuracy of the diagnosis is the general weakness of this population-based study, and it is a limitation of this dataset. However, about 83.8% of hospitalizations were from physicians' service in our study. This may somewhat enhance the reliability of the discharge diagnoses. Despite these limitations, this nationwide population-based study identified the risk of mortality associated with major complications in cirrhotic patients with bacterial infections. In summary, poor hepatic reserve is associated with a poor prognosis in cirrhotic patients with bacterial infections. The presence of three or more cirrhosis-related complications increases mortality almost four folds.

Acknowledgments

This study is based in part on data from the Taiwan National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, which is managed by National Health Research Institutes (Registration Number: 104359). The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

We appreciate the efforts of Dr. Chen-Chi Tsai in designing this study. Although he is no longer alive, we honor his great achievements in this series of population-based studies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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