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Clinical Research Paper

Association of type 2 diabetes with liver cirrhosis: a nationwide cohort study

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ABSTRACT

Background: The link between the subcategories of liver cirrhosis and type 2 diabetes is not well known. We investigated the association of type 2 diabetes mellitus with alcoholic cirrhosis and cirrhosis without alcohol.

Methods: This nationwide cohort study used the Taiwan National Health Insurance Research Database. Cirrhotic individuals and their matched controls were identified from 2001-2008. In all, 9 313 cirrhotic patients aged 20 years or older were matched by age, sex, and index date with the non-cirrhotic individuals (*n* = 37 252). Cirrhosis was categorized into alcoholic cirrhosis and cirrhosis without alcohol. Type 2 diabetes mellitus was identified from January 2001- December 2011.

Results: The incidence densities (per 1 000 person-months) of type 2 diabetes were as follows: 1.14 (95% CI: 1.09-1.20) in the non-cirrhotic group, 1.88 (CI 1.76-2.01) in patients with cirrhosis, 1.62 (CI 1.48-1.78) in patients with cirrhosis without alcohol, and 2.92 (CI 2.64-3.23) in patients with alcoholic cirrhosis. The adjusted hazards ratio (aHR) for type 2 diabetes mellitus among cirrhotic individuals was 0.774 (CI: 0.715-0.8934). Alcoholic cirrhotic men had a significantly higher risk of type 2 diabetes (aHR 1.182, CI: 1.046-1.335) compared with non-cirrhotic individuals. Increased risks were seen in men (aHR 1.690; CI: 1.455-1.963) and women (aHR 1.715; CI: 1.113-2.645) with alcoholic cirrhosis compared to those with cirrhosis without alcohol.

Conclusions: This study indicates that alcoholic cirrhosis is a significant risk factor for type 2 diabetes mellitus compared with cirrhosis without alcohol.

INTRODUCTION

Diabetes mellitus is a global health issue. Alcoholic liver diseases have been associated with increased risk of type 2 diabetes [1]. The prevalence of diabetes in cirrhosis has been reported at 12.3-57% [2]. Previous publications have reported a high prevalence of liver diseases in diabetic patients and a high prevalence of diabetes in patients with liver disease [3, 4]. Increased risks of diabetes have also been reported in patients with cirrhosis due to hepatitis C (HCV) and alcoholic liver disease but not in patients with cirrhosis due to cholestatic liver disease [1, 4]. In Asia, more than half of the liver cirrhosis burden is linked to hepatitis B (HBV) and hepatitis C [5]. The prevalence of cirrhosis among Taiwanese patients with HBV is reported to be 49% [6]. Up to 30% of cirrhotic patients in Taiwan were seropositive for HBeAg while 73% had a serum HBV DNA level >10000 copies/ml [7]. A previous study including Chinese individuals in Taiwan reported that hepatitis B and C virus infection would act independently and synergistically in the development of liver cirrhosis [8]. Huang and colleagues reported that Taiwanese patients with chronic hepatitis B who develop diabetes are at increased risk of liver cirrhosis and its decompensation over time [9]. The exact incidence of liver cirrhosis especially in individual Asian countries is still

unknown. From 2011-2013, the incidence rates of primary biliary cirrhosis in Korea were respectively 0.84, 0.92 and 0.87 per 100,000 population [10]. About 33,379 patients from 58 nationwide hospitals in Japan were diagnosed with liver cirrhosis in 2008 [11]. The prevalence rates of non-alcoholic liver disease (NAFLD) in South-Pacific Asia range from 12% to 24% in population subgroups and is about 11.4-41% in Taiwan [12]. About 69.4% of patients with NAFLD have been reported with type 2 diabetes mellitus (T2DM) [13]. In a prospective follow-up study including 8 663 men, heavy drinking was associated with a 2-fold increased risk of type 2 diabetes compared with moderate drinking [14]. It is worth mentioning that similar studies have not shown such relationships in women [15, 16].

Liver cirrhosis has been strongly associated with type 2 diabetes [3]. However, the association between T2DM and subcategories of cirrhosis is poorly understood. In this study, liver cirrhosis was categorized into two groups: alcoholic cirrhosis and cirrhosis without alcohol to investigate their association with diabetes mellitus.

MATERIALS AND METHODS

Data source

The data sources were the 2005 and 2010 Longitudinal Health Insurance Databases (LHID 2005 and 2010). These datasets contain de-identified secondary data which have been released to the public for research purposes. This study was exempted from full review by the Institutional Review Board. Informed consents were not applicable.

Study population

The study participants included 1 878 196 enrollees sampled from the LHID 2005 and 2010 (Figure 1). All participants were aged 20 years and older. Newly diagnosed cirrhotic patients and their matched controls (comparison individuals) were identified from January 2001-December 2008 and matched 1:4 by age, sex and index date. The index date was the first date of cirrhosis detection. The event date was the first date of T2DM diagnosis or prescription of antihyperglycemic agents. Censoring occurred in case of death or withdrawal from the study. Patients were defined as having alcoholic cirrhosis if they had one inpatient and/or two outpatient claims with reported ICD-9 CM Code: 571.2. Cirrhosis without alcohol was identified using the ICD-9 CM Code: 571.5, 571.6. Patients were classified as having type 2 diabetes mellitus if they had one one inpatient and/or two outpatient claims with reported ICD-9 CM codes: 250.xx, 790.21, 790.22, 791.5x, A181. Patients were also classified as having T2DM if they were prescribed antihyperglycemic agents (alpha-glucosidase inhibitor, biguanides, insulin, meglitinides, sulfonylureas and thiazolidinediones) from 2001-2011.

Baseline characteristics and statistical analysis

The demographic variables included sex, age, low-income, urbanization, and medications (antihypertensives such as ACE inhibitors, β-blocker and diuretics; antihyperlipidemics such as statins and fibrates as well as antiviral drugs). Co-morbidities included hepatitis B (ICD-9: 070.2, 070.3, V02.61), hepatitis C (ICD-9: 070.41, 070.44, 070.51, 070.54,070.7, V02.62), unspecified hepatitis (ICD-9: 070.9, 571.4, 571.8, 571.9), dyslipidaemia (ICD-9: 272), hypertension (ICD-9: 401-405), COPD (ICD-9: 490-505 506.4), cerebrovascular disease (ICD-9: 430-438), myocardial infarction (ICD-9: 410, 412) and renal disease (ICD-9: 582, 583-583.7 585, 586, 588).

The Chi-square test was used for the nominal variables between cirrhotic and comparison individuals. Pearson Chi-square was used to compare the differences in the distribution of variables between patients with alcoholic cirrhosis and those with cirrhosis without alcohol. A two-tailed t-test was used to compare the mean difference between individuals or groups. The incidence density (per 1 000 person months) of DM and its 95 % confidence interval (95% CI) were calculated. Cox proportional hazard model was used to estimate the hazard ratios (HR) and 95% CI of cirrhosis and other covariates. Because of the high rate of patients with cirrhosis, competing-risk regression was also performed using the Fine and Gray model. Statistical analyses were performed using SAS 9.3 software while a p-value <0.05 was considered as statistically significant.

RESULTS

The final enrollment included 9 313 cirrhotic and 37 252 non-cirrhotic individuals (Figure 1). Table 1 shows the demographic characteristics of the study population. A significant proportion of cirrhotic patients were low-income earners (cirrhotic: 1.81% versus non-cirrhotic: 0.75%) and rural inhabitants (14.39 vs. 10.53%). Cirrhotic individuals also had a higher proportion of hepatitis B (22.33 vs. 2.12%), hepatitis C (16.41 vs. 0.80%), unspecified hepatitis (59.74 vs. 12.76%), dyslipidaemia (16.65 vs. 12.45%), hypertension (33.36 vs. 25.94%), COPD (23.70% vs. 17.97%), cerebrovascular disease (10.32 vs. 7.50%), myocardial infarction (1.12 vs. 0.86%), renal disease (7.61 vs. 3.37%), antihypertensive medications, and antihyperlipidemic agents. The proportion of men with alcoholic cirrhosis was higher than that of those with cirrhosis without alcohol (92.97% vs. 63.34%).

The proportion of participants with alcoholic cirrhosis and cirrhosis without alcohol were as follows; low income (3.56 vs. 1.26%), rural inhabitants (17.07 vs. 13.53%), hepatitis B (14.67 vs. 24.77%), hepatitis C (7.65 vs. 19.20%), unspecified hepatitis (55.09 vs. 61.23%), hypertension (23.43 vs. 36.52%), COPD (16.05 vs. 26.13%), cerebrovascular disease (6.14 vs. 11.65%), and renal disease (8.88 vs. 3.65%). In general, 2 315 cirrhotic and 7 289 non-cirrhotic individuals were diagnosed with T2DM from 2001-2010. Among the cirrhotic patients who were newly diagnosed with DM, 1 562 had alcoholic cirrhosis while 753 had cirrhosis without alcohol. The incidence density (per 1 000 person months) of T2DM was 1.88 (1.76-2.01) for individuals with cirrhosis, 1.62 (1.48-1.78) for those with cirrhosis without alcohol, 2.92 (CI 2.64-3.23) for those with alcoholic cirrhosis, and 1.14 (CI: 1.09-1.20) for the comparison individuals (2001-2011). The adjusted HR for T2DM among cirrhotic patients was 0.774 (CI 0.715-0.838) compared to non-cirrhotic individuals (Table 2). In addition, unspecified viral hepatitis was found to be a significant risk factor for T2DM (aHR 1.233, CI 1.147-1.326). However, the hazard ratio was 0.807 (CI 0.711-0.915) in patients with HBV. Compared with the non-cirrhotic individuals, the hazard ratios for T2DM were 1.182 (CI 1.046-1.335) in men and 0.889 (CI 0.601-1.345) in women with alcoholic cirrhosis (Table 3). Those of men and women with cirrhosis without alcohol were 0.723 (CI 0.645-0.810) and 0.549 (CI 0.469-0.644), respectively. Table 4 shows the adjusted hazard ratios for T2DM in patients with alcoholic cirrhosis and cirrhosis without alcohol as the reference group. The hazards ratios were 1.929 (CI: 1.742-2.136) and 1.787 (CI 1.339-2.383) for the alcoholic cirrhotic men and women, respectively.

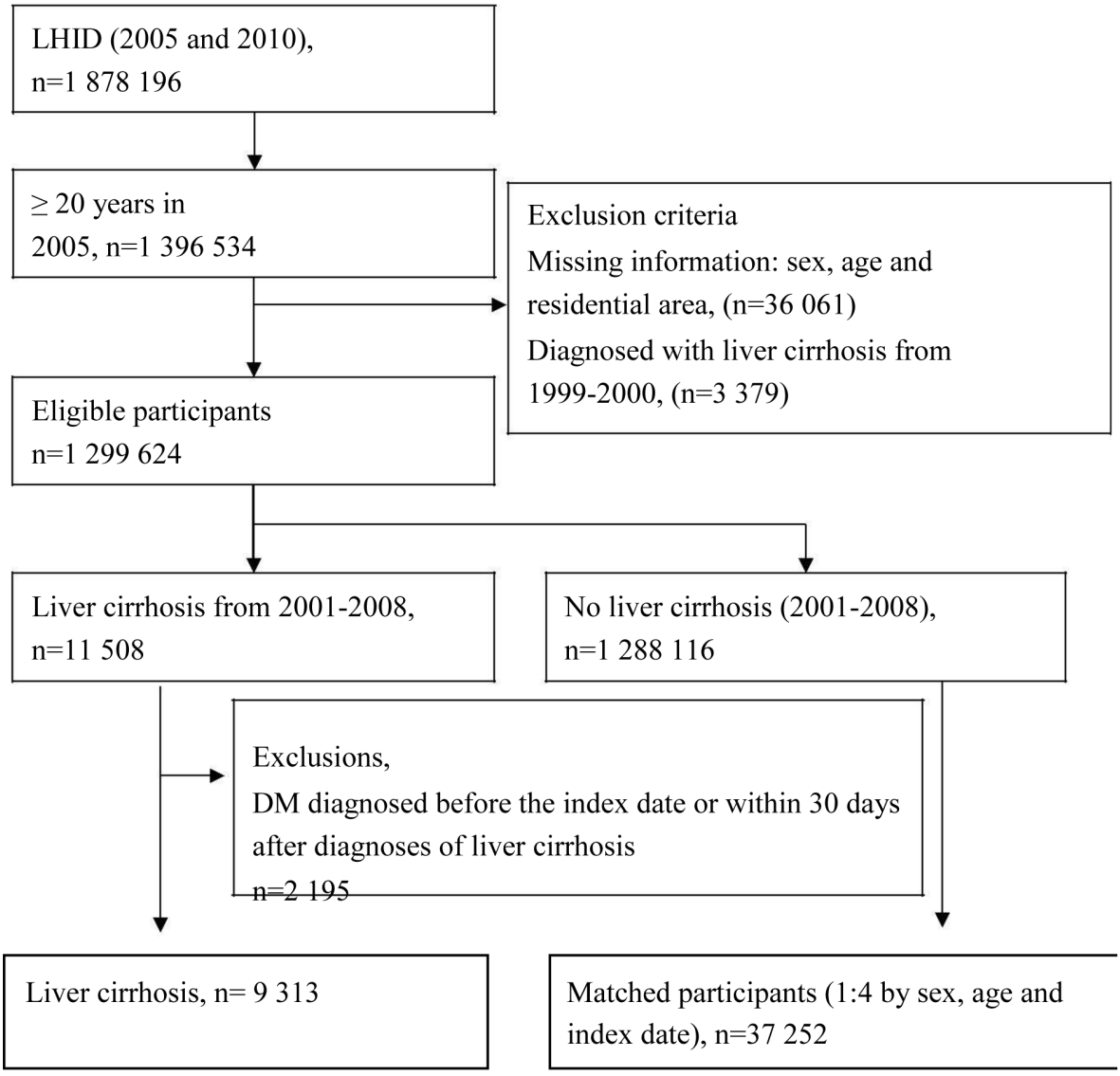

Figure 1: Flowchart of the study participants.

Table 1: Basic characteristics of the study participants

	Control individuals	Cirrhotic individuals		
	No cirrhosis (n = 37 252)	All[☒] (9 313)	Nonalcoholic n = 7 064	Alcoholic n = 2 249
Sex, n (%)[#]				
Male	26 260 (70.49)	6 565 (70.49)	4 474 (63.34)	2 091 (92.97)
Female	10 992 (29.51)	2 748 (29.51)	2 590 (36.66)	158 (7.03)
Age in 2005 (Mean±SD)	54.49±14.92	54.49±14.92	56.87±15.06	47±11.65
Low-income, n (%)[*,#]				
No	36 972 (99.25)	9 144 (98.19)	6 975 (98.74)	2 169 (96.44)
Yes	280 (0.75)	169 (1.81)	89 (1.26)	80 (3.56)
Residents, n (%)[*,#]				
Urban	21 729 (58.33)	4 913 (52.75)	3 823 (54.12)	1 090 (48.47)
Sub-urban	11 601 (31.14)	3 060 (32.86)	2 285 (32.35)	775 (34.46)
Rural	3 922 (10.53)	1 340 (14.39)	956 (13.53)	384 (17.07)
Comorbidity, n (%)				
Hepatitis B[*,#]	790 (2.12)	2 080 (22.33)	1 750 (24.77)	330 (14.67)
Hepatitis C[*,#]	298 (0.80)	1 528 (16.41)	1 356 (19.2)	172 (7.65)
Unspecified hepatitis[*,#]	4 753 (12.76)	5 564 (59.74)	4 325 (61.23)	1 239 (55.09)
Dyslipidemia[*]	4 638 (12.45)	1 551 (16.65)	1 192 (16.87)	359 (15.96)
Hypertension[*,#]	9 662 (25.94)	3 107 (33.36)	2 580 (36.52)	527 (23.43)
COPD[*,#]	6 695 (17.97)	2 207 (23.7)	1 846 (26.13)	361 (16.05)
Cerebrovascular disease[*,#]	2 795 (7.50)	961 (10.32)	823 (11.65)	138 (6.14)
Myocardial infarction[*]	322 (0.86)	104 (1.12)	85 (1.2)	19 (0.84)
Renal disease[*,#]	1 257 (3.37)	709 (7.61)	627 (8.88)	82 (3.65)

[☒]Included alcoholic cirrhosis and cirrhosis without alcohol
*Significantly different between cirrhotic and comparison patients, $p < 0.05$
#Significantly different between patients with alcoholic cirrhosis and cirrhosis without alcohol $p < 0.05$

DISCUSSION

In this large nationwide cohort study, a positive association was found between alcoholic cirrhosis as a risk factor for the development of type 2 diabetes. Previous studies have reported significant proportions of cirrhotic patients with diabetes [17-21]. Nonetheless, cirrhosis was not analyzed by subgroups. In a case-control study, 47% of patients with cryptogenic cirrhosis had T2DM compared to 22% of the controls [22]. Another study showed that the risks of T2DM were 7.6 and 5.3 times higher in hepatitis C and alcoholic cirrhosis, respectively [1]. However, only a few variables were considered during analysis.

In this study, when categorized by sex, a higher risk was found particularly in men with alcoholic cirrhosis. However, after including cirrhosis subgroups in the competing risk analysis, T2DM risk was found to be significantly higher in both men and women. Heavy amounts of alcohol have shown direct diabetogenic effects [23]. One study has reported a significant association between alcohol intake and T2DM with a relative risk of 1.5 per 137.8 g of alcohol intake in the past week [15]. Other studies found that moderate alcohol consumption was negatively correlated with T2DM even with an intake beyond 48 g / day [24]. Alcohol consumption has been inversely associated with fasting and post-load insulin levels [25, 26]. It has also been reported that excess alcohol may reduce insulin-mediated glucose uptake [21] and can cause injury to pancreatic islet β-cells resulting in type 2 diabetes mellitus [27]. In addition, alcohol can also cause fatty liver disease leading to dysfunction of the mitochondria, thereby increasing the risk of T2DM [28, 29].

Table 2: Hazards ratios and 95% confidence interval of type 2 diabetes among patients with liver cirrhosis

	aHR* (95% CI)	*p*-value
Cirrhosis (Reference: Comparison group)		
Cirrhotic individuals	0.774(0.715-0.838)	<.0001
Low-income (Reference: No)		
Yes	1.432(1.138-1.803)	0.0022
Residents (Reference: Urban)		
Sub-urban	0.994(0.913-1.082)	0.8934
Rural	0.958(0.904-1.015)	0.1442
Comorbidity (Reference: No)		
Hepatitis B	0.807(0.711-0.915)	0.0008
Hepatitis C	0.904(0.771-1.060)	0.2121
Unspecified hepatitis	1.233(1.147-1.326)	<.0001
Dyslipidemia	1.650(1.519-1.792)	<.0001
Hypertension	1.732(1.602-1.873)	<.0001
COPD	1.111(1.036-1.192)	0.0033
Cerebrovascular disease	0.958(0.851-1.078)	0.4764
Myocardial infarction	1.203(0.855-1.691)	0.2886
Renal disease	1.176(1.020-1.357)	0.0257

Abbreviation: CI, confidence interval, COPD, chronic obstructive pulmonary disease.
* aHR represented adjusted hazard ratios: adjusted for low-income, residents, comorbidity, antihypertensive, antihyperlipidemics and antiviral drugs

Table 3: Hazard ratios and 95% confidence intervals of type 2 diabetes mellitus associated with cirrhosis and covariates in men and women

	Male		Female	
	aHR* (95% CI)	*p*-value	aHR* (95% CI)	*p*-value
Cirrhosis (Reference: No cirrhosis)				
Cirrhosis without alcohol	0.723(0.645-0.810)	<.0001	0.549(0.469-0.644)	<.0001
Alcoholic	1.182(1.046-1.335)	0.0072	0.899(0.601-1.345)	0.6042
Low income (Reference: No)				
Yes	1.285(0.992-1.666)	0.0577	1.582(0.954-2.625)	0.0756
Residents (Reference: Urban)				
Sub-urban	0.949(0.885-1.017)	0.1402	0.973(0.876-1.079)	0.6022
Rural	1.004(0.907-1.112)	0.9355	0.935(0.803-1.088)	0.3868
Comorbidity (Reference: No)				
Hepatitis B	0.793(0.684-0.919)	0.0020	0.979(0.763-1.255)	0.8653
Hepatitis C	1.022(0.833-1.254)	0.8323	0.904(0.699-1.168)	0.4394
Unspecified hepatitis	1.215(1.114-1.325)	<.0001	1.278(1.121-1.457)	0.0002
Dyslipidemia	1.691(1.523-1.877)	<.0001	1.531(1.336-1.755)	<.0001
Hypertension	1.708(1.547-1.884)	<.0001	1.753(1.541-1.993)	<.0001
COPD	1.092(1.001-1.192)	0.047	1.170(1.039-1.317)	0.0094
Cerebrovascular disease	0.946(0.813-1.101)	0.4745	1.002(0.830-1.209)	0.9838
Myocardial infarction	0.896(0.566-1.419)	0.6402	2.250(1.367-3.704)	0.0014
Renal disease	1.227(1.027-1.465)	0.0241	1.163(0.914-1.481)	0.2195

Abbreviation: CI, confidence interval, COPD, chronic obstructive pulmonary disease.
* aHR represented adjusted hazard ratios: adjusted for low-income, residents, comorbidity, antihypertensive, antihyperlipidemics and antiviral drugs

Table 4: Adjusted hazard ratios of type 2 diabetes mellitus in patients with alcoholic cirrhosis and in patients with cirrhosis without alcohol as the reference group

	Male		Female	
	aHR* (95% CI)	*p*-value	aHR* (95% CI)	*p*-value
Cirrhosis (Reference: cirrhosis without alcohol)				
Alcoholic	1.690(1.455-1.963)	<.0001	1.715(1.113-2.645)	0.0146
Low income (Reference: No)				
Yes	1.157(0.763-1.754)	0.4918	1.643(0.544-4.968)	0.3788
Residents (ref: Urban)				
Sub-urban	0.916(0.782-1.073)	0.2794	0.866(0.665-1.129)	0.2888
Rural	0.953(0.773-1.176)	0.6561	0.839(0.579-1.216)	0.3543
Comorbidity (Reference: No)				
Hepatitis B	0.877(0.729-1.054)	0.1620	0.940(0.671-1.316)	0.7177
Hepatitis C	1.048(0.824-1.333)	0.7043	1.010(0.741-1.377)	0.9501
Unspecified hepatitis	1.148(0.989-1.332)	0.0698	1.217(0.933-1.588)	0.1483
Dyslipidemia	1.312(1.077-1.597)	0.0069	1.632(1.200-2.221)	0.0018
Hypertension	1.735(1.429-2.106)	<.0001	1.571(1.160-2.127)	0.0035
COPD	0.992(0.823-1.196)	0.9301	1.144(0.861-1.519)	0.3538
Cerebrovascular disease	0.967(0.717-1.302)	0.823	0.882(0.559-1.393)	0.5914
Myocardial infarction	0.626(0.235-1.663)	0.3471	2.325(0.721-7.502)	0.1579
Renal disease	1.144(0.819-1.597)	0.4312	1.266(0.818-1.961)	0.2904

Abbreviation: CI, confidence interval, COPD, chronic obstructive pulmonary disease.
* aHR represented adjusted hazard ratios: adjusted for low-income, residents, comorbidity, antihypertensive, antihyperlipidemics and antiviral drugs

Participants who used higher doses of antihypertensive and antihyperlipidemic agents were also found with higher risks of T2DM when compared with non-users. Past studies have associated diuretics and β-blocker with increased risk of diabetes [26]. When analyzed by sex, we found that long-term use of ACEI, β-blocker, diuretic and fibrates women were positively associated with T2DM in both men and women. Therefore, it was important that such confounders be adjusted.

We also found a lower risk of T2DM among patients suffering from HBV. The HR was lower but not significant for HCV. However, unspecified hepatitis was significantly associated with increased risk of T2DM. Previous studies have reported diverging conclusions on the association between HCV and T2DM [30]. Results from a meta-analysis indicate that HBV itself may not be pro-diabetic [31]. Among the cirrhotic individuals in this study, about 22.33 % had HBV. However, whether all the cases of cirrhosis were HBV-derived cannot be fully explained.

Hepatogenous diabetes is a common complication of liver cirrhosis [32, 33]. As noted earlier, recent studies have reported increased risk of diabetes in patients with liver cirrhosis due to hepatitis C and alcoholic liver disease. However, no increased risk was found in patients with liver cirrhosis due to cholestatic liver disease [1]. Nonalcoholic fatty liver disease [34], chronic viral hepatitis [35, 36], hemochromatosis [37], alcoholic liver disease [1, 15] and cirrhosis [27] have been associated with T2DM. However, their relationships may be independent of the lifestyle risk factors and other metabolic diseases [15].

Our study made use of a large sample size with a longer period of follow-up. However, it was not without limitations. First, the severity of cirrhosis could not be determined. Second, there was a dearth of information about lipid and blood glucose levels. Lastly, information on alcohol intake was not available. Alcoholic cirrhosis was defined based on the ICD-9 CM codes, and hence information bias cannot be ruled out.

CONCLUSIONS

In summary, patients with alcoholic cirrhosis were found with a higher risk of type 2 diabetes mellitus compared to those with cirrhosis without alcohol. Monitoring of blood glucose levels is recommended for patients with cirrhosis.

Author contributions

PHH and YPL designed the study, managed the literature searches and summarized previous related work. JYH and ONN analyzed and interpreted the data. PHH, CCL and CCH wrote the manuscript. All authors critically reviewed and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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