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Alcohol use disorders associated with an increased risk of mesenteric ischemia: A nationwide cohort study

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ABSTRACT

Background: To evaluate the relationship of patients with a history of alcohol use disorders (AUD) and its diagnostic categories with risk of subsequent mesenteric ischemia in Taiwan.
Methods: A nationwide population-based cohort study was conducted using data from the Taiwan's National Health Insurance Research Database. We identified 73,583 patients hospitalized for AUD between 2001 and 2010, and matched each case with four comparison patients based on age, gender, Charlson comorbidity index, and the index date. Cox proportional hazard models were used to evaluate the risk of mesenteric ischemia between the AUD and non-AUD cohorts. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated.
Results: Patients with AUD exhibited a significantly increased risk of developing mesenteric ischemia (HR = 2.25; 95% CI 1.92–2.64) compared with those with non-AUD after adjustment for patient sociodemographic, coexisting comorbid conditions, and hospital characteristics. Furthermore, a 2.29- and 2.17-fold higher risk of mesenteric ischemia was observed in patients with alcohol abuse/dependence (HR = 2.29; 95% CI 1.94–2.71) and alcoholic psychosis (HR = 2.17; 95% CI 1.72–2.73), respectively, than in non-AUD comparisons after covariate adjustment.
Conclusions: This study confirmed that the risk of mesenteric ischemia was significantly higher among patients with different diagnostic categories of AUD, particularly for those with alcohol abuse/dependence.

1. Introduction

Alcohol use disorders (AUD), including alcohol abuse and dependence, can result in immediate and long-term health issues (Connor et al., 2016; Griswold et al., 2018). Excessive alcohol exposure may lead to an increased susceptibility to the progression of alcohol-induced liver diseases (Mackenbach et al., 2015), alcoholic psychosis (Jordaan and Emsley, 2014), gastrointestinal (Giesen et al., 2015), and other diseases (Moss and Burnham, 2006). Alcohol use remains a major public health hazard with an estimated 2.8 million deaths worldwide in 2016, which accounted for 6.2% of alcohol use-attributable deaths among males and 1.7% among females (Griswold et al., 2018). In addition, 27% of male deaths and 40% of female deaths resulted from harmful alcohol use in United States, and in Taiwan the proportion of deaths attributable to alcohol use was 10% for men and 1.6% for women (Griswold et al., 2018).

Heavy alcohol consumption is one of the leading causes of emergency department (ED) visits (D'Onofrio et al., 2012; Smith et al., 2015). Individuals with AUD have an increased risk of hospital admissions for liver, cardiovascular, digestive, infectious (Schwarzinger et al., 2018), and kidney diseases (Pan et al., 2018). In addition, alcohol abuse may cause a marked alteration of the gastrointestinal tract

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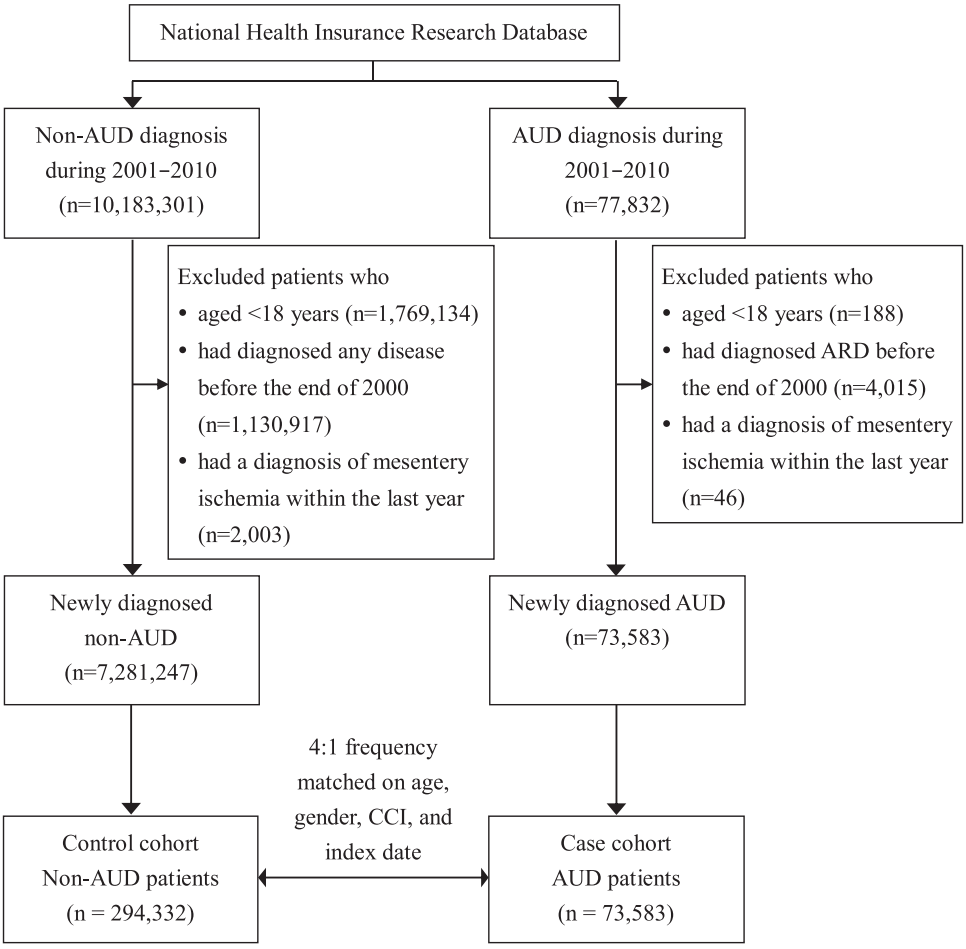

Fig. 1. Flow diagram of the sample selection.

(Molina et al., 2014).

Mesenteric ischemia is a gastrointestinal vascular emergency, accounting for 0.2% of all hospital admissions to the ED (Bala et al., 2017), but has an extremely high fatality rate of 60–80% (El Farargy et al., 2017; Florian et al., 2010). A previous Taiwanese study reported the incidence of mesenteric ischemia in patients with alcoholic intoxication is estimated at 0.06% (Wei et al., 2016). Mesenteric ischemia could present as abdominal pain, and its symptoms range from mild, nonspecific abdominal discomfort to severe pain (Reginelli et al., 2013).

To our knowledge, only a few studies have investigated the effect of heavy alcohol abuse on the extensive bowel ischemia (Lee et al., 2012) and mesenteric ischemia (Wei et al., 2016); however, the association between the symptoms of alcohol addiction and mesenteric ischemia remains unclear. We hypothesized that patients with different symptoms of AUD may have a differential risk of mesenteric ischemia development than those without AUD. Therefore, this study aimed to assess the association of patients with AUD and its symptoms with risk of subsequent mesenteric ischemia in Taiwan.

2. Materials and methods

2.1. Data source

The National Health Insurance (NHI) program in Taiwan is a mandatory universal health insurance that covers nearly 99% of the 23 million person population. The data for this retrospective population-based cohort study were obtained from the Taiwan National Health Insurance Research Database (NHIRD) for hospital admissions between 2000 and 2013. All the datasets included the inpatient expenditures by admissions, registry for beneficiaries, and registry for contracted medical facilities. All variables were linked using the unique personal or hospital identification number that was de-identified and encrypted by the National Health Research Institutes (NHRI) to protect privacy and assure confidentiality. The diagnostic and procedural codes were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding system. The National Health Insurance Administration (NHIA) performed quarterly expert reviews of ambulatory and inpatient records randomly to ensure the accuracy of the claim files. The Institutional Review Board of Kaohsiung Armed Forces General Hospital (KAFGH) approved this study (Approval No. KAFGH 105-043).

2.2. Study sample

We identified patients who were diagnosed with alcoholic psychosis (ICD-9-CM code 291.x) and alcohol abuse/dependence (303.x or 305.0) (briefly named as alcohol use disorders [AUD]) between 2001 and 2010. The index date was defined as the date of the first diagnosis. The control cohort comprised patients without AUD and was frequency matched by age, gender, and Charlson comorbidity index (CCI) at a 1:4 ratio. Comparison cohorts were randomly selected from the population using the frequency matching method by age, gender, and CCI. Frequency matching ensures that AUD and non-AUD cohorts have the same distributions over categorical levels of potential confounders. The index date for control patients was assigned as the same date as those of the matched cases. AUD patients aged less than 18 years and those who had been diagnosed with AUD prior to the end of 2000 and who had a

Table 1
Baseline characteristics of the study population.

	AUD (N = 73,583)		Non-AUD (N = 294,332)		P-value
Age at disease diagnosis (years), mean (SD)	44.5	(12.4)	44.5	(12.4)	1.000
< 20	304	(0.4)	1,216	(0.4)	1.000
20–39	26,978	(36.7)	107,912	(36.7)	
40–59	37,615	(51.1)	150,460	(51.1)	
≥60	8,686	(11.8)	34,744	(11.8)	
Gender					1.000
Female	7,066	(9.6)	28,264	(9.6)	
Male	66,517	(90.4)	266,068	(90.4)	
CCI score					1.000
0	51,420	(69.9)	205,680	(69.9)	
1	14,294	(19.4)	57,176	(19.4)	
≥2	7,869	(10.7)	31,476	(10.7)	
Insurance premium (TWD)					< 0.001
≥45,801	2,319	(3.2)	35,239	(12.0)	
28,801–45,800	10,605	(14.4)	50,619	(17.2)	
15,841–28,800	37,461	(50.9)	87,677	(29.8)	
≤15,840	8,281	(11.2)	18,495	(6.3)	
Dependents	14,917	(20.3)	102,302	(34.7)	
Low income household					< 0.001
No	70,898	(96.3)	291,221	(98.9)	
Yes	2,685	(3.7)	3,111	(1.1)	
Comorbidity					
Hypertension	6,944	(9.4)	33,131	(11.3)	< 0.001
Diabetes mellitus	6,175	(8.4)	33,400	(11.4)	< 0.001
Hyperlipidemia	2,962	(4.0)	10,924	(3.7)	< 0.001
Stroke	1,308	(1.8)	5,600	(1.9)	0.026
Ischemic heart disease	942	(1.3)	7,885	(2.7)	< 0.001
Congestive heart failure	387	(0.5)	3,079	(1.0)	< 0.001
Peripheral artery disease	60	(0.1)	600	(0.2)	< 0.001
COPD	768	(1.0)	3,344	(1.1)	0.033
Obesity	27	(0.05)	249	(0.1)	< 0.001
Alcoholic liver damage	6,376	(8.7)	1,896	(0.6)	< 0.001
Hospital accreditation level					< 0.001
Medical center	20,737	(28.2)	99,099	(33.7)	
Regional hospital	36,407	(49.5)	124,022	(42.1)	
District hospital	16,439	(22.3)	71,211	(24.2)	
Hospital teaching status					< 0.001
Yes	63,620	(86.5)	246,948	(83.9)	
No	9,963	(13.5)	47,384	(16.1)	
Hospital geographic location					< 0.001
Taipei	20,381	(27.7)	87,388	(29.7)	
Northern	8,872	(12.1)	46,017	(15.6)	
Central	15,918	(21.6)	58,960	(20.0)	
Southern	9,508	(12.9)	41,934	(14.3)	
Kao-Ping	15,485	(21.0)	52,129	(17.7)	
Eastern	3,419	(4.7)	7,904	(2.7)	
Medical specialty					< 0.001
Internal medicine	36,229	(49.2)	65,002	(22.1)	
Surgery	7,482	(10.2)	67,480	(22.9)	
Psychiatry	13,885	(18.9)	3,638	(1.2)	
Other	15,987	(21.7)	158,212	(53.8)	
Follow-up period (years), mean (SD)	8.3	(2.9)	8.6	(2.9)	< 0.001

Note: AUD = alcohol use disorders; CCI = Charlson comorbidity index; COPD = chronic obstructive pulmonary disease; SD = standard deviation; TWD = Taiwan dollars.

diagnosis of mesenteric ischemia (557.0, 557.1 or 557.9) within the last year were excluded. Similarly, non-AUD patients aged less than 18 years, and those who had been diagnosed with a disease before the end of 2000 and who had a diagnosis of mesenteric ischemia within the last year were also excluded. The outcome of interest was the occurrence of a mesenteric ischemia event. The follow-up period for both cohorts was from the index date until the date of mesenteric ischemia or the end date of this study (December 31, 2013). A flow diagram of the sample selection is illustrated in Fig. 1.

2.3. Measurement

The primary independent variable was whether or not the patient had a history of AUD. Then, in our analysis, the AUD group was further divided into two categories according to the diagnostic categories of alcohol addictions: alcoholic psychosis and alcohol abuse/dependence.

2.3.1. Covariates

The following covariates were evaluated: characteristics of patients (including age, gender, insurance premium, low-income household status, CCI, other comorbidities, and medical specialty) and hospitals (including accreditation level, teaching status, and geographic location).

Age of patients was divided into four groups: < 20, 20–39, 40–59, and ≥60 years. The monthly insurance premium (as a proxy for socioeconomic status) of an individual was determined by personal salary, and was divided into five groups (≥Taiwan dollars (TWD) 45,801, 28,801–45,800, 15,841–28,800, ≤15,840, and dependents). The dependent group did not have a fixed salary, such as students, housewives, and those dependent on family members. The overall comorbidity burden for each patient was measured by the Deyo-modified CCI scores using ICD-9-CM diagnosis codes in the claims data (Deyo et al., 1992), and the score was divided into three groups (0, 1, and ≥2); this method has been applied by other authors (Kwak et al., 2017). In addition, based on the previous literature (Pan et al., 2018; Wei et al., 2016), the comorbidities were determined by the following ICD-9-CM codes: diabetes mellitus (DM; 250); hyperlipidemia (272); obesity (278); hypertension (401–405); ischemic heart disease (IHD; 410–414); congestive heart failure (CHF; 428); stroke (430–438); peripheral artery disease (PAD; 440–444); chronic obstructive pulmonary disease (COPD; 491, 492 or 496), and alcoholic liver damage (ALD; 571.0, 571.1 or 571.3).

Hospital accreditation in Taiwan was accredited by the Taiwan Joint Commission on Hospital Accreditation, and was divided into medical centers, regional and local hospitals. Geographic locations were divided into six regions (Taipei, northern, central, southern, Kao-Ping, and eastern) based on the NHIA's administrative branches.

2.4. Statistical analysis

All statistical analyses were performed using the SAS version 9.4 (SAS Institute, Cary, NC, USA). A 1:4 frequency matching method was performed to reduce the potential selection bias and to increase the statistical power between the AUD and non-AUD cohorts; this method was also adopted by other researchers (Wei et al., 2016). After frequency matching, the distributions of age, gender and CCI were balanced between the two cohorts. Distribution of patient socio-demographics, comorbidities, and hospital characteristics between the two cohorts were examined using Chi-square or Fisher's exact-tests for categorical variables, and Student's *t*-test for continuous variables, respectively. The incidence rate of developing mesenteric ischemia was calculated by the number of mesenteric ischemia events divided by the sum of person-years of follow-up until the event (per 10,000 person-years). In addition, incidence rate ratios (IRR) with 95% confidence intervals (CI) were calculated for overall incidence and for subgroup comparisons, stratified by AUD cause, age, gender, insurance premium, low income household, and comorbidity. Meanwhile, monthly insurance premiums and low-income household status were tested for collinearity with mesenteric ischemia using the condition indices and variance inflation factor (VIF).

The cumulative incidence of mesenteric ischemia for AUD (including by diagnostic categories) and non-AUD cohorts was estimated using the Kaplan-Meier method. Differences in the development of mesenteric ischemia between groups were tested using the log-rank test. In addition, exposure to mesenteric ischemia was defined as time-varying variables to account for changes in exposure during the follow-

up period after initiation. Univariate and multivariate Cox proportional hazard models with the robust sandwich variance estimator were used to evaluate AUD subgroup and other factors associated with developing mesenteric ischemia. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated. The statistical significance threshold was set at $P < 0.05$.

3. Results

Table 1 shows the basic characteristics of the study population. A total of 73,583 patients with AUD and 294,332 patients with non-AUD were identified during the period of 2001–2010. After matching for age at disease diagnosis, gender, and CCI score, the populations in the two groups were similar. The mean age of the study population was 44.5 ± 12.4 years, with a higher proportion of 40–59-year-old patients. Approximately 90.4% and 69.9% of patients with AUD were men and had a CCI score of 0, respectively. Nearly 51% of AUD patients had monthly insurance premiums of TWD 15,841–28,800, whereas 34.7% of AUD patients belonged to dependent insurance premium group ($P < 0.001$). In addition, 3.7% of AUD patients were low income household compared with 1.1% of non-AUD patients ($P < 0.001$). The results of condition index values ranged between 0.97 and 1.03, and the highest VIF was 1.00, indicating no significant collinearity was found between the monthly insurance premiums and low-income households. AUD patients experienced a higher proportion of hyperlipidemia and ALD, whereas non-AUD patients had a greater percentage of hypertension, DM, stroke, IHD, CHF, PAD, COPD, and obesity. In terms of hospital characteristics, AUD patients were more likely than non-AUD patients to be treated at regional hospitals with teaching status located in Central and Kao-Ping regions. In addition, 49.2% and 18.9% of AUD patients were hospitalized in the internal medicine and psychiatry departments of the hospitals compared with 22.1% and 1.2% of non-AUD patients, respectively ($P < 0.001$). The mean (± standard deviation) follow-up periods were 8.3 (± 2.9) years in AUD patients (including 8.1 years in those with alcoholic psychosis; 8.4 years in those with alcohol abuse/dependence) and 8.6 (± 2.9) years in non-AUD patients (Table 1). The results of Kaplan-Meier analysis showed that the AUD cohort had a greater cumulative incidence of mesenteric ischemia than the non-AUD cohort (log-rank test, $P < 0.001$) (Fig. 1a). In addition, compared with non-AUD patients, patients with alcohol abuse/dependence experienced the highest cumulative incidence of mesenteric ischemia, followed by those with alcoholic psychosis (log-rank test, $P < 0.001$) (Fig. 1b).

The incidence of mesenteric ischemia in the AUD cohort was 4.97 per 10,000 person-years compared with 2.05 per 10,000 person-years in the non-AUD cohort (IRR = 2.42; 95% CI 1.97–2.96) (Table 2). In the subgroup of AUD, 4.57 and 5.24 per 10,000 person-years were in the patients with alcoholic psychosis (IRR = 2.23; 95% CI 1.82–2.73) and those with alcohol abuse/dependence (IRR = 2.55; 95% CI 2.08–3.12) than those with non-AUD, respectively. The IRR of mesenteric ischemia was 4.25 (95% CI 3.46–5.21), 2.52 (95% CI 2.05–3.09), and 1.44 (95% CI 1.18–1.77) for AUD patients in comparison with those with non-AUD aged 20–39, 40–59, and ≥60 years, respectively. Compared with the non-AUD cohort, patients of AUD had an increased IRR of mesenteric ischemia in men (IRR = 1.60; 95% CI 1.31–1.97) and in women (IRR = 2.49; 95% CI 2.03–3.05). The highest IRR of mesenteric ischemia in AUD patients with a monthly insurance premium of ≥ TWD 45,801 (IRR = 4.00; 95% CI 3.26–4.91), whereas the lowest IRR in those with ≤15,840 (IRR = 1.27; 95% CI 1.04–1.56). In addition, AUD patients had a greater IRR of mesenteric ischemia than non-AUD cohort in subjects with low income household (IRR = 1.24; 95% CI 1.01–1.52) and at least one comorbidity (IRR = 1.68; 95% CI 1.37–2.06), respectively (Table 2).

The univariate analysis showed that compared with patients without AUD, patients with AUD had a greater risk of developing mesenteric ischemia (HR = 2.41; 95% CI = 2.09–2.78). The mesenteric ischemia risk was the highest in patients with alcohol abuse/dependence (HR = 2.55; 95% CI = 2.19–2.96), followed by those with alcoholic psychosis (HR = 2.22; 95% CI = 1.78–2.77). In addition, patient's age at diagnosis, gender, monthly insurance premium, low income household, CCI score, coexisting comorbidities, and medical specialties were significantly predictor factors for mesenteric ischemia (Table 3).

The multivariate analysis indicated that after adjustment for patient sociodemographic, coexisting comorbidities, and hospital characteristics, patients with AUD exhibited a significantly higher risk of mesenteric ischemia (HR = 2.25; 95% CI = 1.92–2.64) than those without AUD (Table 3). A 2.29- and 2.17-fold higher risk of mesenteric ischemia was observed in patients with alcohol abuse/dependence (HR = 2.29; 95% CI = 1.94–2.71) and alcoholic psychosis (HR = 2.17; 95% CI = 1.72–2.73) than in non-AUD comparisons after adjustment, respectively. In addition, patients aged ≥60 years (HR = 3.47; 95% CI = 2.80–4.30) and with a monthly insurance premium of ≤ 15,840 TWD (HR = 1.29; 95% CI = 1.05–1.60), a CCI score of ≥2 (HR = 1.54; 95% CI = 1.20–1.98), having coexisting hypertension (HR = 1.35; 95% CI = 1.13–1.62), IHD (HR = 1.54; 95% CI = 1.08–2.20), and ALD (HR = 1.48; 95% CI = 1.06–2.07) had a significantly increased risk of mesenteric ischemia than their counterparts (Fig. 2).

4. Discussion

This nationwide cohort study evaluated the association between patients with a history of AUD and subgroup with risk of mesenteric ischemia during the 13-year period. We found that AUD patients experienced a 2.25-fold higher risk of developing mesenteric ischemia than those who did not suffer with AUD, even after adjusting for sociodemographic, comorbidities, and hospital characteristics. These findings were consistent with those of previous studies (Lee et al., 2012; Wei et al., 2016) on patients with heavy alcohol consumption. However, this study did not select a comparable group of patients with no level of alcohol intoxication as a reference to compare the disease severity at baseline (Wei et al., 2016).

Excessive alcohol consumption and related disorders resulted in the generation of alcohol-induced liver diseases (Heslin et al., 2017; Mackenbach et al., 2015) that may contribute to the increase in alcoholic liver damage (Huang et al., 2017). This present study indicated that the AUD cohort had higher rates of preexisting hyperlipidemia and alcoholic liver damage than the non-AUD cohort. In addition, abdominal pain was a common complaint in patients with a previous history of AUD presenting to the ED (Caulfield et al., 2018; Wei et al., 2016). Abdominal pain in such AUD patients may have an association with subsequent development of mesenteric ischemia. Therefore, the higher incidence of mesenteric ischemia may be as a result of the increase in AUD and alcohol-induced liver diseases.

Furthermore, the greater risk of mesenteric ischemia may be due to the increase in comorbidities. In our study, the risk of mesenteric ischemia increased in patients with a higher CCI score after adjustment. In addition, other comorbidities such as hypertension, ischemic heart disease, and alcoholic liver damage had a significantly higher risk of mesenteric ischemia (Amin-Esmaeili et al., 2017; Wei et al., 2016). Although the complex pathogenesis of mesenteric ischemia is still not fully understood, AUD patients with accompanying comorbidities may present a critical risk factor for development of mesenteric ischemia, which may cause increased mortality and morbidity.

Moreover, we further assessed the risk associated with mesenteric ischemia events for different diagnostic categories of AUD. Compared with non-AUD patients, the greatest risk of developing mesenteric ischemia was found among patients with alcohol abuse/dependence, followed by those with alcoholic psychosis after adjustment for relevant covariates. Prior research reported that alcohol intoxication may be involved in alcoholic psychosis and alcoholic encephalopathy (Kong et al., 2014). In addition, a study found that persons with chronic

Table 2
Incidence and incidence rate ratio of mesentery ischemia stratified by alcohol use disorder (AUD) group, age, gender, Insurance premium, low income household, and comorbidity.

Variable	Alcohol use disorders (AUD)			Non-alcohol use disorders			AUD vs. Non-AUD	
	Event	Person-years	Rate [a]	Event	Person-years	Rate [a]	IRR	(95% CI)
Overall of mesentery ischemia	303	610230.7	4.97	520	2531097.1	2.05	2.42	(1.97–2.96)
ARD group								
Alcoholic psychosis	114	249269.4	4.57	520	2531097.1	2.05	2.23	(1.82–2.73)
Alcohol abuse/dependence	189	360961.3	5.24	520	2531097.1	2.05	2.55	(2.08–3.12)
Age at disease diagnosis (years)								
< 20	2	2570.6	7.78	0	10807.4	0.00	–	–
20–39	88	230263.7	3.82	85	944584.9	0.90	4.25	(3.46–5.21)
40–59	150	305661.2	4.91	247	1267163.4	1.95	2.52	(2.05–3.09)
≥60	63	71735.2	8.78	188	308541.4	6.09	1.44	(1.18–1.77)
Gender								
Female	17	57446.9	2.96	45	243965.4	1.84	1.60	(1.31–1.97)
Male	286	552783.8	5.17	475	2287131.7	2.08	2.49	(2.03–3.05)
Insurance premium (TWD)								
≥45,801	7	18432.1	3.80	28	295079.6	0.95	4.00	(3.26–4.91)
28,801–45,800	45	86189.1	5.22	71	431878.8	1.64	3.18	(2.59–3.89)
15,841–28,800	146	312708.4	4.67	171	761919.0	2.24	2.08	(1.70–2.55)
≤15,840	39	70501.6	5.53	72	165544.7	4.35	1.27	(1.04–1.56)
Dependents	66	122399.5	5.39	178	876675.0	2.03	2.66	(2.17–3.26)
Low income household								
No	290	588054.0	4.93	507	2503535.3	2.03	2.44	(1.99–2.99)
Yes	13	22176.7	5.86	13	27561.8	4.72	1.24	(1.01–1.52)
Comorbidity[b]								
No	138	325893.2	4.23	196	1590790.7	1.23	3.44	(2.80–4.21)
Yes	165	284337.5	5.80	324	940306.4	3.45	1.68	(1.37–2.06)

Note: AUD = alcohol use disorders; IRR = incidence rate ratio; TWD = Taiwan dollars.
[a] Rate represented as the incidence rate (per 10,000 person-years).
[b] Comorbidity was defined as patients with CCI score ≥1 or having hypertension, diabetes mellitus, hyperlipidemia, stroke, ischemic heart disease, congestive heart failure, peripheral artery disease, COPD, obesity, and alcoholic liver damage were classified as the comorbidity group.

alcohol abuse and intoxication may develop alcohol-induced psychotic disorders that were associated with increase in several medical and psychiatric conditions (Jordaan and Emsley, 2014). Hence, the alcohol abuse/dependence may be more likely to suffer a mesenteric ischemia event than the alcoholic psychosis group. Although the pathological mechanisms underlying the onset of mesenteric ischemia is not completely understood, the categories of alcohol addictions may present different degrees of risk with regards to the occurrence of mesenteric ischemia.

In addition, individuals with the lowest insurance premium but not low-income household generated the highest risk of mesenteric ischemia compared with their counterparts, whereas those with the highest insurance premium had the lowest mesenteric ischemia risk. Persons with lower socioeconomic status may have a greater risk for binge drinking, alcohol abuse and dependence that can lead to poor health outcomes (Lui et al., 2018; Mulia and Karriker-Jaffe, 2012). Therefore, this may be an interesting factor to explore in future research.

The strengths of this study, including the nationwide sample and robust adjustment for comprehensive characteristics of patients and hospitals, allowed us to accurately estimate the impact of overall and subgroups of AUD on mesenteric ischemia risk. Moreover, the two cohorts were selected to have an adequate matching by age, gender, CCI score and index date to minimize the effect of selection bias when evaluating the relationship. Finally, the current study highlights the need for awareness of mesenteric ischemia in AUD patients presenting with high-risk conditions.

4.1. Limitations

Several limitations of this study should be noted. First, the detailed information on alcohol consumption, smoking, medications, and the details of the physical examination and laboratory was not available, which may partially influence the risk of developing mesenteric ischemia. However, our analyses adjusted for comorbidities and baseline characteristics when comparing the mesenteric ischemia risk between the AUD and non-AUD cohorts. Second, misclassification of AUD could not be completely avoided in the NHIRD inpatient claims data. Although hospitalized patients with AUD were identified based on specific ICD-9-CM codes to increase the accuracy of diagnosis, it may underestimate the difference in mesenteric ischemia risk between AUD and non-AUD cohorts. Hence, the true difference between the two cohorts might be even larger than observed in this study. Third, the results were not generalized to non-Taiwanese populations or other patients who had unspecified AUD. However, the number of these patients was very low (0.9%) and was therefore unlikely to affect our statistical analysis.

4.2. Future directions

On the basis of these results, we propose that early consideration of mesenteric ischemia for AUD patients who have abdominal pain/discomfort and those with high-risk comorbidities and medication use. These may be the possible mechanisms underlying the higher risk of mesenteric ischemia in AUD patients. Furthermore, prospective clinical–pathological studies are needed to investigate the clinical changes of mesenteric ischemia in different subcategories of AUD.

5. Conclusion

This study provides evidence that patients with AUD had a significantly increased risk of mesenteric ischemia, particularly for those diagnosed with alcohol abuse/dependence. AUD is a risk factor for developing mesenteric ischemia that may be exacerbated by alcohol

Table 3
Univariate and multivariate Cox proportional hazard models of mesentery ischemia in patient with alcohol use disorders (AUD) compared to those without alcohol use disorders.

Variable	Mesentery ischemia event	Univariate model			Multivariate model 1			Multivariate model 2		
		HR	(95% CI)	P-value	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Non-AUD patients	520	1.00			1.00			1.00		
Overall AUD patients	303	2.41	(2.09–2.78)	< 0.001	2.25	(1.92–2.64)	< 0.001			
AUD group										
Alcoholic psychosis	114	2.22	(1.78–2.77)	< 0.001				2.17	(1.72–2.73)	< 0.001
Alcohol abuse/dependence	189	2.55	(2.19–2.96)	< 0.001				2.29	(1.94–2.71)	< 0.001
Age at disease diagnosis (years)										
< 20	2	1.02	(0.26–4.00)	0.982	1.16	(0.30–4.48)	0.829	1.16	(0.30–4.47)	0.830
20–39	173	1.00			1.00			1.00		
40–59	397	1.71	(1.42–2.06)	< 0.001	1.50	(1.24–1.82)	< 0.001	1.50	(1.24–1.82)	< 0.001
≥60	251	4.48	(3.66–5.49)	< 0.001	3.47	(2.80–4.30)	< 0.001	3.47	(2.80–4.30)	< 0.001
Gender										
Female	62	1.00			1.00			1.00		
Male	761	1.30	(1.03–1.66)	0.030	1.09	(0.86–1.39)	0.479	1.09	(0.86–1.39)	0.479
Insurance premium (TWD)										
≥45,801	35	0.38	(0.27–0.52)	< 0.001	0.57	(0.41–0.79)	< 0.001	0.57	(0.41–0.79)	< 0.001
28,801–45,800	116	0.76	(0.62–0.94)	0.010	0.96	(0.78–1.19)	0.707	0.96	(0.78–1.19)	0.706
15,841–28,800	317	1.00			1.00			1.00		
≤15,840	111	1.60	(1.31–1.95)	< 0.001	1.30	(1.05–1.60)	0.017	1.29	(1.05–1.60)	0.017
Dependents	244	0.83	(0.70–0.97)	0.023	0.96	(0.80–1.15)	0.642	0.96	(0.80–1.15)	0.640
Low income household										
No	797	1.00			1.00			1.00		
Yes	26	2.03	(1.42–2.92)	< 0.001	1.32	(0.92–1.91)	0.136	1.32	(0.92–1.91)	0.137
CCI score										
0	465	1.00			1.00			1.00		
1	212	1.68	(1.45–1.94)	< 0.001	1.24	(1.04–1.48)	0.017	1.24	(1.04–1.48)	0.017
≥2	146	2.05	(1.64–2.58)	< 0.001	1.54	(1.20–1.97)	< 0.001	1.54	(1.20–1.98)	< 0.001
Comorbidity										
Hypertension	154	2.01	(1.69–2.38)	< 0.001	1.35	(1.13–1.62)	0.001	1.35	(1.13–1.62)	0.001
Diabetes mellitus	137	1.73	(1.44–2.09)	< 0.001	1.17	(0.95–1.44)	0.149	1.17	(0.95–1.44)	0.152
Hyperlipidemia	38	1.31	(1.02–1.69)	0.034	1.03	(0.79–1.34)	0.840	1.03	(0.79–1.34)	0.849
Stroke	28	1.79	(1.19–2.70)	0.005	0.95	(0.62–1.46)	0.820	0.95	(0.62–1.46)	0.821
Ischemic heart disease	42	2.21	(1.57–3.13)	< 0.001	1.54	(1.07–2.20)	0.019	1.54	(1.08–2.20)	0.019
Congestive heart failure	17	2.25	(1.43–3.54)	< 0.001	1.44	(0.91–2.28)	0.124	1.44	(0.91–2.28)	0.125
Peripheral artery disease	4	2.78	(0.86–8.98)	0.088	1.96	(0.62–6.19)	0.250	1.96	(0.62–6.19)	0.250
COPD	17	1.77	(1.11–2.80)	0.016	0.91	(0.55–1.51)	0.709	0.91	(0.55–1.51)	0.708
Obesity	0	–	–		–	–		–	–	
Alcoholic liver damage	38	2.10	(1.53–2.88)	< 0.001	1.46	(1.05–2.05)	0.025	1.48	(1.06–2.07)	0.023
Hospital accreditation level										
Medical center	249	1.00			1.00			1.00		
Regional hospital	377	1.14	(0.96–1.35)	0.147	1.12	(0.95–1.31)	0.192	1.12	(0.95–1.32)	0.184
District hospital	197	1.00	(0.82–1.21)	0.967	1.18	(0.95–1.46)	0.136	1.18	(0.95–1.47)	0.129
Hospital teaching status										
Yes	709	1.00			1.00			1.00		
No	114	0.82	(0.67–1.00)	0.052	0.85	(0.67–1.08)	0.178	0.85	(0.67–1.08)	0.178
Hospital geographic location										
Taipei	249	1.00			1.00			1.00		
Northern	100	0.76	(0.61–0.95)	0.014	0.82	(0.65–1.03)	0.082	0.82	(0.65–1.03)	0.085
Central	155	0.88	(0.71–1.08)	0.215	0.86	(0.70–1.07)	0.179	0.86	(0.70–1.07)	0.179
Southern	140	1.18	(0.95–1.46)	0.137	1.15	(0.92–1.43)	0.224	1.15	(0.92–1.43)	0.223
Kao-Ping	153	0.96	(0.79–1.15)	0.632	0.94	(0.77–1.14)	0.500	0.93	(0.77–1.14)	0.498
Eastern	26	0.96	(0.74–1.25)	0.769	0.85	(0.64–1.12)	0.254	0.85	(0.64–1.13)	0.264
Specialty										
Internal medicine	324	1.00			1.00			1.00		
Surgery	148	0.63	(0.52–0.77)	< 0.001	1.01	(0.82–1.26)	0.904	1.01	(0.82–1.26)	0.908
Psychiatry	42	0.77	(0.53–1.12)	0.168	0.80	(0.54–1.17)	0.241	0.81	(0.55–1.19)	0.282
Other	309	0.55	(0.47–0.65)	< 0.001	0.85	(0.72–1.02)	0.081	0.85	(0.72–1.02)	0.081

Note: AUD = alcohol use disorders; CCI = Charlson comorbidity index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; TWD = Taiwan dollars.

abuse/dependence. Clinicians should consider mesenteric ischemia as a differential diagnosis for patients of different subcategories of AUD. In addition, these findings suggest that patient assessment and subsequent treatment should take into consideration the presence of comorbidities, which could specifically increase the severity of AUD. Clinical validation through additional prospective studies is still needed to derive the casual relationship between AUD and mesenteric ischemia.

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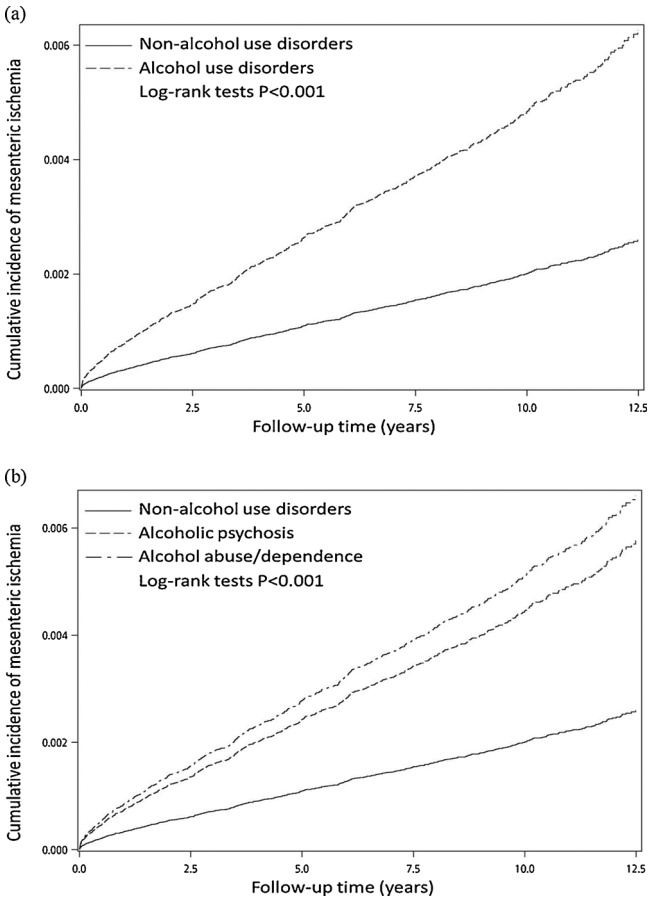

Fig. 2. The cumulative incidence of mesentery ischemia between (a) patients with and without alcohol use disorders; (b) patients with alcoholic psychosis and alcohol abuse/dependence, and those without alcohol use disorders.

Contributors

CFC and CCH conceived of the design and implementation of the study and drafted the manuscript. YTH collected and prepared data and provided analytic suggestions. CFC, SLC, and CCH carried out the data analysis. WTK, KTL, and YTH reviewed drafts of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

No conflict declared.

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