Original Article

Risk of Hemorrhoid in Patients with Alcohol Use Disorder: A Nationwide, Population-based Nested Case-control Study

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Key Words
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Background. The association between alcohol use disorder (AUD) and the risk of developing hemorrhoid is, as yet, to be investigated, and thus we conducted this large-scale, population-based cohort to examine the association in patients from Taiwan.
Methods. Overall, we included 30,988 individuals with newly diagnosed AUD, defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification, and 92,964 gender-, age-, and index day-matched controls without AUD from 2000 to 2013 from the Longitudinal Health Insurance Database (LHID), a subset from the National Health Insurance Research Database (NHIRD) in Taiwan. We measured the cumulative incidence of hemorrhoid in each cohort using the Kaplan-Meier method, and computed hazards ratios (HRs) and accompanying 95% confidence intervals (CIs) for the estimation of the association between AUD and hemorrhoid using the Cox proportional hazards models.
Results. Kaplan-Meier analysis revealed that the cumulative incidence of hemorrhoid was significantly higher in patients with AUD than in those without it (log rank test, $p < 0.001$). After adjustments for age, gender, and comorbidities, patients with AUD were associated with a significantly higher risk of hemorrhoid than those without AUD (adjusted HR = 1.604, 95% CI = 1.515-1.697, $p < 0.001$).
Conclusion. Based on a retrospective follow-up, nationwide study in Taiwan, AUD was associated with an increase in the risk of developing hemorrhoid. Even after adjustments for confounding factors, the patients with AUD exhibited higher risk of developing hemorrhoid.
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Hemorrhoids are a structural gastrointestinal disorder contributing to reduced quality of life and a common and sensitive challenge for patients to manage.[1] Hemorrhoids are vascular cushions within the anal canal, and consist of direct arteriovenous communications, mainly between the terminal branches of the superior rectal and superior hemorrhoidal arteries. Clinical manifestations are highly diverse, ranging from asymptomatic to anal bleeding, and the treatments are equally varied Nowadays, there are variety of option for manage hemorrhoids and surgical methods are surely for those with advanced hemorrhoids

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or sever symptoms.[2] Postoperative bleeding is one of the most annoying complications after interventions for hemorrhoids. Therefore, preventing the development of hemorrhoids or avoiding their worsening has become an important topic in medicine.

Alcohol use disorder (AUD) is defined by regular alcohol consumption, an inability to control drinking, experiencing negative emotions when not drinking, and it encompasses both alcohol dependence syndrome and alcoholism.[3] The 2016 World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study highlighted that alcohol use was the seventh leading cause of death globally and the leading contributor to disability-adjusted life-years.[4]

To further understand the relationship between hemorrhoids and AUD in Asian populations, we conducted a large, nationwide, population-based nested case-control study using Taiwan's National Health Insurance Research Database (NHIRD) to investigate the impact of AUD on the incidence of hemorrhoids.

Methods

Data source

This study was based on the data from the NHIRD in Taiwan. NHIRD run by the government of Taiwan, was started in 1995 and covers more than 99% of the Taiwanese population. We analyzed the Longitudinal Health Insurance Database (LHID), a dataset comprising one million individuals randomly sampled in 2013 from the NHIRD, with each patient's identifying information encrypted to ensure privacy. We collected data on 989,753 individuals with 26,769,418 medical events from January 1, 2000, to December 31, 2013. The demographics and characteristics of individuals registered in the LHID followed a normal distribution. Due to the ability to easily link with population-based screening data for hemorrhoids using personal patient identification numbers, the selected sample of patients with hemorrhoids was free from selection and participation bias.[5]

Study design, participants, and ethics

We performed a nested case-control study to investigate the relationship between alcoholism and hemorrhoids. Diagnoses were identified using the ICD-9-CM coding system, with hemorrhoids defined by codes 455.X and 159. Alcoholism was identified using ICD-9-CM codes 291.0-291.5, 291.81, 291.89, 291.9, 303.00-303.03, 303.90-303.93, 350.00-350.03, 571.0-571.3, 571.40, 571.41, 571.49, V11.3, V61.41, and V79.1.

From 2000 to 2013, a total of 989,753 individuals had medical records (outpatient, emergency, or inpatient visits). Among them, 31,313 were patients with AUD. After applying exclusion criteria (325 excluded), a total of 30,988 patients with AUD were included (matched to 92,964 controls at a 1:3 ratio). The proportion of hemorrhoid occurrence was 6.41% (1,985 out of 30,988) in the AUD group, compared to 3.41% (3,169 out of 92,964) in the control (non-alcohol dependence (alcohol abuse)) group. The difference between the two groups was statistically significant (Log-rank $p < 0.001$). In other words, the risk of developing hemorrhoids was significantly higher in patients with AUD compared to those without (Fig. 1).

Statistical analysis

We examined the descriptive statistics of demographic characteristics and baseline comorbidities between the exposed and non-exposed cohorts using chi-square tests or Student's t-tests, as appropriate. Additionally, we employed the Kaplan-Meier method to estimate the cumulative incidence of hemorrhoids in the study cohorts and used the log-rank test to compare the differences between these curves. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models, adjusting for potential confounders mentioned earlier. All confounders, including psychiatric diagnoses, were calculated separately as covariates and comorbidities. The analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC), with statistical significance set at 0.05 for two-tailed tests.

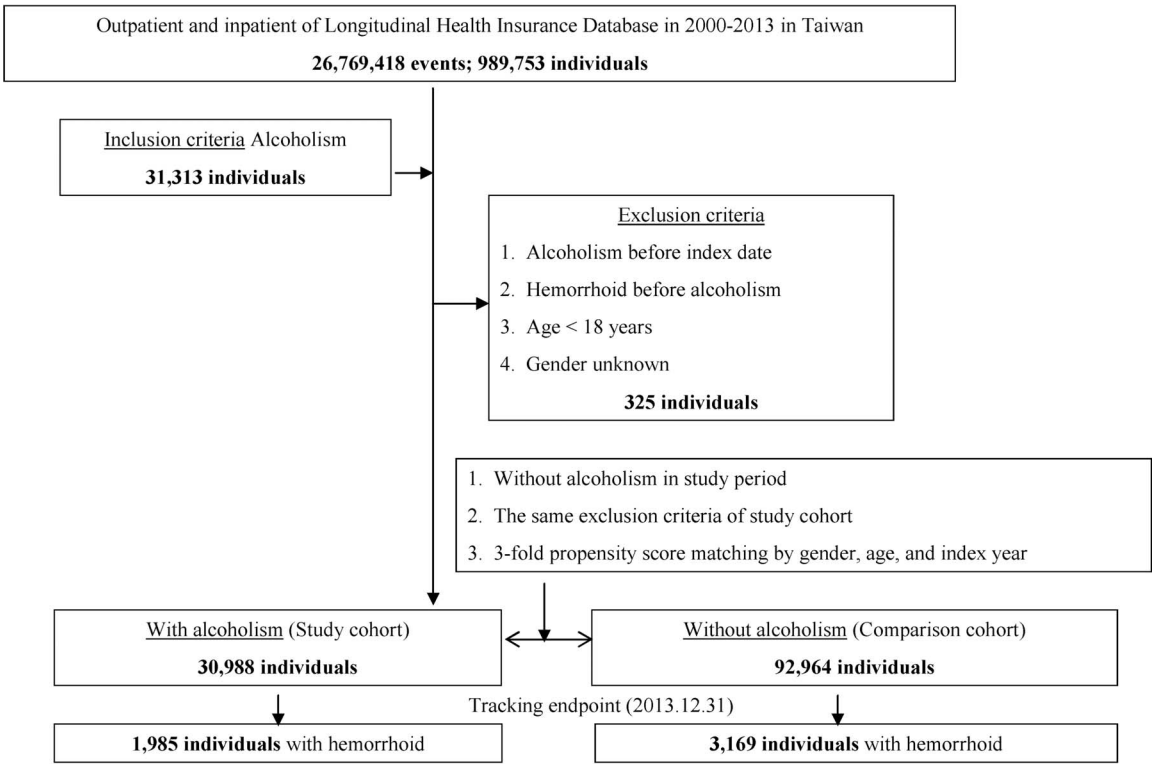

Fig. 1. The flowchart of study sample selection from National Health Insurance Research Database in Taiwan.

Results

Overall, AUD significantly increases the risk of developing hemorrhoids. Individuals with AUD are 1.604 times more likely to develop hemorrhoids compared to the control group, with this finding reaching statistical significance (Log-rank $p < 0.001$) (Fig. 2).

We present the distribution of baseline characteristics for the entire cohort of 123,952 individuals (30,988 in the case group with AUD and 92,964 in the control group without AUD) at the start of follow-up. The distribution of gender and age (due to matching) shows no significant differences between the case and control groups. The proportion of individuals with an insured salary (income) of less than 18,000 NTD is significantly higher in the case group compared to the control group (92.15% vs. 91.73%; $p < 0.001$). The AUD group has a significantly higher prevalence of comorbidities compared to the control group, including COPD (7.74% vs. 5.08%; $p < 0.001$), diabetes mellitus (DM) (12.94% vs. 8.87%; $p < 0.001$), hypertension (HTN) (10.75% vs. 10.24%; $p = 0.011$), hypercholesterolemia (8.16% vs. 2.77%; $p < 0.001$), and

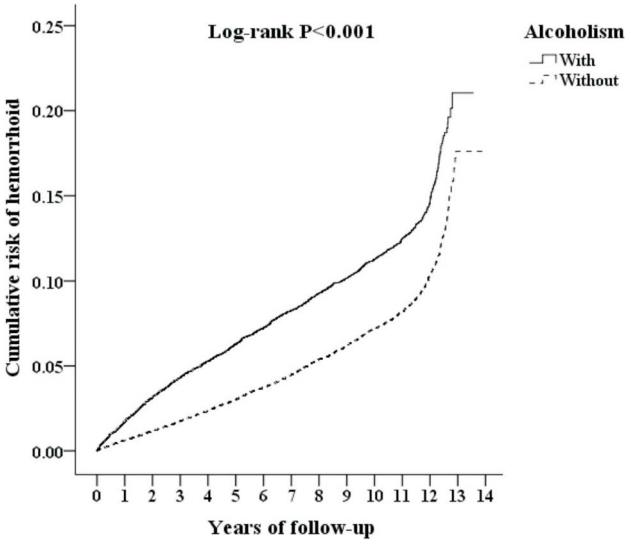

Fig. 2. Kaplan-Meier for cumulative risk of hemorrhoid aged 18 and over stratified by alcoholism with log-rank test.

peptic ulcer (15.22% vs. 6.32%; $p < 0.001$). Seasonally, the case group has a higher proportion of individuals during summer (25.37% vs. 24.73%) and autumn (23.09% vs. 22.48%) compared to the control group ($p < 0.001$). Geographically, a higher propor-

tion of the case group resides in central (32.91% vs. 26.73%), southern (27.97% vs. 26.56%), and eastern (7.92% vs. 5.91%) regions compared to the control group ($p < 0.001$). Additionally, the case group has a higher proportion of individuals living in urbanization level 3 (10.01% vs. 8.16%) and level 4 (28.10% vs. 15.30%) areas compared to the control group ($p < 0.001$). The proportion of individuals seeking medical care at regional hospitals is also higher in the case group (47.02% vs. 40.09%; $p < 0.001$) (Table 1).

Table 2 shows the results of univariate and multivariate analyses of factors influencing hemorrhoid incidence. According to the multivariate analysis results, after controlling for income, individuals with AUD have a 1.604 times higher risk of developing hemorrhoids compared to the control group ($p < 0.001$). Men have a 1.395 times higher risk of developing hemorrhoids compared to women ($p < 0.001$). Individuals aged 65 and above have a 0.714 times lower risk of developing hemorrhoids compared to those aged 18-44 ($p < 0.001$). Individuals with COPD have a 1.669 times higher risk of developing hemorrhoids compared to those without COPD ($p < 0.001$). Those with DM have a 1.663 times higher risk compared to those without DM ($p < 0.001$). Individuals with CAD have a 0.548 times lower risk compared to those without CAD ($p < 0.001$). Those with HTN have a 0.583 times lower risk compared to those without HTN ($p < 0.001$). Individuals with hypercholesterolemia have a 1.667 times higher risk compared to those without hypercholesterolemia ($p = 0.001$). Those with peptic ulcers have a 2.018 times higher risk compared to those without peptic ulcers ($p < 0.001$). Individuals with inflammatory bowel disease (IBD) have an 8.873 times higher risk compared to those without IBD ($p < 0.001$).

Additionally, individuals seeking medical care in summer, autumn, and winter have a 0.879 times ($p < 0.001$), 0.819 times ($p = 0.001$), and 0.878 times ($p < 0.001$) lower risk, respectively, of developing hemorrhoids compared to those seeking care in spring. Individuals seeking medical care in urbanization level 2, level 3, and level 4 areas have a 1.339 times ($p < 0.001$), 1.148 times ($p = 0.001$), and 1.234 times ($p < 0.001$) higher risk, respectively, compared to those in urbanization level 1 areas. Finally, individuals seeking medical care at academic medical centers and regional hospitals have a 0.556 times ($p < 0.001$) and 0.793 times ($p < 0.001$) lower risk, respectively, compared to those seeking care at local hospitals.

The stratified analysis of various variables to understand how much more likely individuals with AUD are to develop hemorrhoids compared to those without (Table 3). The results show that, after controlling for other factors, individuals with AUD have a significantly higher risk of developing hemorrhoids, regardless of gender (male, female), age group (25-44 years, 45-66 years, 65 years and older), presence of COPD, DM, HTN, hypercholesterolemia, peptic ulcer, or IBD, season (spring, summer, autumn, winter), urbanization level (levels 1-4), or hospital level (academic medical center, regional hospital, local hospital). The risk ranges from 1.225 to 9.246 times higher compared to those without AUD ($p < 0.001$, $p = 0.001$). Among males, those with AUD have a 1.611 times higher risk of developing hemorrhoids compared to those without AUD ($p < 0.001$). Among females, the risk is 1.331 times higher ($p < 0.001$). For individuals aged 18-44, those with AUD have a 2.106 times higher risk of developing hemorrhoids compared to those without ($p < 0.001$). For individuals aged 45-64, the risk is 1.459 times higher ($p < 0.001$). For those aged 65 and older, the risk is 1.225 times higher ($p < 0.001$).

Discussion

This large-scale, population-based study indicated that patients with AUD have a significantly higher risk of developing hemorrhoids than those without AUD. AUD is an independent risk factor for hemorrhoids, with a nearly 1.604-fold risk. Kaplan-Meier analysis revealed that hemorrhoids-free rate of patients with AUD is significantly lower than that of the controls. To the best of our knowledge, this retrospective study is the first large cohort analysis showing an increased risk of developing hemorrhoids in patients with alcoholism. The advantage of this study is that it is a nationwide cohort study, which includes a large number of cases and control cohorts with a long follow-up period.[6]

Table 1. Characteristics of study in the baseline

Alcohol use disorder	Total		With		Without		*p*
Variables	n	%	n	%	n	%	
Total	123,952		30,988	25.00	92,964	75.00	
Gender							0.999
Male	98,380	79.37	24,595	79.37	73,785	79.37	
Female	25,572	20.63	6,393	20.63	19,179	20.63	
Age (years)	49.66 ± 17.14		49.79 ± 15.38		49.62 ± 17.69		0.131
Age group (years)							0.999
18-44	54,644	44.08	13,661	44.08	40,983	44.08	
45-64	44,268	35.71	11,067	35.71	33,201	35.71	
≥ 65	25,040	20.20	6,260	20.20	18,780	20.20	
Insured premium (NT$)							< 0.001
< 18,000	113,827	91.83	28,554	92.15	85,273	91.73	
18,000-34,999	8,569	6.91	1,864	6.02	6,705	7.21	
≥ 35,000	1,556	1.26	570	1.84	986	1.06	
COPD							< 0.001
Without	116,828	94.25	28,588	92.26	88,240	94.92	
With	7,124	5.75	2,400	7.74	4,724	5.08	
DM							< 0.001
Without	111,696	90.11	26,977	87.06	84,719	91.13	
With	12,256	9.89	4,011	12.94	8,245	8.87	
CAD							0.150
Without	116,682	94.13	29,119	93.97	87,563	94.19	
With	7,270	5.87	1,869	6.03	5,401	5.81	
HTN							0.011
Without	111,103	89.63	27,657	89.25	83,446	89.76	
With	12,849	10.37	3,331	10.75	9,518	10.24	
Hypercholesterolemia							< 0.001
Without	118,850	95.88	28,458	91.84	90,392	97.23	
With	5,102	4.12	2,530	8.16	2,572	2.77	
Peptic ulcer							< 0.001
Without	113,360	91.45	26,273	84.78	87,087	93.68	
With	10,592	8.55	4,715	15.22	5,877	6.32	
IBD							0.250
Without	123,830	99.90	30,952	99.88	92,878	99.91	
With	122	0.10	36	0.12	86	0.09	
Season							0.001
Spring	32,591	26.29	8,044	25.96	24,547	26.40	
Summer	30,849	24.89	7,863	25.37	22,986	24.73	
Autumn	28,050	22.63	7,155	23.09	20,895	22.48	
Winter	32,462	26.19	7,926	25.58	24,536	26.39	
Location							< 0.001
Northern Taiwan	46,966	37.89	9,542	30.79	37,424	40.26	
Middle Taiwan	35,045	28.27	10,199	32.91	24,846	26.73	
Southern Taiwan	33,362	26.92	8,668	27.97	24,694	26.56	
Eastern Taiwan	7,947	6.41	2,453	7.92	5,494	5.91	
Outlets islands	632	0.51	126	0.41	506	0.54	
Urbanization level							< 0.001
1 (The highest)	39,897	32.19	7,208	23.26	32,689	35.16	
2	50,433	40.69	11,970	38.63	38,463	41.37	
3	10,687	8.62	3,103	10.01	7,584	8.16	
4 (The lowest)	22,935	18.50	8,707	28.10	14,228	15.30	
Level of care							< 0.001
Hospital center	36,632	29.55	8,246	26.61	28,386	30.53	
Regional hospital	35,476	28.62	8,171	26.37	27,305	29.37	
Local hospital	51,844	41.83	14,571	47.02	37,273	40.09	

Note. CCI_R, Charlson comorbidity index removed sleep apnea; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CAD, coronary artery disease; HTN, hypertension; IBD, inflammatory bowel disease.
Spring: March-May, Summer: June-August; Autumn: September-November; Winter: December-Feburary.
p-value (category variable: Chi-square/Fisher exact test; continue variable: t-test).

Table 2. Factors of hemorrhoid by using Cox regression

Variables	Crude HR	95% CI	*p*	Adjusted HR	95% CI	*p*
Alcohol use disorder						
Without	Reference			Reference		
With	1.675	1.584-1.772	< 0.001	1.604	1.515-1.697	< 0.001
Gender						
Male	1.420	1.321-1.528	< 0.001	1.395	1.296-1.501	< 0.001
Female	Reference			Reference		
Age group (years)						
18-44	Reference			Reference		
45-64	0.884	0.830-0.942	< 0.001	0.977	0.915-1.043	0.482
≥ 65	0.554	0.517-0.595	< 0.001	0.714	0.683-0.769	< 0.001
Insured premium (NT$)						
< 18,000	Reference			Reference		
18,000-34,999	0.818	0.638-1.049	0.114	0.782	0.610-1.003	0.053
≥ 35,000	1.122	0.723-1.741	0.607	1.011	0.651-1.570	0.961
COPD						
Without	Reference			Reference		
With	1.621	1.543-1.710	< 0.001	1.669	1.610-1.802	< 0.001
DM						
Without	Reference			Reference		
With	1.543	1.494-1.597	< 0.001	1.663	1.602-1.730	< 0.001
CAD						
Without	Reference			Reference		
With	0.381	0.326-0.444	< 0.001	0.548	0.468-0.642	< 0.001
HTN						
Without	Reference			Reference		
With	0.417	0.378-0.459	< 0.001	0.583	0.508-0.623	< 0.001
Hypercholesterolemia						
Without	Reference			Reference		
With	1.463	1.368-1.584	< 0.001	1.667	1.528-1.643	0.001
Peptic ulcer						
Without	Reference			Reference		
With	2.125	1.958-2.306	< 0.001	2.018	1.858-2.193	< 0.001
IBD						
Without	Reference			Reference		
With	9.052	6.244-13.125	< 0.001	8.873	6.115-12.876	< 0.001
Season						
Spring	Reference			Reference		
Summer	0.885	0.819-0.956	0.002	0.879	0.814-0.950	< 0.001
Autumn	0.817	0.756-0.882	< 0.001	0.819	0.759-0.885	0.001
Winter	0.870	0.805-0.942	0.001	0.878	0.811-0.950	< 0.001
Location						
Northern Taiwan	Reference			Multicollinearity with urbanization level		
Middle Taiwan	1.164	1.090-1.244	< 0.001	Multicollinearity with urbanization level		
Southern Taiwan	0.919	0.855-0.987	0.021	Multicollinearity with urbanization level		
Eastern Taiwan	1.205	1.081-1.344	0.001	Multicollinearity with urbanization level		
Outlets islands	0.803	0.491-1.313	0.381	Multicollinearity with urbanization level		
Urbanization level						
1 (The highest)	0.982	0.905-1.066	0.662	1.339	1.224-1.464	< 0.001
2	0.939	0.869-1.015	0.112	1.148	1.060-1.244	0.001
3	1.254	1.127-1.397	< 0.001	1.234	1.108-1.374	< 0.001
4 (The lowest)	Reference			Reference		
Level of care						
Hospital center	0.575	0.534-0.618	< 0.001	0.556	0.512-0.603	< 0.001
Regional hospital	0.792	0.743-0.844	< 0.001	0.793	0.743-0.846	< 0.001
Local hospital	Reference			Reference		

Note. CCI_R, Charlson comorbidity index removed sleep apnea; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CAD, coronary artery disease; HTN, hypertension; IBD, inflammatory bowel disease.
Spring: March-May, Summer: June-August; Autumn: September-November; Winter: December-Feburary.
p-value (category variable: Chi-square/Fisher exact test; continue variable: t-test).

Table 3. Factors of hemorrhoid stratified by variables listed in the table by using Cox regression

Alcohol use disorder	With			Without			With vs. Without			
Strarified	Event	PYs	Rate	Event	PYs	Rate	Ratio	Adjusted HR	95% CI	*p*
Total	1,985	318,816.63	622.61	3,169	1,056,920.72	299.83	2.077	1.604	1.515-1.697	< 0.001
Gender										
Male	1,676	245,419.96	682.91	2,605	821,222.07	317.21	2.153	1.661	1.561-1.768	< 0.001
Female	309	73,396.66	421.00	564	235,698.65	239.29	1.759	1.331	1.157-1.530	< 0.001
Age group (yrs)										
18-44	787	86,020.77	914.90	1,045	298,049.32	350.61	2.609	2.106	1.916-2.314	< 0.001
45-64	802	125,508.05	639.00	1,158	340,730.46	339.86	1.880	1.459	1.332-1.598	< 0.001
≥ 65	396	107,287.81	369.10	966	418,140.93	231.02	1.598	1.225	1.089-1.378	0.001
Insured premium (NT$)										
< 18,000	1,960	313,121.49	625.96	3,111	1,037,328.01	299.91	2.087	1.610	1.521-1.705	< 0.001
18,000-34,999	21	5,021.81	418.18	42	15,282.04	274.83	1.522	1.109	0.649-1.894	0.706
≥ 35,000	4	673.33	594.07	16	4,310.67	371.17	1.601	1.221	0.341-4.335	0.758
COPD										
Without	1,894	297,828.41	635.94	3,036	982,957.88	308.86	2.059	1.598	1.508-1.693	< 0.001
With	91	20,988.22	433.58	133	73,962.84	179.82	2.411	1.723	1.314-2.261	< 0.001
DM										
Without	1,742	261,125.04	667.11	2,935	899,152.67	326.42	2.044	1.565	1.474-1.662	< 0.001
With	243	57,691.59	421.21	234	157,768.05	148.32	2.840	1.894	1.574-2.279	< 0.001
CAD										
Without	1,932	296,456.24	651.70	3,056	968,909.96	315.41	2.066	1.612	1.522-1.707	< 0.001
With	53	22,360.39	237.03	113	88,010.76	128.39	1.846	1.368	0.981-1.908	0.065
HTN										
Without	1,845	269,362.95	684.95	2,871	860,096.06	333.80	2.052	1.620	1.527-1.719	< 0.001
With	140	49,453.67	283.09	298	196,824.66	151.40	1.870	1.396	1.140-1.709	0.001
HC										
Without	1,943	309,882.11	627.01	3,138	1,025,480.49	306.00	2.049	1.588	1.499-1.681	< 0.001
With	42	8,934.52	470.09	31	31,440.23	98.60	4.768	2.588	1.591-4.210	< 0.001
Peptic ulcer										
Without	1,670	292,132.73	571.66	2,827	995,316.57	284.03	2.013	1.593	1.363-1.863	< 0.001
With	315	26,683.90	1,180.49	342	61,604.15	555.16	2.126	1.603	1.508-1.704	< 0.001
IBD										
Without	1,975	318,736.38	619.63	3,151	1,056,129.11	298.35	2.077	1.595	1.507-1.688	< 0.001
With	10	80.24	12,462.10	18	791.61	2,273.84	5.481	9.246	2.587-33.04	0.001
Season										
Spring	513	73,311.89	699.75	802	243,162.81	329.82	2.122	1.698	1.512-1.908	< 0.001
Summer	500	80,453.98	621.47	800	269,649.90	296.68	2.095	1.582	1.412-1.772	< 0.001
Autumn	509	88,218.00	576.98	843	291,939.54	288.76	1.998	1.525	1.364-1.704	< 0.001
Winter	463	76,832.76	602.61	724	252,168.48	287.11	2.099	1.635	1.461-1.831	< 0.001
Urbanization level										
1 (The highest)	529	86,854.47	609.06	916	329,816.00	277.73	2.193	1.835	1.609-2.093	< 0.001
2	821	140,659.14	583.68	1,353	469,250.92	288.33	2.024	1.548	1.418-1.689	< 0.001
3	205	25,407.53	806.85	318	84,670.68	375.57	2.148	1.703	1.426-2.035	< 0.001
4 (The lowest)	430	65,895.50	652.55	582	173,183.12	336.06	1.942	1.507	1.355-1.675	< 0.001
Level of care										
Hospital center	397	94,729.37	419.09	871	360,923.95	241.33	1.737	1.316	1.167-1.482	< 0.001
Regional hospital	857	137,378.53	623.82	1,372	440,632.11	311.37	2.003	1.587	1.456-1.730	< 0.001
Local hospital	731	86,708.73	843.05	926	255,364.66	362.62	2.325	1.850	1.677-2.041	< 0.001

PYs = Person-years; Adjusted HR = Adjusted hazard ratio: Adjusted for the variables listed in Table 3; Rate (per 105 PYs).
Note. CCI_R, Charlson comorbidity index removed sleep apnea; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CAD, coronary artery disease; HTN, hypertension; HC, hypercholesterolemia; IBD, inflammatory bowel disease.
Spring: March-May, Summer: June-August; Autumn: September-November; Winter: December-Feburary.
p-value (category variable: Chi-square/Fisher exact test; continue variable: t-test).

The National Health Insurance Program (NHIP), initiated in 1995, was designed to provide comprehensive health coverage and now includes over 99% of the population. It functions as a mandatory, government-run insurance system, streamlining the financial aspects of healthcare. In 1997, the National Health Insurance Research Database (NHIRD) was established to support research on healthcare utilization, health economics, preventive medicine, and medical research, while also assisting in the formulation of national health policies. The NHIRD's longitudinal database contains extensive medical records for all insured individuals, including information on visits, prescriptions, and diagnoses. Criteria for diagnosing alcoholism and hemorrhoids were clearly defined using ICD-9-CM codes. The diagnosis of hemorrhoids follows strict clinical protocols, requiring a physician's evaluation, tissue confirmation from surgical procedures, and pathology reports. Final diagnoses are carefully coded by physicians and reviewed by medical experts at the National Health Insurance Administration (NHIA). This rigorous process guarantees the accuracy of diagnoses, including alcoholism and hemorrhoids, as the data is closely monitored by the NHI Bureau for reimbursement purposes.

Interest in the association between AUD and hemorrhoid is increasing rapidly. However, the underlying mechanisms of the association between AUD and hemorrhoids remain unknown. We hypothesize several factors for this association. The development of hemorrhoid is recognized as a multifactorial disease process, which is widely considered to have an effect on hereditary components, genetic factors, dietary habit, long-term lifestyle, environmental factors, and inflammatory conditions of the digestive tract.[3] Previous studies have demonstrated that alcohol consumption is linked to various negative consequences.[7,8] Previous study postulated that the ADH1C polymorphism and ALDH2*2 allele have strong relationships with hemorrhoids.[8] Furthermore, chronic alcohol consumption may also cause intestinal inflammation, which includes changes in intestinal microbiota composition and distribution, increased absorbency of the intestinal epithelium, and alteration of intestinal immune equilibrium.[9,10] However, to date, perturbation studies have not been carried out to conclusively define the association between AUD and hemorrhoid. We have assumed that both AUD and hemorrhoids share similar immunopathologic pathways.

Our finding is consistent with previous studies in the basic prevalence of hemorrhoids among age and sex, which is mainly seen 40s and male.[11,12] Furthermore, several educations and theories explain the alcoholic consumption may increased the incidence of hemorrhoids, but there are few studies showed the direct correlation. Pigot et al. showed alcohol intake with spicy diet and unusual events go with higher risk of acute hemorrhoidal symptoms.[13] We find the direct influence of high alcohol consumption, which we used AUD as the factor, on the incidence of hemorrhoids.

Multiple studies revealed that exposure to ethanol affects cytokine production by various immune cells.[14,15] Among the cells shown to be affected by chronic alcohol exposure, mast cells fill a particularly important role in innate immunity and deleterious tissue remodeling, which are known to affect local vascular conditions through release of their chemical mediators and cytokines, and may influence hemorrhoid symptomatology and progression at this level.[16,17] One of the first and most extensively studied mast cell preformed mediators is histamine, which plays a role in diverse functions associated with allergic reactions including vasodilation and increased capillary permeability, is with respect to the early stages of pathogenesis of hemorrhoids.[18] In addition, alcohol especially red wine, and its first oxidized metabolite acetaldehyde liberate histamine from its store in mast cells and depress histamine elimination by inhibiting diamine oxidase (DAO), resulting in elevated histamine levels in tissues, which intensifies the vicious circle.[19] Alongside this, mast cells also encounter platelet aggregation and thrombosis through degranulation and release of granular constituent, including histamine, cytokines, and proteases, which are common acute complications of hemorrhoid.[1,20] Herein, we postulated that mast cell-mediated histamine regulation related inflammation is one underlying mechanism by which chronic alcohol promotes hemorrhoids.

A study by Giovanni Galati and Antonio De Vincentis demonstrated that hemorrhoidal disease is a

common finding in cirrhotic patients, due to hemorrhoidal plexus is a possible site of porto-systemic venous anastomosis.[21] The venous drainage of the hemorrhoids is collected through the superior hemorrhoidal system which is under increased pressure in patients with portal hypertension. Alcohol is chiefly metabolized in the main parenchymal cells of the liver, which express the highest levels of the major ethanol-oxidizing enzymes, including alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1). ADH and CYP2E1-catalyzed ethanol oxidation generates acetaldehyde, which is highly reactive and toxic by covalently binding to proteins, lipids, and nucleic acids, followed by disruption of the structure and function of these macromolecules, leading to oxidative stress, lipid peroxidation, genetic and epigenetic alterations, intestinal epithelial barrier dysfunction, and immune modulatory effects.[22] Heavy ethanol consumption produces a wide spectrum of hepatic destruction, characterized by gradually swollen, dying hepatocytes and neutrophilic infiltration, refer to the deposition of abnormal amounts of extracellular matrix proteins, leading to progression to late stage of irreversible hepatic scarring that severely compromises the liver's vascular architecture. Cirrhosis development progresses to a decompensated phase where scar tissue fully envelops the organ, which deteriorate to development of portal hypertension. Portal hypertension shunts venous blood from the portal system through the portosystemic anastomosis which present at this site into the systemic venous system, occurs anorectal varices. Such evidence partly explains the linking mechanism between alcoholism related portal hypertension and hemorrhoidal diseases. In addition, there are some theories that might account for the heightened risk of hemorrhoids in patients with AUD. First, those with AUD with higher risk of comorbidities and obesity that increasing stress on the rectal muscle.[23-25] Second, increase the alcohol consumption usually comes along with higher risk of dehydration. Dehydration was noted as second risk factors (14.49%) to the hemorrhoids among adult patients in Saudi Arabia.[26] Third, patients with AUD was associated with liver cirrhosis and those with liver cirrhosis was at higher risk of lower gastrointestinal bleeding. Among them, the mostly noted etiology is the hemorrhoids (37%) in the study by Khalifa A et al.[27] Further studies are needed to clarify the mechanism of AUD and hemorrhoids.

This study has several limitations. First, the diagnoses of AUD and hemorrhoids were determined using ICD-9-CM codes rather than direct medical records, which may introduce registration biases that could act as potential confounders not accounted for in the study. Second, our study was unable to evaluate the dose-response relationship, as the AUD diagnostic criteria focus on the symptoms associated with alcohol use rather than the quantity of alcohol consumed. Third, patients with asymptomatic alcoholism might delay seeking healthcare until they experience significant discomfort, possibly leading to an underestimation of hemorrhoid risk among alcohol consumers.

Conclusion

The use of a nationwide population database with a large sample size and adjustment for certain covariates related to alcoholism allowed us to identify a significant association between AUD and the risk of developing hemorrhoids. Although hemorrhoids are not life-threatening, they can significantly impact quality of life. To our knowledge, this retrospective case-control study is the first to suggest an increased risk of hemorrhoids among Asian patients with alcohol consumption. Further large-scale prospective randomized studies are needed to confirm our findings on the relationship between AUD and hemorrhoids.

Author Contributions

All the authors have substantially contributed to the study and agree with the contents of the manuscript. Conception/design: Je-Ming Hu, Yu-Hong Liu and Nian-Sheng Tzeng. Provision of study materials: Nian-Sheng Tzeng, Wu-Chien Chien. Collection and assembly of data: Je-Ming Hu, Chi-Hsiang Chung, and Wu-Chien Chien. Data analysis and interpretation: all authors. Manuscript preparation: all authors. Final approval of manuscript: all authors.

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Conflicts of Interest

All authors report that there are no conflicts of interest.

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原　著

酒精使用障礙患者罹患痔瘡風險分析：以全國人口為對象之巢式病例對照研究

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目的　酒精使用障礙患者與痔瘡發生風險之間的關聯尚未充分研究。因此，我們進行了這項基於台灣大規模人口的隊列研究，旨在探討這兩者之間的關聯性。

方法　我們從台灣國家健康保險研究資料庫 (NHIRD) 中的長期健康保險資料庫中選取了 30,988 名於 2000 年至 2013 年間新診斷的酒精使用障礙患者，並選取 92,964 名依性別、年齡及指數日配對的非酒精使用障礙患者對照者。利用 Kaplan–Meier 方法計算每組的痔瘡累積發生率，並使用 Cox 比例風險模型估算 AUD 與痔瘡發生之間的風險比 (HR) 及其 95% 信賴區間 (CI)。

結果　Kaplan–Meier 分析顯示，酒精使用障礙患者患者的痔瘡累積發生率顯著高於非酒精使用障礙患者 (log-rank 測試，$p < 0.001$)。在調整年齡、性別及合併症後，AUD 患者與非 AUD 患者相比，發生痔瘡的風險顯著增加 (調整後 HR = 1.604，95% CI = 1.515-1.697，$p < 0.001$)。

結論　根據台灣的回溯性全國性研究，酒精使用障礙患者與痔瘡的發生風險增加有關聯。在調整了混雜因素後，酒精使用障礙患者患者的痔瘡風險仍顯著高於非酒精使用障礙患者患者。

關鍵詞　痔瘡、酒精使用障礙 (AUD)、國家健康保險研究資料庫、巢式病例對照研究。