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Identification and medical utilization of incident cases of alcohol dependence: A population-based case-control study

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ABSTRACT

Background: Patients with alcohol dependence (AD) often seek help from medical professionals due to alcohol-related diseases, but the overall distribution of medical specialties identifying new AD cases is unclear. We investigated how such cases were identified and how medical resources were utilized before the identification of AD in a nationwide cohort.

Methods: We enrolled a population-based cohort (N = 1,000,000) using the National Health Insurance Research Database of Taiwan; 8181 cases with incident AD were retrieved between January 1, 2000, and December 31, 2010. For this nested case-control study, four controls were matched for age and sex with each case based on risk-set sampling. We measured various dimensions of medical utilization before AD was diagnosed, including department visited, physical comorbidity, and medication used. Conditional logistic regression was used for estimating the variables associated with AD.

Results: Patients living in less urbanized areas who were unemployed were more likely to develop AD. The highest proportions (34.2%) of AD cases were identified in the internal medicine department, followed by the emergency (22.3%) and psychiatry (18.7%) departments. AD patients had a higher risk of comorbid chronic hepatic disease (adjusted RR = 2.72, $p < 0.001$) before identification of AD than controls. AD patients also had greater numbers of hospital admissions than controls, including non-psychiatric and psychiatric hospitalizations. Outpatient visit numbers were similar for AD patients and controls.

Conclusions: The findings indicate that clinicians providing care in diverse medical settings should be prepared to screen for unhealthy alcohol use and to mitigate its detrimental effects.

1. Introduction

According to a WHO report (World Health Organization, 2014), harmful use of alcohol causes approximately 3.3 million deaths every year (or 5.9% of all deaths), and 5.1% of the global burden of disease is attributable to alcohol consumption. From a public health view, 4% of the global disease burden is attributable to alcohol, which is almost equal to the negative effect of tobacco and hypertension (Room et al., 2005). Alcohol has associations with more than 60 different medical problems (Rehm et al., 2003), especially liver cirrhosis, cancer, hypertensive disease, and stroke. The WHO (World Health Organization, 2014) reports that cardiovascular and gastrointestinal diseases were the leading causes of alcohol-attributable deaths in 2012 at 33.4% and 16.2% respectively. In a record-linkage study, patients with alcohol dependence (AD) had a higher mortality risk than patients with heroin dependence, and the leading cause was gastrointestinal diseases such as liver cirrhosis (Chen et al., 2001).

AD is a conception that comprises biological elements (e.g., tolerance and withdrawal), cognitive elements (e.g., craving), and behavioral elements (e.g., impaired control) as described in the DSM-IV criteria (American Psychiatric Association, 1994). Before the development of AD, patients can experience the onset of various medical

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consequences (Schuckit et al., 1993). These physical illnesses warrant further investigation. Knowledge gained from these investigations could help clinicians to identify AD earlier in its course.

A substantial proportion of alcohol-related problems are detected in primary care settings (Cherpitel and Ye, 2008; Dawson et al., 2012; Rehm et al., 2015a) and emergency departments (Crane, 2013; Mullins et al., 2017) in most Western countries. For example, in a U.S. national alcohol survey, AD patients used primary care 1.63 times more frequently than non-alcohol users (Cherpitel and Ye, 2008). Another recent U.S. study (Dawson et al., 2012) revealed primary care and student health services were important types of initial medical utilization for patients whose alcohol problems required intervention. A recent large cross-sectional study in Europe pointed out that though general practitioners could identify alcohol dependence, the cases they recognized were different from those identified with the Composite International Diagnostic Interview using the DSM-IV criteria (Rehm et al., 2015a). Another recent study (Mullins et al., 2017) showed that there is an increasing rate of alcohol-related visits to emergency departments in the U.S., revealing a growing burden on the health delivery system. In a 5-year follow-up study, compared to the alcohol-free group, heavy alcohol drinkers had an increasing emergency department and inpatient resource utilization (Kline-Simon et al., 2014). Thus, it seems general or emergency department practitioners identify most new cases of AD. Additionally, patients with AD could visit a psychiatrist to seek abstinence treatment or for alcohol-related mental problems (Hung et al., 2015). The global view of the distribution of the medical specialties identifying incident cases of AD is unclear and deserves investigation.

The treatment gap among AD patients is relatively wide compared to other mental disorders (Kohn et al., 2004; Rehm et al., 2015b). The treatment gap represents the absolute difference between the true prevalence of a disorder and the treated proportion of individuals affected by the disorder (Kohn et al., 2004). AD patients rarely seek help within the addiction treatment system possibly due to a perceived stigma (Kohn et al., 2004). Understanding the health-seeking behavior patterns of AD patients could lead to the detection of alcohol-related problems earlier and, thus, decrease the treatment gap.

In the present study, we enrolled a large Asian nationwide cohort of the general population over a long period, ascertained the incident cases of AD, and investigated how such patients were identified. For selecting suitable controls for comparison and avoiding selection bias, we conducted a nested case-control study with controls derived from the cohort. We then investigated various topics, including the distribution of the specialties that identified the new AD cases, medical utilization within the 1 year before the diagnosis of AD, and the physical comorbidity associated with the development of AD.

2. Methods

2.1. Study population

The single-payer National Health Insurance (NHI) program was launched in Taiwan on March 1, 1995, and covered nearly 99.9% of the Taiwanese population in 2014 (National Health Insurance Administration, 2014). The NHI database contains registration files and original claims data for medical reimbursements. The database is managed by the National Health Research Institute (NHRI), which has established the National Health Insurance Research Database (NHIRD) (http://nhird.nhri.org.tw/en/) to provide data for research purposes.

This study used the Longitudinal Health Insurance Database 2005 (LHID 2005), which contains all the original claims data of 1,000,000 beneficiaries enrolled in 2005 randomly sampled from the 2005 Registry for Beneficiaries (ID) of the NHIRD. There are approximately 25.68 million individuals in this registry. All registration and claims data of these 1,000,000 individuals collected by the NHI program constitute the LHID 2005 (Supplemental e-Figure 1). There was no significant difference in the sex or age distributions between patients in the LHID 2005 and the original NHIRD. Information that can be used to identify beneficiaries and medical care providers is scrambled by the NHI Administration to maintain patient and provider confidentiality. All investigators signed an agreement guaranteeing patient confidentiality before using the database. This study was approved by the Institutional Review Board of the Committee on Human Subjects of Taipei City Hospital, and informed consent was waived due to the retrospective nature of the study.

2.2. Identification of cases of incident alcohol dependence

For sampling, the definition of the population at-risk for the development of AD (Supplemental e-Figure 1), we initially excluded patients with AD (ICD 9 code 303**) or alcohol psychosis (ICD 9 code 291**) between January 1, 1996, and December 31, 1999 (n = 1399). Then, we enrolled the study cohort (N = 998,601) and defined the baseline date as January 1, 2000. We broadly searched all of the claims data from the baseline to December 31, 2010, and consequently, 8181 cases with incident AD were retrieved.

2.3. Nested case-control study

We conducted a nested case-control study to compare the pattern of identification and medical utilization of the patients with AD with the controls. For comparability, we used the controls for each case randomly derived from the study cohort that represented the general population of Taiwan.

We selected four controls for each case subject, matched for age and sex, using risk-set sampling. The date of the newly diagnosed AD was defined as the index date. Controls were assigned the same index date as their corresponding case. Cases that were identified later during the follow-up were eligible to serve as controls for earlier cases. In addition, each control patient had at least one claim record after the corresponding index date to confirm that the controls were alive before the corresponding index date. Finally, 8181 cases were completely matched with 32,724 controls.

2.4. Variables of medical utilization

In this study, demographic variables included sex, age, employment, and urbanization (Table 1) for each case and the corresponding controls. We applied urbanization stratification (Liu et al., 2006) specifically used in Taiwan, and the level of urbanization was categorized as level 1 (highly urbanized area), level 2 (moderately urbanized area), level 3 (newly urbanized area), level 4 (township area), and level 5 (rural area). In addition, we used the Charlson comorbidity score (Quail et al., 2011; Quan et al., 2005) as the severity of physical comorbidity. The Charlson comorbidity score, which is the sum of the weighted scores of 31 comorbid conditions, is widely used to assess general health status (Quail et al., 2011; Quan et al., 2005). The specialty of the medical doctors who identified each case was also collected.

Based on the DSM-IV criteria (American Psychiatric Association, 1994), AD is defined as a maladaptive pattern of alcohol use, occurring at any time in the same 12-month period, leading to clinically significant impairment or distress, as manifested by three (or more) of the seven dependent-related items such as tolerance, withdrawal, loss of control with the use, and failure to control alcohol use. Thus, the medical utilization within the 12 months before AD was identified was investigated. We measured various dimensions of medical usage within the 12-month period before the index date, such as the department visited, numbers and costs of the procedures examined, physical comorbidity, and concomitant use of medications.

The categories of medications were based on information obtained from the Anatomical Therapeutic Chemical Classification system (WHO Collaborating Centre for Drug Statistic Methodology, 2016).

Table 1
Demographic and clinical characteristics of incidence cases with alcohol dependence and control group at the (corresponding) index date.

Characteristics	Cases (N = 8181)	Controls (N = 32724)	Unadjusted risk ratio[a]	99.9% CI	P-value	Adjusted risk ratio[b]	99.9% CI	P-value
	N (%)	N (%)						
Sex								
Male	6413 (78.4)	25652 (78.4)	Reference					
Female	1768 (21.6)	7072 (21.6)	–					
Age[a], yr (mean, SD)	43.6 (13.1)	43.6 (13.1)						
18–29	1241 (15.2)	4964 (15.2)	Reference			Reference		
30–39	2127 (26.0)	8508 (26.0)						
40–49	2468 (30.2)	9872 (30.2)						
50–59	1404 (17.2)	5616 (17.2)						
60–69	622 (7.6)	2488 (7.6)						
70–79	263 (3.2)	1052 (3.2)						
≥80	56 (0.7)	224 (0.7)						
Charlson comorbidity Index[d]								
0	4890 (59.8)	26154 (79.9)	Reference			Reference		
1	1807 (22.1)	4102 (12.5)	2.58	2.31 – 2.88	< 0.001*	1.51	1.30–1.75	< 0.001*
≥2	1484 (18.1)	2468 (7.5)	3.88	3.40–4.42	< 0.001*	1.69	1.43–2.00	< 0.001*
Urbanization[c]								
Level 1	2237 (27.3)	11461 (35.0)	Reference			Reference		
Level 2	2410 (29.5)	9994 (30.5)	1.23	1.11–1.37	< 0.001*	1.28	1.11–1.47	< 0.001*
Level 3	1134 (13.9)	4635 (14.2)	1.26	1.10–1.44	< 0.001*	1.51	1.26–1.81	< 0.001*
Level 4	1094 (13.4)	4032 (12.3)	1.40	1.22–1.60	< 0.001*	1.44	1.19–1.73	< 0.001*
Level 5	1306 (16.0)	2602 (8.0)	2.57	2.24–2.94	< 0.001*	2.69	2.23–3.26	< 0.001*
Employment[c]								
Yes	4481 (54.8)	22761 (69.6)	Reference			Reference		
No	3700 (45.2)	9963 (30.4)	2.00	1.83–2.19	< 0.001*	1.77	1.57–1.99	< 0.001*
Hospital type[d]								
Medical center	1708 (20.9)	2338 (7.1)	Reference			Reference		
Regional hospital	3583 (43.8)	3025 (9.2)	1.63	1.41–1.89	< 0.001*	1.56	1.34–1.82	< 0.001*
Local hospital	2308 (28.2)	3050 (9.3)	1.05	0.90–1.22	0.322	0.99	0.84–1.16	0.794
Local clinic	582 (7.1)	21964 (67.1)	0.04	0.03–0.04	< 0.001*	0.04	0.03–0.46	< 0.001*
No visit	0 (0.0)	2347 (7.2)	0.00	–	–	0.00	–	–

[a] Estimated using univariate conditional logistic regression.
[b] Estimated using multivariate conditional logistic regression (the model for case identification). We conducted the multivariate regression based on the strategy of backward variable selection. The variables with a very strong association (P < 0.001) were retained in the final model.
[c] At the (corresponding) index date.
[d] Cases: at the index date. Controls: the visit closest to the index date (within 1 year); if no visit within 1 year before or after the index date, then coded as "no visit".
* < 0.001.

2.5. Statistical analyses

We conducted conditional logistic regression analyses to investigate the association between all variables and the development of AD. The variables regarding medical utilization, such as admissions, outpatient visits, hospital expenditures, and the procedures examined within the 12 months before the index date were also analyzed.

The regression analysis was conducted using the Proc Phreg function of SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA). We set a rigorous significance level for this study, and a value of $p < 0.001$ was considered statistically significant for all analyses. We next conducted the multivariate regression based on the strategy of backward variable selection. The variables with a powerful association ($p < 0.001$) were retained in the final model.

Depending on the different dimensions, two explanatory models were used, i.e., the model for case identification (Table 1), and the model for physical comorbidity and concomitant medications (comorbidity model) (Table 2). First, we investigated the sociodemographic and clinical conditions at the time the cases were initially identified, including urbanization, unemployment, sex, age, hospital type, and Charlson comorbidity scale. Second, we explored comorbid physical illnesses and concomitant use of medications as the potential factors related to the development of AD.

3. Results

3.1. Demographic and clinical characteristics of cases and controls

Based on the nested case-control study design, Table 1 shows the matching characteristics of four controls for each case for which the distribution of sex and age between cases and controls are the same. Among the cases, there was a greater proportion of men than of women (78.4% vs. 21.6%), and patient age ranged from 30 to 49 years.

Based on univariate regression, the case group with newly diagnosed AD had higher Charlson comorbidity index scores in the year before the index date compared to the controls. Persons in less urbanized areas were more likely to become the cases with incident AD, and the risk showed an increased trend (e.g., level 5 had the highest risk, risk ratio [RR] = 2.69, p < 0.001). The cases with incident AD were likely to be unemployed compared to the controls (RR = 1.77, p < 0.001). Most patients with AD were identified at regional hospitals (RR = 1.56, p < 0.001). In general, the results of multivariate analyses were similar to the results of the univariate analyses.

3.2. Specialists who identified new alcohol dependence

Regarding the distribution of the specialties of the medical doctors who identified the incident AD cases, the department of internal medicine identified the highest proportion of cases (34.2%), followed by the emergency department (22.3%) and psychiatry department (18.7%) (Fig. 1).

Table 2
Patterns of physical comorbidity and concomitant use of medications within 12 months before the index date among patient with alcohol dependence (cases) and the control group (1:4), derived from a nationwide cohort, from 1997 to 2011 (N = 998,601).

Characteristics	Case (N = 8181)	Controls (N = 32724)	Unadjusted risk ratio[a]	99.9% CI	P-value	Adjusted risk ratio[b]	99.9% CI	P-value
Within 1 year before the index date	N (%)	N (%)						
Comorbid physical illnesses								
Cardiovascular disease	2297 (28.1)	5546 (15.7)	2.11	1.90–2.34	< 0.001			
Diabetes mellitus	726 (8.9)	1884 (5.8)	1.61	1.38–1.88	< 0.001			
Cerebrovascular disease	241 (3.0)	486 (1.5)	2.04	1.56–2.67	< 0.001			
Chronic hepatic disease	1676 (20.5)	2082 (6.4)	3.85	3.41–4.34	< 0.001	2.72	2.38–3.10	< 0.001*
Cancer	199 (2.4)	485 (1.5)	1.66	1.25–2.21	< 0.001			
Asthma	349 (4.3)	734 (2.2)	1.94	1.56–2.42	< 0.001	1.32	1.04–1.69	< 0.001*
Upper respiratory tract infection	1258 (15.4)	5065 (15.5)	0.97	0.87–1.10	0.451	0.80	0.70–0.90	< 0.001*
Delirium†	5 (0.1)	8 (0.0)	2.51	0.39–16.37	0.106			
Concomitant drugs								
Cardiovascular drugs								
Antihypertensive agents	311 (3.8)	921 (2.8)	1.38	1.10–1.73	< 0.001			
Beta blocking agents	1636 (20.0)	2910 (8.9)	2.67	2.38–3.00	< 0.001	1.30	1.12–1.49	< 0.001*
Calcium channel blockers	1224 (15.0)	2818 (8.6)	2.00	1.76–2.28	< 0.001	1.31	1.11–1.54	< 0.001*
Agents acting on the renin-angiotensin system	786 (9.6)	2232 (6.8)	1.48	1.27–1.73	< 0.001	0.82	0.68–0.99	< 0.001*
Lipid modifying agents	496 (6.1)	1400 (4.3)	1.43	1.20–1.72	< 0.001			
Respiratory drugs++	5678 (69.4)	20107 (61.4)	1.34	1.23–1.46	< 0.001			
Drugs used in diabetes	592 (7.2)	1599 (4.9)	1.51	1.28–1.79	< 0.001			
Antithrombotic agents	846 (10.3)	2197 (6.7)	1.67	1.44–1.94	< 0.001			
Corticosteroids for systemic use	2121 (25.9)	6201 (18.9)	1.48	1.35–1.63	< 0.001			
Anti-Parkinson drugs	423 (5.2)	741 (2.3)	2.32	1.89–2.84	< 0.001			
Mood stabilizers	353 (4.3)	435 (1.3)	3.28	2.59–4.17	< 0.001			
Antipsychotics	985 (12.0)	932 (2.9)	4.53	3.87–5.30	< 0.001	1.77	1.47–2.12	< 0.001*
Antidepressants	1176 (14.4)	1136 (3.5)	4.59	3.97–5.30	< 0.001	1.85	1.56–2.19	< 0.001*
Benzodiazepines	4036 (49.3)	6362 (19.4)	4.19	3.83–4.59	< 0.001	2.83	2.55–3.15	< 0.001*

[a] Estimated using univariate conditional logistic regression.

[b] Estimated using multivariate conditional logistic regression. Adjusted for physical illnesses and concomitant medications that remained in the final model. We conducted the multivariate regression based on the strategy of backward variable selection. The variables with a very strong association (P < 0.001) were retained in the final model.

† Based on ICD-9 code, including presenile dementia with delirium, senile dementia with delirium, arteriosclerotic dementia with delirium, alcohol withdrawal delirium, drug-induced delirium, acute delirium, subacute delirium.

++ Based on ATC code, including nasal preparations, throat preparations, drugs for obstructive airway diseases, cough and cold preparations, antihistamines for systemic use, other respiratory.system products.

* < 0.001.

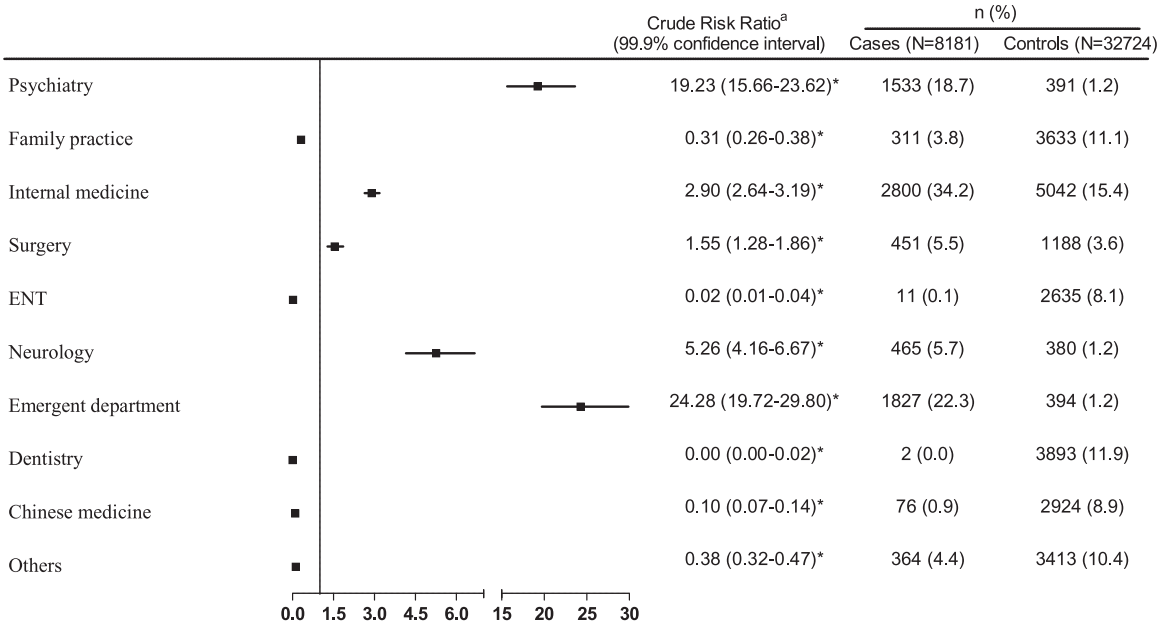

Fig. 1. Risk ratios for the departments of medical doctors who identified the incident cases of alcohol dependence relative to the control group (1:4) in the general population in Taiwan.
Note: ENT: ear, nose, and throat.
[a]Estimated using univariate conditional logistic regression.
*P < 0.001.

Compared to the general population, the patients who were first identified with AD were most likely to visit the emergency department (RR = 24.28, $p < 0.001$), followed by the psychiatry (RR = 19.23, $p < 0.001$) and neurology departments (risk ratio = 5.26, $p < 0.001$).

3.3. Physical comorbidity and concomitant medications before identification of alcohol dependence

As expected, the univariate analysis showed that case subjects had more comorbid physical illnesses and use of various medications within the year before AD was identified than controls (Table 2). More specifically, the multivariate analysis showed the variables remained significantly associated with the development of alcohol dependence with a strong effect size (adjusted RR > 2) including comorbid chronic hepatic disease (adjusted RR = 2.72, $p < 0.001$) and the use of benzodiazepines (adjusted RR = 2.83, $p < 0.001$). In addition, the variables with moderate effect size (adjusted RR = 1.5–2.0) included the use of antipsychotics (adjusted RR = 1.77, $p < 0.001$) and the use of antidepressants (adjusted RR = 1.85, $p < 0.001$).

3.4. Patterns of medical utilization within the 1 year before identification of alcohol dependence

Table 3 shows medical utilization within 1 year before the index date for cases and controls. Case subjects had more hospital admissions than control subjects, including both non-psychiatric and psychiatric hospitalizations. The numbers of outpatient visits were similar for both groups.

Further analyses showed that, among the specialists who case subjects had ever visited before the identification of AD, intriguingly, the department of internal medicine had the highest number of visits (mean, 3.9), then family practice (mean, 2.6), and Chinese medicine (mean, 1.5).

Additionally, case subjects had the highest mean number of digestive diseases (supplement, e-Table 1), followed by respiratory diseases, diseases of the musculoskeletal system, and injury, poisoning, and mental diseases.

As expected, the mean cumulative medical expenditure for cases was significantly higher than that of controls, including hospitalization and outpatient services. A majority of cases had undergone electrocardiographic examinations (EKG) (51.90%) and sonography (43.65%), which were significantly higher than in the control group. A substantial portion of cases had used endoscopy (17.46%), which was also higher than in the control group.

4. Discussion

The major strength of the present study is its representative, nationwide sample of the general population in the Taiwan healthcare system, in which we investigated the factors related to the first identification of AD and compared the patterns of medical utilization before the case identification with that of suitably matched controls.

We found that AD cases were strongly associated with comorbid chronic hepatic diseases and benzodiazepine usage before identification of AD. Patients with AD were more likely to visit the internal medicine department, emergency department, psychiatry, and then neurology clinics. AD patients rarely sought help within the addiction treatment system possibly due to a perceived stigma (Kohn et al., 2004). Understanding the health-seeking behavior patterns of AD patients could lead to the detection of alcohol-related problems earlier. This study provides valuable evidence-based information to understand the contexts in which AD patients seek healthcare and could increase the early detection rates of alcohol-related problems.

4.1. Risk factors for incident alcohol dependence

The results showed that the case subjects were predominantly men living in less urbanized areas and were unemployment. Moreover, the risk of alcohol dependence was counter-correlated to the degree of urbanization. Our findings were comparable to the epidemiologic data

Table 3
Patterns of medical utilization within 12 months before the index date among patients with alcohol dependence (cases) and control group (1: 4).

Characteristics	Case (N = 8181)	Controls (N = 32724)	Unadjusted risk ratio[a]	99.9% CI	P-value
Within 1 year before the index date					
Number of hospital admissions	Mean (SD)	Mean (SD)			
Non-psychiatric	0.36 (1.09)	0.10 (0.44)	2.02	1.93–2.12	< 0.001
Psychiatric	0.04 (0.30)	0.01 (0.13)	2.47	2.11–2.88	< 0.001
Number of outpatient visits					
Non-psychiatric	17.11 (18.88)	12.54 (14.77)	1.02	1.02–1.02	< 0.001
Psychiatric	1.04 (3.99)	0.23 (1.91)	1.11	1.10–1.12	< 0.001
Specialist (number of outpatient visits)[b]	Mean (SD)[a]	Mean (SD)[a]			
ALL	18.2 (19.9)	12.8 (15.0)	1.02	1.018–1.023	< 0.001
Psychiatry	1.0 (4.0)	0.2 (1.9)	1.11	1.095–1.131	< 0.001
Family practice	2.6 (6.6)	1.5 (4.7)	1.04	1.027–1.043	< 0.001
Internal medicine	3.9 (7.6)	2.5 (5.8)	1.04	1.029–1.042	< 0.001
Surgery	0.9 (2.8)	0.5 (2.0)	1.07	1.055–1.092	< 0.001
ENT	0.8 (2.7)	1.0 (2.6)	0.97	0.950–0.986	< 0.001
Neurology	0.3 (1.6)	0.2 (1.6)	1.03	1.005–1.055	< 0.001
Emergency department	0.5 (1.6)	0.1 (0.5)	2.10	1.947–2.244	< 0.001
Dentistry	0.9 (2.1)	1.1 (2.2)	0.95	0.933–0.974	< 0.001
Chinese medicine	1.5 (4.4)	1.4 (4.1)	1.01	0.996–1.015	0.072
Others	5.8 (9.4)	4.3 (7.4)	1.02	1.019–1.029	< 0.001
Prior 1 years mean (SD) cumulative medical expenditure, USD[c]					
Hospitalization	448.1 (1771.7)	142.3 (1074.0)	1.00	1.000–1.000	< 0.001
Outpatient service	569.3 (2554.6)	390.3 (1200.3)	1.00	1.000–1.000	< 0.001
Procedures done	N (%)	N (%)			
Sonography	3571 (43.65)	6053 (18.50)	2.66	2.401–2.951	< 0.001
Endoscopy	1428 (17.46)	2474 (7.56)	2.50	2.182–2.868	< 0.001
EKG[d]	4246 (51.90)	4709 (14.39)	3.88	3.487–4.309	< 0.001

[a] Analyzed by means of univariate conditional logistic regression.
[b] Mean number (SD) of visits per subject.
[c] US dollar (1 USD = 30 NTD).
[d] Electrocardiographic examination.

on AD in the U.S. showing that individuals with AD were men with low incomes; however, our results for urbanization differed from those in the U.S. (Grant et al., 2015; Hasin et al., 2007). In a meta-analysis, there was no urban-rural difference in substance use disorders (Peen et al., 2010). In an Indian door-to-door survey, alcohol use was greater in transitional towns than in urban or rural regions(Girish et al., 2010). Another meta-analysis in India showed a higher prevalence of AD in rural than in urban areas (Singh and Pradhan, 1999). A possible explanation for the inconsistency remains speculative but includes the application of different instruments, methodologies, and the various cultural backgrounds.

4.2. Identification of alcohol use disorder by specialty

Research on psychiatrists newly identifying incident AD was quite rare. Interestingly, in the present study, almost one-fifth (18.7%) of the incident AD cases were identified by psychiatrists, internists and emergency physicians identified most cases. These findings add valuable evidence-based information for developing effective strategies for intervention. We assume that the poor general health of patients with AD, including digestive problems and alcohol-related trauma and mental disorders, would prompt these patients to visit the specialists frequently and raise the doctors' awareness of the AD problem.

According to our data, internists and emergency physicians are in prominent positions to identify AD; therefore, enhancing screening for unhealthy alcohol use and early intervention in such medical settings could improve the consequences. Our data are consistent with the results of prior studies reporting that substantial portions of AD cases are identified in the emergency department (Crane, 2013; Mullins et al., 2017). However, the present study showed the cases were more likely to be identified in the department of internal medicine instead of family practice, which is inconsistent with prior studies (Cherpitel and Ye, 2008; Dawson et al., 2012; Rehm et al., 2015a). In Taiwan, there is a medical referral system for specialists, but its use is not mandatory. Thus, people could visit a medical specialist without the referral of a primary care physician. One possible explanation for cases to have been identified by an internal medicine specialist is the easier accessibility to the specialized department of medicine in this study. The differences in medical seeking behaviors of Taiwanese and Western patients might partially account for the discrepancy.

4.3. Physical comorbidity and concomitant medications used before identification of alcohol dependence

Based on multivariate analysis, there was much higher mean frequency of chronic hepatic disease in the AD group than the general population within 1 year before the diagnosis. Alcohol is well-known to be associated with liver and pancreatic diseases (Rehm et al., 2010).

Based on the alcohol-related causes of death as an index marker, some studies (Holst et al., 2017; Rehm et al., 2012) showed liver diseases having the highest risk of death in those with AD. A recent national cohort study in Denmark showed AD patients had higher hazards of liver disease in comparison to the control population (Holst et al., 2017). Additionally, in a large European study, liver cirrhosis was the leading death cause both in men and women with AD, followed by cancer and cardiovascular disease (Rehm et al., 2012).

In contrast, some studies reported cardiovascular disease accounted for the majority of alcohol-related deaths. In Norwegian long-term prospective study, the leading cause of death among AD was cardiovascular diseases, then malignant tumors and accidents (Rossow and Amundsen, 1997). In a Swedish long-term follow-up community cohort, diseases of the circulatory system accounted for up to 50% of the causes of death in alcohol-related disorders (Ojesjo et al., 1998).

Our findings were in line with those of Chen et al. (2001) conducted in Taiwan, whose study indicated the leading cause of death among patients with AD was a gastrointestinal disease (mostly hepatic disease), followed by cardiovascular diseases. Additionally, the high prevalence of hepatitis B virus infection in Taiwan (Yang et al., 2011) might also have accounted for this discrepancy.

Our study showed that patients with AD used more benzodiazepines, antipsychotics, and antidepressants before the identification of AD. These findings suggest that individuals developing AD subsequently had a severe form of alcohol use disorder and needed medication due to possible anticipated alcohol-related consequences.

4.4. Medical utilization before identification of alcohol dependence

Our findings showed that both numbers of psychiatric and non-psychiatric admissions and outpatient visits were larger in AD patients than in controls within 1 year before AD was diagnosed. The utilization of procedures including EKG, sonography, and endoscopy was also higher in AD cases than in controls before the identification of AD. This phenomenon may imply that the case subjects had a poor physical condition before they were identified, confirming earlier findings of a high frequency of physical problems in patients with alcohol use disorder (Cargiulo, 2007; Chen et al., 2001; Rehm et al., 2009; Rehm et al., 2003; Room et al., 2005; World Health Organization, 2014).

Due to the higher frequency of medical setting visits and procedure usage, the cumulative medical expenditure in cases was much higher than in the control group, as we expected. This finding reconfirms that of Laramee et al., who reported excessive alcohol consumption represents a significant health system burden in Europe (Laramee et al., 2013).

It is noteworthy that AD patients were more likely to visit the emergency department, then psychiatry and neurology than general population before they were diagnosed with AD. This use of resources may indicate that the AD patients had more comorbidity such as injury, psychiatry disorders, and negative impact on the nervous system compared to that of the general population even they had not already been diagnosed. This finding was in agreement with that of previous studies (Grant et al., 2015; Harper and Kril, 1990; Helzer and Pryzbeck, 1988; Li et al., 1998; Rehm et al., 2015b).

Although the use of the internal medicine, family practice, and Chinese medicine outpatient departments occurred in the same order for AD patients and controls, the mean frequency of outpatient visits was higher in the AD group. One caveat is the low rate of AD identified by family practice clinicians in our study. The result reconfirms that of Rehm et al., who reported AD was prevalent among patients in primary health care settings, with low treatment rates (Rehm et al., 2015b). Although general practitioners (or family practitioners in our study) were one of the key physician groups to recognize AD in our study, appropriate public health interventions are warranted, such as enhancing the family practitioners' ability to identify AD in patients and provide adequate treatment.

4.5. Medical utilization and costs

In contrast to our study, some studies did not show that AD patients had higher utilization than controls. In a 5-year follow-up study (Kline-Simon et al., 2014), compared to the alcohol-free group, heavy drinkers had increased emergency department and inpatient utilization, with no difference in primary care costs between the two groups. In an Australian National Survey of Mental Health and Wellbeing (Proudfoot and Teesson, 2009; Proudfoot et al., 2002), AD did not predict more utilization, despite the higher frequency of visits to general practitioners for comorbid mental disorders. One possible explanation is that heavy drinkers had to overcome the stigma of AD and hesitated to use health care services (Fleury et al., 2014). However, the present study revealed higher medication utilization of inpatient and outpatient services. One explanation for higher usage could be the high coverage rate of the NHI system in Taiwan and easy access to the health care delivery system, which could have overcome the possible stigma.

4.6. Limitations

The findings in this study are limited in several ways. First, the patients with AD were identified by the physicians in various medical departments who might not have received the reliability study for the diagnosis of AD based on DSM diagnostic system. However, physicians recognize that AD, a severe form of alcohol use disorder, has a long-term course and poor consequences.

Second, heavy drinkers had to overcome the stigma associated with AD to use health care services (Fleury et al., 2014). Thus, some people with AD in the community did not seek medical help and were not included in the database.

Third, the case group could have lower rates of adherence to treatment and regular follow-up than the controls. Such a condition tends to be underestimated for the analysis of the medical utilization.

Fourth, this study identified 8181 cases with AD derived from a large-scale cohort (N = 998,601), which indicates a substantial portion of individuals with AD remained unrecognized. The AD cases identified in this study were in a more severe state of AD due to the medical departments they more frequently visited (such as emergency, neurology, and psychiatry), as well as the type of physical comorbidity present (e.g., hepatic disease). Further community-based research is needed to learn how to detect the unrecognized individuals with alcohol-related problems who were not retrieved in the health care delivery system and provide intervention before the severity of AD becomes grave.

5. Conclusions

The results showed that before the identification of AD, patients were more likely to visit the departments of internal medicine, emergency medicine, and then psychiatry and neurology. This pattern of high usage of medical specialties places an increased burden on the health care service system. AD patients had a higher risk of chronic hepatic disease and benzodiazepine usage before identification of AD. Based on these clinical findings, this study highlights that clinicians providing care in diverse medical settings (i.e., internal medicine, emergency department, psychiatry) should be prepared to screen for unhealthy alcohol use and mitigate the consequences of unhealthy alcohol use through counseling, pharmacotherapy, or referral to an abstinence program. Earlier treatment of AD could improve the overall health of the people and reduce the economic burden of AD.

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Contributors

CHP and CJK led the conception and design of the research study. CHP and CJK wrote and revised the manuscript. TWP, MCH, and CCC were responsible for field investigation. SSS performed the experiments. CJK, YNH, and CCC conducted the analysis and participated in the data interpretation. CHP, MSL, and CJK reviewed and edited the manuscript. All authors approved the final version of the submitted manuscript. YNH, MSL, and CJK contributed equally to this article.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2018.03.046.

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