Chulalongkorn Medical Journal

Volume 66 | Issue 1 Article 8

1-1-2022

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Recommended Citation

Kalayasiri, Rasmon and Sareedenchai, Pairoj (2022) "Associated factors of delirium tremens in the inpatients receiving psychiatric consultation-liaison service for alcohol-related problems," *Chulalongkorn Medical Journal*: Vol. 66: Iss. 1, Article 8.
DOI: 10.14456/clmj.2022.8
Available at: https://digital.car.chula.ac.th/clmjournal/vol66/iss1/8

Original article

Associated factors of delirium tremens in the inpatients receiving psychiatric consultation-liaison service for alcohol-related problems

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Background: Alcohol withdrawal delirium or delirium tremens (DTs) is found variably between 3.0 - 48.5% in different settings.
Objective: The study aims to investigate the prevalence of DTs in the inpatients of a university hospital who had alcohol use problems and were sent to receive psychiatric consultation-liaison service and to identify related factors for DTs in this cohort.
Methods: Demographics, alcohol use variables, and blood chemistry were obtained from fifty-three inpatients with alcohol problems that were sent to receive psychiatric consultation-liaison service at the Department of Psychiatry, King Chulalongkorn Memorial Hospital, Thailand. The severity of alcohol withdrawals and delirium were measured by using the Clinical Institute Withdrawal Scale for Alcohol-revised (CIWA-Ar) and the Delirium Rating Scale-Revised 98 (DRS-R-98), respectively.
Results: Of the 53 inpatients, 50 (94.3%) were male (mean age 45 years) and 31 (58.5%) had DTs. Patients with DTs were more likely to have a trend toward drinking the higher amount of maximum alcohol consumption per day (> 30 standard drinking units) and drinking liquor than the non-DTs group. Level of bicarbonate, creatinine, aspartate transaminase were associated with DTs at admission ($P < 0.05$). Abnormal alkaline phosphatase level was associated and nearly associated with severity of delirium and alcohol withdrawal symptoms respectively. Logistic regression analysis showed that bicarbonate and creatinine were risk factors for DTs.
Conclusion: Prevalence of DTs is high in the inpatients receiving psychiatric consultation-liaison service for alcohol-related problems. Blood chemistry, especially those involved with kidney and liver function at the time of admission, may be used to predict the occurrence and severity of DTs.

Keywords: Alcohol, alcohol withdrawal, delirium tremens, consultation-liaison.

The use of alcohol, a central nervous system depressant, is legal in almost all of the countries. In 2011, an estimation of 73.6 million of global population misused alcohol, and 2.5 million died from the alcohol related causes each year. [1] In Thailand, number of adult drinkers (aged 15 years or more) has been estimated to increase from 29.3% in 2007 to 34.5% in 2014 [2] who consumed unusual high amount of pure alcohol of 21 litres per person in 2014. [3]

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Received: January 29, 2020
Revised: April 27, 2021
Accepted: May 18, 2021

Alcohol consumption causes acute and long-term effects on host's physical health and mental health. Alcohol use is ranking the eighth leading risk factor for death and the third leading risk factor for disease and disability globally in 2004. In 2015, alcohol use accounted for 5.9% of deaths in males and 4.0% in females. [4] When individuals with chronic alcohol users stop or reduce their drinking, they may experience withdrawal symptoms. The withdrawal symptoms may accelerate to a severe withdrawal syndrome called alcohol withdrawal delirium or delirium tremens (DTs); a severe form of the alcohol withdrawal syndrome occurs in chronic heavy alcohol drinkers after a few days of the reduction of the amount of alcohol consumption. DTs is characterised by having other alcohol withdrawal symptoms with

the disturbance of consciousness (i.e., disorientation to time, place, and person), hallucination and autonomic hyperactivity. [5]

Previous study revealed a low prevalence of alcohol withdrawal symptoms in adult population with alcohol dependence. [6] However, in a hospital setting, the prevalence of DTs was 12.8% of the medical and surgical patients with alcohol dependence. [7] The prevalence of DTs is ranging between 3.0% and 49.0% among drinkers with alcohol dependence in various settings of the studied population.[7 - 11] DTs may complicate other medical conditions that may extend the hospital stay. Similar to high mortality among patients with delirium of organic causes [12], the mortality rate of DTs is about 10.0% among patients at risk.[13]

Prevalence and predictors of DTs in the psychiatric consultation-liaison service are lacking despite the high prevalence of patients with alcohol problems in medical and surgical hospital wards that may request for the service. In general, several factors were found to be associated with the occurrence of DTs including long latency to the peak of alcohol withdrawal severity, having history of severe alcohol withdrawal symptoms, brain lesions, low platelet concentration, low plasma potassium [8, 14], unstable vital signs (i.e, high blood pressure, fever [10], or increased pulse rate [15, 16]), and/or abnormal serum enzymes (i.e., alanine aminotransferase [11, 17], creatinine kinase [18]).

Nevertheless, a systematic review and meta-analysis revealed that having a prior episode of DTs is the most reliable predictor for DTs and well established while some laboratory results, such as low platelet count and low potassium level, are correlated with DTs and still inconclusive.[19] Further study on other demographics and drinking pattern as predictors for DTs is suggested. Our study aims to study the prevalence of DTs, related factors for DTs and severity of DTs in the inpatients who have alcohol use problems and being sent for psychiatric consultation-liaison service at a tertiary-care, university-based treatment centre in Bangkok, Thailand.

Materials and methods

Demographics, alcohol-use pattern, the occurrence of DTs, and recent available laboratory results including complete blood count, liver function test, blood urea nitrogen, creatinine, and electrolytes were obtained from the Hospital Psychiatric Consultation Form of the fifty-three medical and/or surgical inpatients, aged 18 years or more, who had alcohol- related problems that were sent to receive the consultation-liaison service from the Department of Psychiatry, King Chulalongkorn Memorial Hospital between July 2012 - December 2012. This is a cross-sectional descriptive study planned before the year 2012. Alcohol-related issues that caused the patients to receive the service included alcohol abuse/ dependence, alcohol withdrawal symptoms or suspicious of alcohol withdrawal symptoms. All above individuals were included by using convenience sampling. Sample size was calculated by using Taro Yamane formula. DTs was determined based on Diagnostic and Statistical Manual of Mental Disorders - Fourth Version (DSM-IV) [20] by the clinical diagnosis performed by psychiatric residents and confirmed by an attending psychiatrist at the consultation-liaison service and by the Delirium Rating Scale-Revised 98 (DRS-R-98), Thai version. Informed consent was obtained from each participant. The Ethics Committee of the Faculty of Medicine, Chulalongkorn University has approved the study (IRB no. 112/55).

Measurement

Clinical Institute Withdrawal Scale for Alcohol-Revised (CIWA-Ar), Thai version and DRS-R-98, Thai version were used to assess patients once a day for severity of alcohol withdrawal and severity of delirium, respectively at the time of the consultation-liaison request for at least three days (the average duration of delirium after alcohol drinking cessation). The highest score of the three days was used for further analysis to ensure the endorsement of non-DTs. In case of DTs, the assessment was continued until the patients were recovered (CIWA-Ar = 15 or lower). The CIWA-Ar was developed in 1978 with 15 items and decreased to 10 items by Sullivan JT, *et al*. in 1989 [21], comprised symptoms of nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, and headache with scores ranging between 0 - 7 and orientation and clouding of sensorium with scores ranging between 0 - 4. Mild, moderate, and severe alcohol withdrawal symptoms were determined by taking the sum of the score 0 - 7, 8 - 15, and 15 or more, respectively.

DRS-R-98 was used to diagnose delirium with higher sensitivity (92.0%) and specificity (92.0%) [22] comprised of 16 items, which examining disturbances

of sleep-wake cycle, hallucinations, delusions, emotional instability, language and process of thinking, agitation, retardation, disturbances of orientation to time, place, or person, attention, short term and long term memory, and visuospatial function. The Thai version had high sensitivity (97.0%) and specificity (91.0%).[23] The cut-off point at score 15 was used in the Thai version.

Laboratory findings, including complete blood count, electrolytes, blood urea nitrogen, creatinine, and liver function test, were obtained at the beginning of receiving psychiatric consultation-liaison service. Vital signs, including systolic and diastolic blood pressure, pulse rate, and body temperature, were also recorded.

Statistical analysis

Continuous variables including age, age of alcohol use onset, duration of alcohol drinking, and maximum standard drinks per day were tested for distribution and subjected to being recorded as categorical variables in non-normal distribution. Standard drink unit was calculated based on the Semi-Structured Assessment for Drug Dependence and Alcoholism - Thai version's alcohol equivalencies (1 litre of liquor = 25.4 units, 1 large bottle of beer = 2 units). Laboratory results and vital signs were presented as abnormal or not by using references from the hospital's cut-off point. Chi-square test and Fisher's Exact Test were used to compare demographics, pattern of alcohol use, laboratory results and vital signs between individuals with and without DTs. Two-tail unpaired Student's *t* - test was used to compare severity scores of alcohol withdrawals among demographics, pattern of alcohol use, laboratory results and vital signs. Significant or nearly significant variables ($P < 0.1$) from initial analyses were subjected to enter into the logistic regression analysis, forward LR, to control for the occurrence of DTs. Each participant was excluded if the variables were missing. P - value < 0.05 was considered as statistically significant.

Results

Demographic data and alcohol/substance-use variables

Almost all of the participants were male. The mean age of the studied sample was 45.5 ± 10.2 years, and the mean age of alcohol use onset was 22.3 ± 7.9 years. The average duration of continued alcohol drinking was 22.3 ± 11.4 years, and the average maximum amount of alcohol per day was 32.4 ± 24.5 standard drinking units. The average number of days from alcohol cessation before the time of receiving current consultation-liaison service was 2.4 ± 2.1 days.

Of the 53 inpatients, 31 (58.5%) had DTs during the time of current hospitalisation with the mean duration was 1.9 ± 1.8 days. There was a trend that the DTs group was more likely to report maximum drinking more than 30 drinks per day and more likely to report drinking liquor than non-DTs group (41.9% *vs* 18.2% $P = 0.068$ and 80.7% *vs* 59.1% $P = 0.086$, respectively), however, these findings did not reach the significant level ($P > 0.05$). In addition, there was a trend that individuals with earlier onset of alcohol use at age 18 years or less had more severe alcohol withdrawal symptoms than later onset of alcohol use (CIWA-Ar score = 26.2 ± 112.8 (n = 14) vs 16.6 ± 10.6 (n = 10); $P = 0.074$, two - tail *t* - test). Inpatients who had a duration of DTs for three days or more had higher scores on alcohol withdrawal symptoms (34.6 ± 5.7 *vs* 13.4 ± 7.7; $P < 0.001$) and on delirium (33.2 ± 4.3 *vs* 15.8 ± 10.2; $P < 0.001$) than those with fewer than three days of duration of DTs ($P < 0.001$). None of the other alcohol or substance use variables, including cigarette smoking and duration of alcohol drinking and the demographic variables, including gender, age, current marital status, and the reasons for current admission, was associated with the occurrence of DTs (Table 1) or the severity of alcohol withdrawal symptoms or severity of delirium ($P > 0.05$).

Laboratory results of complete blood count and blood chemistry

A panel of blood chemistry, including bicarbonate, creatinine, aspartate transaminase (SGOT) was associated with the occurrence of DTs ($P < 0.05$) (Table 2). In addition, individuals with abnormal alkaline phosphatase level had more score on delirium scale (34.7 ± 2.1 *vs* 20.7 ± 11.7; $P = 0.02$) and a trend toward having more severe alcohol withdrawal symptoms (33.2 ± 5.0 *vs* 20.0 ± 12.6; $P = 0.075$) than those with normal level. Interestingly, individuals with abnormal bicarbonate had a trend toward having a lower level of delirium and alcohol withdrawal symptoms ($P < 0.1$).

Multivariate analysis

Logistic regression analysis, forward LR by entering age, gender, maximum amount of alcohol drinking per day, liquor use, and abnormal blood chemistry in the model show that normal level of bicarbonate and abnormal kidney function, including creatinine were associated with the occurrence of DTs in the studied sample (P = 0.020, ORs = 0.219, $Wald_1$ = 5.390 and P = 0.035, ORs = 4.089, $Wald_1$ = 4.451, respectively) (Table 3).

Table 1. Demographics and pattern of alcohol use of individuals receiving consultation-liaison services because of alcohol problems with and without DTs.

	DTs (n = 31)		Non-DTs (n = 22)		*P* - values
	n	%	n	%	
Demographics					
Gender					
Female	2	6.5	1	4.5	1.000[a]
Male	29	93.5	21	95.5	
Age (years)					
≤ 44	18	58.1	10	45.4	0.365
≥ 45	13	41.9	12	54.6	
Current marital status					
Married	16	51.6	15	68.2	0.228
Not married	15	48.4	7	31.8	
Reasons for current admission					
Alcohol withdrawal	13	41.9	10	45.5	0.799
Other medical conditions	18	58.1	12	54.5	
Cigarette smoking	16	51.1	11	50.0	0.908
Alcohol-use variables					
Age of alcohol onset (years)					
≤ 18	11	35.5	5	22.7	0.319
> 18	20	64.5	17	77.3	
Maximum alcohol (standard drinks) per day					
≤ 30	18	58.1	18	81.8	0.068
> 30	13	41.9	4	18.2	
Duration of alcohol drinking (years)					
≤ 25	23	74.2	14	63.6	0.409
> 25	8	25.8	8	36.4	
Types of alcoholic beverages					
Beer	9	40.9	10	45.4	0.219
Liquor	25	80.7	13	59.1	0.086

[a] Fisher's Exact Test

Table 2. Abnormal vital sign and laboratory blood chemistry of individuals receiving consultation-liaison services because of alcohol problems with and without DTs.

	DTs (n = 31)		Non-DTs (n = 22)		*P* - values
	N	%	N	%	
Vital signs[b]					
Abnormal systolic blood pressure	18	58.1	8	34.8	0.119
Abnormal diastolic blood pressure	12	38.7	6	27.3	0.386
Abnormal pulse rate	13	41.9	6	27.3	0.273
Abnormal respiratory rate	5	16.1	5	22.7	0.724[a]
Fever	2	6.5	1	4.6	1.000[a]
Blood chemistry and complete blood count[c]					
Abnormal hematocrit	10	32.3	9	40.9	0.518
Abnormal MCV[d]	11	35.5	7	31.8	0.781
Abnormal white blood cell count	7	22.6	5	22.7	1.000[a]
Abnormal platelet count	20	64.5	13	59.1	0.688
Abnormal sodium	15	48.4	6	28.6	0.153
Abnormal potassium	19	61.3	8	34.8	0.100
Abnormal chloride	17	54.8	7	33.3	0.127
Abnormal bicarbonate	7	22.6	13	61.9	0.004**
Abnormal total protein	5	16.7	6	30.0	0.311[a]
Abnormal albumin	8	25.8	9	42.9	0.198
Abnormal total bilirubin	17	56.7	11	52.4	0.762
Abnormal direct bilirubin	29	96.7	19	90.5	0.561[a]
Abnormal SGOT[d]	31	100	17	81.0	0.022*,[a]
Abnormal SGPT[d]	20	64.5	10	47.6	0.226
Abnormal alkaline phosphatase	10	33.3	4	19.1	0.261
Abnormal calcium	11	40.7	6	31.6	0.256
Abnormal phosphate	11	36.7	7	35.0	0.904
Abnormal blood urea nitrogen	12	38.1	7	33.3	0.693
Abnormal creatinine	19	61.3	5	23.8	0.008**
Abnormal magnesium	12	40.0	8	42.1	0.884

* *P* - values < 0.05, Chi-square test
** *P* - values < 0.01, Chi-square test
[a] Fisher's Exact Test
[b] Abnormalities were determined by blood pressure > 140/90 mmHg, pulse rate > 100 beats per minute, respiratory rate > 20 per minute, and body temperature > 37.8°C.
[c] Reference of abnormal laboratory result from the hospital's cut-off point. Hypo- or hyper- values were grouped as abnormal for statistical analysis purpose.
[d] MCV = mean corpuscular volume, SGOT = Serum glutamic-oxaloacetic transaminase, SGPT = Serum glutamic-pyruvate transaminase

Table 3. Logistic regression analysis for the risk factors of the occurrence of DTs.

	B	SE	Wald	*P* - values	Odds ratio
Abnormal bicarbonate	-1.517	0.653	5.390	0.020	0.219
Abnormal creatinine	1.408	0.668	4.451	0.035	4.089
Constant	-0.211	1.553	0.018	0.892	0.810

* $P < 0.05$, binary logistic regression analysis, forward LR by entering age, gender, maximum amount of alcohol drinking per day, liquor use, and abnormal blood chemistry found in the chi square analysis.

Discussion

The prevalence of alcohol withdrawal syndrome was high among medical and/or surgical inpatients with alcohol problems who were sent for psychiatric consultation service for alcohol-related problems. Our results support the notion that blood chemistry may be used as risk factors for DTs. Several variables known for being risk factors for DTs from previous studies were identified to have a trend associated with DTs in the present study, including amount of alcohol consumption and type of alcoholic beverages. The longer duration of DTs was associated with the more severe alcohol withdrawal and delirium. To our knowledge, this study is the first to study the prevalence and related factors of DTs of the alcohol-related inpatients receiving psychiatric consultation-liaison service.

The present study shows the prevalence of DTs in the extreme alcohol use population that usually had high amount and long duration of alcohol consumption until having alcohol related problems and/or complication that needs medical attention. Prevalence of DTs in the present study, therefore, was different from previous studies that investigated DTs in different settings. For example, of the population voluntarily to receive treatment for alcohol dependence, only 8.0% had DTs.[6] In a general hospital inpatient setting, of the patients with chronic alcohol dependence, 13.5% had DTs.[9] Surprisingly, a study from a Thai hospital found a high prevalence of DTs (52.6%) in persons came to the hospital for alcohol detoxification [24] which is comparable to the present study. The mortality rate was of around 20.0% in DTs and around 50.0% after 1 year of having delirium in the Intensive Care Unit [12], nevertheless, no death was found in the current studied sample, partly may be due to that the patients were in a special service.

The present study found that blood chemistry, especially those related to kidney function and liver function, is a risk factor of the occurrence and/or severity of DTs. The kidney is an organ responsible for eliminating byproduct and waste from the body. When the kidney does not function well, the waste, including blood urea nitrogen and creatinine, will accumulate in the body. Alcohol consumption can cause the reduction of blood creatinine level [25] and/or increase calculated creatinine clearance and glomerular filtration rate.[26] In contrast, abnormal creatinine, as a result of alcohol intake, is found in the animal study.[27] Abnormal creatinine is also associated with DTs in previous studies. [28]

The present study shows that bicarbonate is also a risk factor for DTs. Another critical function of the kidney is to maintain body's electrolytes such as salt and potassium, maintain acid-base balance by excreting hydrogen ion, and to absorb bicarbonate from the urine. In previous studies, acid-base imbalance was found in DTs [29], though maybe inconsistent in an animal study.[30] The mechanisms of acid-base imbalance that may be used to explain the phenomenon including abnormal respiratory rate and abnormal level of electrolytes. For example, alcohol drinking causes increased respiratory rate that may result in respiratory alkalosis. However, when high amount of alcohol was consumed, it can cause respiratory depression leading to respiratory acidosis. The respiratory acidosis may then affect blood bicarbonate level.

Abnormal level of aspartate transaminase or SGOT, an enzyme produced by the liver, is associated with the occurrence of DTs though did not pass the statistical significance in the logistic regression analysis. Almost the entire of the studied sample had an abnormal level of SGOT confirming that chronic and high amount of alcohol drinking can result in abnormal liver function. To diagnose alcoholic hepatitis, both SGOT and alanine aminotransferase or SGPT are usually 2 - 7 times higher than normal and the ratio is higher than 1. Having hepatitis may also be one of the risk factors for the chronic alcohol drinker to have DTs. One study found that normal SGOT and mean corpuscular volume at admission nearly exclude the possibility of having DTs at a trauma service.[31]

Alkaline phosphatase, another liver enzyme, is associated with severity of DTs. Alkaline phosphatase was found to be associated with delirium from other general medical conditions or DTs. [17, 32] Nevertheless, no evidence clearly supported that alkaline phosphatase can differentiate between DTs and non-DTs, but the enzyme is increased in the persons who had a biliary obstruction. Biliary obstruction usually was found in severe liver disease which may result in the accumulated bilirubin. Though not found associated to DTs in the present study, previous studies found that bilirubin is a risk factor for delirium from medical conditions in intensive care unit and may be the cause of abnormal brain dysfunction.[33, 34]

Other factors, though did not pass the statistical significance in the logistic regression and had only a

trend statistical significance in the initial analysis, deserve mentions. High amount of alcohol consumption usually reflects the severity of alcohol use which, in turn, results in the poor health condition that may precipitate the severe withdrawal syndrome. Liquor is a type of alcoholic beverages that has a high degree (about 40.0% of pure alcohol) and may result in more severe effects from alcohol in persons who select liquor as alcohol type of preference. In addition, people who started drinking at a younger age had higher severity of DTs. The brain usually fully developed at age 25 - 30, therefore, starting psychoactive substance especially alcohol which is a central nervous system depressant during early age may prime the brain for a further poor outcome from chronic alcohol use than those who start drinking at later onset.

Selection bias is a significant limitation of the study. Since inpatients with alcohol problems who were sent for psychiatric consultation service usually had some symptoms that might interfere the major diseases that were the reasons for hospitalisation which was mainly alcohol withdrawal. Therefore, the persons with alcohol problems in the study usually had severe alcohol problems and had more tendencies to develop DTs resulting in the high prevalence of DTs in the present setting. Demographics and drinking pattern were obtained directly from the participants and subjected to recall bias, being underreport, or inaccuracy. In addition, several known predictors for DTs were not included in the present study. Our study had a small sample size and could be considered as a pilot study for finding the risk factors for DTs to predict having DTs in the current setting. Lastly, some of the non-DTs group had alcohol withdrawal symptoms but not severe to have DTs. The study that includes patients without alcohol withdrawal symptoms as a control group may show different results from the present study. Nevertheless, the result may be used to increase awareness at the time of admission patients to the service to prevent the occurrence of DTs in medical patients admitted to staying in a hospital.

Conclusion

Prevalence of DTs is high in the inpatients receiving psychiatric consultation-liaison service for alcohol-related problems at a tertiary-care, university-based treatment. High amount of maximum alcohol consumption per day (> 30 standard drinking units), drinking liquor, blood chemistry, especially those involved with kidney and liver function at the time of admission, were associated with DTs. Logistic regression analysis showed that bicarbonate and creatinine were risk factors for DTs and may be used to predict the occurrence and severity of DTs.

Acknowledgements

We would like to thank participants and staff of King Chulalongkorn Memorial Hospital (KCMH) for facilitating data collection. Rasmon Kalayasiri is supported by the Centre for Addiction Studies (CADS), Thailand Health Promotion Foundation and the Fogarty International Center of the National Institutes of Health (NIH) under the subaward of the award number D43TW009087 for research activities.

Conflict of interest

The authors, hereby, declare no conflict of interest.

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