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RESEARCH REPORT

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Mortality and alcohol-related morbidity in patients with delirium tremens, alcohol withdrawal state or alcohol dependence in Norway: A register-based prospective cohort study

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Abstract

Background and Aims: Little is known about long-term consequences of delirium tremens (DT). This study aimed to compare all-cause and cause-specific mortality and alcohol-related morbidity between patients with: (i) DT, (ii) alcohol withdrawal state (AWS) and (iii) alcohol dependence (AD).

Design: A national longitudinal health registry study with linked data from the Norwegian Patient Registry and the Norwegian Cause of Death Registry.

Setting: Norway.

Participants: All patients registered in the Norwegian Patient Registry between 2009 and 2015 with a diagnosis of AD (ICD-10 code F10.2), AWS (F10.3) or DT (F10.4) and aged 20–79 years were included (n = 36 287).

Measurements: Patients were categorized into three mutually exclusive groups; those with DT diagnosis were categorized as DT patients regardless of whether or not they had received another alcohol use disorder diagnosis during the observation period or not. Outcome measures were: annual mortality rate, standardized mortality ratios (SMR) for all-cause and cause-specific mortality and proportion of alcohol-related morbidities which were registered in the period from 2 years before to 1 year after the index diagnosis.

Findings: DT patients had higher annual mortality rate (8.0%) than AWS (5.0%) and AD (3.6%) patients, respectively. DT patients had higher mortality [SMR = 9.8, 95% confidence interval (CI) = 8.9–10.7] than AD patients (SMR = 7.0, 95% CI = 6.8–7.2) and AWS patients (SMR = 7.8, 95% CI = 7.2–8.4). SMR was particularly elevated for unnatural causes of death, and more so for DT patients (SMR = 26.9, 95% CI = 21.7–33.4) than for AD patients (SMR = 15.2, 95% CI = 14.2–16.3) or AWS patients (SMR = 20.1, 95% CI = 16.9–23.9). For all comorbidities, we observed a higher proportion among DT patients than among AWS or AD patients (P < 0.001).

Conclusions: People treated for delirium tremens appear to have higher rates of mortality and comorbidity than people with other alcohol use disorders.

KEYWORDS
Alcohol use disorder, alcohol withdrawal, alcohol-related morbidity, delirium tremens, mortality, standardized mortality rates

INTRODUCTION

Alcohol use disorder (AUD) causes substantial morbidity and mortality [1,2]. Among AUD patients, approximately half experience major withdrawal symptoms when tapering alcohol consumption. Delirium tremens (DT) is the most severe form of alcohol withdrawal; potentially life-threatening and particularly resource-demanding [3]. DT occurs in a small proportion of AUD patients, ranging from 3 to 15% [1, 4–7], although higher prevalence has been observed [8].

DT develops after sudden cessation or reduction of heavy and prolonged drinking, most often 2–4 days after last alcohol intake [4]. The condition is characterized by a state of confusion and autonomous hyperactivity. Impairment of cognitive function, attention, memory and/or consciousness is often seen. Many DT patients experience hallucinations—most often visual, although they may be tactile or auditory. There is often psychomotor agitation and disturbed sleep. Other clinical features include tachycardia and hypertension, increased sweating and fever, but also anxiety [9].

The natural course of DT will usually run to 3–4 days but may last up to 8 days, most often ending with a period of prolonged sleep. Untreated in this phase, DT has a high mortality, perhaps up to 35% [10]. Treated correctly, mortality can be significantly reduced [11]. Correct treatment usually involves hospitalization, and the goal of the treatment is to control agitation and decrease the risk of seizures, injury and death [7]. The condition should be monitored during treatment in hospital using a validated and clinically useful scoring instrument, such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) [4, 12].

While the literature on alcohol withdrawal state (AWS) and DT is somewhat extensive with regard to short-term treatment regimens, predisposing factors and short-term outcomes in the clinical setting [4, 13], few studies have examined the long-term outcomes of AWS and DT [4]. Wolters *et al*. found that DT patients, compared to other intensive care patients, had a higher crude mortality risk and poorer cognitive function at 1 year follow-up [14]. One study from Finland [15] reported that 31% of DT patients died during the 8-year follow-up period.

Moreover, there are indications that risk of DT increases with the severity of AUD [4, 8, 16, 17]. Thus, it may be assumed that the long-term mortality risk is higher in DT patients compared to AUD patients who have not experienced DT. In the present study we aimed to test this assumption, employing registry data on specialized treatment of alcohol-dependent patients in Norway. Specifically, we aimed at comparing all-cause and cause-specific mortality between DT patients, other AWS patients and alcohol-dependent patients without AWS or DT. Moreover, we aimed at examining whether DT patients bear signs of more severe alcohol dependence (AD), in terms of alcohol-related morbidity, compared to other AUD patients with or without AWS.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies [18].

Setting and participants

The Norwegian Patient Registry is a national registry which covers all episodes in publicly funded specialized inpatient or outpatient treatment in Norway. The study cohort comprised all patients aged 20–79 years who were registered at least once during the period of 1 January 2009 to 31 December 2015, with one of the following as diagnosis: DT (ICD-10 diagnostic code F.10.4), AWS (F10.3) or AD (F10.2). Diagnoses in the Norwegian Patient Registry are entered based on clinical reports from attending physicians. The unique 11-digit national personal identifier, recorded at each treatment episode, allowed for identifying individuals over time within the Norwegian Patient Registry and for linking patient data to other national registers, such as the Norwegian Cause of Death Registry. Some patients (n = 4428, 12.2%) received more than one of these diagnoses, and these patients were hierarchically assigned to mutually exclusive groups; hence, the diagnosis DT was given priority over AWS which, in turn, was given priority over AD, regardless of when these diagnoses were set during the observation period. Thus, during the observation period, AD patients had not been hospitalized with AWS or DT, and AWS patients had not been hospitalized with DT. This was conducted under the assumption that the diagnoses AD, AWS and DT—in this order—represent increasing severity of AUD. Within each of these groups, the first contact in the period with the assigned diagnosis was considered the index episode. The cohort comprised three groups; 30 478 patients received an AD diagnosis only, 3993 patients received an AWS diagnosis and 1816 patients received a DT diagnosis, in total 36 287 patients. In the following, we will refer to these three patient groups as AD, AWS and DT, respectively.

All patients were followed prospectively from the index episode until 31 December 2015, or the date of censoring (i.e. death, emigration from Norway or 31 December the year they turned 79 years, whichever came first). Patients who were already hospitalized as of 1 January 2009 were followed from this date (n = 368). The average observation time from the index episode to censoring or 31 December 2015 was 43.9 months for AD patients, 37.2 months for AWS patients and 36.2 months for DT patients.

Measures

Mortality

Information regarding whether the cohort participants had died or emigrated during the observation period (from the index episode to 31 December 2015, or censoring) was obtained from the National Population Registry. All-cause mortality within the study cohort was described as: (i) the percentage of patients who died within the first month after the index episode; (ii) the percentage who died within the whole observation period after the index episode; and (iii) the crude annual mortality rate (i.e. the number of deaths divided by person-years under observation from the index episode to censoring or 31 December 2015). For all deaths, we obtained data on cause of death from the Norwegian Cause of Death Registry, which includes 98% of all deaths in Norway [19]. Causes of death were coded according to ICD-10. Natural causes of death (A00–R99) were grouped into cardiovascular disease (I00–I99), respiratory disease (J00–J99), cancer (C00–C97) and other natural causes. Unnatural causes of death (V01–Y98) were grouped into poisoning (X40–X49), suicide (X60–X84 and Y87.0) and other unnatural causes (including accidents V01–V89).

The standardized mortality ratio (SMR) was calculated as the observed number of deaths divided by the expected number of deaths in the general population with the same age and gender distribution per calendar year. Data on annual number of deaths in gender-stratified 5-year age groups in the general population was obtained from the Norwegian Institute of Public Health [20], and annual population figures in the age groups 20–79 years during the period 2009–15 were obtained from Statistics Norway. The SMR was calculated for all-cause and cause-specific mortality with 95% confidence intervals (CI).

Alcohol-related morbidity

For all cohort participants we obtained data from the Norwegian Patient Registry on whether they were diagnosed in specialized health services with any of the following emergencies, diseases or injuries that are often seen in AUD patients [1, 21]: acute alcohol intoxication (ICD-10: F10.0), alcoholic liver disease (K70), alcoholic-induced chronic pancreatitis (K86.0), polyneuropathies (G60–G64), dementia (F00–F03, F05.1, G311.1) and head injury (S00–S09). Psychiatric comorbidities were not included. Each patient could have more than one alcohol-related morbidity. We assumed that the presence of one or several of these morbidities was indicative of more severe AD. For each of these alcohol-related morbidities we compared the proportion of patients being diagnosed (at least once) in a 2-year period before the index episode (from 1 January 2009) and in a 1-year follow-up period after the index episode (to 31 December 2015, or censoring) throughout the three patient groups (AD, AWS and DT).

Data on the patient's registered gender (binary measure) and age at the time of the index episode were obtained from the National Population Registry. Data were taken from central health registries that can be accessed only after application to the owners.

Data analysis

We compared the three patient groups regarding gender, age, all-cause mortality and alcohol-related morbidity using the χ^2 test for categorical variables and Student's *t*-test for continuous variables.

We analyzed whether all-cause mortality differed between the three patient groups, adjusting for age and gender, in Cox regression models. First, mortality was regressed on patient group, using age as time variable. Next, we included gender as covariate in the analysis. Hazard ratios (HR) estimated in Cox regression models and SMRs were considered statistically significantly different if the *P*-value was less than 0.05.

The analyses were carried out using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary, NC, USA. This explorative study was not pre-registered.

All patient data were completely de-identified for the researchers, which is required for data from health registries where the participants are not asked for consent. Legal basis and exemption from duty of confidentiality for the use of personal data in research were granted by the Regional Committee for Medical and Health Research Ethics (2014/72/REK North).

RESULTS

During the study period after the index episode, we observed 2937 episodes of DT in 1816 DT patients, 9168 episodes of AWS in 3993 AWS patients and 537 742 episodes of AD in 30 478 AD patients. Observation time before the index episode was 39.5, 41.1 and 34.7 person-months for DT, AWS and AD, respectively. Observation time after the index episode was 36.2, 37.2 and 43.9 person-months, respectively. DT patients were older and more often male compared to both AWS and AD patients (both $P < 0.001$) (Table 1). Compared to AD patients and AWS patients, DT patients had a higher mortality rate, both in the first month and in the total observation period after the index episode (both $P < 0.001$), and hence crude annual mortality rate was higher in DT patients (8.0%) compared to AWS and AD patients (5.0 and 3.6%, respectively) (Table 1). These findings are reflected in the Kaplan–Meier plot (Fig. 1).

Table 2 shows that DT patients had a higher all-cause mortality risk (HR = 1.56, 95% CI = 1.41–1.72) compared to AD patients (reference), when adjusting for age (i.e. using age as time variable in the analysis). Compared to AD patients, AWS patients also had an increased mortality risk (HR = 1.17, 95% CI = 1.07–1.27). Additional adjustment for gender did not substantially alter these differences in mortality risk.

The distribution of causes of death was similar among the three patient groups (Table 3) and across genders (Supporting information, Table S1). SMRs for all-cause mortality was high in all three patient groups, and higher in DT patients (SMR = 9.8, 95% CI = 8.9–10.7) compared to AD patients (SMR = 7.0, 95% CI = 6.8–7.2) and AWS patients (SMR = 7.8, 95% CI = 7.2–8.4). For all three patient groups, the SMRs were higher for unnatural than for natural causes of death; for AD patients 15.2 (95% CI = 14.2–16.3) versus 6.1 (95%CI = 5.9–6.4), for

TABLE 1 Demographic characteristics and measures of crude mortality by patient group.

		Alcohol dependence (AD) *n* = 30 478	Alcohol withdrawal state (AWS) *n* = 3993	Delirium tremens (DT) *n* = 1816	*P*-value[a]
Age at inclusion	Mean (SD)	48.4 (14.0)	52.3 (12.2)	55.9 (11.4)	< 0.001
Male	*n* (%)	21 528 (70.6)	3151 (78.9)	1457 (80.2)	< 0.001
Mortality					
First month after the index episode	*n* (%)	366 (1.2)	23 (0.6)	45 (2.5)	< 0.001
Throughout the observation period	*n* (%)	4048 (13.3)	622 (15.6)	437 (24.1)	< 0.001
Annual mortality rate	%	3.6	5.0	8.0	

[a]Significance tested with χ^2 test for categorical variables and Student's *t*-test for continuous variables.

FIGURE 1 Kaplan–Meier curves displaying the survival probability for patients with alcohol dependence syndrome (AD) (blue curve), alcohol withdrawal state (AWS) (red curve) or delirium tremens (DT) (green curve) after index episode.

AWS patients 20.1 (95% CI = 16.9–23.9) versus 6.7 (95% CI = 6.1–7.3) and for DT patients 26.9 (95% CI = 21.7–33.4) versus 8.6 (95% CI = 7.7–9.5). Moreover, DT patients had significantly higher SMRs for all categories of unnatural causes of death compared to AD patients (Table 3). In all three patient groups, SMR was particularly elevated for poisoning as the cause of death, and among DT patients, death from poisoning occurred 60 times more often than in the general population (Table 3). Alcohol poisoning accounted for 113 of the 394 poisoning deaths (28.7%), and of these 24.3% were among the AD patients, 36.0% among the AWS patients and 61.3% among the DT patients. Gender-specific analyses showed that the SMRs were somewhat higher for women than for men but, overall, the same pattern for all-cause and cause-specific mortality was observed across the three patient groups (Supporting information, Table S1).

Table 4 shows, for each of the three patient groups, the proportion with various alcohol-related morbidities indicative of severe AD within two periods: prior to the index episode and after the index episode. In the period prior to the index episode, DT patients were more often admitted with alcohol intoxication, liver disease, pancreatitis, polyneuropathy or head injury compared to AD patients. Also, during the observation period after the index episode DT patients were, compared to AD patients, more often admitted with alcohol intoxication or head injury or alcohol-related morbidities such as liver disease, pancreatitis, polyneuropathy or dementia. Several of the alcohol-related morbidities were also more frequently observed among DT patients than other AWS patients in the period before index admission, in the period after, or both.

DISCUSSION

Using data from the Norwegian Patient Registry we identified 36 287 alcohol use disorder (AUD) patients who were diagnosed with alcohol

TABLE 2 Cox regression models for all-cause mortality by patient group. Hazard ratios [with 95% confidence intervals (CI)] (n = 36 287).

Models	Alcohol dependence (AD) Hazard ratio	Alcohol withdrawal state (AWS) Hazard ratio (95% CI)	Delirium tremens (DT) Hazard ratio (95% CI)
(1) Adjusted for age	1.0 (ref.)	1.17 (1.07–1.27)	1.56 (1.41–1.72)
(2) Adjusted for gender and age	1.0 (ref.)	1.14 (1.05–1.24)	1.52 (1.38–1.68)

TABLE 3 Distribution of causes of death and standardized mortality ratios (SMR) for all-cause and cause-specific mortality by patient group; alcohol dependence only, alcohol withdrawal state and delirium tremens for all patients and for men and women separately.

	Alcohol dependence (AD)		Alcohol withdrawal state (AWS)		Delirium tremens (DT)	
	Died, *n* (%)	SMR (95% CI)	Died, *n* (%)	SMR (95% CI)	Died, *n* (%)	SMR (95% CI)
All-cause mortality	4026 (100.0)	7.0 (6.8–7.2)	621 (100.0)	7.8 (7.2–8.4)	437 (100.0)	9.8 (8.9–10.7)[a,b]
Natural causes of death	3129 (77.7)	6.1 (5.9–6.4)	473 (76.2)	6.7 (6.1–7.3)	347 (79.4)	8.6 (7.7–9.5)[a,b]
Cardiovascular death	690 (17.1)	5.4 (5.0–5.8)	109 (17.6)	6.0 (5.0–7.2)	79 (18.1)	7.4 (6.0–9.3)[a]
Respiratory death	402 (10.0)	9.8 (8.9–10.8)	55 (8.9)	9.6 (7.4–12.5)	46 (10.5)	13.1 (9.8–17.5)
Cancer	723 (18.0)	3.2 (2.9–3.4)	79 (12.7)	2.5 (2.0–3.1)	52 (11.9)	2.9 (2.2–3.8)
Other natural causes of death	1314 (32.6)	13.5 (12.8–14.2)	230 (37.0)	17.1 (15.0–19.5)	170 (38.9)	22.5 (19.3–26.1)[a,b]
Unnatural causes of death	805 (20.0)	15.2 (14.2–16.3)	130 (20.9)	20.1 (16.9–23.9)	82 (18.8)	26.9 (21.7–33.4)[a,b]
Poisonings	313 (7.8)	28.5 (25.5–31.8)	50 (8.1)	40.4 (30.6–53.3)	31 (7.1)	60.6 (42.6–86.2)[a]
Suicide	259 (6.4)	14.1 (12.5–16.0)	32 (5.2)	14.8 (10.4–20.9)	23 (5.3)	24.5 (16.3–36.9)[a]
Other unnatural causes of death	233 (5.8)	10.1 (8.9–11.5)	48 (7.7)	16.1 (12.2–21.4)	28 (6.4)	18.1 (12.5–26.2)[a]

[a]SMR for DT patients is statistically significantly larger ($P < 0.05$) than for AD patients.
[b]SMR for DT patients is statistically significantly larger ($P < 0.05$) for DT patients than for AWS patients.

dependence (AD), alcohol withdrawal state (AWS), or delirium tremens (DT) in the years 2009 to 2015. DT patients were at significantly higher risk of all-cause mortality compared to AWS or AD patients; their annual mortality rate was 8.0%, and the standardized mortality ratio (SMR) was just short of 10. Regarding cause-specific mortality in DT, SMR was particularly elevated for poisonings. Alcohol-related morbidities were more frequent among DT patients than AD patients both before and after the index episode.

This study adds to a small literature on long-term outcomes of DT. To the best of our knowledge, this study is the first to examine long-term mortality and alcohol-related morbidity among DT patients in comparison to other alcohol-dependent patients, and is the first study to describe long-term outcomes in DT patients based on national registry data and a large cohort of DT patients. We observed that, among AUD patients, the share of patients with DT was one in 20, which is of the same magnitude as reported in some previous studies [6, 7], but slightly lower than observed in other studies [8, 13, 16, 22]. The substantial variation in the reported proportion of DT among all AUD patients may reflect differences in methodology among studies but, to some extent, it may also reflect differences in the treatment of serious alcohol withdrawal symptoms. When AWS is treated aggressively, it is known to prevent the development of DT [4, 23, 24].

We found that among DT patients, almost one in four died during an average observation time of 36 months. This mortality rate among DT patients is higher than that reported in a Finnish study, where 31% died during 8-year follow-up [15], and approximately similar to that in a German study [25]. This finding indicates that mortality is not only an issue around the time of the DT episode, but very much so in the months and years thereafter. The crude annual mortality rate in DT patients in our study exceeds the average mortality rate among, for instance, male cancer patients [26] or injecting heroin users [27] in Norway.

All-cause mortality rate and SMRs were significantly higher for DT patients compared to AD or AWS patients, and correspondingly alcohol-related morbidities were more prevalent among DT than among AD or AWS patients. These findings fitted well the assumption that AWS, and even more so DT, are more likely to occur in patients with severe AD [4, 7, 8] and they corroborate previous findings that mortality risk in AUD patients increases with severity of the disorder [28]. The SMRs for all three patient groups in our study exceeded what is generally reported for AUD patients (i.e. in the magnitude of 3–4) [2]. One possible explanation for the higher excess mortality in our study compared to most previous studies is that treatment access for people with AD is low in Norway compared to other European countries [29, 30]. This may imply that when entering treatment, AUD patients in Norway are more severely ill and at a more advanced stage of AUD, and therefore at higher risk of premature death. Another contributing factor to the elevated SMR is the low premature mortality in the Norwegian general population compared to other European countries [31]. The particularly elevated SMRs for unnatural causes of death in our study resemble that reported in previous studies of

TABLE 4 Presence of alcohol-related morbidities prior to and after index episode by patient group (%).

	Alcohol-related morbidities prior to episode					Alcohol-related morbidities after episode				
	n (%)					*n* (%)				
	Alcohol dependence (AD)	Alcohol withdrawal state (AWS)	Delirium tremens (DT)	*P*-value	*Post hoc*	Alcohol dependence (AD)	Alcohol withdrawal state (AWS)	Delirium tremens (DT)	*P*-value	*Post hoc*
Alcohol-related morbidities										
Alcohol intoxication	2521 (8.3)	792 (19.8)	386 (21.3)	< 0.001	2 < 3/4	3756 (12.3)	1053 (26.4)	498 (27.4)	< 0.001	2 < 3/4
Liver disease	2086 (6.8)	494 (12.4)	264 (14.5)	< 0.001	2 < 3 < 4	3450 (11.3)	729 (18.3)	419 (23.1)	< 0.001	2 < 3 < 4
Pancreatitis	253 (0.8)	74 (1.9)	43 (2.4)	< 0.001	2 < 3/4	414 (1.4)	95 (2.4)	50 (2.8)	< 0.001	2 < 3/4
Polyneuropathy	508 (1.7)	134 (3.4)	86 (4.7)	< 0.001	2 < 3 < 4	944 (3.1)	205 (5.1)	137 (7.5)	< 0.001	2 < 3 < 4
Dementia	163 (0.5)	22 (0.6)	17 (0.9)	0.083	NS	571 (1.9)	77 (1.9)	80 (4.4)	< 0.001	2/3 < 4
Head injury	3559 (11.7)	724 (18.1)	355 (19.5)	< 0.001	2 < 3/4	3925 (12.9)	692 (17.3)	385 (21.2)	< 0.001	2 < 3 < 4

Note: The *P*-values are given for χ^2 tests of the overall distribution. The *post-hoc* tests indicate statistically significant ($P < 0.05$) pairwise differences between patient groups; 2 = DT, 3 = AWS, 4 = DT. For instance, 3 < 4 means that the proportion among DT is statistically significantly larger than the proportion among AWS, whereas 2 < 3/4 means that there is no statistically significant difference between DT and AWS, but the proportions in these groups are larger than that in AD.
Abbreviation: NS = not statistically significant.

cause-specific mortality in AUD [32]. Poisoning and suicide were frequent unnatural causes of death in DT patients and in AD and AWS patients, similar to that reported in previous studies of cause-specific mortality in AUD [32].

We compared alcohol-related morbidities throughout the three patient groups in two periods: prior to and after the index episode. For all morbidities we found that these were more prevalent among DT patients than the other AUD patients, in either one or both periods. This may suggest that at the time of the index episode DT patients represented a more severe AUD group, being at a more advanced stage of AUD compared to the other patient groups [4, 7]. The higher age among DT patients is also suggestive of a more advanced disease stage. The presence of some of these morbidities prior to first DT episode, including acute alcohol intoxication, dementia and head injury, may not only be symptomatic of disease stage, but may also be risk factors for—or even part of—the aetiological pathway to DT [4, 11, 33]. In the follow-up period after the index episode, we found that DT patients were more often hospitalized with dementia, much in line with the reported elevated risk of incident poor cognitive function among DT patients [14]. The observation that DT patients are frequently also hospitalized with alcohol-related morbidities in the period after their first episode of DT suggests that DT patients, on average, also remain more severely ill in the long term after treatment. This may, at least in part, explain the observed elevated mortality.

The three patient groups were observed over more than 3 years on average. During the observation period, the course of illness may have developed differently both within and between the groups, and we know little about this apart from our outcome measures: alcohol-related morbidity and mortality. We know, however, that AD patients were not hospitalized with AWS or DT, and AWS patients were not hospitalized with DT. Our findings thus suggest that, among AUD patients, the single event of hospitalization with AWS or DT is indicative of extensive comorbidity and high mortality risk, and particularly so for those with DT. Hence, these patients require close follow-up and medical attention not only during the acute episode, but also in the years following the incident.

Limitations

This study used data from two linked health registries; the Norwegian Patient Registry and the Norwegian Cause of Death Registry, both of which have almost complete coverage. However, the reported findings may possibly be biased. Specifically, many people with AUD are not treated in specialized health services and such undertreatment seems to be more prevalent in Norway than in most other European countries [29, 30]. If this implies that only the more severely ill people with AUD are treated in specialized health services, the observed crude mortality rates and SMRs are probably upward-biased. Correspondingly, the observed figures for alcohol-related morbidities may also be upward-biased. However, it is possible that many patients with AWS and DT were diagnosed with withdrawal symptoms when hospitalized for other reasons than AD. Given this, the treatment

barrier may have been lower for AWS and DT patients than for AD patients. In this scenario, the differences in mortality and morbidity between AD patients and AWS and DT patients could have been downward-biased.

It may also be argued that if socio-economic status (SES) is associated with hospital treatment for DT or AWS, SES would be a confounder and should be accounted for in the analyses. However, data on SES were not available in this study. Furthermore, all data were gathered from the Norwegian specialized health services. Here, diagnoses are set clinically by the attending physician, who is most often a specialist, but no second opinion or quality control is performed on the diagnosis, leaving the study open to clinical flaw. Moreover, our assumption that hospitalization with ASW or DT typically occurs among people at a more advanced and severe stage of AUD than those hospitalized with AD may not be accurate in two respects. First, hospitalizations with ASW and DT may also occasionally appear in patients not fulfilling the criteria for AD. However, in most cases this assumption is probably true. Secondly, within each of the three patient categories, there may be substantial differences in the course of illness, but we had no data to examine this.

Because, for example, alcohol intoxication within the F10 code of Chapter V in ICD-10 is included in our study, we have chosen the term 'alcohol-related morbidity' instead of 'comorbidity'. The nomenclature AUDs and alcohol-related morbidities may, however, be discussed. In agreement with ICD-10, we have included AWS, even if it may be viewed as a somewhat non-specific diagnosis. Also, deaths from unnatural causes among people with AUD probably constitute a significant part of unnatural deaths in the general population, which is used as reference. This may have led us to underestimate the difference, as pointed out in an earlier study using the same kind of linked data from registries [34]. However, such flaws may, to a large extent, occur randomly and thus have little impact upon the results of the study. Finally, we followed the patients for a limited period, and hence we know little about morbidity and mortality in DT and other AUD patients over a substantially longer observation period.

CONCLUSION

Patients with AUDs generally have very high mortality and morbidity. In this study we showed that DT occurred in 5% of patients treated with AUD in Norway. The mortality in DT patients was 10 times higher than in the general Norwegian population, and DT patients also had higher levels of mortality and alcohol-related morbidity compared to other AUD patients. The high morbidity and mortality in DT patients shown in this study underlines that DT is a serious condition, probably representing the most severe end of an AUD spectrum.

AUTHOR CONTRIBUTIONS

Jørgen G. Bramness conceptualised the study with methods input from Ina Heiberg and Ingeborg Rossow. Ina Heiberg curated the data and conducted the statistical analyses with inputs from Jørgen G. Bramness and Ingeborg Rossow. Jørgen G. Bramness drafted the first manuscript and all authors contributed equally to the development of the last version, which was also approved by all authors.

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DECLARATION OF INTERESTS

None.

DATA AVAILABILITY STATEMENT

Data were taken from central health registries, that can be accessed only after application to the owners.

DISCLAIMER

Data from the Norwegian Patient Registry and the Norwegian Cause of Death Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by any of these registries is intended nor should be inferred.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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