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Article

Article

Long-Term Mortality of Patients with an Alcohol-Related Wernicke–Korsakoff Syndrome

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Abstract

Aims: To characterize a series of contemporary patients with alcohol-related Wernicke's encephalopathy (WE) or Korsakoff's syndrome (KS) and to update the current prognosis of disease.
Methods: Retrospective and prospective study of patients diagnosed with an alcohol-related WE or KS between 2002 and 2011 in a tertiary hospital. Socio-demographic, alcohol use characteristics, signs and symptoms, co-morbidity and blood parameters were obtained at admission. Patients were followed up until 2013 and causes of death were ascertained through the review of charts.
Results: Sixty-one patients were included (51 with WE and 10 with KS). Among patients with WE, 78% were men and age at diagnosis was 57 years (interquartile range (IQR): 49–66). Twenty-three percent fulfilled the classic WE triad. Regarding Caine's criteria for WE, 70.6% presented with at least two out of four signs or symptoms. Median follow-up of patients with WE syndrome was 5.3 years (IQR: 2.6–8.8), the cumulated mortality was 45% and death rate of 7.4 × 100 person-years (95% confidence interval (CI): 4.8–10.9). Overall, 50% of patients would be expected to die within 8 years of WE episode and main causes of death included serious bacterial infections (44.5%) and cancer (33.3%).
Conclusions: Survival of patients with an alcohol-related Wernicke–Korsakoff syndrome is poor; pursuing treatment of alcohol use disorder and early diagnosis of thiamine deficiency is a priority for improving clinical outcomes.

INTRODUCTION

Wernicke's encephalopathy (WE) is an acute neurological disease due to thiamine deficiency. The clinical picture is characterized by the onset of mental status changes with confusion, ophthalmoplegia and ataxia, as described by Carl Wernicke in 1881. Acute cases recognized early respond to treatment with thiamine, but in chronic forms or Korsakoff's syndrome (KS) the disease evolves into a psychosis and memory deficits (Victor *et al.*, 1971, 1989).

Alcohol use disorder (AUD) is a recognized risk factor for the development of Wernicke–Korsakoff syndrome in western countries; ethanol contributes to a diminished capacity of the liver to store vitamins and to the inhibition of thiamine transport across the intestinal mucosa (Thomson, 2000). Some studies have determined that up to 90% of WE cases are related to unhealthy alcohol use (i.e. a chronic alcohol misuse associated with inadequate dietary intake of thiamine) (Harper, 1983, 1995; Thomson, 2000), and that 13% of patients with AUD develop WE (Harper *et al.*, 1986).

Thiamine, in its biologically active form thiamine pyrophosphate, is an essential coenzyme in several biochemical pathways in the brain. The cerebellar vermis is the anatomical zone commonly observed to be damaged by ethanol; the cerebellum and the brainstem structures, through a neuronal loss, are particularly sensitive to a lack of thiamine, and this mechanism could be involved in the reversible and irreversible neurological symptoms (Butterworth, 1993; Lavoie and Butterworth, 1995; Baker *et al.*, 1999). One study showed that 30% of patients with unhealthy alcohol use had signs of cerebellar ataxia and 27–42% showed atrophy of the cerebellar vermis, according to neuroimaging data (Maschke *et al.*, 2005).

Studies have described the prevalence of WE as falling between 0.8 and 2.8% of the general population (Lishman, 1981; Charness *et al.*, 1989; Torvik, 1991). However, the prevalence reaches up to 12% among AUD patients, according to brain damage data obtained during autopsies (Torvik *et al.*, 1982).

The diagnosis of WE is clinical and often goes unnoticed (Sechi and Serra, 2007; Galvin *et al.*, 2010). In 1997, new clinical criteria were included in order to improve the sensitivity of diagnosis compared with the classic triad of WE, which is only seen in one in four patients (Caine *et al.*, 1997). Actually, neuroimaging techniques can aid in the diagnosis of WE but the absence of abnormalities in magnetic resonance imaging (MRI) examinations does not exclude the disease; in fact, the sensitivity of WE diagnosis by MRI is 53% although the specificity is high (93%) (Antunez *et al.*, 1998). The misdiagnosis of WE implies that the disease is undertreated thus increasing the risk of chronic forms of the disease as described by Sergei Korsakoff in 1889. Some studies have reported that in AUD patients diagnosed with WE, progression to KS was seen in 56–84% of cases (Victor *et al.*, 1971; Wood *et al.*, 1986; Thomson and Marshall, 2006).

Studies conducted in past decades have estimated that mortality of patients with WE is ~17%, and that 10% of patients die during the acute phase of the disease (Victor *et al.*, 1971, 1989). Nevertheless, current data on mortality and long-term prognosis are scarce even after the introduction of more sensitive diagnostic criteria and MRI techniques.

In this study, we aimed to characterize a series of contemporary patients with alcohol-related WE and KS. We hypothesized that alcohol-related cases of the syndrome continue to be diverse in its clinical presentation. Furthermore, we also looked at the severity of clinical course and long-term prognosis of patients focusing on the impact of unhealthy alcohol use in the survival of disease.

MATERIALS AND METHODS

Retrospective and prospective longitudinal study of patients diagnosed with alcohol-related WE and KS in a tertiary hospital in Badalona, Spain, between 1 January 2002 and 31 December 2011. The University Hospital Germans Trias i Pujol is a 500-bed facility serving a population of 400,000 in an urban area north of Barcelona, Spain. The hospital provides clinical and surgical services including emergency medicine, intensive care, maternity and pediatric care as well as >20 specialties including internal medicine, neurology and general surgery. There are no specific beds for the hospitalization of acute and chronic psychiatric conditions. The hospital serves an average of 200 emergencies per day, and up to 20,000 discharges per year.

For the retrospective objective of study, clinical charts were reviewed for the patients admitted between 1 January 2002 and 31 December 2011 and the following codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) were used: 291.1, alcohol-induced persisting amnestic disorders; 294.0, amnestic disorder in conditions classified elsewhere; and 265.1, other and unspecified manifestations of thiamine deficiency. The ICD-9-CM codes were agreed upon by internists participating in a multi-center study on the incidence and treatment of WE cases in Spain (Chamorro and Marcos, 2012). The disease coding system follows the Spanish regulation of the whole of National Health System hospitals in relation with hospital admittance episodes. Disease codes were classified by Groups of Related Diagnosis (GRD) in the version 'All patients' (AP-GRD v25.0) (Ministerio de Sanidad Servicios Sociales e Igualdad, 2014), and recorded in a Minimum Basic Data Set (MBDS) that included the principal diagnosis code and nine secondary codes; codification was performed by the hospital documentation unit and patients were classified according to whether they presented WE or KS (Fig. 1).

Socio-demographic variables, clinical signs and symptoms of WE (ataxia, ophthalmoplegia and mental changes/confusion) and Caine's criteria (Caine *et al.*, 1997) (at least two out of dietary deficiency, ocular disturbances, cerebellar dysfunction and altered mental state) were collected through the revision of charts. In addition, information on co-morbidity at admission, hematological and biochemical parameters, and the length of stay were also variables of interest.

The clinical course of an acute WE episode was considered favorable if patients exhibited complete remission of the clinical signs and symptoms at discharge. For the purposes of this study, the majority of patients were followed up in the hospital outpatient clinics between the date of discharge and 31 December 2013. In addition, cross-checks with the national death registry were performed in all cases.

The study was approved by the Ethics Committee of the Hospital Universitari Germans Trias I Pujol, and the research methods complied with the ethical norms for medical investigations and good practice principles established in the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were expressed as the median and interquartile range (IQR) for continuous variables and as absolute frequencies and percentages for categorical variables. The chi-square test and Fisher's F test for categorical variables and one-factor ANOVA for continuous variables were used to explore differences in patient characteristics.

Incidence rates were calculated in person-years (p-y); p-y represents the time that all patients contribute to a longitudinal study. Rates in p-y are the quotient of the number of events observed during the study period and the sum of all the individual follow-up time. The long-term prognosis for WE was analyzed through Kaplan–Meier survival curves using the log-rank test for the comparison of the curves in relation to the variables of interest.

Values of $P < 0.05$ were considered to be statistically significant. The statistical analysis was performed with SPSS 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Between 1 January 2002 and 31 December 2011, 61 patients met the criteria for inclusion; of them, 51 were diagnosed with WE and 10 with KS. The majority of the diagnoses (74.6%) were carried out in the departments of Neurology and Internal Medicine. WE and KS were found among the three principal diagnostic codes in 67% of the cases. Among the 51 patients with WE, 78.4% were men, median age at admission was 57 years (IQR: 49–66 years) and the

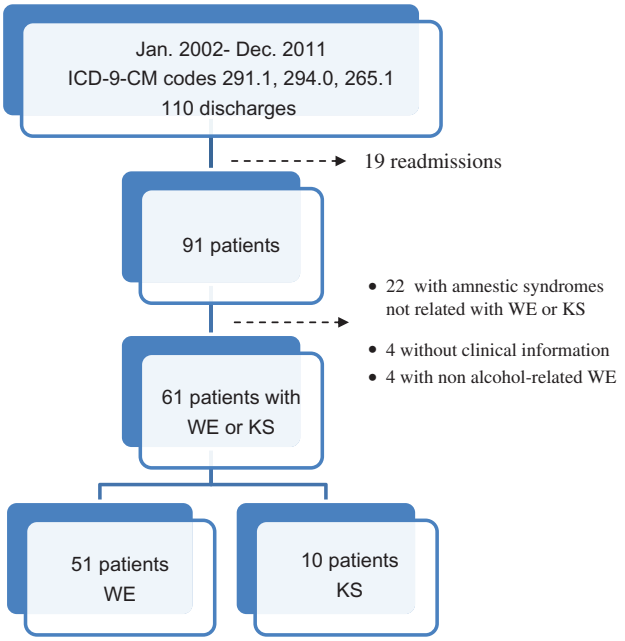

Fig. 1. Selection of the study population. Patients with WE and KS diagnosed in a tertiary hospital. Hospital Universitari Germans Trias i Pujol. Badalona, Spain.

length of stay was 10 days (IQR: 5–24 days). Socio-demographic and clinical characteristics of patients are shown in Table 1.

Regarding symptoms and signs of WE, 60.8% of the patients presented with ocular disturbances, 82.4% with ataxia, 41.2% altered mental state and 18 (35.3%) had dietary deficiencies. Overall, 63% showed one or more symptom or sign, 23.5% fulfilled the classic WE triad and 11.8% had neither signs nor symptoms of classic triad. As to the diagnosis of WE according to Caine's criteria, 70.6% of patients had two out of four criteria, 17.6% showed all four and 9.8% none. The majority of patients without signs or symptoms of disease presented with nausea and vomiting at admission; in these patients, MRI and/or levels of thiamine were used to confirm WE.

At the time of WE, 55% of the patients were tobacco smokers, 11.8% of patients had diabetes mellitus, 15.7% hypertension and 25.5% chronic liver disease. With respect to biological parameters, median hemoglobin was 13.4 g/dl (IQR: 12.4–14.7 g/dl), mean corpuscular volume was 101 fl (IQR: 96–108 fl), leukocyte count was 9×10^9 cells/l (IQR: 8–12 $\times 10^9$ cells/l) and platelet count was 198×10^9 cells/l (IQR: 119–257 $\times 10^9$ cells/l). The clinical and biological characteristics of patients are shown in Table 2. Complete recovery of those with an acute WE episode was obtained in 42.6% of the cases.

In-hospital mortality

Two patients died during their hospital stay. The first died of heart failure and the autopsy showed dilated hypertrophic cardiomyopathy and left atrium thrombosis. The second, admitted for ataxia and delirium, presented with severe malnutrition and subsequently developed gastrointestinal bleeding, kidney failure, urinary sepsis (*Escherichia coli*) and died 44 days after admission.

Follow-up and outcomes

Median follow-up after discharge was 5.3 years (IQR: 2.6–8.8 years). The majority (80%) of patients diagnosed with WE were regularly visited in the outpatient clinics and 20% were lost to follow-up. The cumulative mortality at the end of the study, in 31 December 2013, was 45.1% (23 patients); overall mortality rate was 7.4 × 100 p-y (95% CI: 4.8–10.9 × 100 p-y). In the 23 patients who died during follow-up, time between hospital discharge and death was 4.8 years (95% CI: 1.8–7.0 years). Overall, 44.5% of deaths were due to serious bacterial infections and 33.3% were due to cancer. More information on clinical outcomes is shown in Table 3.

Figure 2 shows the Kaplan–Meier survival estimates for WE. Median of survival was 8 years (95% CI: 5.3–10.7 years) and mortality was not associated with sex ($P = 0.408$), medical co-morbidity at admission (liver disease, $P = 0.791$; hypertension, $P = 0.419$; gastrointestinal surgery, $P = 0.839$; cancer, $P = 0.555$) and clinical signs of WE (classic triad, $P = 0.940$; Caine's criteria, $P = 0.810$). Although not statistically significant, patients older than 57 years ($P = 0.106$) at admission and those with diabetes mellitus ($P = 0.520$) had lower survival (5.9 and 5.1 years, respectively).

Overall, two thirds of patients continued to drinking alcohol after discharge, 6% of presented with a new WE episode, 25% were diagnosed with cancer (incidence rate, 5 × 100 p-y; 95% CI: 2.5–9.3 × 100 p-y) and 25% with progressive cognitive impairment.

Table 1. Characteristics of patients with WE admitted between January 2002 and December 2011

	$N = 51$, n (%)
Male	40 (78.4)
Age (years), median (IQR)	57.3 (48.8–66.0)
Period of admission	
2002–2006	33 (64.7)
2007–2011	18 (35.3)
Cause of admission	
≥1 sign or symptom of WE	32 (62.7)
Gastrointestinal symptoms	7 (13.7)
Malaise, fever, constitutional syndrome	7 (13.7)
Treatment of AUD	2 (3.9)
Other[a]	3 (6.0)
Duration of admission (days), median (IQR)	10 (5–24)
ICD-9-CM codes	
265.1—Unspecified manifestations of thiamine deficiency	23 (45.1)
291.1—Alcohol-induced amnestic disorders	25 (49.0)
294.0—Amnestic disorder	3 (5.9)

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[a]Seizures in one case, polyneuropathy in one case and femur fracture in one case.

Korsakoff's syndrome

Patients with KS ($n = 10$) were predominantly male (90%) and older (60.5 years (IQR: 51.3–68.4 years)) than those with WE. One patient died during hospitalization due to bacterial infection in the context of pharyngeal carcinoma, and three died during follow-up (mortality rate 7.3 × 100 p-y (95% CI: 2.3–17.7 × 100 p-y)); causes of death included respiratory tract infections, liver disease and cancer. The four deceased patients had been institutionalized due to marked cognitive impairment.

DISCUSSION

WE is an acute, neuropsychiatric syndrome leading to permanent brain lesions if treatment with thiamine is delayed. Patients with

Table 2. Clinical and biological characteristics of patients with WE admitted to a tertiary hospital between January 2002 and December 2011

	$N = 51$, n (%)
Classic triad	12 (23.5)
Ataxia	42 (82.4)
Ophthalmoplegia	31 (60.8)
Confusion	17 (33.3)
Caine's criteria[a]	36 (70.6)
Dietary deficiency	18 (35.3)
Ocular disturbances	31 (60.8)
Cerebellar dysfunction	42 (82.4)
Altered mental state	21 (41.2)
Co-morbidity at admission	
Liver disease	13 (25.5)
Hypertension	8 (15.7)
Gastrointestinal surgery[b]	5 (9.8)
Diabetes mellitus	6 (11.8)
Cancer	3 (5.9)
Blood parameters at admission	
Hemoglobin (g/dl) ($n = 49$)	13.4 (12.4–14.7)
Mean corpuscular volume (fl) ($n = 45$)	101 (96–108)
Leukocytes ($\times 10^9$ cells/l) ($n = 49$)	9 (8–12)
Platelets ($\times 10^9$ cells/l) ($n = 48$)	198 (119–257)
Glycemia (mg/dl) ($n = 46$)	113 (95–145)
Urea (mg/dl) ($n = 44$)	31 (20.6–39.5)
Sodium (mEq/l) ($n = 47$)	135 (133–138)
Aspartate aminotransferase (U/l) ($n = 43$)	56 (32–104)
Alanine aminotransferase (U/l) ($n = 35$)	31 (23–47)
Gamma glutamyl transferase (U/l) ($n = 31$)	124 (37–243)

[a]At least two out of four criteria are necessary in WE.
[b]Cholecystectomy in three cases and gastrectomy in two cases.

Table 3. Outcomes of interest at the end of study

	$N = 51$, n (%)
Total follow-up (person-years)	310
Median follow-up (years) [IQR]	5.3 [2.6–8.8]
Cumulative mortality	23 (45.1)
Death rate [95% CI] (×100 p-y)	7.4 [4.8–10.9]
Age at death [IQR] (years)	65 [54–76]
Causes of death ($N = 18$)[a]	
Infection	8 (44.5)
Cancer	6 (33.3)
Severe malnutrition and medical co-morbidity	2 (11.1)
Heart failure	2 (11.1)

Cumulative mortality and causes of death in 51 patients with an alcohol-related episode of WE.
[a]In five patients, the cause of death was unknown.

AUD are particularly at risk of developing thiamine deficiency if they are malnourished or have severe co-morbidities. This study in an urban area confirms the relative poor survival of disease in a contemporary series of middle-aged patients. In fact, median survival after an episode of WE is 8 years, which confirms the poor prognosis of the disease. To our knowledge, this is the first longitudinal study that analyzes long-term outcomes of the syndrome in AUD patients.

It is interesting to note that with respect to causes of death, 50% were related to serious bacterial infections, the majority being respiratory tract infections in the context of chronic AUD and chronic liver disease. One longitudinal study from our group reported that among patients seeking treatment of AUD the main causes of death were liver related, cancer and cardiovascular disease (Rivas *et al.*, 2013). However, neuropathology necropsies of 51 WE cases established that 52% of deaths were caused by bronchopneumonia (Harper, 1979); another study with post-mortem analysis reported that up to 77% of WE/KS patients die of infections (Victor *et al.*, 1989). Furthermore, a recent study in a cohort of patients with acute WE shows that half of them had serious infections (i.e. pneumonia, urinary tract and abdominal), thus suggesting a relationship between thiamine deficiency and the risk of infection (Wijnia *et al.*, 2016).

In this study, cancer was the second cause of death which is in agreement with previous studies. Moreover, it is well known that the combination of alcohol consumption and tobacco smoking (55% of our study population) is associated with an increased risk for certain malignant tumors (Lee and Hashibe, 2014). In this regard, the association between unhealthy alcohol use and some malignancies has been well established, but research is needed to analyze the role of thiamine deficiency in the risk of cancer (Galvin *et al.*, 2010).

Systemic inflammation, oxidative stress and immune alterations are involved in the pathogenesis of diseases associated with AUD. The oxidative stress in these patients could have been induced not only by alcohol itself but also by thiamine deficiency (Sechi *et al.*, 2016). It is known that alcohol consumption causes oxidative stress leading to impair cellular functions such as proliferation, apoptosis and inflammatory response (Napoli *et al.*, 2001; Grasselli *et al.*, 2014; Rajbanshi and Pandanaboina, 2014). On the other hand, low levels of thiamine may lead to a decreased α-ketoglutarate dehydrogenase activity, which triggers a cascade of alterations that increase the oxidative stress.

Also regarding mortality, 10% of WE cases from this study died during the episode. While there is not sufficient data on mortality during the acute phase of WE, this result is in the lower range of previous studies (Victor *et al.*, 1989; Chamorro *et al.*, 2017).

Interestingly, one in four patients with WE showed progressive cognitive impairment during follow-up. This finding is not surprising considering that 50% of patients continued to drinking alcohol and that thiamine pyrophosphate is an essential coenzyme in different biochemical pathways in the brain. A recent study among middle-aged participants suggests that heavy drinking is associated with more rapid decline in cognitive function (Sabia *et al.*, 2014).

Underdiagnosis of WE and heterogeneity of thiamine doses for the treatment of the disease is widely recognized (Sechi and Serra, 2007; Galvin *et al.*, 2010; Thomson *et al.*, 2013). The high percentage of undiagnosed WE has been associated with the low recognition of clinical manifestations, the lack of sensitive diagnostic markers and the low detection of unhealthy alcohol use by history taking. In this study, the proportion of patients with classic WE symptoms is similar to that previously described (15–30%) (Harper *et al.*, 1986; Munir *et al.*, 2001). In contrast, the percentage of patients with mental confusion at admission (33.3%) was lower than observed in other studies (Harper *et al.*, 1986), which may suggest incomplete assessment of the condition at emergency room admissions where initial physical examinations might be centered in the level of consciousness.

On the other hand, the percentage of patients without clinical signs (12%) of the classic triad was lower than in previous series (Harper *et al.*, 1986). In the context of an acute episode of WE, signs and symptoms such as nausea, vomiting, weakness, anxiety or

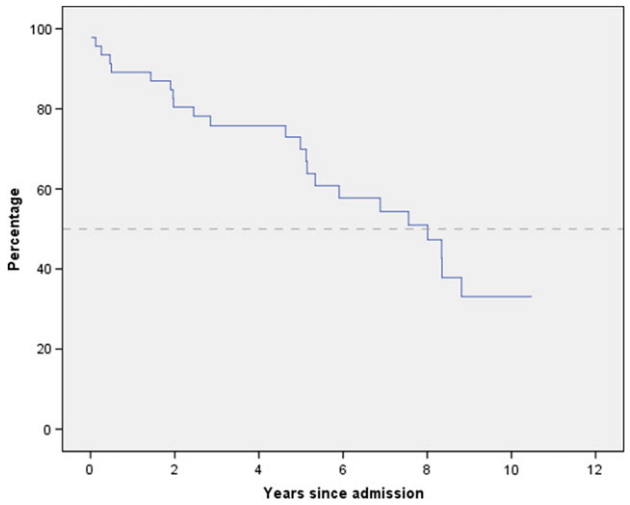

Fig. 2. Kaplan–Meier survival estimates of 51 patients with an alcohol-related episode of WE diagnosed between January 2002 and December 2011.

emotional changes may appear (Thomson *et al.*, 2008a, 2008b). In our study, up to 14% of the patients suffered from vomiting at admission and the majority had neither classic WE symptoms nor the Caine's clinical criteria (data not shown). Since diagnosis of the disease remains clinical, attempts are underway to find markers for increasing the sensitivity of diagnosis. A recent review of biomarkers associated with Wernicke–Korsakoff highlights the poor results obtained until now, although certain markers of microglial activation (CD68, leukocyte antigen-DR in brain tissue and lactate in serum and cerebrospinal fluid) may be associated with delirium in thiamine deficiency (Wijnia and Oudman, 2013; Sechi *et al.*, 2016)

The present study found that survival was reduced in WE patients with diabetes mellitus. The association between unhealthy alcohol use and the metabolic complications of diabetes mellitus is recognized (Pietraszek *et al.*, 2010; Kim and Kim, 2012). In addition, thiamine plays a role in the carbohydrate metabolism, and diabetic patients with AUD have an increased risk of developing WE (Chamorro *et al.*, 2009; Wijnia *et al.*, 2012). On the other hand, it is well known that supplementation with carbohydrates can precipitate thiamine deficiency and the appearance of WE (Sechi and Serra, 2007). In any case, these findings suggest that assessment of comorbidity is relevant in the prognosis WE (Rivas *et al.*, 2013).

It is noteworthy that survival of WE patients in this study was not associated with age, sex or clinical presentation of the disease. The lack of statistically significant associations may be related not only to the small sample size but also to the few clinical variables available. In addition, key cofactors such as malnutrition, alcohol-related liver disease and parameters measuring systemic inflammation were not collected. In patients with AUD, surrogate markers of chronic inflammation have been associated with poor prognosis (Fuster *et al.*, 2015). This study has other limitations that should be mentioned. First, doses of thiamine for treating the WE episode were not available; in this sense, a recent review on the prevention and treatment of WE and KS concludes that there is insufficient evidence to guide clinicians in doses, frequency, route of administration and duration of the treatment (Day *et al.*, 2013). Second, MRI was not available in the majority of cases; MRI is regarded as the most valuable neuroimaging technique aiding in the diagnosis of WE. Third, incidence of WE could have been underestimated if patients with alcohol-related delirium, encephalopathy, cognitive impairment or psychoses were misclassified. Finally, data on history of alcohol consumption and nutrition are scarce partly because this information is poorly recorded in clinical charts. Rather, the strength of this study relays in the long-term follow-up and clinical outcomes of patients that allowed us to update the prognosis of a preventable disease. Additional studies are required to identify AUD patients at risk of developing both WE and KS.

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CONFLICT OF INTEREST STATEMENT

None declared.

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