



Treatment variability and its relationships to outcomes among patients with Wernicke's encephalopathy: A multicenter retrospective study

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ABSTRACT

Background: Despite guidelines and recommendations, Wernicke's encephalopathy (WE) treatment lacks evidence, leading to clinical practice variability.

Aims: Given the overall lack of information on thiamine use for WE treatment, we analyzed data from a large, well-characterized multicenter sample of patients with WE, examining thiamine dosages; factors associated with the use of different doses, frequencies, and routes; and the influence of differences in thiamine treatment on the outcome.

Methods: This retrospective study was conducted with data from 443 patients from 21 centers obtained from a nationwide registry of the Spanish Society of Internal Medicine (from 2000 to 2012). Discharge codes and Caine criteria were applied for WE diagnosis, and treatment-related (thiamine dosage, frequency, and route of administration) demographic, clinical, and outcome variables were analyzed.

Results: We found marked variability in WE treatment and a low rate of high-dose intravenous thiamine administration. Seventy-eight patients out of 373 (20.9%) received > 300 mg/day of thiamine as initial dose. Patients fulfilling the Caine criteria or presenting with the classic WE triad more frequently received parenteral treatment. Delayed diagnosis (after 24 h hospitalization), the fulfillment of more than two Caine criteria at diagnosis, mental status alterations, and folic acid deficiency were associated significantly with the lack of complete recovery. Malnutrition, reduced consciousness, folic acid deficiency, and the lack of timely thiamine treatment were risk factors for mortality.

Conclusions: Our results clearly show extreme variability in thiamine dosages and routes used in the management of WE. Measures should be implemented to ensure adherence to current guidelines and to correct potential nutritional deficits in patients with alcohol use disorders or other risk factors for WE.

1. Introduction

Wernicke's encephalopathy (WE) is caused by thiamine (vitamin B1) deficiency and is characterized by ocular signs, mental status changes, and motor disturbances, such as gait incoordination and ataxia. Excessive alcohol intake is the most common risk factor, but conditions such as intestinal malabsorption, cancer, and hyperemesis also predispose individuals to WE development (Galvin et al., 2010; Mateos-Díaz et al., 2022; Thomson et al., 2013). Although this disease is likely to be underdiagnosed, its prevalence has been estimated to be approximately 0.4–2.8% in the general population and 12.5–35% in patients with excessive alcohol consumption. Additionally, untreated WE may lead to irreversible sequelae, such as Korsakoff syndrome (Galvin et al., 2010; Mateos-Díaz et al., 2022).

Regarding treatment of this disease, the mainstay is early parenteral thiamine administration (Thomson et al., 2013), but little evidence is available to establish recommendations regarding optimal treatment regimen. Indeed, a 2004 Cochrane review concluded that evidence was insufficient to establish the adequate thiamine dose, dosing interval, route of administration, and duration of treatment (Galvin et al., 2010), and little information has accumulated subsequently (Dingwall et al., 2022; Mateos-Díaz et al., 2022; Wijnia, 2022).

In this context of lack of evidence, experts have made several recommendations for thiamine regimens: Thomson and coworkers (Thomson et al., 2013) recommended 500 mg thiamine given intravenously (iv) every 8 h for at least 5 days, and Sechi and Serra (Sechi and Serra, 2007) recommended 500 mg given iv every 8 h for 2–3 days, followed by 250 mg daily for 3–5 days. In contrast, European guidelines (Galvin et al., 2010) recommend 200 mg thiamine administered iv every 8 h until no further improvement in clinical signs or symptoms occurs, based on the findings of one of the few trials published (Ambrose et al., 2001). Differences in recommendations may also reflect the availability of parenteral preparations in different countries (Agabio, 2005; Mateos-Díaz et al., 2022). Apart from thiamine, common WE treatment recommendations are the correction of other nutritional deficits, such as magnesium deficiency, which are particularly common among people

with alcohol use disorders (AUDs) (Thomson et al., 2013), and the avoidance of intravenous glucose administration before thiamine is given due to the potential risk of precipitating the occurrence of WE (Schabelman and Kuo, 2012).

Despite these recommendations, several surveys and audits have shown that the treatment of suspected or confirmed WE is inadequate in many cases, characterized by the use of inappropriately low doses or oral instead of parenteral therapy (Agabio, 2005; Thomson et al., 2013). This inadequacy is of special interest, as Victor and coworkers (Victor et al., 1971) showed that patients with WE given low parenteral doses of thiamine (50–100 mg/daily) had high mortality (~20%) and low full recovery (16%) rates.

Given the overall lack of information and the uncertainty associated with thiamine treatment for WE, we analyzed data from a large, well-characterized multicenter sample (Chamorro et al., 2017; Novo-Veleiro et al., 2022) of patients with WE. We examined the doses used, factors associated with the use of different doses, treatment frequency and route, and potential influence of differences in thiamine treatment on the outcome.

2. Patients and methods

2.1. Patient selection and data collection

A multi-center retrospective case note review study was conducted through the Wernicke Group of the Spanish Society of Internal Medicine (SEMI) with the participation of 21 centers from Spain (Chamorro et al., 2017; Novo-Veleiro et al., 2022). The study was performed in accordance with the ethical standards of the Declaration of Helsinki, and with the approval of the ethics committees of all participating hospitals.

As described previously (Chamorro et al., 2017), we searched all hospital discharge diagnoses recorded at each participating center during a 13-year period (from 2000 to 2012). In brief, this search was restricted to International Classification of Diseases (ICD) Ninth Revision codes 291.1, 294.0, and 265.1 and Tenth Revision codes E51.2 and F0 (Novo-Veleiro et al., 2022). ICD codes were identified through the Admission and Clinical Documentation Departments of participating hospitals. Epidemiological, clinical, laboratory, and radiological data (including age and sex; comorbidities; WE risk factors, signs, and

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Table 1
Caine criteria for the clinical diagnosis of Wernicke Encephalopathy.

Criteria	Evidenced by one or more of the following
Cerebellar signs	Ataxia, gait disturbances, or other signs of cerebellar dysfunction.
Oculomotor abnormalities	Ophthalmoplegia, nystagmus, or gaze palsy.
Dietary deficiencies	Body mass index < 18.5 kg/m ² , hypoalbuminemia and/or record of clearly impaired dietary intake.
Altered mental status	Confusion, stupor, or disorientation.
or	
Mild memory impairment	Lack of success to remember two or more words in the four item memory test or other test of memory function.

The clinical diagnosis of Wernicke Encephalopathy is made when two of these criteria are present (modified from Caine et al. (1997) according to study protocol).

symptoms; imaging and laboratory findings; alcohol consumption; liver disease diagnosis; treatment; duration of hospital stay; and hospital outcome) from these cases were coded using a specific protocol. Missing data were assumed to be missing at random and therefore we did not impute missing data.

2.2. Diagnostic criteria and variable definitions

WE diagnostic criteria were recorded according to Caine criteria (Caine et al., 1997), according to the presence of cerebellar signs (ataxia, gait disturbances, or other signs of cerebellar dysfunction), oculomotor abnormalities (ophthalmoplegia, nystagmus, or gaze palsy), dietary deficiencies (body mass index < 18.5 kg/m², hypoalbuminemia and/or record of clearly impaired dietary intake), and altered mental status (confusion, stupor, or disorientation) or mild memory impairment (Table 1). These are operational criteria for the diagnosis of WE and the presence of the items defining each of the criteria was assessed in the medical records. The presence of the classic WE triad (altered mental status, ataxic gait, and ophthalmoplegia) and concomitant symptoms (fever, seizures, dyskinesia, or tremor) was also recorded. All patients with definitive clinical WE diagnoses, as determined by the clinical diagnosis documented in the medical records, even those who did not meet at least two Caine criteria, were included in this study.

We defined AUD as high-risk alcohol consumption (>28 standard drink units (SDU)/week or 280 g ethanol/week for men and >17 SDU/week or 170 g ethanol/week for women) or active alcohol consumption with a previously established diagnosis. These criteria were in use in Spain during the data collection period (Gual et al., 2001), and one SDU is equivalent to 10 g absolute alcohol in this country. Smoking and the use of other drugs of abuse (cocaine, heroin, and cannabis) was also recorded. Regarding alcoholic liver disease (ALD), patients with histological diagnoses or unequivocal clinical, endoscopic, and/or ultrasonographic findings were considered to have cirrhosis. Other forms of ALD were identified with the application of clinical, imaging, and biochemical criteria.

Findings from biochemical, hematological, and coagulation tests upon admission were documented when available. Hypomagnesemia was defined as serum magnesium level < 1.5 mg/dL, hyponatremia as serum sodium value < 135 mmol/L, and hypokalemia as potassium level < 3.5 mg/dL.

When available, we registered the dates of thiamine treatment initiation and termination, the route of administration, dosage, posology, and changes in the treatment regimen during hospitalization. We also recorded the administration of glucose solution before or after thiamine and concomitant treatments such as magnesium supplementation.

The timing of WE diagnosis, duration of hospitalization, recovery status at the time of hospital discharge, date of in-hospital death, and cause of death were also registered. WE diagnoses made within the first

24 h after admission were considered to be early, and hospital stays > 10 days were classified as prolonged. The absence of WE signs or symptoms at the time of discharge was considered as complete recovery; partial recovery was defined as improvement during hospitalization with the persistence of signs or symptoms at discharge; and the lack of recovery was defined as no improvement or worsening of signs or symptoms during hospitalization.

Magnetic resonance imaging (MRI) findings were classified according to lesion location (mammillary bodies, thalamus, hypothalamic nuclei, periaqueductal-periventricular region, midbrain, fornix, cerebellum, or cerebral cortex) and symmetry. According to previous reports (Galvin et al., 2010; Sechi and Serra, 2007; Zuccoli et al., 2009), symmetrical signal intensity alterations in the mammillary bodies, thalamus, midbrain, and periaqueductal-periventricular area were considered to be typical of WE.

2.3. Statistical analysis

Categorical variables are presented as absolute and relative frequencies. Variables are presented as medians with ranges [min-max]. Categorical variables were compared using the χ^2 test and Fisher's exact test, and continuous variables were compared using Student's *t* test and the Mann-Whitney *U* test. Two-tailed *P* values < 0.05 were considered to be significant. The Spearman rank correlation coefficient (*r*) was used to identify correlations between ordinal variables, and multivariable logistic regression analysis was used to independently analyze the relationships of baseline variables and treatment characteristics to mortality and recovery. The statistical analyses were performed using SPSS software (version 20.0; IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

The initial cohort comprised 569 patients discharged with WE diagnosis codes. We excluded 33 patients due to the lack of clinical WE diagnosis during hospitalization (because of prior WE diagnosis or inconsistent or missing data) and another 93 patients due to the lack of detailed information about their treatment regimens. Thus, a total of 443 patients were included in this study.

The median age of the patients was 54.6 years and range was 68.1 (20.9–89.0), and 358 (80.8%) patients were male. The existence of an AUD was established for 417 (94.1%) patients, with a median active alcohol consumption of 84 (range = 333 [3–336]) SDU/week; 84 (range = 313 [7–320]) SDU/week in men and 70 (range = 333 [3–336]) SDU/week in women. In addition, 63.2% of the patients were also smokers and 5.2% consumed other drugs. The presence of dietary deficiencies was established in 218 (49.2%) patients.

3.2. Treatment characteristics and factors related to the choice of treatment route or dosage

Thiamine treatment was initiated within 48 h before or after the recorded date of WE diagnosis in 373 (84.2%) patients. The remaining 70 patients received thiamine more than 48 h before (*n* = 48) or after (*n* = 7) diagnosis, or did not receive thiamine during hospitalization (*n* = 15).

Among patients who received thiamine treatment within an adequate timeframe, the initial treatment route was intramuscular for 196 (52.5%) patients, intravenous for 145 (38.9%) patients, and oral for 32 (8.6%) patients. Among the 341 patients who received parenteral (intravenous or intramuscular) treatment, 272 (79.8%) also received oral treatment during or after this treatment.

Among patients who received parenteral treatment within an adequate timeframe, the initial dosage was >500 mg/day for 4 (1.1%)

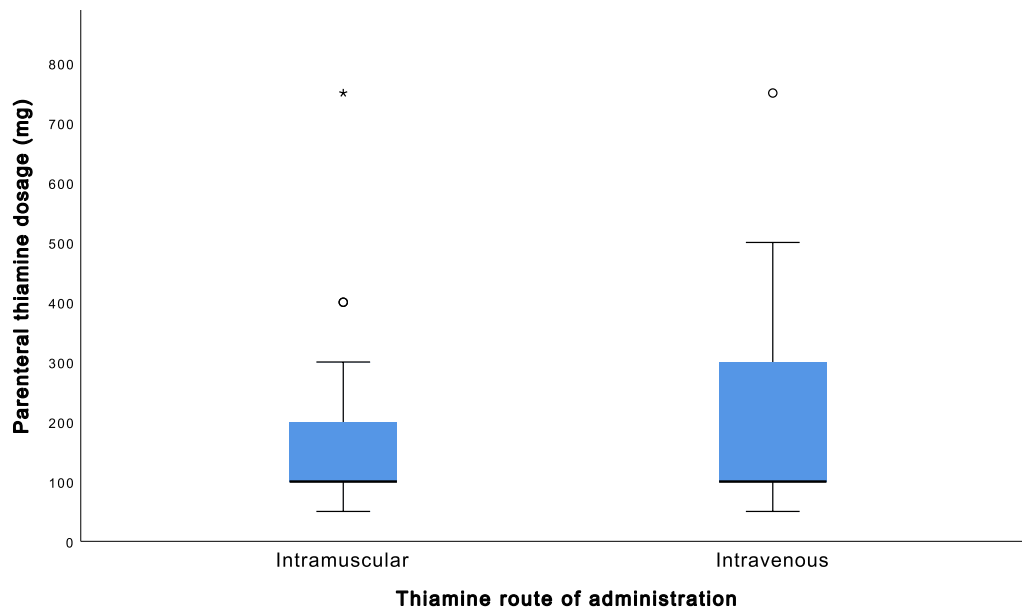


Fig. 1. Parenteral thiamine dosage initiated during the first 24 h of hospitalization according to the route of administration. IM: intramuscular, IV: intravenous.

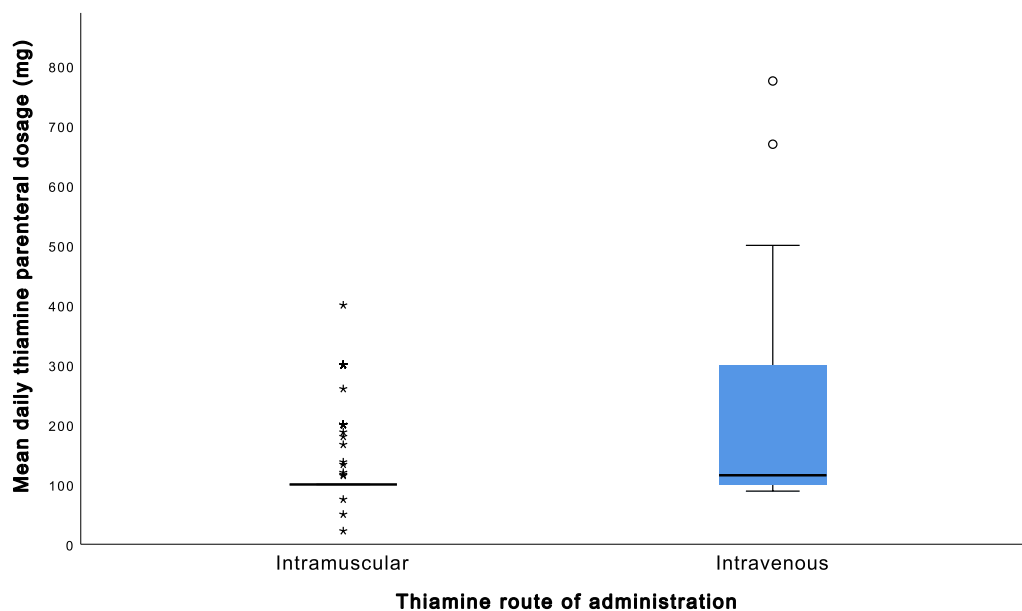


Fig. 2. Mean daily parenteral thiamine dosage according to the route of administration. IM: intramuscular, IV: intravenous.

patients and 300–500 mg/day for 74 (19.8%) patients. For 232 (61.9%) patients, the initial dosage was <200 mg/day, with wide dispersion of the data (Fig. 1). The median daily intravenous and intramuscular doses received during hospitalization was 115 (range = 90–1000) and 100 (range = 1480 [20–1500]), respectively (Fig. 2). The median durations of intravenous and intramuscular treatment were 6 (range = 29 [1–30]) and 5 (SD = 33 [1–34]) days, respectively.

Patients who fulfilled the Caine criteria were significantly more likely to receive initial parenteral instead of oral treatment than were those who did not fulfill the criteria [92.7% vs. 81.0%, $P = 0.010$]; the same was true for patients presenting and not presenting with the classic WE triad (95.7% vs. 88.9%, $P = 0.025$). Other factors related to the selection of parenteral treatment were oculomotor abnormalities ($P < 0.001$), cerebellar dysfunction ($P = 0.023$), ataxia ($P = 0.023$), and folic acid deficiency ($P = 0.021$) (Table 2). Only folic acid deficiency was related to the choice of intravenous rather than oral or intramuscular

administration ($P = 0.015$).

Factors related to higher initial thiamine dosages (>300 mg) for parenteral treatment initiated during first 24 h were chronic liver disease ($P < 0.001$); clinical presentation with tremor ($P = 0.003$), flapping ($P = 0.009$), cerebellar dysfunction ($P = 0.009$), oculomotor abnormalities ($P = 0.018$) or delirium ($P = 0.006$); and coexisting alcohol withdrawal syndrome ($P < 0.001$). The same variables were related to average daily thiamine doses > 300 mg (Table 3).

Of 15 patients with hypomagnesemia, 5 received magnesium supplementation. Another 14 patients with no reported hypomagnesemia received such supplementation, resulting in a total of 19 (5%) patients who received this treatment.

3.3. Influence of thiamine treatment on outcomes

The median length of hospital stay in the cohort of 443 patients was

Table 2
Associations of variables with the choice of thiamine administration route.

	Exclusive oral treatment (n = 32)	Parenteral treatment (n = 341)	P	OR (95% CI)	Oral or intramuscular treatment (n = 228)	Intravenous treatment (n = 145)	P	OR (95% CI)
Chronic liver disease	9 (28.1)	68 (19.9)	0.274	0.64 (0.28–1.44)	45 (19.7)	32 (22.1)	0.588	1.26 (0.74–2.15)
Cirrhosis	3 (9.4)	22 (6.5)	0.527	0.67 (0.19–2.36)	18 (7.9)	7 (4.8)	0.248	0.61 (0.24–1.54)
Alcohol use disorder	31 (96.9)	317 (93.0)	0.397	0.43 (0.06–3.26)	215 (94.3)	133 (91.7)	0.332	0.72 (0.32–1.66)
Cancer	3 (9.4)	20 (5.9)	0.430	0.60 (0.17–2.15)	11 (4.8)	12 (8.3)	0.177	2.12 (0.84–5.33)
Malnutrition	10 (31.3)	91 (26.7)	0.579	0.80 (0.37–1.76)	63 (27.6)	38 (26.2)	0.763	0.96 (0.59–1.56)
Gastrointestinal surgery	2 (6.3)	28 (8.2)	0.697	1.34 (0.31–5.91)	14 (6.1)	16 (11.0)	0.090	1.90 (0.87–4.16)
Classic triad	6 (18.8)	132 (38.7)	0.025	2.74 (1.10–6.83)	80 (35.1)	58 (40.0)	0.338	1.10 (0.71–1.71)
Seizures	3 (9.4)	31 (9.1)	0.957	0.97 (0.28–3.36)	19 (8.3)	15 (10.3)	0.511	1.30 (0.62–2.72)
Oculomotor abnormalities	10 (31.2)	228 (66.9)	<0.001	4.44 (2.03–9.69)	143 (62.7)	95 (65.5)	0.584	0.90 (0.57–1.42)
Cerebellar dysfunction	19 (59.4)	264 (77.4)	0.023	2.35 (1.11–4.97)	173 (75.9)	110 (75.9)	0.997	0.86 (0.51–1.43)
Ataxia	19 (59.4)	264 (77.4)	0.023	2.35 (1.11–4.97)	173 (75.9)	110 (75.9)	0.997	0.86 (0.51–1.43)
Tremor	6 (18.8)	51 (15.0)	0.568	0.76 (0.30–1.94)	30 (13.2)	27 (18.6)	0.153	1.64 (0.90–2.98)
Flapping	3 (9.4)	22 (6.5)	0.527	0.67 (0.19–2.36)	16 (7.0)	9 (6.2)	0.760	0.93 (0.39–2.24)
Alcohol withdrawal syndrome	8 (25.0)	63 (18.5)	0.369	0.68 (0.29–1.59)	38 (16.7)	33 (22.8)	0.144	1.63 (0.94–2.82)
Hepatic encephalopathy	2 (6.3)	10 (2.9)	0.275	0.45 (0.10–2.16)	6 (2.6)	6 (4.1)	0.303	2.07 (0.57–7.48)
Delirium	6 (18.8)	91 (26.7)	0.328	1.58 (0.63–3.96)	53 (23.2)	44 (30.3)	0.128	1.38 (0.85–2.24)
Altered mental status	28 (87.5)	279 (81.8)	0.421	0.64 (0.22–1.90)	187 (82.0)	120 (82.8)	0.855	1.12 (0.64–1.96)
Confusional syndrome	23 (71.9)	246 (72.1)	0.974	1.01 (0.45–2.27)	168 (73.7)	101 (69.7)	0.398	0.81 (0.50–1.30)
Low level of consciousness	1 (3.1)	28 (8.2)	0.304	2.77 (0.36–21.08)	15 (6.6)	14 (9.7)	0.279	1.39 (0.64–3.01)
Caine >2	24 (75.0)	307 (90.0)	0.010	3.01 (1.26–7.22)	206 (90.4)	125 (86.2)	0.217	0.67 (0.35–1.27)
B12 vitamin deficit	2 (9.5)	14 (5.7)	0.474	0.57 (0.12–2.70)	10 (6.1)	6 (5.8)	0.912	1.03 (0.35–3.07)
Folic acid deficiency	2 (7.7)	78 (28.8)	0.021	4.85 (1.12–21.01)	56 (32.2)	24 (19.5)	0.015	0.42 (0.24–0.74)
Anemia	10 (31.3)	95 (28.1)	0.706	0.86 (0.40–1.88)	56 (24.8)	49 (34)	0.054	1.66 (1.03–2.68)

Variables are presented as absolute frequencies (percentages) and were compared using the χ^2 and Fisher's exact tests.

14 (range = 205 [1–206]), and 284 (64.1%) patients had prolonged stays. The median time until WE diagnosis was 1 (range = 51 [0–51]) day, and 295 (66.6%) patients were diagnosed during the first 24 h of hospitalization. Such early diagnosis was significantly more frequent among patients with AUDs (68.3% vs 38.5%, odds ratio [OR] = 3.45, 95% confidence interval [CI] 1.53–7.82, $P = 0.002$) and those presenting with oculomotor abnormalities (72.1% vs 58.4%, OR = 1.84, 95% CI 1.23–2.74, $P = 0.003$), whereas more patients presenting with confusion (37% vs 23.3%, OR = 1.94, 95% CI 1.19–3.15, $P = 0.007$), altered mental status (36.1% vs 18.8%, OR = 2.43, 95% CI 1.28–4.61, $P = 0.005$), delirium (41.5% vs 30.3%, OR = 1.63, 95% CI 1.06–2.51, $P = 0.026$), or reduced consciousness (55% vs 31.3%, OR = 2.69, 95% CI 1.39–5.19, $P = 0.002$) received late diagnoses. Prolonged hospital stays were significantly more frequent among patients with malnutrition (74% vs 60.9%, OR = 1.83, 95% CI 1.16–2.89, $P = 0.009$) and in those presenting with confusion (71.2% vs 46.6%, OR = 2.84, 95% CI 1.83–4.40, $P < 0.001$), altered mental status (69.5% vs 39.1%, OR = 3.54, 95% CI 2.08–6.02, $P < 0.001$), and delirium (78.7% vs 59.3%, OR = 2.53, 95% CI 1.56–4.13, $P < 0.001$).

Detailed information about 418 patients' recovery was available.

Among them, 105 (23.7%) patients achieved complete clinical recovery, 275 (62.1%) had partial recovery, and 38 (8.6%) patients showed no improvement during hospitalization. In univariate analyses, the main factors on admission related to the lack of complete recovery at discharge were cerebellar dysfunction ($P = 0.015$), confusional syndrome ($P = 0.002$), ataxia ($P = 0.015$) or altered mental status ($P = 0.007$), fulfillment of more than two Caine criteria at diagnosis ($P < 0.001$), previous diagnosis of cirrhosis ($P = 0.043$), folic acid deficiency ($P < 0.001$), and pathological MRI findings ($P = 0.041$) (Table 4). Early diagnosis ($P = 0.008$) and receipt of any thiamine treatment within an adequate timeframe ($P = 0.042$) were associated significantly with complete recovery, but only a trend toward better recovery of patients who received intravenous treatment was observed ($P = 0.052$). On logistic regression analysis, variables associated independently with the lack of complete recovery were the fulfillment of more than two Caine criteria at diagnosis (OR = 2.98, 95% CI 1.48–6.03, $P < 0.01$), mental status alterations (OR = 2.50, 95% CI 1.29–4.85, $P < 0.01$), folic acid deficiency (OR = 2.82, 95% CI 1.39–5.76, $P < 0.01$), and delayed diagnosis (OR = 1.93, 95% CI 1.05–3.53, $P = 0.03$).

Twenty-two (4.9%) patients died during hospitalization. Factors

Table 3

Associations of variables with initial parenteral thiamine doses > 300 mg during the first 24 h or mean daily parenteral dose > 300 mg.

	Initial dose ≥300 mg (first 24 hours) (N = 74)	Initial dose <300 mg (first 24 hours) (N = 267)	P	OR (95% CI)	Mean daily dose ≥300 mg (N = 69)	Mean daily dose <300 mg (N = 272)	P	OR (95% CI)
Chronic liver disease	26 (35.1)	42 (15.7)	<0.001	2.90 (1.63–5.18)	25 (36.2)	43 (15.8)	<0.001	3.03 (1.68–5.45)
Cirrhosis	8 (10.8)	14 (5.2)	0.077	2.19 (0.88–5.44)	7 (10.1)	15 (5.5)	0.132	1.93 (0.76–4.95)
Alcohol use disorders	68 (91.9)	249 (93.3)	0.684	0.82 (0.31–2.14)	62 (89.9)	255 (93.8)	0.259	0.59 (0.24–1.49)
Cancer	3 (4.1)	17 (6.4)	0.454	0.62 (0.18–2.18)	3 (4.3)	17 (6.3)	0.548	0.68 (0.19–2.40)
Malnutrition	15 (20.3)	76 (28.5)	0.158	0.64 (0.34–1.20)	14 (20.3)	78 (28.7)	0.161	0.63 (0.33–1.20)
Gastrointestinal surgery	2 (2.7)	26 (9.7)	0.051	0.26 (0.06–1.11)	1 (1.4)	27 (9.9)	0.022	0.13 (0.02–1.00)
Classic triad	25 (33.8)	107 (40.1)	0.326	0.76 (0.44–1.31)	22 (31.9)	110 (40.4)	0.192	0.69 (0.39–1.21)
Seizures	11 (14.9)	20 (7.5)	0.051	2.16 (0.98–4.73)	11 (15.9)	21 (7.7)	0.036	2.28 (1.04–4.96)
Oculomotor abnormalities	41 (55.4)	187 (70.0)	0.018	0.53 (0.31–0.90)	39 (56.5)	189 (69.5)	0.041	0.57 (0.33–0.98)
Cerebellar dysfunction	49 (66.2)	215 (80.5)	0.009	0.47 (0.27–0.84)	44 (63.8)	221 (81.3)	0.002	0.41 (0.23–0.72)
Ataxia	49 (66.2)	215 (80.5)	0.009	0.47 (0.27–0.84)	44 (63.8)	221 (81.3)	0.002	0.41 (0.23–0.72)
Tremor	19 (25.7)	32 (12.0)	0.003	2.54 (1.340–4.81)	19 (27.5)	33 (12.1)	0.001	2.75 (1.45–5.23)
Flapping	10 (13.5)	12 (4.5)	0.009	3.32 (1.37–8.03)	9 (13.0)	13 (4.8)	0.018	2.99 (1.22–7.31)
Alcohol withdrawal syndrome	25 (33.8)	38 (14.2)	<0.001	3.08 (1.70–5.56)	23 (33.3)	40 (14.7)	<0.001	2.90 (1.59–5.30)
Hepatic encephalopathy	3 (4.1)	7 (2.6)	0.374	1.57 (0.40–6.22)	2 (2.9)	8 (2.9)	0.672	0.99 (0.20–4.75)
Delirium	29 (39.2)	62 (23.2)	0.006	2.13 (1.23–3.68)	27 (39.1)	64 (23.5)	0.009	2.09 (1.20–3.65)
Altered mental status	61 (82.4)	218 (81.6)	0.877	1.05 (0.54–2.07)	57 (82.6)	222 (81.6)	0.849	1.07 (0.53–2.14)
Confusional syndrome	47 (63.5)	199 (74.5)	0.061	0.60 (0.34–1.03)	43 (62.3)	202 (74.3)	0.049	0.57 (0.33–1.00)
Low level of consciousness	8 (10.8)	20 (7.5)	0.357	1.50 (0.63–3.55)	6 (8.7)	22 (8.1)	0.870	1.08 (0.42–2.78)
Caine >2	57 (77.0)	250 (93.6)	<0.001	0.22 (0.11–0.47)	52 (75.4)	256 (94.1)	<0.001	0.19 (0.09–0.40)
B12 vitamin deficit	6 (12.2)	8 (4.0)	0.038	3.31 (1.09–10.05)	5 (11.4)	9 (4.4)	0.081	2.76 (0.88–8.69)
Folic acid deficiency	11 (16.9)	67 (32.5)	0.015	0.42 (0.21–0.86)	10 (16.4)	68 (32.5)	0.014	0.41 (0.20–0.85)
Anemia	25 (34.2)	70 (26.4)	0.187	1.45 (0.83–2.53)	25 (36.8)	70 (25.9)	0.076	1.66 (0.95–2.92)

Variables are presented as absolute frequencies (percentages) and were compared using the χ^2 and Fisher's exact tests.

associated with mortality in univariate analyses were previous diagnosis of cancer ($P = 0.038$), gastrointestinal surgery ($P = 0.020$), malnutrition ($P = 0.027$), cirrhosis ($P = 0.028$), folic acid deficiency ($P = 0.004$), and reduced consciousness at the time of diagnosis ($P = 0.002$) (Table 5). Timely thiamine treatment ($P = 0.003$) and early diagnosis ($P = 0.031$) were related to lower mortality. On logistic regression analysis, independent prognostic factors for death during hospitalization were malnutrition (OR = 3.07, 95% CI 1.03–9.17, $P = 0.04$), reduced consciousness (OR = 3.51, 95% CI 1.04–11.79, $P = 0.04$), folic acid deficiency (OR = 3.61, 95% CI 1.21–10.68, $P = 0.02$), and the lack of adequate treatment (OR = 3.36, 95% CI 1.12–10.09, $P = 0.03$).

4. Discussion

This study revealed a high degree of variability in clinical WE treatment, with overall use of lower doses than currently recommended by international guidelines and recommendations (Galvin et al., 2010). Although no global consensus has been established, current guidelines recommend intravenous treatment with 200 mg thiamine three times a

day, beginning as soon as possible after WE diagnosis (Galvin et al., 2010; Pruckner et al., 2019). Although current guidelines were not published until 2010, most patients included in our study, even those receiving intravenous treatment, were undertreated. Such inadequacy has been highlighted previously by other authors, not only with regard to WE treatment (Crook and Sriram, 2014; Isenberg-Grzeda et al., 2012), but also in cases of acute illness and high WE risk, in which early thiamine administration can prevent WE development (Pawar et al., 2022). Although the lack of high-quality evidence from clinical trials may favor variability in the clinical management of WE, the potential benefits and safety profile of high-dose intravenous thiamine treatment are clear (Pruckner et al., 2019; Thomson et al., 2019, 2013). Thus, there seems to be a clear need to implement existing recommendations. An automated electronic system designed to enhance the prescription of high-dose thiamine for patients with AUDs has been proposed and has shown promising results (Wai et al., 2019).

Regarding factors associated with treatment characteristics, we found that patients fulfilling the Caine criteria or presenting with the classic WE triad, which furthers the clinical suspicion of WE, were more

Table 4
Associations of variables with recovery status.

	No recovery or partial recovery (N = 313)	Complete recovery (N = 105)	P	OR (95% CI)
Chronic liver disease	77 (24.6)	18 (17.1)	0.115	0.63 (0.36–1.12)
Cirrhosis	32 (10.2)	4 (3.8)	0.043	0.35 (0.12–1.01)
Alcohol use disorders	291 (93.0)	102 (97.1)	0.119	2.57 (0.75–8.77)
Cancer	21 (6.7)	5 (4.8)	0.475	0.70 (0.26–1.89)
Malnutrition	95 (30.4)	26 (24.8)	0.274	0.76 (0.46–1.25)
Gastrointestinal surgery	22 (7.0)	9 (8.6)	0.602	1.24 (0.55–2.79)
Classic triad	117 (37.4)	36 (34.3)	0.569	0.87 (0.55–1.39)
Seizures	26 (8.3)	9 (8.6)	0.932	1.04 (0.47–2.29)
Oculomotor abnormalities	190 (60.7)	62 (59.0)	0.764	0.93 (0.60–1.46)
Cerebellar dysfunction	248 (79.2)	71 (67.6)	0.015	0.55 (0.34–0.90)
Ataxia	248 (79.2)	71 (67.6)	0.015	0.55 (0.34–0.90)
Tremor	53 (16.9)	23 (21.9)	0.253	1.38 (0.80–2.38)
Flapping	25 (8.0)	4 (3.8)	0.145	0.46 (0.16–1.34)
Alcohol withdrawal syndrome	66 (21.1)	28 (26.7)	0.236	1.36 (0.82–2.27)
Hepatic encephalopathy	16 (5.1)	2 (1.9)	0.127	0.36 (0.08–1.59)
Delirium	93 (29.7)	23 (21.9)	0.122	0.66 (0.39–1.12)
Altered mental status	273 (87.2)	80 (76.2)	0.007	0.47 (0.27–0.82)
Confusional syndrome	244 (78.0)	66 (62.9)	0.002	0.48 (0.30–0.77)
Low level of consciousness	33 (10.5)	5 (4.8)	0.075	0.42 (0.16–1.12)
Caine >2	287 (91.7)	83 (79.0)	<0.001	0.34 (0.18–0.63)
B12 vitamin deficiency	10 (4.5)	7 (8.9)	0.124	2.07 (0.76–5.64)
Folic acid deficiency	83 (34.7)	11 (12.4)	<0.001	0.27 (0.13–0.53)
Anemia	94 (30.2)	29 (27.9)	0.651	0.89 (0.55–1.46)
Pathologic findings in MRI	153 (88.4)	45 (77.6)	0.041	0.45 (0.21–0.98)
Intravenous treatment	95 (37.0)	46 (48.4)	0.052	1.60 (1.00–2.58)
Parenteral treatment	192 (83.1)	70 (77.8)	0.267	1.69 (0.87–3.30)
Adequate treatment*	257 (82.1)	95 (90.5)	0.042	2.07 (1.02–4.22)
Mean parenteral daily dose >300 mg	45 (19.3)	24 (26.7)	0.148	1.52 (0.86–2.68)
First 24 h parenteral dose >300 mg	50 (19.9)	26 (28.3)	0.099	1.58 (0.91–2.74)
Early diagnosis	197 (62.9)	81 (77.1)	0.008	1.99 (1.19–3.31)

MRI, magnetic resonance imaging. Variables are presented as absolute frequencies (percentages) and were compared using the χ^2 and Fisher's exact tests. *Initiation of thiamine treatment within 48 h before or after Wernicke's encephalopathy diagnosis.

likely to receive parenteral treatment. In addition, most factors related significantly to the administration of higher thiamine doses (chronic liver disease; clinical presentation with seizures, tremor, flapping, or delirium; and coexisting alcohol withdrawal syndrome) enhance the

Table 5
Main factors linked to mortality.

	Died (n=22)	Survivors (n=421)	P	OR (95% CI)
Chronic liver disease	8 (36.4)	91 (21.6)	0.092	2.07 (0.84–5.09)
Cirrhosis	5 (22.7)	32 (7.6)	0.028	3.58 (1.24–10.32)
Alcohol use disorder	20 (90.9)	397 (94.3)	0.510	0.61 (0.13–2.74)
Cancer	4 (18.2)	23 (5.5)	0.038	3.85 (1.20–12.29)
Malnutrition	11 (50.0)	118 (28.0)	0.027	2.57 (1.08–6.08)
Gastrointestinal surgery	5 (22.7)	29 (6.9)	0.020	3.98 (1.37–11.55)
Classic triad	4 (18.2)	154 (36.6)	0.079	0.39 (0.13–1.16)
Seizures	2 (9.1)	35 (8.3)	0.565	1.10 (0.25–4.91)
Oculomotor abnormalities	11 (50.0)	254 (60.3)	0.335	0.66 (0.28–1.55)
Cerebellar dysfunction	13 (59.1)	320 (76.0)	0.073	0.46 (0.19–1.10)
Ataxia	13 (59.1)	320 (76.0)	0.073	0.46 (0.19–1.10)
Tremor	6 (27.3)	72 (17.1)	0.173	1.82 (0.69–4.80)
Flapping	1 (4.5)	28 (6.7)	0.570	0.67 (0.09–5.15)
Alcohol withdrawal syndrome	5 (22.7)	90 (21.4)	0.527	1.08 (0.390–3.01)
Hepatic encephalopathy	2 (9.1)	17 (4.0)	0.242	2.38 (0.51–11.00)
Delirium	10 (45.5)	113 (26.8)	0.057	2.27 (0.96–5.40)
Altered mental status	21 (95.5)	353 (83.8)	0.116	4.05 (0.54–30.58)
Confusional syndrome	19 (86.4)	308 (73.2)	0.170	2.32 (0.68–8.00)
Low level of consciousness	7 (31.8)	33 (7.8)	0.002	5.49 (2.09–14.40)
Caine >2	20 (90.9)	370 (87.9)	0.497	1.38 (0.31–6.07)
B12 vitamin deficiency	1 (7.1)	17 (5.5)	0.561	1.32 (0.16–10.67)
Folic acid deficiency	10 (62.5)	91 (27.2)	0.004	4.47 (1.58–12.65)
Anemia	10 (45.5)	119 (28.5)	0.088	2.09 (0.88–4.98)
Pathologic findings in MRI	9 (81.1)	201 (86.3)	0.470	0.72 (0.15–3.47)
Intravenous treatment	2 (15.4)	143 (39.7)	0.077	0.28 (0.06–1.26)
Parenteral treatment	15 (71.4)	346 (84.0)	0.117	0.48 (0.18–1.27)
Adequate treatment*	13 (59.1)	360 (85.5)	0.003	0.25 (0.10–0.60)
Mean parenteral daily dose >300 mg	2 (15.4)	68 (20.7)	0.482	0.70 (0.15–3.22)
First 24 h parenteral dose >300 mg	2 (9.1)	75 (19.3)	0.182	0.56 (0.12–2.53)
Early diagnosis	10 (45.5)	285 (67.7)	0.031	0.40 (0.17–0.94)

MRI, magnetic resonance imaging. Variables are presented as absolute frequencies (percentages) and were compared using the χ^2 and Fisher's exact tests. *Initiation of thiamine treatment within 48 h before or after Wernicke's encephalopathy diagnosis.

clinical suspicion of WE. On the other hand, and for unknown reasons, oculomotor abnormalities, ataxia, and cerebellar dysfunction were associated with the receipt of lower thiamine doses in our sample. As we reported previously, differences in the clinical presentation of WE may be related to the presence of ALD or AUDs, whose clinical characteristics could act as confounders leading to delayed WE diagnosis and inadequate treatment (Chamorro et al., 2017; Novo-Veleiro et al., 2022). The

broad dispersion of dosages and routes combined with the observational and retrospective nature of our study render the drawing of definite conclusions about these associations difficult.

Better prognosis (clinical recovery and reduced mortality) was associated in our univariate analyses with early diagnosis and the timely receipt of thiamine treatment, as in other studies (Day and del Campo, 2014; Patel et al., 2018). These findings reinforce the key roles of early diagnosis and treatment, which clearly appears to improve the prognosis of WE. It has been previously highlighted the need for maximal clinical suspicion in high-risk patients and the potential benefit of early treatment, which far outweighs possible risks (Mateos-Díaz et al., 2022; Mifsud et al., 2022).

We also found that more patients with AUDs and those presenting with oculomotor abnormalities received early WE diagnoses, whereas an atypical presentation with altered mental status and reduced consciousness were linked to late diagnosis and greater risks of incomplete recovery and mortality. These findings could reflect the reduced clinical suspicion of WE in daily practice in the absence of AUDs and in cases with atypical presentations, leading to delayed diagnosis, lower rates of parenteral treatment, and undertreatment (Galvin et al., 2010; Harper, 1983; Sanvisens et al., 2017).

Malnutrition was linked to a higher mortality rate and folic acid deficiency was related to the lack of complete recovery and mortality in this study. Malnutrition is a major risk factor for WE development, even in the absence of alcohol consumption, and could be additionally linked to multiple nutrient (e.g., folic acid) deficiencies (Chamorro et al., 2017; Oudman et al., 2021). Although specific recommendations regarding folic acid and WE are lacking, the restoration of a normal folic acid level could be useful to reduce neurological damage and cognitive impairment (Puga et al., 2021; Rotstein et al., 2022) and our findings may support the empirical folic acid supplementation during WE treatment until serum results are available. Patients with malnutrition and a high risk of WE development, such as those with AUDs, should be included in specific nutritional programs (Oudman et al., 2021).

Finally, although the timely receipt of thiamine treatment was associated with lower mortality in our series, the dose and route of administration had no significant effect on prognosis. In line with this finding, a recent randomized controlled trial revealed no significant difference in cognitive or neurological function according to the thiamine dosage (100 mg/day, 100 mg tid, and 300 mg tid), which may reflect the lack of clear benefit of higher doses or methodological limitations that hamper the detection of this effect, even in such trials (Dingwall et al., 2022). Thus, clinicians must be aware of initiating treatment with intravenous thiamine as soon as WE is suspected. Given the reported safety of this treatment (Wrenn et al., 1989), higher intravenous doses should be used following the current guidelines, but there is no clear evidence for a specific thiamine dosage. Larger and high-quality clinical trials should be conducted to answer this question.

Although our study had the strength of a relevant sample comprising a large number of patients from 21 centers for whom detailed daily treatment data were recorded (one of the largest series published to date), our analysis was limited by the retrospective nature of our study and the potential inadequate assessment of clinical criteria, the risk of selection bias toward more severe cases, and the lack of randomization. Statistical comparisons between treatment regimens and correlation with outcomes were difficult due to the extreme variability in treatment regimens. In addition, our data may not fully reflect current practice due to collection dates, we did not examine potential side effects of thiamine treatment and we did not carry out a long-term follow-up of patients in order to assess the development of complications such as Korsakoff syndrome.

In conclusion, our results clearly show extreme variability in thiamine dosages and routes used for the management of WE. Although our data support the prognostic benefit of prompt thiamine treatment after early diagnosis, the impact of the administration of very high thiamine doses remains unclear. Available data and methodological limitations

make the availability of conclusive evidence in the short term for the establishment of treatment recommendations based on high-quality evidence unlikely.

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CRedit authorship contribution statement

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Declaration of Competing Interest

All authors declare no competing interests.

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