Low serum magnesium and 1-year mortality in Alcohol Withdrawal Syndrome

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Abstract

Background:

In 2014, the WHO reported that 6% all deaths were attributable to excess alcohol consumption. The aim of the present study was to examine the relationship between serum magnesium concentrations and mortality in patients with alcohol withdrawal syndrome (AWS).

Methods:

A retrospective review of 700 patients with documented evidence of previous AWS indicating a requirement for benzodiazepine prophylaxis or evidence of alcohol withdrawal syndrome between November 2014 and March 2015.

Results:

Of 380 patients included in the sample analysis, 64 (17%) were dead at 1 year following the time of treatment for AWS. The majority of patients had been prescribed thiamine (77%) and a proton pump inhibitor (66%). In contrast, the majority of patients had low circulating magnesium concentrations (<0.75mmol/l) (64%) and had not been prescribed magnesium (90%). The median age of death at one year was 55 years (p=0.002). On univariate analysis, age (p<0.05), GMAWS (p<0.05), BDZ (p<0.05), bilirubin (p<0.001), alkaline phosphatase (p<0.001), albumin (p<0.001), CRP (p<0.05), AST:ALT ratio >2 (p<0.001), sodium (p<0.05), magnesium (p<0.001), platelets (p<0.05) and the use of proton pump inhibitor medication (p<0.001) were associated with death at 1 year. On multivariate binary logistic regression analysis, age >50 years (OR 3.37, 95%CI 1.52-7.48, p<0.01), AST:ALT ratio >2 (OR 3.10, 95%CI 1.38-6.94, p<0.01) and magnesium <0.75 mmol/L (OR 4.11, 95%CI 1.3-12.8, p<0.05) remained independently associated with death at 1 year.

Conclusion:

Overall, 1-year mortality was significantly higher among those patients who were magnesium deficient (<0.75 mmol/L) when compared to those who were replete ($\geq$ 0.75 mmol/L) (p<0.001).

Introduction

In 2014, the WHO reported that 5% of the global burden of disease and 6% all deaths were attributable to excess alcohol consumption (1). Some areas of the world are more severely affected than others (2). For example, over half of all deaths in Russia between 1990 and 2001 were attributed to alcohol (3), while in Scotland it is estimated that one in four adults currently consume alcohol at harmful or hazardous levels (4). Despite public health measures, alcohol consumption has continued to rise in the U.K. and U.S.A. over the past three decades (1, 4, 5), while alcohol related mortality among women has more than doubled in Scotland over the past decade (6).

Recent recognition of alcohol as a carcinogen may have contributed to these epidemiological estimates of alcohol related morbidity and mortality (7), however little data is available in the literature relating to expected mortality for patients diagnosed with severe alcohol use disorder, as defined by a simple tool such as the Focused Alcohol Screening Test (FAST) score or following an episode of acute alcohol withdrawal (8). The Glasgow Modified Alcohol Withdrawal Score (GMAWS) is a validated score of severity of alcohol withdrawal syndrome that allocates a score (0-2) to five clinical characteristics (tremor, anxiety, sweating, orientation, hallucinations) (8). The benzodiazepine treatment dose is titrated and the time interval to re-administering the GMAWS scoring test are determined by the score achieved (i.e. the severity of alcohol withdrawal). A GMAWS ≥ 4 is considered severe, and is approximately equivalent to a Clinical Institute Withdrawal Assessment - Alcohol Revised (CIWA-Ar) scale ≥ 16 (8).

It is reported that 40% of patients admitted to a general hospital and 33% of patients admitted to the intensive care unit (ICU), fulfil the criteria for diagnosis of alcohol use disorder (9). Alcohol withdrawal syndrome is reported to occur in 10% of patients who fulfil the criteria for alcohol use disorder patients (10). An episode of severe alcohol withdrawal syndrome is reported to extend the length of stay in hospital by a median of 4 days (11) and more than double the length of stay in ICU settings (12). Indeed, patients who experience excited delirium are reported to have

20% higher acute mortality in a cardiac intensive care setting (12), and 37% mortality at 8 years (13), which is comparable to patients diagnosed with several severe malignant disease processes (14, 15).

Alcohol exerts direct and indirect effects on cellular energy metabolism and alcohol use disorder is a complex psychological and pathophysiological problem. Nutritional and social factors may be protective or contributory, however a threshold may be reached beyond which alcohol related compromise of oxidative resilience manifests in accelerated organ/ system specific final common pathways of biochemical and clinical deterioration. The occurrence of alcohol withdrawal syndrome (AWS) may represent the crossing of that threshold.

The aim of the present study was to examine the relationship between clinicopathological characteristics, circulating magnesium concentrations and 1- year mortality in patients with AWS.

Patients and methods

A retrospective case-note review of electronic patient records of sequential patients, who were referred to the hospital addictions team between November 2014 and March 2015, was carried out (n=700). The hospital Alcohol and Drugs Addiction Team in Glasgow Royal Infirmary (GRI) serves an urban population in the north and east of the city, which has a high burden of socio-economic (SE) deprivation (6, 16). GRI is a general hospital that offers the full spectrum of adult acute receiving specialties to patients over 16 years old. This review of patients was carried out as an audit and was approved by the Greater Glasgow and Clyde NHS Caldecott Guardian.

The availability of age, sex, BMI and documented evidence of AWS were considered minimal criteria for inclusion (n=380). From the original cohort of 700 patients, 320 patients were excluded in the final analysis as they did not fulfil the entry criteria of either contemporaneous BMI (+/- 3 month time period from study related attendance) or documented evidence of AWS.

Duplicate referrals were removed and data from the earliest time of referral was recorded. Data was analysed according to 1-year mortality and serum magnesium concentrations. Standard thresholds were applied to the data. Continuous data were analyzed using the Mann-Whitney U test and categorical data were analyzed using the Chi-squared test. Data that reached a p-value <0.10 on univariate analysis were included in the multivariate binary logistic regression analysis. Data was analyzed in SPSS (Version 24.0. SPSS Inc., Chicago, IL, USA).

Results

Of the 700 patients, 380 patients fulfilled the criteria for inclusion with age, sex, BMI and documented evidence of alcohol withdrawal syndrome. The clinicopathological characteristics are shown in Table 1. The majority of patients were <50 years old (53%), male (76%), not underweight (80%), had a severe alcohol withdrawal score (GMAWS max score $\geq$ 4) and the total 'diazepam-equivalent' dose of benzodiazepine (BDZ) administered was less than 120mg (81%). Of the laboratory analysis, the majority of patients had bilirubin (58%), alkaline phosphatase (71%), albumin (56%), CRP (57%), AST/ALT ratio (62%), glucose (66%), urea (66%), sodium (70%), potassium (76%), MCV (88%) and platelets (67%) within the laboratory reference range. The majority of patients had been prescribed thiamine (77%) and a proton pump inhibitor (PPi) (66%). In contrast, the majority of patients had circulating magnesium concentrations that could be considered to be low (<0.75mmol/l) (64%) and had not been prescribed magnesium (90%). When patients from this cohort were followed up at their next admission the majority of patients still had magnesium (65%) below the reference range (median = 0.69 mmol/L, range 0.32 – 0.97 mmol/L, median time interval between samples = 128 days) (Figure 1).

At one year, 64 patients with AWS had died giving a mortality rate of 17%. Sepsis (40%) and complications of chronic liver disease (36%) were the commonest causes of death (see Table 2). The relationship between 1-year mortality and clinicopathological characteristics are shown in Table 1. On univariate analysis, age ($p<0.05$), GMAWS ($p<0.05$), BDZ ($p<0.05$), bilirubin ($p<0.001$), alkaline phosphatase ($p<0.001$), albumin ($p<0.001$), CRP ($p<0.05$), AST:ALT ratio ($p<0.001$), sodium ($p<0.05$), magnesium ($p<0.001$), platelets ($p<0.05$) and treatment with PPi's ($p<0.01$) were associated with death at 1 year. On multivariate binary logistic regression analysis, age >50 (OR 3.37, 95% CI 1.52-7.48, $p<0.01$), AST:ALT ratio >2 (OR 3.10, 95% CI 1.38-6.94, $p<0.01$) and magnesium <0.75 mmol/L (OR 4.11, 95% CI 1.3-12.8, $p<0.05$) remained independently associated with death at 1-year.

The majority of patients had a documented history of alcohol withdrawal seizures (54%) and 5% of patients included in the present study had experienced a seizure in relation to the study related admission. No association was found between previous AWS seizure and 1-year mortality. The majority of patients (95%) presenting to the Emergency Department with AWS had a temperature $<37.5^0$C. The median temperature of patients was 36.2^0C ($33 – 39.1^0$C). No association between 1-year mortality or severity of AWS was found with temperature.

The FIB4 score is a validated scoring system for severity of liver fibrosis (17). In this cohort of patients FIB4 >1.45 was associated with low serum magnesium concentrations ($p<0.001$), 1-year mortality ($p<0.001$), a documented history of chronic liver disease ($p<0.01$) and elevated plasma lactate ($p<0.05$).

The relationship between low circulating magnesium concentrations and clinicopathological characteristics is shown in Table 3. Low circulating magnesium concentrations were associated with a lower median GMAWS max ($p<0.05$), elevated bilirubin ($p<0.01$), elevated alkaline phosphatase ($p<0.05$), low albumin ($p<0.001$), elevated AST:ALT ratio ($p<0.001$), low sodium ($p<0.001$), low potassium ($p<0.001$), low platelets ($p\leq0.001$), elevated MCV ($p<0.05$), low follow-up magnesium concentration ($p<0.001$), and no supplemental magnesium treatment ($p<0.001$). The odds ratios for 1-year mortality associated with serum magnesium concentrations for patients with AWS in this study are shown in Table 4.

Discussion

In a comprehensive analysis of factors associated with 1-year mortality, the results of the present study show that the majority of patients with AWS had low magnesium concentrations at presentation and without treatment remained low on follow-up. Furthermore, low magnesium was independently associated with increased risk of mortality (approximately 4 fold) at 1-year. These results highlight the importance of a low circulating magnesium concentration and its lack of treatment in outcome of patients presenting with AWS.

Circulating magnesium concentrations are tightly regulated. However, there is on-going debate as to the serum magnesium concentration threshold below which a patient may be considered to be deficient (18, 19). Most epidemiological studies have defined concentrations below 0.70mmol/l as "very low" (20-22) whilst others have suggested concentrations below 0.75mmol/l as "low" (22, 23). In the present study approximately 65% of patients with AWS had low circulating concentration of magnesium (< 0.75mmol/l) and this was independently associated with mortality. In comparison and using the "low" threshold (< 0.75mmol/l), Zhang and co-workers examined data from the NHANES epidemiologic follow-up study of more than 14,000 apparently healthy subjects and reported that approximately 7% had a low circulating magnesium concentration, and this was associated with greater all cause mortality (22). Therefore, since it is clear that low circulating magnesium concentrations are much more common in patients with AWS (24, 25), it is plausible that such low concentrations may contribute to mortality in this patient group.

The basis of such low concentrations of magnesium is not clear since only 1% of the whole body pool of magnesium is in the circulation and there is a tight homeostatic control of circulating magnesium concentrations (26). Furthermore, there is a poor correlation between circulating magnesium and dietary magnesium intake (27-29). Nevertheless, low circulating magnesium concentrations would suggest that there is a net redistribution of magnesium from the circulation to the cells.

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In the present study low circulating magnesium concentrations were associated with an elevated bilirubin, alkaline phosphatase and AST:ALT ratio. They were also associated with low platelets, albumin and potassium. Taken together these results may suggest that low magnesium concentrations, given their independent prognostic value, compromise liver and renal function. Indeed, chronic alcohol use is recognised to damage liver cells as part of the detoxification process (30). As part of substantial liver cell breakdown there will be an increase in circulating bilirubin, alkaline phosphatase and the AST:ALT ratio, and a reduction of albumin synthesis. In addition, chronic alcohol use is recognised to cause tubular dysfunction in the kidney (24, 31). Such renal dysfunction results in an increase in the loss of magnesium, potassium and albumin in the urine (31). Clearly, low magnesium, given its role as an enzyme cofactor in the cytoplasm and mitochondria of the liver and the kidney may further compromise the ability of these organs to withstand chronic exposure to alcohol (32). Specifically, alcohol mediated magnesium depletion may result, through compromised enzyme function, in a cycle of reduced ATP production (33), magnesium extrusion (34), loss of mitochondrial inner-membrane potential and cell death (35).

In the present study it was of interest that thiamine, although rarely measured (only 1 patient in the cohort had a thiamine measurement), was frequently administered to patients with AWS. In contrast, magnesium was frequently measured but rarely administered, particularly in those patients with a low circulating magnesium concentration. The reasons for this clinical paradox are not clear but in the case of thiamine it probably reflects the delay in getting thiamine results (approximately two weeks) and the established clinical appreciation of the importance of thiamine deficiency in exacerbating symptoms in patients with AWS. In contrast, in the case of magnesium, although results are obtained within hours, the clinical appreciation of the importance of a low magnesium concentration is probably less well-established in patients with AWS. Therefore, further studies are required to clarify the relative importance of thiamine and magnesium measurement and treatment in patients with AWS. Nonetheless, on the basis of the present findings, it may be considered that magnesium may represent a potential therapeutic target in this patient group. As such, oral

magnesium supplementation represents a potential low-cost treatment option. However, it should be recognized that gastrointestinal side effects of oral magnesium supplementation may compromise patient compliance. Further studies are therefore required to clarify the dose and frequency of oral magnesium supplementation that may optimize patient compliance.

The present study had a number of limitations. In particular, the nature of observational studies even with longitudinal follow-up precludes establishing a causal relationship between a low circulating magnesium concentration and mortality. Further prospective studies including randomised clinical trials are required to test and establish such a causal relationship.

Conclusion

In summary, the results of the present study implicate low circulating magnesium concentrations (<0.75 mmol/L), and the lack of magnesium treatment, in short-term mortality for patients presenting with alcohol withdrawal syndrome.

Declaration and acknowledgements

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Table 1. The relationship between clinicopathological characteristics and 1-year mortality in patients with AWS (n=380)

	1-year Mortality Univariate analysis			1-year Mortality Multivariate analysis		
	Alive (n = 316)	Dead (n = 64)	P-value[1]	Odds Ratio	95% CI	P-value[2]
Age (years)	47 (21 - 85)	54 (29 - 88)	0.002			
Age (<50 / $\geq$50 y)	176/140	24/40	0.008	3.37	(1.52 – 7.48)	0.003
Male/ Female	243/73	45/19	0.239			
BMI (kg/m^2)	23.6 (14 - 52.5)	22.9 (14.4 -40.4)	0.542			
BMI ($\geq$ 20 / < 20kg/m^2)	256/60	47/17	0.170			
Clinical						
Alcohol intake (U/Day)	30 (1 – 120) [a]	23 (3 - 80) [a]	0.133			
FAST (<9/$\geq$9)	24/212	5/35	0.657			
GMAWS (at presentation)	2 (0 - 9)	2 (0 - 6)	0.307			
GMAWS (max)	4 (0 – 10)	3 (0 - 8)	0.055			
GMAWS max (<4 / $\geq$ 4)	112/180	32/26	0.020			
BDZ total (mg)	170 (10 – 1130)	110 (10 - 570)	0.052			
BDZ total (<120 / $\geq$120 mg)	181/135	46/18	0.034	0.452	(0.199 – 1.03)	0.058
Laboratory						
Bilirubin (umol/L)	16 (2 - 309)	29 (5 - 462)	<0.001			
Bilirubin (< 20 / $\geq$ 20 umol/L)	197/117	24/39	<0.001			
Alk phos (U/L)	96 (31 - 524)	129 (43 - 475)	<0.001			
Alk phos (<130/ $\geq$130 U/L)	237/77	33/30	<0.001	2.25	(0.959 – 5.30)	0.062
Albumin (g/L)	36 (16 - 53)	29 (13 - 48)	<0.001			
Albumin ($\geq$ 35 / < 35 g/L)	193/121	18/45	<0.001	2.25	(0.959 – 5.30)	0.062
CRP (mg/L)	5 (<1 - 286)	10 (<1 - 221)	<0.001			
CRP ($\leq$10 / > 10 mg/L)	189/118	29/33	0.031			

AST: ALT	1.5 (0.5 - 6.6)	2.3 (0.9 - 7.4)	<0.001			
AST: ALT (<2 / $\geq$2)	214/89	23/40	<0.001	3.10	(1.38 – 6.94)	0.006
GGT (U/L)	164 (7 - 2889)	221 (42 - 2281)	0.337			
GGT (<50/ $\geq$50 U/L)	21/86	2/21	0.220			
Glucose (mmol/L)	5.8 (3.0 - 81)	6.1 (2.7 - 30.8)	0.810			
Glucose (< 7/ $\geq$7 mmol/L)	205/54	47/11	0.311			
Lactate (mmol/L)	2.3 (0.4 - 19.2)	2.8 (1.0 - 12.9)	0.212			
Lactate (<2.0/$\geq$ 2.0 mmol/L)	27/86	3/21	0.222			
Urea (mmol/L)	3.3 (0.5 - 21.2)	3.1 (0.8 - 78.0)	0.341			
Urea ($\geq$2.5 / < 2.5 mmol/L)	209/91	40/16	0.755			
Sodium (mmol/L)	138 (106 - 165)	136 (105 - 149)	<0.001			
Sodium ($\geq$135 /<135 mmol/L)	230/84	37/26	0.021			
Potassium (mmol/L)	3.9 (2.3 - 6.2)	4.2 (2.2 - 7.3)	0.434			
Potassium ($\geq$3.5 / <3.5 mmol/L)	245/54	45/16	0.142			
Magnesium (mmol/L)	0.70 (0.25 - 1.19)	0.62 (0.28 - 0.95)	<0.001			
Magnesium ($\geq$ 0.75 / < 0.75 mmol/L)	93/135	6/42	<0.001	4.11	(1.3 – 12.8)	0.015
MCV (fl)	95.1 (60.1 - 116.3)	94.8 (70.6- 123.5)	0.854			
MCV ($\leq$96 / > 96 fl)	156/143	34/27	0.464			
Platelets (10^9/L)	201 (15 - 725)	158 (29 – 515)	0.003			
Platelets ($\geq$150 / <150 x 10^9/L)	219/95	35/28	0.029			
Medications						
Thiamine (Yes/No)	233/51	59/3	0.477			
Magnesium (Yes/No)	24/264	9/48	0.034			
PPi (Yes/No)	196/119	53/10	0.001	2.45	(0.96 – 6.25)	0.062

Continuous data are presented as median values, ranges are presented in parenthesis.

[1]Continuous data were analysed with Mann-Whitney U test and categorical data were analysed with Chi-squared test

2 Binary logistic regression analysis

(a) alive: n = 226; dead: n = 44

Table 2. Cause of death in patients (n=64) within 1-year in patients with AWS (n=380)

Cause of death at 1-year in patients with AWS	Total
Cancer	3
Cardiovascular (AMI, PE)	3
Coma – cause unknown	2
Deliberate self poisoning	1
Deliberate self harm	1
Trauma – accidental - brain injury	1

ALD complications e.g. hepatic encephalopathy, hepatorenal syndrome, bleeding oesophageal varices	23
Sepsis	25
Seizure	3
Acute mesenteric ischaemia	1
COPD	1

Table 3. The relationship between low circulating magnesium concentrations and clinicopathological characteristics in patients with AWS (n=275)

	Magnesium (mmol/L)		
	$\geq$ 0.75 (n = 98)	< 0.75 (n = 177)	*P*-value[1]
Age (< 50 / $\geq$ 50 y)	56/42	92/85	0.337
Male/ Female	77/21	128/49	0.175
BMI ($\geq$ 20 / < 20kg/m^2)	78/20	134/43	0.505
Dead at 1-year (Yes/No)	6/92	42/135	< 0.001
Clinical			
Alcohol intake (U/Day)	28 (2 – 120) [a]	30 (1-120) [b]	0.368

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FAST (< 9/ ≥ 9)	4/70	13/110	0.212
GMAWS (at presentation) (<4 / ≥ 4)	55/39	130/44	0.296
GMAWS (max)	4 (0 – 10)	3 (0-9)	0.338
GMAWS max (< 4 / ≥ 4)	28/60	81/86	0.011
BDZ total (mg)	120 (10 – 1130)	90 (10- 840)	0.241
BDZ total (≤ 120 / > 120 mg)	52/46	107/70	0.195
Laboratory			
Bilirubin (< 20 / ≥ 20 umol/L)	66/31	82/94	<0.001
Alk phos (< 130/ ≥ 130 U/L)	77/20	114/62	0.007
Albumin (≥ 35 / < 35 g/L)	65/32	74/102	<0.001
CRP (≤ 10 / > 10 mg/L)	58/37	90/83	0.118
AST: ALT (<2 / ≥ 2)	68/25	90/81	0.001
Glucose (< 7 / ≥ 7 mmol/L)	68/13	117/38	0.176
Lactate (< 2.0 / ≥2.0 mmol/L)	9/25	15/58	0.496
Urea (≥ 2.5 / < 2.5 mmol/L)	67/26	102/63	0.117
Sodium (≥ 135 /< 135 mmol/L)	72/25	113/63	0.108
Potassium (≥ 3.5 / < 3.5 mmol/L)	80/9	120/50	0.001
Follow-up Magnesium (≥ 0.75 / < 0.75 mmol/L)	45/25	27/110	<0.001
MCV (≤ 96 / > 96 fl)	56/38	76/89	0.031
Platelets (≥ 150 / <150 x 10^9/L)	76/22	101/74	0.001
Medications			
Thiamine (Yes/No)	75/13	142/21	0.821
Magnesium (Yes/No)	1/89	31/122	<0.001
PPi (Yes/No)	64/34	125/50	0.256

[1] Continuous data were analysed with Mann-Whitney U test and categorical data were analysed with Chi-squared test

(a) n = 69 (b) n = 125

Focused Alcohol Screening Test (FAST); Glasgow Modified Alcohol Withdrawal Score (GMAWS); Diazepam equivalent dose of
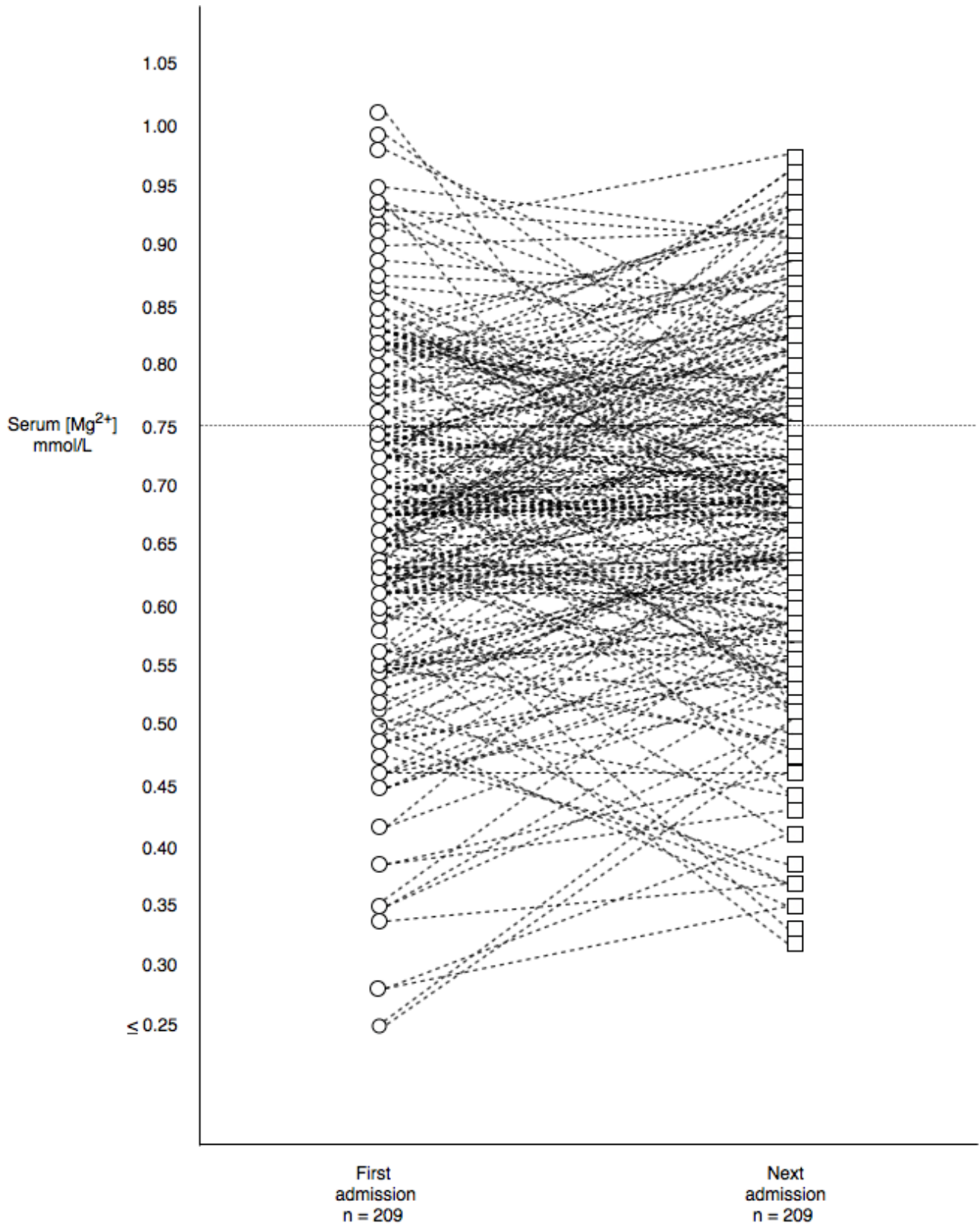
benzodiazepine (BDZ); Proton pump inhibitor (PPi)

Figure 1. Change in serum Mg^{2+} concentrations for patients with AWS at first admission and next admission.

Table 4. Odds ratio of death at 1-year in relation to serum magnesium thresholds (n=275)

Serum Magnesium (mmol/L)	Odds Ratio Death at 1-year	p-value[1]
0.60	2.50	0.004
0.65	2.50	0.004
0.70	4.70	<0.001
0.75	5.90	<0.001
0.80	4.50	0.006
0.85	3.00	0.079

[1] Univariate logistic regression analysis