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1 Whole blood thiamine, intravenous thiamine supplementation and 2 delirium occurrence in the intensive care unit: retrospective cohort 3 analyses

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34 Whole blood thiamine, intravenous thiamine supplementation and 35 delirium occurrence in the intensive care unit: retrospective cohort 36 analyses

37

38 Abstract

39 **Background:** Thiamine di-phosphate is an essential cofactor in glucose metabolism, glutamate
40 transformation and acetylcholinesterase activity, pathways associated with delirium occurrence. We
41 hypothesised that a deficiency in whole blood thiamine and intravenous thiamine supplementation
42 could impact delirium occurrence.

43 **Aim:** To establish whether a deficiency in whole blood thiamine and/or intravenous thiamine
44 supplementation within 72 hours of intensive care admission is associated with delirium occurrence.

45 **Method:** The first dataset was secondary analysis of a previous study in an intensive care unit in the
46 Netherlands, reported in 2017. The second dataset contained consecutive intensive care admissions
47 2 years before (period 1: October 2014 to October 2016) and after (period 2: April 2017 to April
48 2019) routine thiamine supplementation was introduced within 72 hours of admission. Delirium was
49 defined as a positive Confusion Assessment Method-Intensive Care Unit score(s) in 24 hours.

50 **Results:** Analysis of the first dataset (n=57) using logistic regression showed no relationship between
51 delirium and sepsis or whole blood thiamine, but a significant association with age (p=0.014). In the
52 second dataset (n=3074), 15.1% received IV thiamine in period 1 and 62.6% during period 2.
53 Hierarchical regression analysis reported reduction in delirium occurrence in the second period; this
54 did not reach statistical significance, OR =0.81 (95% CI: 0.652 – 1.002); p=0.052.

55 **Conclusion:** No relationship was detected between whole blood thiamine and delirium occurrence
56 on admission, at 24 and 48 hours. It remains unclear whether routine intravenous thiamine
57 supplementation during intensive care admission impacts delirium occurrence. Further prospective
58 randomised clinical trials are needed.

59 Keywords

60 Critical care; Delirium; Intensive care; Retrospective studies; Thiamine.

61

62 **Impact of findings on practice**

- 63 • Whole blood thiamine (WBT) may be helpful in assessing thiamine deficiency and could
64 inform thiamine supplementation in critical illness
- 65 • Intravenous (IV) thiamine supplementation on intensive care unit (ICU) admission could
66 impact delirium occurrence
- 67 • Adherence to an IV thiamine supplementation regime could be enhanced by the presence of
68 an ICU pharmacist
- 69 • Future research into IV thiamine supplementation and delirium occurrence is needed; the
70 impact of IV thiamine supplementation on delirium occurrence is yet to be fully established.

71 Introduction

72 Delirium is common in critical illness with a reported prevalence of up to 50%, and higher in patients
73 who are mechanically ventilated (1–3). Delirium is associated with poor outcomes including
74 increased length of hospital and intensive care unit (ICU) stay, costs and long-term cognitive
75 impairment after critical illness (4). Clinically, patients with delirium present with a number of
76 symptoms including inattention, confusion, emotional distress and agitation which can be severe.
77 Delirium results from one or more causes including sepsis and septic shock, metabolic disturbances,
78 sedation, respiratory failure with hypoxia, SARS-Co-V2 infection and/or environmental factors (1, 5,
79 6). In delirium, brain glucose demands increase, and this may not be met in patients presenting or
80 developing thiamine depletion in the central nervous system (7). Thiamine in its active form,
81 thiamine di-phosphate (TDP), is an essential cofactor in glucose metabolism, glutamate
82 accumulation and acetylcholine synthesis, all of which are associated with delirium occurrence (8). It
83 is therefore scientifically plausible that thiamine depletion or supplementation could impact delirium
84 occurrence in ICU.

85 Deficiency of whole blood thiamine (WBT) has been sporadically reported in ICU patients over the
86 last 15 years (7, 9–12). In 2020, Heming et al. reported erythrocyte levels of total thiamine, free
87 thiamine, thiamine mono-, di- and tri-phosphate (TMP, TDP, and TTP respectively), the erythrocyte
88 transketolase activity (ETKA), and the effect of TDP on ETKA were measured in septic patients and
89 correlated with arterial lactate (n=28)(7). Total thiamine and TDP concentration were significantly
90 higher in ICU survivors than in non-survivors ($p=0.03$) (7). In 2018, Pourhassan et al. reported lower
91 WBT in patients with delirium (54.2 ng/mL), when compared to those without delirium (66.4 ng/mL)
92 ($p=0.002$) (13).

93 In 2021, a systematic review (SR) and meta-analysis in critical illness reported that intravenous (IV)
94 thiamine supplementation resulted in a 42% lower odds of developing ICU delirium (2). The authors
95 did not report adjusting for residual confounding factors such as alcohol dependence or existing

96 vitamin supplementation. Moslemi et al. reported a reduction in delirium in ICU patients after IV
97 thiamine supplementation (14). Branco et al. reported reduction in encephalopathy in severe COVID-
98 19 patients after IV thiamine supplementation (15).

99 We hypothesised: 1) WBT deficiency is associated with delirium occurrence in ICU, and 2) routine IV
100 thiamine supplementation on ICU admission reduces delirium occurrence during ICU stay.

101 Aim

102 To establish whether a WBT deficiency and/or IV thiamine supplementation within 72 hours after
103 ICU admission is associated with delirium occurrence.

104 Ethics approval

105 This study was performed in line with the principles of the Declaration of Helsinki. Both parts of the
106 study were approved by the local Gelre Hospital ethics committee (LTC 09.24, July 14, 2009) (12).

107 Method

108 Patients and Settings

109 The study took place in the (ICU of Gelre Hospitals, a mixed medical and surgical teaching ICU in
110 Apeldoorn, The Netherlands. Gelre has long-term experience in ICU related delirium research. The
111 study consisted of two parts, based on retrospective cohort analysis of two datasets:

112 part one: Secondary analysis of data reported by van Snippenburg et al. in 2017 (12)

113 part two: Exploratory analysis of a 2-year period before and 2 years after introduction of
114 routine IV thiamine supplementation on ICU admission.

115 Demographics

116 Patient demographics for Part one and two included: age, gender, ICU length of stay, Richmond
117 Agitation and Sedation Score (RASS) – lowest score at admission day to the ICU, Acute Physiology
118 and Chronic Health Evaluation (APACHE) II score on admission, Simplified Acute Physiology Score
119 (SAPS) II score on admission, and hospital mortality.

120

121 Delirium presence

122 Delirium screening for both parts was undertaken twice daily as part of routine practice by trained
123 nursing staff using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU). For the
124 analysis, a day in delirium was defined as one or more positive CAM-ICU scores in a 24-hour period.

125

126 Part one: Whole blood thiamine (WBT) and delirium presence

127 Patients were included in the first analysis if thiamine supplementation was not administered before
128 ICU admission. Blood samples (EDTA and fluoride tubes, Vacutainer; Becton-Dickinson, Franklin
129 Lakes, New Jersey, USA) for measurement of Whole Blood Thiamine (WBT) were collected on
130 admission, at 24- and 48-hours post ICU admission. WBT concentration was determined by ultra-
131 pressure liquid chromatography with fluorescence detection (System/column: Waters, Etten-Leur,
132 the Netherlands; method: Chromsystems, Munich, Germany). The pathology range for WBT
133 deficiency was determined, apriori, at $\leq 100\text{nmol/litre}$, in line with the normal reference range
134 provided at the local pathology unit at Gerle hospital (12). Data were analysed to explore the
135 relationship between WBT deficiency (at t-0 hrs, t-24 hrs, or t-48 hrs) and delirium occurrence during
136 ICU stay.

137

138 Part Two: IV thiamine supplementation and delirium presence

139 For part two, we evaluated the relationship between routinely prescribed IV thiamine
140 supplementation and delirium occurrence. IV thiamine supplementation was prescribed as 300 mg
141 IV once only, followed by 100 mg IV daily for 5 days as part of the ICU-admission medication order-
142 set in the electronic patient record. This was implemented at Gelre after reporting of low WBT levels
143 in a significant proportion of acutely admitted ICU patients (12). Anonymised patient data was
144 collected continuously for 24 months before and 24 months after introduction of IV thiamine
145 supplementation in September 2016 with a 6-month washout period. Data was collected for the
146 periods: October 2014 to October 2016 (period 1) and April 2017 to April 2019 (period 2). All ICU

147 patients who had received any dose(s) of routine IV thiamine supplementation within 72 hours of
148 admission were compared against those who did not receive IV thiamine supplementation within
149 their respective periods, but comparisons were also made between the two periods. The rate of
150 adherence to the IV thiamine intervention was additionally assessed.

151

152 Analysis

153 Shapiro-Wilk test was used to determine use of parametric or nonparametric test. For data not
154 conforming to normal distribution, comparisons were made using Mann-Whitney U test. Chi-square
155 test was used to compare groups with nominal variables. $p < 0.05$ was considered statistically
156 significant. Statistical analyses were performed using the IBM Statistical Package for the Social
157 Sciences (SPSS) version 29.0.

158

159 For part one, the relationship between WBT and delirium presence was expressed as odds ratio (OR)
160 and 95% confidence interval (CI). Secondary outcomes were explored by analysing confounding
161 factors associated with delirium presence in ICU (5, 16). Data included duration of mechanical
162 ventilation, presence of sepsis and septic shock, sedation depth, age, and severity of illness.

163 Following univariate analysis, logistic regression analysis was performed adjusting for age and sepsis,
164 as only two confounders were eligible for the model due to the small sample size and these are two
165 of the most common risk factors for ICU delirium (17).

166

167 For part two, the relationship between IV thiamine supplementation and delirium presence was
168 investigated. The analyses are reported as odds ratio (OR) and 95% confidence interval (CI) to
169 determine significance of association between presence or absence of IV thiamine supplementation
170 on admission and delirium occurrence at any time during ICU admission. As the intention of the
171 change in practice was an attempt to ensure all ICU admissions received IV thiamine, the positivity
172 condition was present. However, the decision to actually prescribe was left to the attending
173 physician. As such, not all patients received the suggested thiamine infusion. Nevertheless, there

174 was a greater than zero chance that patients in the second phase of the study would receive
175 thiamine compared to those in the first phase of the study when thiamine prescription was not part
176 of a routine protocol in the hospital's digital system.

177 Hierarchical logistic regression analysis was performed to evaluate impact of IV thiamine
178 supplementation on delirium presence, and known risk factors of delirium: sepsis, age, duration of
179 ventilation, severity of illness (APACHE II) and length of stay in ICU (5, 16, 18, 19). This is a variant of
180 the multiple regression procedure that introduces variables in a stepwise manner to identify the most
181 influential variables within the model and allow better understanding of the relationship between
182 these factors and delirium occurrence.

183 Results

184

185 Part One: Whole blood thiamine (WBT) and delirium occurrence

186 There were 66 patients that met the inclusion criteria for WBT analysis collected between August
187 2009 and February 2010, and previously reported in 2017 (12). Eight patients receiving IV thiamine
188 supplementation before ICU admission were excluded, with a further loss of one patient due to
189 insufficient data, resulting in 57 patients available for analysis (Table 1). WBT levels within thiamine
190 deficient patients were observed from admission to 48 hours of ICU admission (Supplemental Table
191 S1).

192 Delirium was detected, at any time, during ICU stay in 36.4% patients with normal WBT on
193 admission, and 38.1% patients at 48 hours (Table 2). In those that were WBT deficient, delirium was
194 detected in 45.8% patients on admission and 46.7% patients at 48 hours. Exploratory analysis
195 reported delirium presence during ICU stay in those with normal WBT (> 100 nmol/litre) compared
196 to those that were WBT deficient (≤ 100 nmol/litre) at t-0, t-24h, and t-48h, (OR: 0.68 [95%
197 confidence interval (CI): 0.23-1.97]), (OR: 0.63 [95% CI: 0.20-2.00]) and (OR: 0.70 [95% CI: 0.21-2.31])
198 respectively.

199 Using age and sepsis as confounding variables alongside WBT in a binary logistic regression model, a
200 significant relationship was observed between aging and delirium (OR= 1.075; 95% CI: 1.015-1.140; *P*
201 = 0.014) (Supplemental Table S2). No significant relationship was observed between delirium and
202 sepsis or WBT on admission.

203

204 Part Two: Routine prescription of IV thiamine supplementation and delirium occurrence

205 For part two, 3074 ICU admissions were evaluated, 1508 in period one and 1566 in period two (Table
206 3).

207 During period one, 228 of 1508 (15.1%) patients received IV thiamine supplementation in the first 72
208 hours. In period two, adherence to any dose of IV thiamine was observed in 980 of 1566 (62.6%)
209 patients; 37.4% of ICU admitted patients did not receive IV thiamine (Table 3).

210 IV thiamine supplementation, delirium, and outcome

211 In both periods, patients receiving IV thiamine had higher APACHE II score and SAPS II scores on ICU
212 admission (Table 3). In period one (pre-October 2016), those not receiving IV thiamine had a lower
213 mean APACHE II of 15.9 (\pm 6.93), compared to those who did, with 19.9 (\pm 7.64), *p* <0.001; Mann-
214 Whitney U test (Table 3). In period two (after April 2017), the same correlation was observed. SAPS II
215 scores also supported this finding (Table 3).

216

217 The median length of stay (LOS) in ICU was greater for the group receiving IV thiamine during period
218 one, 4 (IQR= 2-9), compared to those not receiving thiamine, 2 (IQR=2-4), *p*<0.001; Mann-Whitney U
219 test. The same correlation was true for period two.

220

221 An overall reduction in delirium occurrence during period two (0.16) was found in an unadjusted
222 analysis, compared to period one (0.20); OR: 0.78 [95% CI: 0.65- 0.94; *P*=0.009; Chi-square test]
223 (Table 3). Hierarchical logistic regression analysis was carried out for delirium occurrence using
224 known risk factors for delirium: hours of mechanical ventilation, age, sepsis on ICU admission,
225 APACHE II on admission, ICU LOS and period of study; a reduction in delirium occurrence was

226 identified in the second period, although this did not reach statistical significance, OR =0.81 (95% CI:
227 0.652 – 1.002); $p=0.052$ (Supplemental Table S3).

228
229 A second hierarchical logistic regression analysis was performed where all patients receiving IV
230 thiamine were compared against all patients not receiving IV thiamine, irrespective of the period.
231 With inclusion of the same confounders in the model, more delirium occurrence was observed in
232 those receiving IV thiamine compared to those not receiving IV thiamine (OR = 1.40 [1.12-1.73]; $p=$
233 0.003) (Supplemental Table S4).

234 Discussion

235 Statement of key findings

236 In this analysis of two distinct datasets, we describe that WBT levels at ICU admission are not related
237 to delirium occurrence during ICU admission, and it was unclear whether routinely prescribing IV
238 thiamine on ICU admissions resulted in an overall reduction in delirium occurrence during ICU stay.

239 Strengths and weaknesses

240 There are a number of limitations: In both parts, sample size calculations were not performed due to
241 the retrospective and pre-determined nature of the studies; however, all available data were utilised
242 for analysis.

243 Part one was an observational single center analysis with a small sample size. Further, the WBT
244 samples were collected between 2009 and 2010; however, we decided to include these results
245 because: whole blood samples are more challenging to store for subsequent analysis, plasma or
246 serum is more stable and can be frozen for clinical or research purposes. Therefore there is paucity
247 of WBT evidence in ICU literature, and WBT is the gold standard for thiamine detection (20). Despite
248 the data's age, we believe the findings are important, as there is still an absence of proven
249 pharmacotherapies for delirium prevention and management. Part two is a large observational
250 dataset obtained during routine ICU care and thus subject to observational bias. Of note, a 62.6%

251 adherence to the IV thiamine supplementation is low, although those not receiving IV thiamine
252 during this period had a lower severity of illness and ICU length of stay. The poor adherence could
253 additionally be attributed to difficulties in changing clinical behaviour in ICU (21). Our focus was to
254 compare two different periods following the decision to routinely introduce IV thiamine
255 supplementation. Over the 4.5-year study duration, while delirium occurrence was higher overall
256 among IV thiamine recipients, we attribute this to their higher illness severity and poor adherence to
257 IV thiamine regime on admission. To improve compliance, implementation strategies could explore
258 the inclusion of a dedicated ICU pharmacist to support prescribing adherence; this was not standard
259 practice in the Netherlands during the study period (22–24). This is relevant as pharmacists have
260 been reported to be underutilised in prevention and management of delirium, especially as 50% of
261 pharmacists' recommendations have been reported to be frequently or always accepted by delirium
262 treating teams (25). In part two, we were unable to detect thiamine deficiency because of challenges
263 in storing whole blood. This is unfortunate, because the greatest benefit in IV thiamine
264 supplementation could be in those who are thiamine deficient.

265 In Gelre ICU, the overall delirium occurrence was low (18%); in UK ICUs, where a higher delirium
266 prevalence is reported, our results may have been very different (26). Higher disease severity in UK
267 patients with higher APACHE-II scores may in part account for the difference. This could additionally
268 be attributed to patient selection, where a shortage of ICU beds in the UK compared to other
269 countries including the Netherlands could result in a more severely unwell patient cohort. Further
270 work is required to establish whether the differences are related to local practices for delirium
271 management or patient population.

272 CAM-ICU remains the most commonly used screening tool for delirium detection, despite its
273 limitations (27, 28). Scores were collected following routine documentation by trained nursing staff
274 in the ICU, potentially reducing the variation in inter-rater reliability that is observed with this tool
275 among untrained users (29).

276 Thiamine (vitamin B1) is a water-soluble vitamin, with a short elimination half-life (30) and in
277 refeeding and alcohol dependence, the recommended dose of IV thiamine is up to 750 mg three
278 times a day for 5 days followed by oral supplementation (31, 32). Studies that report a reduction in
279 encephalopathy or delirium after thiamine supplementation consistently prescribed a regimen at
280 higher doses and for longer duration than those observed in these datasets (33).

281 Interpretation

282 A retrospective study (n=233) on older patients with delirium reported a significantly lower mean
283 WBT compared to those without delirium (13). However, the setting was a geriatric acute care ward
284 with substantial malnutrition risk (47%). Similar to our study, high performance liquid
285 chromatography (HPLC) was used to measure WBT. Another single-centre retrospective study of 71
286 cancer patients reported serum-thiamine deficiency in 45.1% of delirium cases (34). Not all patients
287 underwent thiamine level assessments, suggesting potential selection bias favoring those with
288 severe delirium symptoms. WBT levels were investigated for delirium prevention in 61 patients post-
289 allogenic hematopoietic stem cell transplantation (35). IV thiamine was administered at 200 mg
290 three times daily for seven days and compared to placebo. Although the thiamine group exhibited
291 significantly higher WBT levels, Delirium Rating Scale scores showed no significant differences.
292 While using comparable chromatography, deficiency threshold was lower (70 nmol/L) compared to
293 our study (100 nmol/L). The sample size was small, similar to our study, and the population very
294 different from ICU.

295 A recent meta-analysis of IV thiamine supplementation in ICU, encompassing three RCTs,
296 demonstrated lower incidence of delirium with thiamine (2). Two RCTs were underpowered and had
297 narrow patient focuses (gastrointestinal and cardiac surgery), potentially affecting the
298 generalisability of findings to wider critical care patients (14, 36). All patients who received IV
299 thiamine supplementation in our second dataset had significantly higher severity of illness and
300 longer stays in ICU, suggesting selection bias. This could potentially have influenced the clinical

301 decision by the attending intensivist to prescribe IV thiamine supplementation introducing
302 performance bias. Unfortunately, we do not have data to test this hypothesis. It is worth noting in
303 critical care trials greater effects may be observed in patients with higher severity of illness (37, 38);
304 although we are aware that the opposite can also be true (39).

305 Further research

306 More investigation is needed to explore the impact of IV thiamine on delirium in the ICU, preferably
307 in a randomised controlled clinical trial. Finally, thiamine is concentrated in the brain and in the
308 heart, and a higher dose may be required to replenish thiamine stores in the brain and impact
309 delirium (40). Therefore, it could well be that a higher dose administered more than once a day for 5
310 to 7 days, may have achieved a very different outcome. Data with regards to renal replacement
311 therapy was not available for this study, which could have contributed further to the dosing
312 discussion. Future work should also focus on the pharmacokinetics and pharmacodynamics of IV
313 thiamine in critical illness and its impact on delirium.

314 Conclusion

315 In these two retrospective observational analyses, we could not establish whether either WBT
316 depletion or IV thiamine supplementation had an impact on delirium occurrence. Prospective
317 multicenter randomised controlled studies, taking appropriate dosing regimen of IV thiamine and
318 associated whole blood thiamine levels into account, are needed to assess the impact of IV thiamine
319 supplementation on delirium occurrence and duration in ICU.

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328 Conflicts of interest

329 The authors declare that there is no conflict of interest.

330

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432

433 **Tables**

434 **Table 1: Patient demographics: Whole blood thiamine dataset**

	All Patients	Thiamine Deficient on admission (≤100 nmol/L)	Not thiamine deficient on admission (>100 nmol/L)
<i>n (%)</i>	57	24 (42.1%)	33 (57.9%)
<i>Age, years, median (IQR)</i>	73 (62-79)	76 (65-81)	72 (61-77)
<i>>60 years, n (%)</i>	44 (77.2%)	19 (79.2%)	25 (75.8%)
<i>Male, n (%)</i>	36 (63.2%)	14 (58.3%)	22 (66.7%)
<i>ICU stay, days, median (IQR)</i>	9 (4-19)	9 (5-18)	7 (4-19)
<i>Hospital stay>7 days before ICU admission, n (%)</i>	12 (21.1 %)	7 (29.2%)	5 (15.2%)
<i>Surgery within 1 week before ICU admission, n (%)</i>	31 (54.4%)	19 (79.2%)	12(36.4%)
<i>Sepsis on ICU admission, n (%)</i>	13 (22.8%)	8 (33.3%)	5 (15.2%)
<i>APACHE- II Score on ICU admission, median (IQR)</i>	19 (12-25)	18 (12-21)	20 (16-26)
<i>SAPS-II Score on ICU admission, median (IQR)</i>	45 (34-54)	44 (34-53)	47 (34-54)
<i>Hospital Mortality, n (%)</i>	7 (12.3%)	2 (8.3%)	5 (15.2%)

435

436 Abbreviations: WBT, Whole Blood Thiamine, APACHE, Acute Physiology, Age and Chronic Health Evaluation; ICU, intensive
 437 care unit; SAPS, Simplified Acute Physiology Score, IQR= interquartile range.

438 ^a Results are shown as median with interquartile range or as absolute number with percentage of group

439

440 **Table 2: Part one- relationship between WBT and delirium occurrence ICU admission (t-0), 24 hours (t-24h)**
 441 **and 48 hours (t-48h).**

	On admission		24 hours		48 hours	
	<i>Delirium</i>	<i>Not delirium</i>	<i>Delirium</i>	<i>Not delirium</i>	<i>Delirium</i>	<i>Not delirium</i>
Normal WBT (>100 nmol/L)	12	21	14	25	16	26
WBT Deficient (≤100 nmol/L)	11	13	8	9	7	8
Odds ratio (95% CI)	0.68 (0.23 - 1.97)		0.63 (0.20 – 2.00)		0.70 (0.21 - 2.31)	

442
 443 Abbreviations: WBT = whole blood thiamine. ICU = Intensive Care Unit. CI = Confidence Interval
 444

Table 3: Relationship between intravenous thiamine and delirium, ventilation, sepsis, disease severity, ICU length of stay and mortality

	<i>Overall</i>	<i>Period 1</i>	<i>Period 2</i>	<i>p-value</i>	<i>Period 1 (thiamine)</i>	<i>Period 1 (no thiamine)</i>	<i>p-value</i>	<i>Period 2 (thiamine)</i>	<i>Period 2 (no thiamine)</i>	<i>p-value</i>
<i>Patient No, n (%)</i>	3074	1508 (49.1%)	1566 (50.9%)	-	228 (15.1%)	1280 (84.9%)	-	980 (62.6%)	586 (37.4%)	-
<i>Age (IQR)</i>	67 (55-75)	67 (57-76)	66 (54-75)	-	66 (57-72)	68 (57-76)	-	68 (58-75)	61 (45-72)	-
<i>Delirium, n (%)</i>	545 (17.7%)	295 (19.6%)	250 (16.0%)	-	87 (38.2%)	208 (16.3%)	-	201 (20.5%)	49 (8.4%)	-
<i>Delirium occurrence</i>	0.18	0.20	0.16	0.009	0.38	0.16	-	0.21	0.08	-
<i>Sepsis*, n (%)</i>	485 (15.8%)	218 (14.5%)	267 (17.1%)	-	52 (22.8%)	166 (13.0%)	-	211 (21.5%)	56 (9.6%)	-
<i>APACHE II*, mean ± SD</i>	16.4 ± 7.09	16.5 ± 7.18	16.4 ± 6.99	-	19.9 ± 7.64	15.9 ± 6.93	<0.001	17.9 ± 6.63	13.8 ± 6.84	<0.001
<i>SAPS II*, mean ± SD</i>	35.8 ± 15.97	36.4 ± 15.91	35.24 ± 16.02	-	43.8 ± 16.94	35.0 ± 15.34	<0.001	38.7 ± 15.51	29.4 ± 15.18	<0.001
<i>ICU LOS, median (IQR)</i>	3 (2-5)	3 (2-5)	3 (2-5)	-	4 (2-9)	2 (2-4)	<0.001	3 (2-6)	2 (2-3)	<0.001
<i>Mortality, n (%)</i>	430 (14.0%)	198 (13.1%)	232 (14.8%)	-	42 (18.4%)	156 (12.2%)	-	165 (16.8%)	67 (11.4%)	-

Abbreviations: APACHE, Acute Physiology, Age and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score, LOS, length of stay; IQR= interquartile range.

*on ICU admission

Supplementary materials

Supplemental Table S1: Part one- Whole blood thiamine levels on admission, at 24 hours and 48 hours

	All patients (n=57)	Thiamine deficient (≤ 100 nmol/L) (n=24)	Not thiamine deficient (> 100 nmol/L) (n=33)
<i>WBT on ICU admission, nmol/L, median (IQR)</i>	109 (90-152)	87 (71-92)	147 (126-157)
<i>WBT at 24h post ICU admission, nmol/L, median (IQR)</i>	127 (96-159)	91 (83-118)	157 (132-190)
<i>WBT at 48h post ICU admission, nmol/L, median (IQR)</i>	129 (99-159)	99 (84-124)	150 (125-178)

Abbreviations: IQR= Interquartile range. ICU = Intensive Care Unit

Supplemental Table S2: Part one- regression analysis: factors impacting delirium on admission

	OR (CI)	P-value
WBT	1.011 (0.307-3.325)	0.986
Age	1.075 (1.015-1.140)	0.014
Sepsis	3.745 (0.833-16.841)	0.085

Supplemental Table S3: Part two- hierarchical logistic regression analysis of delirium with *thiamine period*, APACHE II, ventilation hours, length of stay in ICU, age and sepsis

	OR (CI)	p-value
Ventilator hours	1.004 (1.003-1.006)	<0.001
Age	1.031 (1.022-1.041)	<0.001
Sepsis	1.372(1.052-1.790)	0.02
APACHE II	1.056 (1.038-1.073)	<0.001
LOS ICU	1.094 (1.066-1.122)	<0.001
Thiamine Period	0.81 (0.652-1.002)	0.052

Supplemental Table S4: Part two- hierarchical logistic regression analysis of delirium with *thiamine*, APACHEII, ventilation hours, length of stay in ICU, age and sepsis.

	OR (95 % C.I.)	P-value
Thiamine	1.40 (1.12 – 1.73)	0.003
APACHEII	1.04 (1.03- 1.06)	<0.001
Ventilation hours	1.88 (1.49 – 2.37)	<0.001
Length of stay in ICU	1.12 (1.10 – 1.15)	<0.001
Age	1.03 (1.03-1.04)	<0.001
Sepsis	1.38 (1.06-1.80)	0.016