

Prevalence of Thiamine Deficiency in Cirrhotic Patients

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ABSTRACT

OBJECTIVE: This study aimed to evaluate the prevalence of thiamine deficiency in outpatient cirrhosis and compare thiamine deficiency between alcoholic cirrhosis and non-alcoholic cirrhosis, whether there are any factors or clinical outcomes associated with thiamine deficiency, and short-term follow-up after vitamin B1 replacement.

METHODS: This cross-sectional study included patients who were diagnosed with cirrhosis at the Gastrointestinal and Hepatology Division of Vajira Hospital in outpatient settings. All patient data characteristics were collected and also baseline laboratory and erythrocyte transketolase activity (ETKA), which is a standard test for the diagnosis of thiamine deficiency. Patients who were diagnosed with thiamine deficiency were identified as ETKA ≥ 1.25 . Thiamine deficiency patients were tested for clinical outcomes; ophthalmoplegia, nystagmus, ataxia, and Adult ADHD self-report scale v.1.1 and all of them underwent replacement with vitamin B1 for 3 months.

RESULTS: From January 2020 to December 2020, 121 eligible cirrhotic patients were enrolled. Alcoholic cirrhosis comprised 41/121 (33.9%), and non-alcoholic cirrhosis amounted to 80/121 (66.1%). The comparison of prevalence in alcoholic and non-alcoholic cases was 14.6% vs. 11.2% (P=0.59). Neither the severity of disease nor baseline nutritional status was related to thiamine deficiency. The prevalence of hepatocellular carcinoma (HCC) was higher in the thiamine deficiency group compared to the others (46.7% vs. 12.3%; p=0.003). In univariate analysis, HCC was the only factor related to thiamine deficiency. Almost all thiamine deficiency status cases did not have either neurologic abnormality or any attention deficit.

CONCLUSION: Thiamine deficiency was found in end-stage liver disease, irrespective of cirrhotic etiology. HCC was considered an associated factor of the thiamine deficiency. The occurrence of HCC may be emphasized as a proxy for the condition of thiamine deficiency.

KEYWORDS:

alcoholic cirrhosis, non-alcoholic cirrhosis, thiamine deficiency

INTRODUCTION

Thiamine or vitamin B1 is an essential co-enzyme in multiple metabolism pathways, especially glucose metabolism, and is a factor for producing neurotransmitters¹. Clinical presentation in thiamine deficiency is varied depending on the

stage, ranging from asymptomatic, through nonspecific symptoms such as fatigue, memory disturbance, sleep-wake disturbance, anorexia, abdominal pain, and constipation. It can present with cardiac beriberi, lactic acidosis, bradycardia, edema, Wernicke-Korsakoff syndrome, delirium,

ventricular thickening, and brain edema in the end terminal stage^{1,2,6,16}. The diagnosis of thiamine deficiency in this study is confirmed when erythrocyte transketolase activity (ETKA) is equal to or more than 1.25⁷⁻⁸.

The most common cause of thiamine deficiency in Thailand is chronic alcoholism, though other causes include the consumption of raw food that contains thiaminase⁶, renal replacement therapy in end-stage renal disease (ESRD) patients, acute illness, hyperthyroidism, pregnancy, and lactation¹. Around 40% of thiamine is found in tissue, with the remainder being accumulated in the heart, liver, kidney, and brain, respectively. Therefore, chronic liver disease patients were associated with thiamine deficiency¹⁵. In a previous study, the incidence was 80% in alcoholism. Until now, there has been no known defined mechanism for thiamine deficiency. Probable hypotheses encompass multiple factors: poor intake, decreased accumulation in the hepatocyte, and decreased absorption of thiamine in the gastrointestinal tract from ethanol toxicity^{1,4-5}. In addition to thiamine deficiency, deficiencies in other minerals, including vitamins A and D are associated with negative effects on the prognosis of liver cirrhosis³.

In this study, we compared thiamine deficiency status in alcoholic cirrhosis and non-alcoholic cirrhosis, and evaluated the clinical manifestation of thiamine deficiency in patients while examining other factors associated with thiamine deficiency. Moreover, patients who were diagnosed with thiamine deficiency underwent thiamine replacement for three months due to previous data showing improving liver enzymes, increase survival, and prevention of cirrhotic complications after thiamine replacement⁴⁻⁵.

METHODS

This was a cross-sectional, analytical, single center study. Ethical approval by Faculty of Medicine Vajira Hospital Navamindradhiraj University COA 018/2563. Patients were recruited

from the outpatient department of the Gastrointestinal and Hepatology Division, Department of Medicine, Navamindradhiraj University, between February 2020 and December 2020. The trial was approved by the institutional ethics review committee. The patients provided informed consent before enrolling.

Cirrhotic patients were screened for the following criteria of eligibility: age 15-80 years, diagnosed with cirrhosis by ultrasound, computer tomography scan (CT), transient elastography above 13 kPa, magnetic resonance imaging (MRI), or by liver biopsy⁹⁻¹⁴. Key exclusion criteria included patients who were diagnosed with thiamine deficiency or use of thiamine replacement therapy before enrolling, acute illness in 2 weeks, pregnant women, hyperthyroidism, ESRD and on renal replacement therapy, or gastrointestinal tract surgery with anastomosis.

The medical records of each cirrhotic patient were reviewed. The patients who had fulfilled the aforementioned enrollment criteria were selected. Blood tests were performed at the baseline: liver function test, coagulogram, renal function test, sodium, and ETKA. Other data were collected from medical records including gender, age, body weight, height, body mass index, etiology of cirrhosis, alcohol consumption, method for diagnosis of cirrhosis, Child Turcotte Pugh score (CTP), Model for End Stage Liver Disease (MELD) score, and comorbid diseases. Patients were also evaluated for nutritional status and malnutrition by the Royal Free Hospital-Nutritional Prioritizing tool (RFH-NPT)¹⁸⁻¹⁹. Society of Parenteral and Enteral Nutrition of Thailand (SPENT) nutritional screening tool, and followed by Nutrition Alert Form (NAF)²⁰ if the score from SPENT was equal to or greater than 2.

The patients who were diagnosed with thiamine deficiency by ETKA equal to or greater than 1.25 were physically examined for nystagmus, ophthalmoplegia, and ataxia to evaluate Wernicke-Korsakoff syndrome, and were tested for adult attention deficit hyperactivity disorder (ADHD) using the Adult ADHD Self

Report Scale (ASRS) screen version 1.1 to diagnose attention deficit if the score was higher than 4¹⁶. These patients received vitamin B1-6-12 (Patar3B) which contained 100 mg thiamine twice daily for three months, followed up with ETKA, neurological signs, and ASRS V1.1 at 3 months, including side effects of thiamine replacement.

The primary outcome is the comparison for the prevalence of thiamine deficiency between alcoholic cirrhosis and non-alcoholic cirrhosis. The secondary assessment included the following: (1) factors influencing thiamine deficiency other than the etiology of cirrhosis; (2) clinical manifestation of thiamine deficiency patients in neurologic signs and symptoms and attention deficit; (3) improvement of thiamine deficiency after replacement for 3 months.

Based on the previous trial by Rossouw⁷, it was estimated that there was 70.6% thiamine deficiency in alcoholic cirrhosis and 42.8% in non-alcoholic cirrhosis. The number of patients needed to evaluate the prevalence in this study was calculated to be at least 200 with a significance level of 0.05 (one-tailed). All patients enrolled in the study were analyzed. Categorical variability was presented as proportion or frequency, while continuous variables were presented as mean with standard deviation or median (interquartile range). P-values correspond to the independent t-test or Mann-Whitney U and Chi-square tests. Logistic regression was also used to evaluate the association between thiamine deficiency and baseline demographic data. All tests were two-tailed and P<0.05 was considered to indicate statistical significance.

RESULTS

A total of 121 cirrhotic patients were enrolled in this study, with the mean age of 58 ± 10.5 years, of whom 88 (73%) were male. Alcoholic etiology was found in 41 patients (33.9%). Non-alcoholic cirrhosis in this study included chronic hepatitis B (CHB), chronic hepatitis C (CHC), non-alcoholic steatohepatitis (NASH), cardiac cirrhosis, cryptogenic cirrhosis,

and autoimmune hepatitis (AIH). The most common cause of cirrhosis was CHC (31.4%), followed by CHB (19%). The median duration of cirrhosis was 20.9 months. Due to the outpatient setting, the severity of cirrhosis was mostly mild. Most cases were in child A (81.8%) and the mean MELD score was 9.78±3.85. Only one patient could not undergo evaluation of severity due to concurrent warfarin consumption, while 20 of 121 cases (16.5%) had hepatocellular carcinoma (HCC) at the time of enrollment. In terms of nutritional status, most of the patients had a low risk of malnutrition when assessed by RFH-NTP (86 from 121, 71%). The baseline parameters are summarized in [Table 1](#).

Table 1 The baseline parameters of 121 cirrhotic patients

Baseline parameter	
Gender N (%)	
Male	88 (73)
Age (Mean ± SD)	58.03 ± 10.5
Etiology N (%)	
Alcoholic cirrhosis	41 (33.9)
CHC	38 (31.4)
CHB	23 (19)
NASH	14 (11.6)
CHB and CHC	2 (1.6)
Cardiac cirrhosis	1 (0.8)
Cryptogenic cirrhosis	1 (0.8)
AIH	1 (0.8)
Child-Pugh score (N)	
A	99
B	15
C	6
MELD score (Mean ± SD)	9.78 ± 3.85
RFH-NTP	
Low risk	86 (71.1)
Moderate risk	19 (15.7)
High risk	16 (13.2)

Abbreviations: CHC, chronic hepatitis C; CHB, chronic hepatitis B; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; RFH-NTP, Royal Free Hospital-Nutritional Prioritizing tool

Of 121 cirrhotic patients, thiamine deficiency in this study affected 15 patients, and the prevalence was 12.4% ([figure 1](#)). There was no difference in the prevalence of thiamine deficiency between alcoholic vs. non-alcoholic etiology (14.6% vs. 11.3%; p=0.59) ([figure 2](#)). Moreover, more than half (60%) of the thiamine deficiencies were within non-alcoholic cirrhosis. In a non-alcoholic setting, mostly CHC 5 (33.3%) patients, followed by CHB 4 (26.7%) ([table 2](#)).

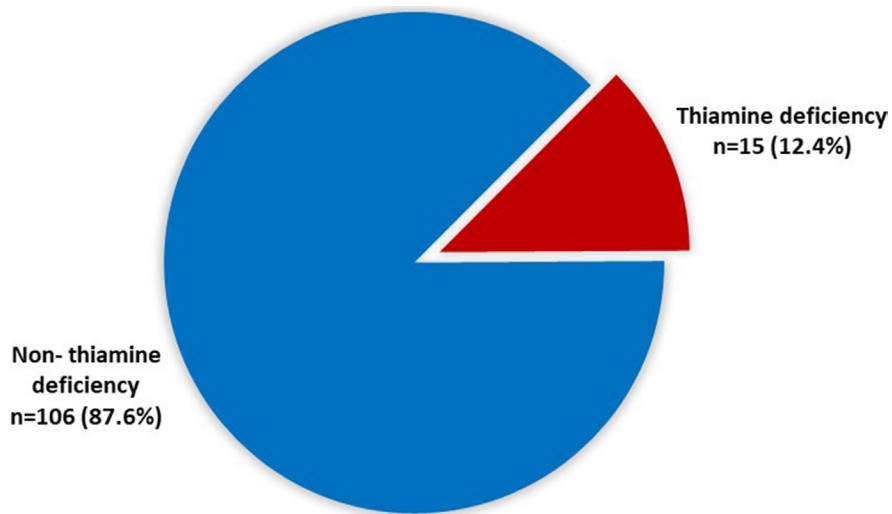


Figure 1 Prevalence of thiamine deficiency

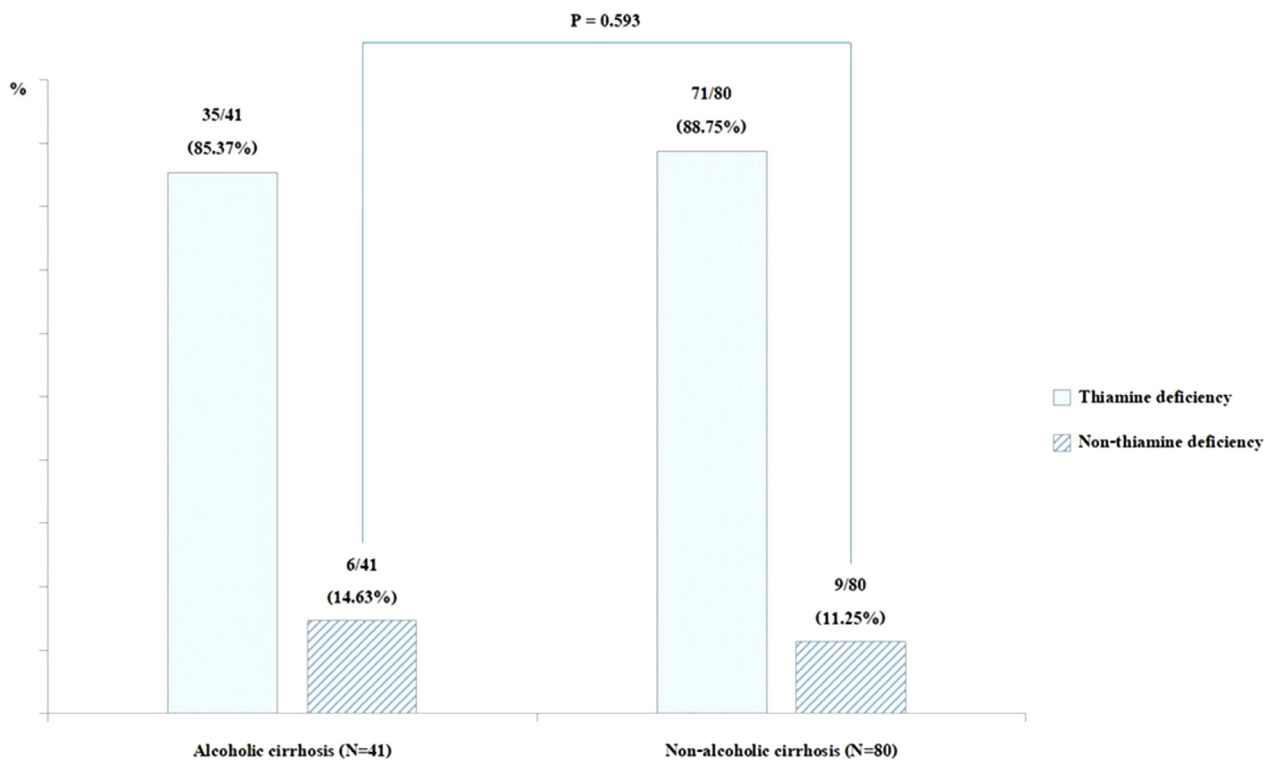


Figure 2 Comparison of the prevalence of thiamine deficiency in alcoholic and non-alcoholic cirrhosis

Table 2 Comparison of the demographic data and ETKA level between the thiamine deficiency group and the non-thiamine deficiency group, along with subgroup analysis

	Thiamine deficiency (n=15)	Non thiamine deficiency (n=106)	P-value
Gender			
Male	12 (80%)	76 (71.7%)	0.758
Female	3 (20%)	30 (28.3%)	0.758
Age (years) [#]	57.07 ± 6.72	58.17 ± 10.89	0.701
<50	2 (13.3%)	27 (25.5%)	0.518
≥50	13 (86.7%)	79 (74.5%)	0.518
Body weight (kg) [#]	71.87 ± 14.94	66.92 ± 14.4	0.218
Height (cm) [#]	167.43 ± 10.09	163.42 ± 9.88	0.157
BMI (kg/m ²) [#]	25.93 ± 4.67	25.1 ± 4.76	0.528
Etiology of cirrhosis			
Alcoholic cirrhosis	6 (40%)	35 (33%)	0.593
Non-alcoholic cirrhosis	9 (60%)	71 (67%)	0.593
Non-alcoholic cause			
CHC	5 (33.3%)	33 (31.1%)	0.864
CHB	4 (26.7%)	19 (7.9%)	0.419
CHB, CHC	0 (0%)	2 (1.9%)	1.000
AIH	0 (0%)	1 (0.9%)	1.000
Cardiac cirrhosis	0 (0%)	1 (0.9%)	1.000
cryptogenic	0 (0%)	1 (0.9%)	1.000
NASH	0 (0%)	14 (13.2%)	0.212
Amount of alcohol (gm/d) [#]	116.83 ± 81.65	137 ± 97.01	0.634
No	9 (60%)	71 (67%)	0.575
<50 gm/d	1 (6.7%)	6 (5.7%)	1.000
50-100 gm/d	3 (20%)	13 (12.3%)	0.418
100-200 gm/d	1 (6.7%)	11 (10.4%)	1.000
>200 gm/d	1 (6.7%)	5 (4.7%)	0.556
Drinking duration (months) [#]	140 ± 61.97	258.86 ± 132.87	0.039*
Cessation alcohol (months) [#]	63.83 ± 97.75	46.54 ± 89.67	0.669
<3 months	2 (13.3%)	17 (16%)	1.000
3-6 months	0 (0%)	1 (0.9%)	1.000
>6 months	4 (26.7%)	17 (16%)	0.293
Transient elastography (kPa) [#]	36.86 ± 20.34	28.9 ± 15.67	0.295
Duration of diagnosis cirrhosis [#]	40.86 ± 92.92	18.24 ± 21.04	0.380
Child-Pugh score			
A	12 (80%)	87 (82.1%)	0.735
B	3 (20%)	12 (11.3%)	0.397
C	0 (0%)	6 (5.7%)	1
Child-Pugh score [#]	5.67 ± 0.98	5.86 ± 1.46	0.625
MELD score [#]	8.5 ± 1.99	9.95 ± 4.01	0.486
Comorbidity			
Diabetic mellitus	5 (33.3%)	23 (21.7%)	0.334
Hypertension	4 (26.7%)	29 (27.4%)	1
HIV infection	0 (0%)	5 (4.7%)	1
HCC	7 (46.7%)	13 (12.3%)	0.003*

Table 2 Comparison of the demographic data and ETKA level between the thiamine deficiency group and the non-thiamine deficiency group, along with subgroup analysis (continued)

	Thiamine deficiency (n=15)	Non thiamine deficiency (n=106)	P-value
SPENT nutrition tool			
0	4 (26.7%)	39 (36.8%)	0.570
1	11 (73.3%)	63 (59.4%)	0.401
2	0 (0%)	4 (3.8%)	1.000
NAF	N/A	8.25 ± 4.92	N/A
NAF level			
1	0 (0%)	2 (1.9%)	1.000
3	0 (0%)	2 (1.9%)	1.000
RFH-NPT			
low risk	11 (73.3%)	75 (70.8%)	1.000
moderate risk	2 (13.3%)	17 (16%)	1.000
high risk	2 (13.3%)	14 (13.2%)	1.000
ETKA level at diagnosis [#]	1.43 ± 0.21	1.03 ± 0.11	<0.001*

Abbreviations: N/A, not available; CHC, chronic hepatitis C; CHB, chronic hepatitis B; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; NAF, nutrition alert form; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing tool; ETKA, erythrocyte transketolase activity

* Indicates P < 0.05

[#] Values are reported as mean ± SD

Neither the amount of alcohol nor the abstinence time before ETKA was different in mean thiamine levels (116.8 ± 81.6 gm/day vs. 137 ± 97 gm/day; P=0.63 in amount of alcohol, 63.8 ± 97.8 months vs. 46.5 ± 89.7 months; P=0.67 in abstinence duration). However, drinking duration was shorter in thiamine deficiency (140 ± 61.97 months vs. 258.86 ± 132.87 months; P=0.039). In the thiamine deficiency group, 12 patients (80%) were CTP A, 3 (20%) were CTP B cirrhosis, and there was no CTP C in this group. The mean MELD score was 8.5 ± 1.99 (table 2).

In the part of nutritional status, 4 from 15 (26.7%) had a score of 0, 11 from 15 (73.3%) had a score of 1 from the SPENT nutrition screening tool, so in cases where the score was less than 2, nobody in this group was evaluated for NAF level. And most of the patients (11, 73.3%) were classified in the low-risk group for malnutrition by RFH-NTP. In the thiamine deficiency group, the mean of ETKA was 1.43 ± 0.21 at diagnosis (table 2).

Of the 15 patients with thiamine deficiency from ETKA diagnosis, 12 patients underwent complete neurological examination and performed the ASRS V1.1 test at the baseline before thiamine replacement, but the remaining 3 patients (20%) were lost at follow up and did not have thiamine replacement. At baseline neurologic signs, one patient had peripheral nystagmus, and another patient had an abnormal ASRS test. After 3 months of thiamine supplementation, a persistent abnormal ASRS test but the disappearance of peripheral nystagmus could be seen. During follow up, a total of 5 (4.1%) patients did not survive: 1 from 15 (6.7%) in the thiamine deficiency group died from the advanced stage of HCC after 2 months of diagnosis, and of the remaining 4 from 106 (3.8%) in the non-thiamine deficiency group, 2 patients died from liver-related causes (1 ruptured HCC, 1 severe alcoholic hepatitis), and the others died from sepsis; Figure 3 No statistically significant variance was found in deaths between the 2 groups; P = 0.598.

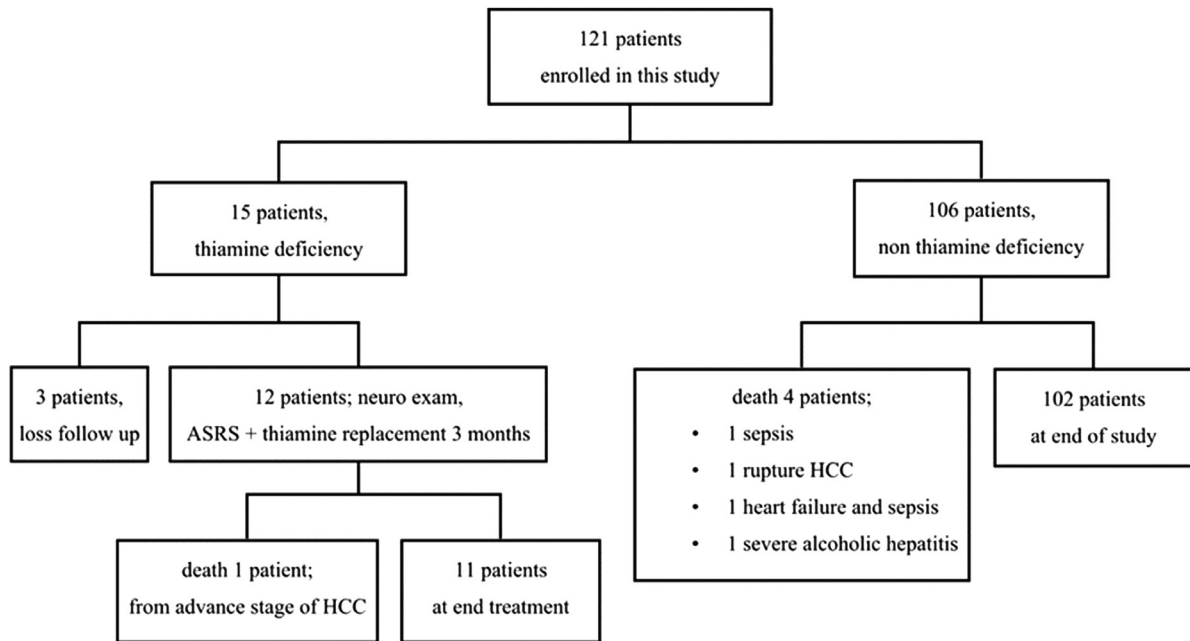


Figure 3 Patient flow chart, follow up diagram

Among the 2 groups who were diagnosed with thiamine deficiency and non-thiamine deficiency, there was no difference in terms of baseline age, etiology, and severity of liver disease: male gender, age, alcoholic cirrhosis, non-alcoholic cirrhosis, CHB cirrhosis, CHC cirrhosis, liver stiffness, CTP score, MELD score, and comparable in nutritional status when evaluated by SPENT and RFH-NPT tests (table 2). For logistic regression, HCC patients were 4.42

times (95% CI 1.18, 10.08) significantly greater in the thiamine deficiency group (46.7% vs. 12.3%; $P=0.003$) (table 3). Most of the HCC patients were in the intermediate stage based on the Barcelona Clinic Liver Cancer (BCLC) criteria. Moreover, we found nearly one-third of HCC cases had thiamine deficiency, mostly CHB 4 patients, CHC 2 patients, followed by 1 patient in alcoholic cirrhosis.

Table 3 Logistic regression analysis to evaluate factors associated with thiamine deficiency

	Univariate	
	OR (95%CI)	P-value
Etiology of cirrhosis		
Alcoholic cirrhosis	1.35 (0.4, 4.6)	0.593
Non-alcoholic cirrhosis	0.74 (0.2, 2.7)	0.593
Child-Pugh score		
A	0.89 (0.3, 2.9)	0.735
B	1.77 (0.6, 5.5)	0.397
C	N/A	1
Hepatocellular carcinoma	4.42 (1.8, 10.8)	0.003*
RFH-NPT		
Low risk	1.12 (0.4, 3.3)	1.000
Mod risk	0.83 (0.2, 3.4)	1.000
High risk	1.01 (0.3, 4.1)	1.000

Abbreviations: N/A, not available; NAF, nutrition alert form; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing tool

Mean ETK activity at the baseline was 1.43 ± 0.21 in the thiamine deficiency group. After 3 months of 200 mg/day of thiamine replacement in 11 patients, the mean ETKA decreased to a level of 1.04 ± 0.15 . Significant improvement of mean ETKA was -0.41 ± 0.26 ; $P < 0.001$. ETKA improvement did not depend on the etiology and severity of disease. In only 1 from 11 patients did ETKA not return to normalization.

DISCUSSION

In this study, we report data from a prospective cohort on thiamine deficiency status in cirrhotic patients. As thiamine status is not easy to evaluate and unavailable in general hospitals, data concerning the exact prevalence of thiamine deficiency in cirrhosis are scarce. In this study, we observed that thiamine deficiency was found to be 12.4% in stable cirrhotic patients, while 80% were CTP A. This is similar to the trial of Bandidwattanawong in 2019, for which the prevalence of thiamine deficiency was 13.2% in cirrhosis with complications, although half of enrolled patients (52.6%) were CTP B²¹. These data may imply that the severity of disease was not correlated to the thiamine level. Consistent with the trial of Stephane Levy in 2002¹⁷, thiamine deficiency was 21.6% in alcoholic and CHC cirrhosis, classified to CTP A 21%, B 47%, and C 31%. Because thiamine deficiency is related to multiple factors, such as food type, medication, and acute infection which can occur in any stage of the disease, the severity of disease alone cannot predict thiamine status. And in this study might be under estimate of prevalence thiamine deficiency in cirrhosis because most case in Child pugh A. So, we need more data and sample size to analyze association between thiamine deficiency and severity of cirrhosis.

Prevalence of thiamine deficiency was varied, in comparison to the trial of Rossouw in 1978⁷. The prevalence in our study was lower, as 14.6% (6/41) had thiamine deficiency status in the current study compared to 70.6% in the Rossouw trial in alcoholic cirrhosis, and 11.3% (9/80) vs.

42.8% from the Rossouw trial in the non-alcoholic cirrhosis setting. Since the previous study enrolled severely ill-patients, in each case there were at least two of the following features: hepatic encephalopathy, jaundice, ascites, low albumin, and coagulopathy, which may result in predisposition to a higher prevalence of thiamine deficiency. Focusing on etiology, the current study found no difference in thiamine status in alcoholic and non-alcoholic etiology ($P=0.59$), consistent with the Stephane Levy trial, and no difference in frequency of thiamine deficiency was found between alcoholic and chronic hepatitis C cirrhosis (25% vs. 19%; $P=0.09$)¹⁷. And because sample size in this study are less than calculation that might not show significant different of both groups.

Neither the amount of alcohol consumption nor the abstinence time was different in mean thiamine levels. However, the duration of consumption was longer in the non-thiamine deficiency group in this study. This may be due to unreliable alcoholic habitual information from patients or binge drinking of alcohol rather than regular consumption in the thiamine deficiency group. Therefore, gamma glutamyl-transferase (GGT) is possibly helpful in determining alcoholic status at the time of enrollment.

Wernicke's encephalopathy is often mentioned in thiamine deficiency. The triad of nystagmus, ophthalmoplegia, and mental status change was found in only 16% of patients²². In this study, only one (8.3%) had peripheral nystagmus and another one had attention deficit. Due to the small sample size of the thiamine deficiency group, and no confirmatory test by imaging, neurological abnormality is not significant in this study.

In the current study, hepatocellular carcinoma (HCC) is the only associated factor of thiamine deficiency status (OR 4.42, 1.81-10.8). There is no prevalence of thiamine deficiency in HCC in previous studies, but among patients with all cancers, a high rate of thiamine deficiency was observed. Thiamine deficiency was found in 55.3%

of cancer patients for which hepatopancreatobiliary was 7.4% in the Isenberg-Grzeda trial 2017²³. In our study, HCC may be a predisposing factor of thiamine deficiency due to loss of appetite, receiving transarterial chemoembolization (TACE) in most cases, and increasing metabolic demands which is the mechanism of relative thiamine deficiency²³.

Our study has the strength of a cross-sectional study, together with detailed demographic baseline characteristics, etiology of cirrhosis, and HCC data. Data from the real-life cohort represent a spectrum of patients wider than randomized controlled trials. This result applies to routine clinical practice. Nonetheless, our study has some limitations. First, the sample size of cirrhotic patients was less than the 200 calculated to be enrolled at first due to the limited duration of the study and the COVID-19 outbreak, causing fewer patients to present at the outpatient department. Second, the current trial was studied in a single center, so it cannot be used to validate data for other centers. Third, this is a single-arm study with no placebo arm for comparing the efficacy of thiamine replacement therapy. Fourth, we did not record compliance with thiamine replacement or document food types that may be associated with the improvement of ETKA. And the last one, HCC usually arises from cirrhosis and prone to be more nutritional deficiency, so we cannot definitely summarize that HCC is only one factor of thiamine deficiency.

In future studies, outcomes after thiamine replacement such as improvement of CTP, MELD score, or cirrhotic complications are needed. Following cessation of thiamine replacement is interesting, whether or not there is a return to deficiency status.

CONCLUSION

All etiologies of cirrhosis are associated with thiamine deficiency, not only alcoholic cirrhosis. Hepatocellular carcinoma also associated with thiamine deficiency, but not in end stage liver disease, child B and C. The possible cause of this

association is still doubtful, because it did not show in advanced liver disease, especially child C. Empirical replacement of thiamine in cirrhosis and HCC may be beneficial. Consistent with European Association for the Study of the Liver (EASL) clinical practice guidelines on nutrition in chronic liver disease (2019), supplementary oral multivitamins are recommended in decompensated cirrhosis because of the cost effectiveness and lack of serious side effects²⁴.

CONFLICT OF INTEREST

The authors report no relevant conflicts of interest for this article.

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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