An association between dietary habits and traffic accidents in patients with chronic liver disease: A data-mining analysis

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Abstract. The incidence of traffic accidents in patients with chronic liver disease (CLD) is high in the USA. However, the characteristics of patients, including dietary habits, differ between Japan and the USA. The present study investigated the incidence of traffic accidents in CLD patients and the clinical profiles associated with traffic accidents in Japan using a data-mining analysis. A cross-sectional study was performed and 256 subjects [148 CLD patients (CLD group) and 106 patients with other digestive diseases (disease control group)] were enrolled; 2 patients were excluded. The incidence of traffic accidents was compared between the two groups. Independent factors for traffic accidents were analyzed using logistic regression and decision-tree analyses. The incidence of traffic accidents did not differ between the CLD and disease control groups (8.8 vs. 11.3%). The results of the logistic regression analysis showed that yoghurt consumption was the only independent risk factor for traffic accidents (odds ratio, 0.37; 95% confidence interval, 0.16-0.85; P=0.0197). Similarly, the results of the decision-tree analysis showed that yoghurt consumption was the initial divergence variable. In patients who consumed yoghurt habitually, the incidence of traffic accidents was 6.6%, while that in patients who did not consume yoghurt was 16.0%. CLD was not identified as an independent factor in the logistic regression and decision-tree analyses. In conclusion, the difference in the incidence of traffic accidents in Japan between the CLD and disease control groups was insignificant. Furthermore, yoghurt consumption was an independent negative risk factor for traffic accidents in patients with digestive diseases, including CLD.

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Abbreviations: CLD, chronic liver disease; BCAA, branched-chain amino acids; CON, control; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST to platelet ratio index

Key words: road traffic accident, liver cirrhosis, dietary habits, nutrition, subclinical hepatic encephalopathy

Introduction

The development of antiviral treatment, anticancer therapy and endoscopic treatment for esophageal varix, along with nutritional care has significantly improved the prognosis of chronic liver disease (CLD) (1-3). Thereby, management of complications of CLD in addition to liver failure, hepatocellular carcinoma and esophageal varices is important. Infection and diabetes mellitus are major complications of CLD (2,4). In addition, cognitive dysfunction is frequently observed in patients with CLD (5-7), as ammonia and proinflammatory cytokines affect the central nervous system through the liver-brain axis (8).

Cognitive dysfunction occurs without signs of hepatic encephalopathy, and affects daily function and health-related quality of life, and causes falls in CLD patients (9,10). Additionally, cognitive dysfunction has been reported to be associated with poor driving performance (11). Disease-related traffic accident is a serious social issue worldwide (12), and the incidence of traffic accidents is high in patients with liver cirrhosis in the USA (13,14). However, traffic conditions and the characteristics of CLD patients, including age and etiology of CLD, in Japan differ from those of CLD patients in the USA. Thus, the impact of CLD on traffic accidents in Japan remains to be elucidated.

Cognitive function is regulated by various factors. Alcohol consumption, starvation, malnutrition, advanced liver cirrhosis, constipation and psychotropic medication

are known risk factors for cognitive dysfunction in patients with CLD (10,12,15). By contrast, supplementation with branched-chain amino acids (BCAA) and treatment with lactulose for hyperammonemia alleviate cognitive dysfunction in patients with CLD (12,16). Furthermore, habitual consumption of coffee or yoghurt enhances attention (17-20). Although these factors are thought to affect the occurrence of traffic accidents, limited information is available on the impact of these dietary factors on traffic accidents in patients with CLD.

The aim of the present study was to investigate the incidence of traffic accidents in patients with CLD in Japan. In addition, the risk factors and the clinical profiles associated with traffic accidents were investigated.

Subjects and methods

Ethics. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, as reflected in the prior approval of the Institutional Review Board of Kurume University (Kurume, Fukuoka, Japan; approval no. 12142). Written informed consent for participation in the study was obtained from each subject. None of the subjects were institutionalized.

Study design. Between August 2012 and June 2015, a cross-sectional case-control study was performed to investigate the impact of CLD on the incidence of traffic accidents in Japan.

Subjects. Inclusion criteria were patients: i) With CLD (case) or other digestive diseases [disease control (disease CON)], ii) whose performance status was 0 or 1, iii) who regularly drive any type of vehicle (car, motorcycle or bicycle), and iv) who agreed with the study protocol. Exclusion criteria were patients with hepatic encephalopathy, active alcohol intake (in the 3 months before the study), epilepsy, syncope, severe hypoglycemia, severe sleep disorder, manic-depressive psychosis and dementia. Severe hypoglycemia was defined as a blood glucose level <50 mg/dl or symptoms that promptly resolve with oral carbohydrate or intravenous glucose, as previously described (21). Severe sleep disorder was defined as sleep episodes that are present daily and at times of physical activities that require mild to moderate attention, as previously described (22). According to the International Classification of Disease 10th revision, dementia was defined as a disorder with deterioration in memory and thinking, which is sufficient to impair personal activities of daily living (23).

A total of 256 patients were enrolled and, of these, 2 patients were excluded as they did not provide answers to questions regarding traffic accidents (Fig. 1). In total, 254 patients were classified into the following two groups: i) The CLD group (total n=148; hepatitis C virus, n=91; hepatitis B virus, n=18; alcoholic liver disease, n=13; nonalcoholic steatohepatitis, n=4; others, n=22) and ii) the disease CON group (total n=106; pancreatic malignancy, n=20; gastric cancer, n=18; colon polyp, n=16; bile duct cancer, n=11; esophageal cancer, n=6; bile duct stone, n=6; ulcerative colitis, n=5; colitis, n=3; pancreatitis, n=2; others, n=19). The diagnoses of CLD and digestive diseases were based on the results of clinical examination, serological examination, imaging and histological examination.

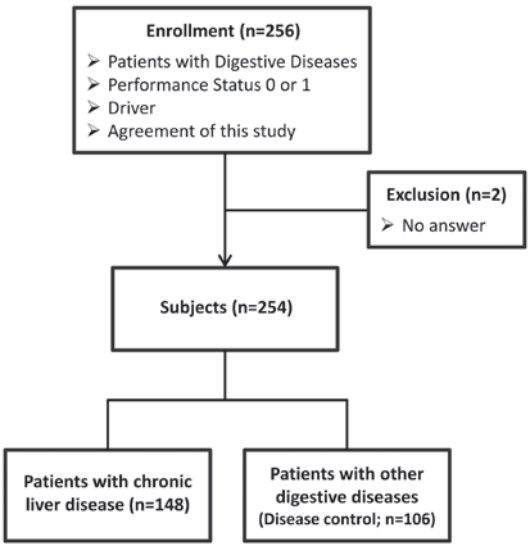

Figure 1. Study design. A total of 256 patients with digestive diseases were enrolled. Of these, 2 patients were excluded as they did not provide answers to questions regarding traffic accidents. The remaining 254 patients were classified into the chronic liver disease (CLD) group (n=148) or disease control (disease CON) group (n=106).

Clinical characteristics and lifestyle. Data regarding the clinical characteristics and lifestyle factors of the subjects, including age, gender, sleep disturbance, constipation, muscle cramp, habitual coffee consumption and habitual yoghurt consumption, were collected prior to any invasive diagnostic or therapeutic procedures. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2).

Definition of habitual coffee and yoghurt consumptions. Habitual coffee consumption was defined as drinking ≥1 cup of coffee/day (>180 ml/day) (24). Habitual yoghurt consumption was defined as consuming ≥1 cup of yoghurt/day (>100 g/day) (25).

Laboratory examinations. Venous blood samples were collected in the morning after a 12-h overnight fast. Platelet count; prothrombin activity; serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, and creatinine levels; and blood glucose, urea nitrogen, and ammonia levels were measured using standard clinical methods (Department of Clinical Laboratory, Kurume University Hospital). The stage of liver fibrosis was assessed by the AST-to-platelet ratio index (APRI): Serum AST level (U/l)/upper limit of normal AST (33 U/l) x 100/platelet count ($x10^4$/ml) (26). Patients with APRI values of ≤1.5 were diagnosed with chronic hepatitis, and those with APRI values >1.5 were diagnosed with liver cirrhosis (26).

Medications. Data regarding the use of psychotropic medication, BCAA-related medication or lactulose were collected from the medical records of the patients.

Erroneous stepping on the accelerator and brake, near miss of a traffic accident, and traffic accident. Among the subjects who drive a car, the experience of erroneous stepping on the

Table I. Patient characteristics.

Characteristics	CLD group	Disease CON group	P-value
Total, n	148	106	
Median age, years (range)	71 (17-85)	65 (24-86)	0.0006
Male/female, n	103/45	60/46	0.0332
Median body mass index, kg/m^2 (range)	23.2 (15.8-35.7)	21.6 (15.0-34.1)	0.0023
Lifestyle, n			
Sleep, hypersomnia/good/insomnia	8/120/20	4/89/13	0.7848
Constipation, yes/no	1/147	6/100	0.0167
Muscle cramp, yes/no	71/75	34/72	0.0085
Use of psychotropic medication, yes/no	18/129	10/95	0.4980
Habitual coffee consumption, yes/no	80/68	69/37	0.0781
Habitual yoghurt consumption, yes/no	101/46	65/41	0.2223
History of alcohol consumption, yes/no	14/134	10/96	0.5848
Median biochemical examinations (range)			
AST, IU/l	48 (13-693)	24 (8-550)	<0.0001
ALT, IU/l	37 (5-473)	20 (3-637)	<0.0001
Total bilirubin, mg/dl	0.93 (0.15-18.58)	0.74 (0.05-23.18)	0.0019
Albumin, g/dl	3.53 (2.23-4.85)	4.00 (1.7-5.04)	<0.0001
Creatinine, mg/dl	0.72 (0.30-8.84)	0.71 (0.33-2.43)	0.2002
Prothrombin activity, %	81 (21-140)	103 (22-140)	<0.0001
Platelet count, x10^3/mm^3	11.1 (3.6-40.3)	21.6 (4.5-64.3)	<0.0001
CLD-related variables			
Presence of liver cirrhosis, n (yes/no)	81/67	N/A	N/A
Median APRI (range)	1.64 (0.19-8.37)	N/A	N/A
Median ammonia, µg/dl (range)	51 (15-200)	N/A	N/A
Use of BCAA-related medication, n (yes/no)	54/94	N/A	N/A
Use of lactulose, n (yes/no)	16/132	N/A	N/A

AST, aspartate aminotransferase; ALT, alanine aminotransferase; N/A, not applicable; APRI, AST-to-platelet ratio index; BCAA, branched-chain amino acid; CLD group, chronic liver disease group; disease CON group, disease control group.

accelerator and brake was investigated using a questionnaire sheet. For all the subjects, the experience of a near miss of a traffic accident and a traffic accident was investigated using a questionnaire sheet. A near miss of a traffic accident was defined as the experience for avoidance of any type of traffic accidents, including property damage. A traffic accident was defined as the experience of any type of traffic accidents, including property damage.

Statistical analysis. Non-parametric comparisons were made using the Wilcoxon signed-rank test, and categorical comparisons were made using Fisher's exact test. A logistic regression model was used for multivariate stepwise analysis to identify any independent variables that were associated with traffic accidents, as previously describe (27). A decision-tree algorithm was constructed to identify profiles associated with traffic accidents, as previously described (28,29).

A stratification analysis was also performed for patients with CLD. Multivariate stepwise and decision-tree analyses were performed to identify any independent variables that were associated with traffic accidents. All the statistical analyses were conducted using JMP Pro version 11.0 (SAS Institute, Cary, NC, USA). Data are expressed as number or median (range). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The patient characteristics are summarized in Table I. Age, male-to-female ratio, BMI and prevalence of muscle cramp were significantly higher in the CLD group compared to the disease CON group. However, no significant difference was identified between the CLD and disease CON groups in the prevalence of sleep disturbance, constipation and use of psychotropic medication. No significant difference was apparent between the CLD group and the disease CON group in the prevalence of habitual coffee, yoghurt and alcohol consumption (Table I).

The results of biochemical examinations showed a significant elevation in the serum AST, ALT and total bilirubin levels in the CLD group, as compared to the levels in the disease CON group. The serum albumin level, prothrombin activity

Table II. Driving status.

Driving variables	CLD group	Disease CON group	P-value
Car/motorcycle/bicycle, n	124/4/20	89/3/14	0.9959
Median driving time, min (range)	60 (5-540)	60 (10-540)	0.6648

CLD group, chronic liver disease group; CON, control group.

Table III. Logistic regression analysis for the incidence of traffic accidents and habitual yoghurt consumption.

	Logistic regression analysis		
Factor	Odds ratio	95% CI	P-value
Habitual yoghurt consumption	0.37	0.16-0.85	0.0197

CI, confidence interval.

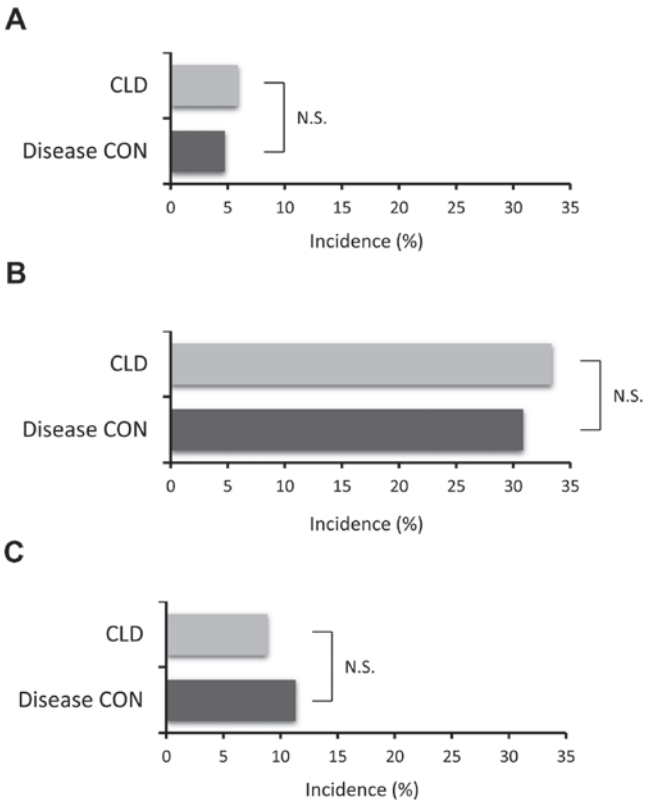

Figure 2. Incidence of (A) erroneous stepping on the accelerator and brake, (B) a near miss of a traffic accident and (C) traffic accidents. CLD, chronic liver disease; CON, control.

and platelet count were significantly lower in the CLD group compared to the corresponding values in the disease CON group (Table I).

In the CLD group, the prevalence of liver cirrhosis was 54.7% (81/148) and the median blood ammonia level was 51 μg/dl. Use of BCAA-related medication and lactulose was observed in 36.5% (54/148) and 10.8% (16/148) of the patients in the CLD group, respectively (Table I).

Driving status and incidence of traffic accidents. No significant difference was observed between the CLD and disease CON groups in the type of vehicle and driving time (Table II). In the CLD group, the incidence of erroneous stepping on the accelerator and brake was 5.6% (7/119; Fig. 2A), and that of a near miss of a traffic accident was 25.0% (37/111; Fig. 2B). These incidence rates did not differ from those in the disease CON group (Fig. 2A and B). The incidence of traffic accidents was 8.8% (13/148) in the CLD group, and did not differ from that in the disease CON group (Fig. 2C).

Logistic regression analysis for the incidence of traffic accidents. In a logistic regression analysis for traffic accident incidences, age, gender, sleep status, constipation, muscle cramp or use of psychotropic medication were not identified as independent factors associated with traffic accidents. Furthermore, CLD, liver cirrhosis or a history of alcohol consumption were not identified as independent factors associated with traffic accidents. Habitual yoghurt consumption was the only independent negative risk factor for traffic accidents [odds ratio (OR), 0.37; 95% confidence interval (CI), 0.16-0.85; P=0.0197)] (Table III).

Decision-tree algorithm for traffic accidents. To clarify the profile associated with traffic accidents, a decision-tree algorithm was created using 2 divergence variables and classified the patients into three groups (Fig. 3). Habitual yoghurt consumption was the initial divergence variable. The traffic accident incidence in patients with habitual yoghurt consumption was 6.6% (group 1 in Fig. 3), whereas that in patients with no habitual yoghurt consumption was 16.0%. Among patients with no habitual yoghurt consumption, use of psychotropic medication was the variable for the second classification. Thus, in patients with no habitual yoghurt consumption and no use of psychotropic medication, the traffic accident incidence was 11.8% (group 2 in Fig. 3). By contrast, in patients with no habitual yoghurt consumption and use of psychotropic medication, the traffic accident incidence was 45.5% (group 3 in Fig. 3). In this analysis, neither CLD nor liver cirrhosis was identified as a divergence variable for the incidence of traffic accidents.

Stratification analysis according to CLD. In the CLD group, the incidence of traffic accidents did not significantly differ between patients with chronic hepatitis and those with liver cirrhosis (Table IV). Furthermore, no significant difference was identified between BCAA-related medication, lactulose, HCV-infection and muscle cramp and the incidence of traffic accidents (Table IV). By contrast, the incidence of traffic accidents was significantly higher in CLD patients with a history of alcohol consumption compared to those with no history of alcohol consumption.

In the CLD group, logistic regression and decision analyses were performed to clarify the independent factor and the profile associated with traffic accidents. In the logistic

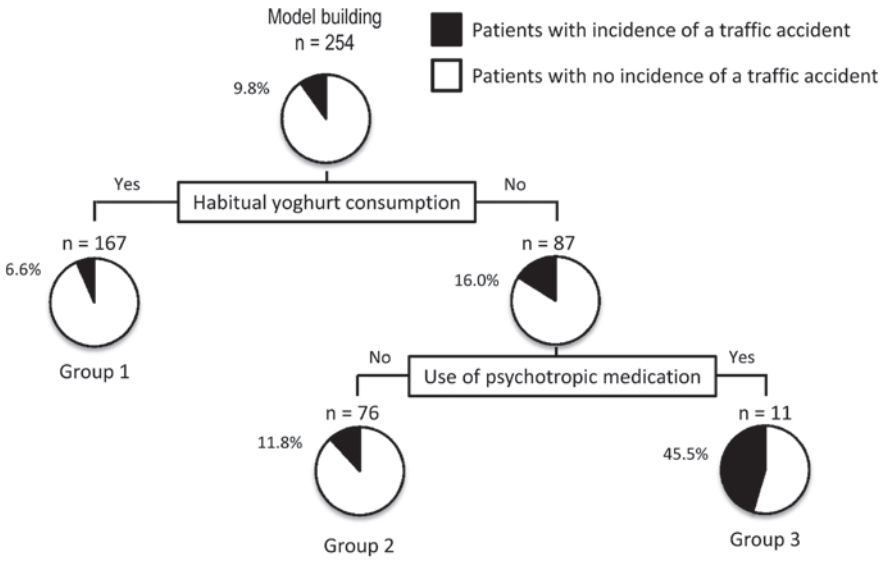

Figure 3. A decision-tree algorithm for the incidence of traffic accidents. The subjects were classified according to the indicated variables. The pie graphs indicate the proportion of patients with no incidence of a traffic accident (white) and those with an incidence of a traffic accident (black) in each group.

Table IV. Stratification analysis according to hepatic fibrosis, branched-chain amino acids (BCAA)-related medication, lactulose use and alcohol consumption for the incidence of traffic accidents in patients with chronic liver disease.

	Traffic accidents, n		
Factors	Incidence	No incidence	P-value
Chronic hepatitis	7	60	
Liver cirrhosis	6	75	0.5154
Use of BCAA-related medication			0.4484
Use	6	48	
No use	7	87	
Lactose			0.7046
Use	1	15	
No use	12	120	
Alcohol consumption			0.006
History	4	10	
No history	9	125	

Table V. Logistic regression analysis for the incidence of traffic accidents in patients with chronic liver disease and use of psychotropic medication.

	Logistic regression analysis		
Factor	Odds ratio	95% CI	P-value
Use of psychotropic medication	5.81	1.57-20.3	0.0100

CI, confidence interval.

regression analysis, use of psychotropic medication was the only independent risk factor for traffic accidents (OR, 5.81; 95% CI, 1.57-20.3; P=0.0100) (Table V). In this analysis, liver cirrhosis, etiology of liver disease, blood ammonia level, use of BCAA-related medication, or lactulose use were not identified as independent factors associated with traffic accidents (Table V).

In this stratification analysis, a decision-tree algorithm was created using 2 divergence variables to classify the patients into three groups (Fig. 4). Use of psychotropic medication was the initial classification variable. In CLD patients who were not administered psychotropic medication, the traffic accident incidence was 6.2% (group 1 in Fig. 4), whereas in those who were administered psychotropic medication, the traffic accident incidence was 27.8%. Among patients who were administered psychotropic medication, habitual yoghurt consumption was the variable for the second classification. Thus, in patients who were administered psychotropic medication and habitually consumed yoghurt, the traffic accident incidence was 9.1% (group 2 in Fig. 4), whereas in patients who used psychotropic medication and did not habitually consume yoghurt, the traffic accident incidence was 57.1% (group 3 in Fig. 4). In this analysis, liver cirrhosis, etiology of liver disease, blood ammonia level, use of BCAA-related medication or lactulose use were not identified as divergence variables for the incidence of traffic accidents.

Discussion

In the present study, no significant difference was observed between the incidence of traffic accidents in CLD patients from that in patients with other digestive diseases. In addition, CLD was not an independent risk factor for the incidence of traffic accidents. Habitual yoghurt consumption was also found to be an independent negative risk factor for traffic accidents.

In the present study, the incidence of traffic accidents was 8.8% in CLD patients, and no significant difference was identified for this incidence and for that in patients

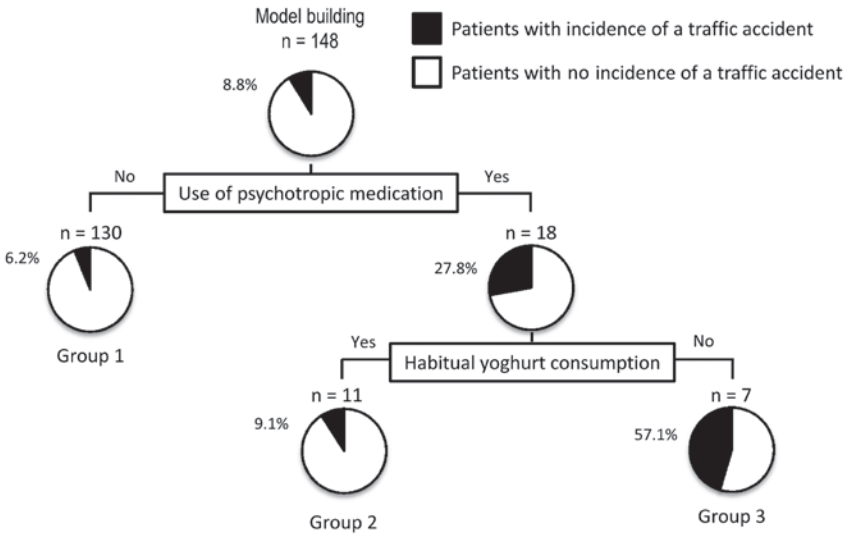

Figure 4. A decision-tree algorithm for the incidence of traffic accidents in patients with CLD. The subjects were classified according to the indicated variables. The pie graphs indicate the proportion of patients with no incidence of a traffic accident (white) and those with an incidence of a traffic accident (black) in each group.

with other digestive diseases. By contrast, as reported by Bajaj *et al* (14,30), 17.0% of patients with liver cirrhosis experience traffic accidents in the USA, and this incidence is significantly higher compared to that in their control group. The reason for the difference in the incidence of traffic accidents between the previous studies and the present study remains to be elucidated. In the present study, the disease CON group included patients with pancreatic malignancy and ulcerative colitis. These diseases have poor health-related quality of life, suggesting that the incidence of traffic accidents may be high due to these diseases. The incidence of traffic accidents in the area is 1.23% (41,618 accidents/3,329,884 automobiles owned in the area) according to Ministry of Land, Infrastructure, Transport and Tourism in Japan (31). Although there is no data for age and physical condition in automobile owners of the area, the incidence of traffic accidents in CLD patients may be higher than that in the healthy population.

Liver cirrhosis was not identified as an independent risk factor or a divergence variable for traffic accidents in the present study. According to the previous studies, liver cirrhosis may influence the incidence of traffic accidents (14,30) and the possible explanations for the present observation are the differences in the medication for liver cirrhosis and etiology of CLD between Japan and the USA. In the present study, 50.6% of patients with liver cirrhosis were treated with BCAA-related medication. Nutritional management, including treatment with BCAA, has been reported to alleviate minimal hepatic encephalopathy 5, which is a neurocognitive dysfunction associated with traffic accidents (15,32). In addition, alcohol consumption was observed in 24.6% of patients with liver cirrhosis in a previous study (14). By contrast, alcohol consumption was observed in 9.5% of the subjects in the present study. Alcohol consumption is the main factor in traffic accident fatalities (33,34). In the present study, a history of alcohol consumption in CLD patients was significantly associated with the incidence of traffic accident; this finding suggests that the incidence of traffic accident is associated with the alcohol consumption.

The present study examined the current factor(s) associated with the incidence of traffic accidents in Japan, and found that habitual yoghurt consumption was an independent negative risk factor for traffic accidents, according to the results of the logistic regression analysis. Similarly, habitual yoghurt consumption was the initial divergence variable in the decision-tree algorithm for traffic accidents. Furthermore, in CLD patients, habitual yoghurt consumption was the second divergence variable followed by the use of psychotropic medication in the decision-tree algorithm for traffic accidents. A decision tree analysis was also performed for near-miss of a traffic accident. However, as opposed to clinical profile of traffic accidents, gender is the initial divergence variable and habitual yoghurt consumption was not identified as a variable associated with near-miss of a traffic accident (data not shown). Patients with experience of near-miss of a traffic accident could avoid traffic accidents. This data also implies that habitual yoghurt consumption is a specific factor associated with the incidence of traffic accidents.

A causal association between habitual yoghurt consumption and traffic accidents could not be examined in this study, and none of the previous studies have reported an association between yoghurt consumption and traffic accidents. However, the impact of the gut-brain axis on human health and disease is apparent. Yoghurt consumption is known to affect the activity of brain regions that control the central processing of emotion and sensation (20). In addition, yogurt supplementation is known to alleviate minimal hepatic encephalopathy in patients with cirrhosis (35). Gut microbiota regulates circulating tumor necrosis factor-α and interferon-γ levels through mucosal immune mechanisms (36,37). Gut microbiota also regulates the metabolism of tryptophan and short-chain fatty acids (38,39). These microbiota-associated factors are known to alter hippocampal expression of brain-derived neurotrophic factor (37), a modulator of cognitive function (40). In addition to this mechanism, gut microbiota influences the brain function through neuroactive substances and enterochromaffin cell-mediated vagal activation (39).

Taken together, the previous findings and the present results suggest that habitual yoghurt consumption inhibits cognitive dysfunctions and thereby has a beneficial role in traffic accidents.

Various types of yoghurts are now commercially available. Although the present study did not evaluate the type of probiotic bacteria in yoghurt, Bravo *et al* (41) reported that the *Lactobacillus* strain directly regulates brain function via reduction of GABA (Aα2) mRNA expression in the prefrontal cortex and amygdala. Certain Japanese diets and supplementations contain the *Lactobacillus* species, including Miso, a Japanese traditional fermented soybean paste, and lactic acid supplementation. Thus, a dietary survey may provide further beneficial information for prevention of traffic accidents.

In conclusion, no significant difference was identified in the incidence of traffic accidents between CLD patients and patients with digestive diseases. Furthermore, to the best of our knowledge, this is the first study to show that habitual yoghurt consumption was an independent negative risk factor for traffic accidents in patients with digestive diseases and those with CLD.

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