Observational Study

Presence of columnar-lined esophagus is negatively associated with the presence of esophageal varices in Japanese alcoholic men

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AIM
To determine whether the presence of columnar-lined esophagus (CLE) is associated with the presence of esophageal varices in Japanese alcoholic men.
esophageal varices (EVs) in male Japanese alcoholics.

METHODS
The subjects were 1614 Japanese alcohol-dependent men (greater than or equal to 40 years of age) who had undergone upper gastrointestinal endoscopic screening. Digitalized records of high-quality endoscopic images that included the squamocolumnar junction and esophagogastrovascular junction were retrospectively jointly reviewed by four expert endoscopists for the purpose of diagnosing CLE. The authors investigated whether and to what extent there were associations between the presence of CLE and the presence of EVs, especially in the group with liver cirrhosis (LC).

RESULTS
CLE greater than or equal to 5 mm in length was found in 355 subjects (greater than or equal to 30 mm in 6 of them), LC without EVs in 152 subjects, LC with EVs in 174 subjects, and EVs without LC in 6 subjects. Advanced EVs, i.e., nodular, large or coiled forms, red color sign, or post-treatment, were found in 88 subjects. The incidence of CLE greater than or equal to 5 mm decreased in the following order (P less than 0.0001): 23.3% in the group without EVs, 17.4% in the group with small and straight EVs, and 5.7% in the group with advanced EVs. The multivariate ORs (95% CI) for EVs and advanced EVs in the group with LC were lower when CLE greater than or equal to 5 mm was present [0.46 (0.23-0.93) and 0.24 (0.08-0.74), respectively, vs 0-4 mm CLE].

CONCLUSION
The presence of CLE in male Japanese alcoholics was negatively associated with the presence of EVs.

Key words: Alcohol; Columnar-lined esophagus; Hiatal hernia; Liver cirrhosis; Portal hypertension; Esophageal varices

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Core tip: A positive association between excessive drinking and the presence of short-segmental columnar-lined esophagus (CLE) has been reported in Asians. Endoscopic screening of 1614 Japanese alcohol-dependent men revealed the presence of CLE greater than or equal to 5 mm in length in 355 subjects and esophageal varices (EVs) in 180 subjects. The presence of CLE was negatively associated with the presence of EVs, and even more negatively associated with the presence of advanced forms of EVs. Since the first resistance vessels to EVs are the mucosal palisade vessels and submucosal veins at the lower end of the esophagus, the development of CLE may impede the development of EVs.

INTRODUCTION
Esophageal varices (EVs) develop as a result of portal hypertension, which is mainly due to liver cirrhosis (LC) in alcoholics, and excessive alcohol drinking increases the risk of variceal bleeding and mortality [4-8]. Excessive alcohol consumption has been reported to be associated with the presence of gastroesophageal reflux disease (GERD) and a short-segmental columnar-lined esophagus (CLE) in East-Asian studies [4-6]. Long-segmental CLE is rare in Asians [8], and a large pooled analysis of the cases in Western studies did not show a positive association between heavy drinking and GERD or long-segmental CLE [9]. The differences between the results in East Asia and the West may be attributable to the differences between East Asia and Western countries in abdominal obesity, incidences of Helicobacter pylori infection, and gene polymorphisms of alcohol-metabolizing enzymes.

Our empirical impression based on the results of endoscopic screening examinations of Japanese alcoholic men is that EVs are less common among men with short-segmental CLE. The development of CLE has been shown to be accompanied by several histological changes around the palisade vessels, including the development of a double muscularis mucosae [10,11]. Since dilatation of the palisade vessels at the lower end of the esophagus has been suspected of being one of the major initial events in the development of EVs secondary to portal hypertension [12,13], some of the histological changes accompanying the development of CLE may protect against the development of EVs.

It is widely accepted that genetic polymorphisms of alcohol dehydrogenase-1B (ADH1B, rs1229984) and aldehyde dehydrogenase-2 (ALDH2, rs671) affect the susceptibility of East-Asians to alcoholism [14-16], and the presence of fast-metabolizing ADH1B encoded by the ADH1B*2 allele in Japanese alcoholics has been reported to be positively associated with the presence of advanced liver disease [17,18].

The aim of the present study was to determine whether and to what extent associations exist between the presence of EVs and the presence of CLE in Japanese alcoholic men based on the results of endoscopic screening examinations and their ADH1B/ALDH2 genotypes.

MATERIALS AND METHODS
Subjects
The reference population of this study consisted of 1902 Japanese alcoholic men 40 years of age and over who: [1] Came to the Kurihama Medical and Addiction Center for treatment of alcohol dependence for the first
time between May 2004 and December 2011; (2) Were evaluated for the presence of physical comorbidities; (3) Underwent routine upper gastrointestinal endoscopic screening; (4) And underwent ADH1B and ALDH2 genotyping. After excluding the 194 subjects with a history of either gastrectomy or treatment for esophageal cancer and the 94 subjects without a digitalized record of high-quality endoscopic images that included the squamocolumnar junction and esophagogastric junction, 1614 patients were selected as subjects.

All of the alcoholics who participated in this study met the DSM-IV criteria for alcohol dependence. Just before the endoscopic screening examination we asked each participant when he was in a sober state about his drinking and smoking habits. Usual alcohol consumption during the preceding year was expressed in grams of ethanol per day calculated by using standard conversion factors for alcoholic beverages. Beer and low-malt beer were assumed to be 5% ethanol (v/v); wine, 12%; sake, 16%; shochu, 25%; and whiskey, 40%.

The clinical diagnoses of comorbidities were made after alcohol detoxification. Patients received a routine examination that included a physical examination, blood tests, chest X-ray and abdominal X-ray, upper gastrointestinal endoscopy, abdominal ultrasound examination, and abdominal computed tomography. The clinical diagnosis of LC was made on the basis of the results of the physical examination, blood tests, and imaging studies or detection of esophagogastric varices during the endoscopic examination. The severity of LC was graded according to the Child-Pugh scoring system based on the findings at the first visit. Hepatitis B surface (HBs) antigen and second generation anti-hepatitis C (HCV) antibody were measured with Abbott enzyme immunosorbent assays (Abbott Japan Inc., Tokyo).

**Endoscopic procedure**
Endoscopy was performed with an Olympus XQ230, Q240, Q240Z, or Q260 panendoscope (Olympus Optical Co. Ltd., Tokyo, Japan). Esophagogastric varices were diagnosed according to the grading system for esophagogastric varices adopted by the Japanese Society for Portal Hypertension; e.g., based on their form [small and straight (F1), nodular (F2), and large or coiled (F3)] and red color (RC) sign (Figure 1). The severity of portal hypertensive gastropathy (PHG) was evaluated according to Toyonaga’s grading system, which has been adopted by the Japanese Society for Portal Hypertension (Figure 2); All PHG lesions exhibit a snake-skin (mosaic) pattern in their background mucosa; Grade 1, erythematous flecks or maculae; Grade 2, red spots or diffuse redness; and Grade 3, intramucosal or luminal hemorrhage. Three patients could not be evaluated for PHG because of food residue in the stomach.

**Assessment for columnar-lined esophagus and hiatal hernia**
The digitalized images that included the squamocolumnar junction and esophagogastric junction acquired before advancing the endoscope into the stomach were stored by the medical imaging communication system. The endoscopic digitalized images were retrospectively assessed during a joint review by four expert endoscopists (Yokoyama A, Hirata K, Nakamura R, Omori T) to diagnose CLE and hiatal hernia according to the classification system adopted by the Japan Esophageal Society. The endoscopic esophagogastric junction was defined as the lower limit of the palisade longitudinal vessels (Figure 3). It was defined as the upper limit of the gastric mucosal folds when the lower limit of the palisade vessels was unclear. The greatest axial lengths of CLE were classified into four categories: 0-4 mm, 5-9 mm, 10-29 mm, and ≥ 30 mm. The axial length of a hiatus hernia was defined as the distance between the esophagogastric junction and the hiatus represented by the diaphragmatic pinch. The images were examined for the presence or absence of a hiatal hernia whose axial length was ≥ 10 mm.

**Alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 genotyping**
ADH1B and ALDH2 genotyping of every subject was performed by PCR-RFLP methods on a lymphocyte DNA sample.

**Statistical analysis**
The data have been summarized as means and standard errors or as percentage values. Student’s t-test was used to compare normally distributed continuous variables between groups; the Mann-Whitney U-test was used to compare non-normally distributed continuous variables between groups; and Fisher’s exact test or Cochran-Mantel-Haenszel test for trend was used to compare proportions between groups. Multiple logistic regression models were used to calculate adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). A P value less than 0.05 was considered statistically significant. All analyses were performed by a biomedical statistician (Yokoyama T) using the SAS statistical package (version 9.4; SAS Institute, Cary, NC United States).

**RESULTS**
LC without EVs was diagnosed in 152 subjects, LC with EVs in 174 subjects, and EVs without LC in 6 subjects. The EVs were classified as F1 in 92 subjects, F2 or F3 in 41 subjects, RC-sign-positive in 21 subjects, and post-treatment in 26 subjects, 17 of whom were reported to have been treated for variceal rupture. All of the EVs in the subjects without LC were classified as F1. Table 1 shows the background factors of the 1614
Subjects according to whether they had EVs. There were no significant differences between the group with EVs and the group without EVs in age, usual alcohol consumption, smoking, hepatitis C and B infection status, or ALDH2 and ADH1B genotypes. LC, gastric varices, and higher grade PHG were more common in the group with EVs than in the group without EVs ($P < 0.0001$). Most of the gastric varices in the group without EVs were found in the fornix alone, and gastric varices located in the cardia or cardia plus fornix predominated in the group with EVs.

CLE $\geq 5$ mm was found in 355 (22.0\%) of the subjects (5-9 mm, 13.6\%; 10-29 mm, 8.1\%; and $\geq 30$ mm, 0.4\%; Table 2). When advanced forms of EVs were defined as F2 - F3 varices, RC-sign-positive varices, and post-treatment varices, the proportion of subjects with CLE $\geq 5$ mm decreased in the following order ($P < 0.0001$): 23.3\% in the group without EVs, 17.4\% in the group with F1 varices, and 5.7\% in the group with advanced varices, and the findings were similar in the subgroup of subjects with LC ($P = 0.0004$). The incidence of CLE $\geq 5$ mm in the group of subjects with advanced EVs did not differ significantly according to whether they had or had not received endoscopic treatment (7.7\% and 4.8\%, respectively, $P = 0.63$). The proportions with a hiatal hernia $\geq 10$ mm (24.4\%, 20.7\%, and 13.6\%, respectively) decreased in the same order as the order in which the proportions of subjects with CLE $\geq 5$ mm decreased ($P = 0.017$), but the trend was not significant in the subgroup of subjects with LC.

Table 1  Background of the Japanese alcoholic men with and without esophageal varices n (%)  

| Esophageal varices       | Absent | Present | $P$ value |
|-------------------------|--------|---------|-----------|
| n                       | 1434   | 180     |           |
| Age (yr) mean ± SE      | 55.8 ± 0.3 | 54.4 ± 0.7 | 0.079    |
| Alcohol consumption (g ethanol/d) mean ± SE | 121 ± 2 | 133 ± 7 | 0.066 |
| Ever smoker             | 1310 (91.4) | 159 (88.3) | 0.21    |
| Liver cirrhosis Absent  | 1282 (89.4) | 6 (3.3) |         |
| Present                 | 152 (10.6) | 174 (96.7) | < 0.0001|
| GC/Vs                   | 1418 (98.9) | 147 (81.7) |         |
| Cardia, cardia/fornix   | 2 (0.1) | 23 (12.8) |         |
| Fornix                  | 14 (1.0) | 10 (5.6) | < 0.0001|
| Portal hypertensive gastropathy | 1432 | 179 |         |
| Absence                 | 1172 (81.8) | 59 (33.0) |         |
| Grade 1                 | 191 (13.3) | 80 (44.7) |         |
| Grade 2                 | 53 (3.7) | 25 (14.0) |         |
| Grade 3                 | 16 (1.1) | 15 (8.4) | < 0.0001|
| Anti-HCV antibody positive | 69 (4.8) | 13 (7.2) | 0.20    |
| HBs antigen positive    | 17 (1.2) | 4 (2.2) | 0.28    |
| ALDH2 genotype          |        |         |           |
| *1/*1                   | 1216 (84.8) | 161 (89.4) |         |
| *1/*2                   | 218 (15.2) | 19 (10.6) |         |
| *2/*2                   | 0 (0.0) | 0 (0.0) | 0.12    |
| ADH1B genotype          |        |         |           |
| *1/*1                   | 406 (28.3) | 41 (22.8) |         |
| *1/*2                   | 470 (32.8) | 69 (38.3) |         |
| *2/*2                   | 558 (38.9) | 70 (38.9) | 0.20    |

ADH1B: Alcohol dehydrogenase-1B; ALDH2: Aldehyde dehydrogenase-2; $P$ values were calculated by Student's $t$-test for mean values, and Fisher's exact test for percent data.
Table 3 shows the background factors of the 1614 subjects according to whether they had CLE $\geq 5$ mm, and there were no significant differences between the two groups in age, usual alcohol consumption, smoking, or ALDH2 and ADH1B genotypes. Hiatal hernia was more common in the group with CLE $\geq 5$ mm than in the other group (45.9% vs 17.3%, $P < 0.0001$). There was a significant difference between the group with CLE $\geq 5$ mm and the group without CLE $\geq 5$ mm in the proportions of 'no LC and no EVs' subjects, 'LC and no EVs' subjects, and the 'EVs' subjects they contained ($P = 0.001$). There were no significant difference between the group with CLE $\geq 5$ mm and group without CLE $\geq 5$ mm in the presence of gastric varices or the grade of PHG.

A multiple logistic regression analysis to predict the presence of CLE $\geq 5$ mm showed that the ORs (95%CI) for CLE $\geq 5$ mm increased with age per +10 years [1.15 (1.00-1.32)] and with the presence of hiatal hernia $\geq 10$ mm [4.33 (3.31-5.67)] and decreased with the presence of EVs [0.47 (0.26-0.87); Table 4]. The presence of LC, presence of gastric varices, and grade of PHG were not associated with the presence of CLE $\geq 5$ mm.

Table 5 shows the background factors of the 326 subjects with LC according to whether they had EVs, and there were no significant differences between the two groups in age, usual alcohol consumption, smoking, hepatitis C and B infection status, or ALDH2 and ADH1B genotypes. The absence of CLE $\geq 5$ mm ($P = 0.003$), presence of gastric varices ($P < 0.0001$), and higher grade PHG ($P < 0.0001$) were all more common in the LC group with EVs than in the LC group without EVs. Advanced Child-Pugh class ($P = 0.011$) was more common in the LC group with advanced EVs.

A multiple logistic regression analysis showed

| Table 2  | Columnar-lined esophagus and hiatal hernia and the degree of esophageal varices $n$ (%) |
|----------|--------------------------------------------------------------------------------------------|
|          | Esophageal varices | Absent | F1 varices | Advanced varices | $P$ value |
|----------|-------------------|--------|------------|-----------------|-----------|
|          |                   | n      | n          | n               |           |
| Columnar-lined esophagus |                    |        |            |                 |           |
| 0-4 mm | 1100 (76.7)       | 76 (82.6) | 83 (94.3)  |                 |           |
| $\geq 5$ mm | 334 (23.3) | 16 (17.4) | 5 (5.7)    | $< 0.0001$    |           |
| 5-9 mm  | 208 (14.5)        | 8 (8.7) | 3 (3.4)    |                 |           |
| 10-29 mm | 120 (8.4) | 8 (8.7) | 2 (2.3)    |                 |           |
| $\geq 30$ mm | 6 (0.4) | 0 (0.0) | 0 (0.0)    |                 |           |
| Hiatal hernia $\geq 10$ mm |                    |        |            |                 |           |
| Absent | 1084 (75.6)       | 73 (79.3) | 76 (86.4)  |                 |           |
| Present | 350 (24.4) | 19 (20.7) | 12 (13.6)  | 0.017          |           |
| Number of patients with liver cirrhosis |                    |        |            |                 |           |
| Columnar-lined esophagus |                    |        |            |                 |           |
| 0-4 mm | 117 (77.0) | 73 (84.9) | 83 (94.3)  |                 |           |
| $\geq 5$ mm | 35 (23.0) | 13 (15.1) | 5 (5.7)    | 0.0004         |           |
| 5-9 mm  | 22 (14.5)        | 8 (9.3) | 3 (3.4)    |                 |           |
| 10-29 mm | 12 (7.9) | 5 (5.8) | 2 (2.3)    |                 |           |
| $\geq 30$ mm | 1 (0.7) | 0 (0.0) | 0 (0.0)    |                 |           |
| Hiatal hernia $\geq 10$ mm |                    |        |            |                 |           |
| Absent | 124 (81.6)       | 71 (82.6) | 76 (86.4)  |                 |           |
| Present | 28 (18.4) | 15 (17.4) | 12 (13.6)  | 0.36           |           |

Advanced varices: F2-F3 varices, red-color-sign positive varices, or post-treatment varices. $P$ values are for trend calculated by the Cochran-Mantel-Haenszel test.

Figure 2  Portal hypertensive gastropathy lesions exhibiting a snake-skin (mosaic) pattern in their background mucosa. A: Grade 1, erythematous flecks or maculae; B: Grade 2, red spots or diffuse redness; C: Grade 3, intramucosal or luminal hemorrhage.
that the ORs (95%CI) for EVs and advanced EVs in the subgroup of subjects with LC decreased with the presence of CLE $\geq$ 5 mm [0.46 (0.23-0.93) and 0.24 (0.08-0.74), respectively, vs CLE 0-4 mm; Table 6]. Child-Pugh class was not associated with EV status. The ORs for EVs and advanced EVs increased with progression of the grade of PHG, and the OR for advanced EVs increased with the presence of gastric varices.

**DISCUSSION**

The analysis of the results of endoscopic screening of 1614 Japanese alcoholic men in this study demonstrated that the presence of CLE was negatively associated with the presence of EVs, and even more negatively associated with the presence of advanced forms of EVs. The prevalence of CLE $\geq$ 30 mm has been reported to be very low (0.0%-0.2%) in Asians[8,25-27]. The prevalence of CLE $\geq$ 30 mm in the present study was 0.4%, and most of the CLE was short-segmental. The presence of a hiatal hernia was a strong determinant of the presence of CLE in this study, a finding that was consistent with the results of previous studies[5,7,8,26,28], suggesting that GERD in patients with a hiatal hernia contributes to the development of CLE. Asian studies have demonstrated positive associations between excessive alcohol consumption and both GERD and short-segmental CLE[4-8,26]. The prevalence of CLE $\geq$ 10 mm has been reported to be 1.8% in unselected Taiwanese, 4.0% in symptomatic Koreans[27], and 5.3% in a group of Japanese who underwent an endoscopic examination in a university hospital[8]. Thus, the high prevalence (8.1%) of CLE $\geq$ 10 mm in the population of alcoholics in our study was at least in part attributable to chronic heavy drinking.

As expected, the presence of EVs was positively associated with the presence of LC, gastric varices, and PHG. However, these factors were not associated with the presence of CLE, and adjustment for these factors revealed a negative association between the presence of CLE and the presence and severity of EVs. These findings taken together suggested a special relationship between CLE and EVs in the presence of LC and portal hypertension.

In the majority of LC patients the left gastric vein is the afferent vein to the EVs[29], and the first resistance vessels to the EVs are the mucosal palisade vessels and submucosal veins at the lower end of the
esophagus, where there are many palisade vessels and few submucosal veins\textsuperscript{[12,13]}. The palisade vessels penetrate the muscularis mucosae and connect to the submucosal veins 3-5 cm above the esophagogastric junction, the critical area for EV rupture\textsuperscript{[12,30,31]}. Greatly enlarged palisade vessels disrupt the muscularis mucosae and form EVs across the proper mucosae and the submucosa\textsuperscript{[13]}, and they cause advanced EVs by

| Table 4  Multivariate analyses to predict the presence of columnar-lined esophagus in Japanese alcoholic men |
|-----------------|-----------------|-----------------|-----------------|
| Independent variables | OR | 95%CI | P value |
|-----------------|-----------------|-----------------|-----------------|
| Age, per +10 yr | 1.15 | (1.00-1.32) | 0.043 |
| Usual alcohol consumption, per +22 g ethanol | 0.99 | (0.96-1.03) | 0.75 |
| Ever smoker vs never smoker | 0.75 | (0.49-1.14) | 0.17 |
| Hiatal hernia ≥ 10 mm, presence vs absence | 4.33 | (3.31-5.67) | < 0.0001 |
| Liver cirrhosis, presence vs absence | 1.04 | (0.68-1.60) | 0.86 |
| Esophageal varices, presence vs absence | 0.47 | (0.26-0.87) | 0.015 |
| Gastric varices, presence vs absence | 0.59 | (0.21-1.64) | 0.31 |
| Portal hypertensive gastropathy | | | |
| Absent | 1.00 | Referent | |
| Grade 1 | 1.23 | (0.86-1.78) | 0.26 |
| Grade 2,3 | 0.91 | (0.52-1.60) | 0.74 |
| Anti-HCV antibody, positive vs, negative | 0.93 | (0.53-1.66) | 0.81 |
| HBs antigen, positive vs, negative | 0.56 | (0.13-2.47) | 0.44 |
| ALDH2 genotype, *1/*1 vs *1/*2 | 0.94 | (0.67-1.33) | 0.73 |
| ADH1B genotype, *2 carrier vs *1/*1 | 0.97 | (0.73-1.28) | 0.81 |

ADH1B: Alcohol dehydrogenase-1B; ALDH2: Aldehyde dehydrogenase-2; OR: Multivariate odds ratio; CI: Confidence interval; CLE: Columnar-lined esophagus. ORs and CIs were calculated by using a multiple logistic regression model.

| Table 5  Background of the Japanese alcoholic men with liver cirrhosis according to whether they had esophageal varices | |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Esophageal varices | Absent | All forms | P value | Advanced forms | P value |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| n | 152 | 174 | 88 | 152 | 174 | 88 |
| Age (yr) | | | | | | |
| mean ± SE | 55.9 ± 0.7 | 54.5 ± 0.7 | 0.16 | 54.3 ± 1.0 | 0.21 |
| Alcohol consumption (g ethanol/d) | | | | | | |
| mean ± SE | 124 ± 7 | 133 ± 7 | 0.37 | 142 ± 11 | 0.18 |
| Ever smoker | 132 (86.8) | 155 (89.1) | 0.61 | 83 (94.3) | 0.081 |
| Columnar-lined esophagus ≥ 5 mm | 35 (23.0) | 18 (10.3) | 0.003 | 5 (5.7) | 0.0005 |
| Hiatal hernia ≥ 10 mm | 28 (18.4) | 27 (15.5) | 0.55 | 12 (13.6) | 0.37 |
| Child-Pugh class | | | | | | |
| A | 93 (61.2) | 88 (50.6) | 41 (46.6) | 0.011 |
| B | 50 (32.9) | 64 (36.8) | 32 (36.4) | 0.01 |
| C | 9 (5.9) | 22 (12.6) | 0.053 | 15 (17.0) | 0.011 |
| Gastric varices | | | | | | |
| Absent | 137 (90.1) | 141 (81.0) | 65 (73.9) | 0.011 |
| Cardia, cardia and fornix | 2 (1.3) | 2 (1.3) | 17 (19.3) | 0.011 |
| Fornix | 13 (8.6) | 10 (5.7) | < 0.0001 | 6 (6.8%) | < 0.0001 |
| Portal hypertensive gastropathy | | | | | | |
| Absent | 88 (58.3) | 55 (31.8) | 27 (30.7) | 0.0001 |
| Grade 1 | 50 (33.1) | 78 (45.1) | 39 (44.3) | 0.0001 |
| Grade 2 | 10 (6.6) | 25 (14.5) | 12 (11.4) | 0.0001 |
| Grade 3 | 3 (2.0) | 15 (8.7) | < 0.0001 | 15 (8.4) | < 0.0001 |
| Anti-HCV antibody positive | 8 (5.3) | 13 (7.5) | 0.50 | 8 (9.1) | 0.29 |
| HBs antigen positive | 4 (2.6) | 4 (2.3) | 1.00 | 1 (1.1) | 0.65 |
| ALDH2 genotype | | | | | | |
| *1/*1 | 134 (88.2) | 156 (89.7) | 77 (87.5) | 0.0001 |
| *1/*2 | 18 (11.8) | 18 (10.3) | 11 (12.5) | 0.0001 |
| *2/*2 | 0 (0.0) | 0 (0.0) | 0.72 | 0 (0.0) | 1.00 |
| ADH1B genotype | | | | | | |
| *1/*1 | 32 (21.1) | 36 (20.7) | 15 (17.0) | 0.0001 |
| *1/*2 | 51 (33.6) | 68 (39.1) | 37 (42.0) | 0.0001 |
| *2/*2 | 69 (45.4) | 70 (40.2) | 0.55 | 36 (40.9) | 0.41 |

\textsuperscript{1}Advanced forms of EVs vs no EVs. ADH1B: Alcohol dehydrogenase-1B; ALDH2: Aldehyde dehydrogenase-2; EVs: Esophageal varices; P values were calculated by Student's t-test for mean values, and Fisher's exact test for percent data.
connecting with submucosal veins or sub- and intra-epithelial channels accompanied by ‘varices on varices’ and positive RC signs\textsuperscript{[12,13,32]}. Although there is no difference between the maximal size of the palisade vessels in the CLE and normal lower esophagus\textsuperscript{[11]}, it is conceivable that the development of CLE may change the microenvironment of the interstitium around the palisade vessels, e.g., increased interstitial fibrosis and the formation of the shallow muscularis mucosae of a double muscularis mucosae. A double muscularis mucosae was seen in 71% of the specimens obtained by endoscopic resection of a CLE\textsuperscript{[11]}. The double muscularis mucosae in CLE divides the proper mucosae into two restricted compartments, and may increase the resistance to enlargement of palisade vessels and prevent the vessels from communicating with the submucosal vessels or sub- and intra-epithelial channels\textsuperscript{[12,32]}, thereby inhibiting the development of enlarged EVs and RC signs. Scars secondary to endoscopic ligation or sclerotherapy were present in some of the LC subjects with post-treatment varices and their presence may have influenced the development of CLE. However, the incidence of CLE in the LC group did not differ significantly according to whether there was a history of endoscopic treatment.

The presence of the \textit{ADH1B*2} allele in Japanese alcoholics has been demonstrated to be positively associated with the presence of advanced liver disease and the progression of Child-Pugh class\textsuperscript{[17-19]}, but the results of the present study showed no significant associations between the genetic polymorphism and the presence of EVs. The effect of the \textit{ADH1B*2} allele on EVs was probably eclipsed, because 46.6% of the LC subjects lacked EVs.

Our study had several potential limitations. The first potential limitation was that it was a cross-sectional study based on the results of the endoscopic screening, and the progression of CLE and EVs was not evaluated directly. Identification of a causal relationship between these endoscopic findings would require longitudinal follow-up examinations. The second potential limitation was that we evaluated the degree of CLE by retrospectively reviewing the endoscopic images, however, the review was performed jointly by four expert endoscopists. Pathological studies of autopsied cirrhotic subjects are warranted to clarify the pathological background underlying the negative association between the presence of CEL and the presence of EVs. We did not observe any effects of alcohol consumption during the preceding year on the presence of CLE or EVs, but that may have been because of the homogeneity of the study population in terms of their extremely high alcohol consumption. Generalization of the results obtained in our study based on investigations of alcoholic men treated in the Center requires confirmation in various drinking populations, including in a population with mild alcoholism.

\textit{Helicobacter pylori} infection and chronic atrophic gastritis protect against the development of GERD and CLE\textsuperscript{[5,6,33]}\textsuperscript{,} if the observed associations between CLE and EVs and advanced EVs reflect causal relationships, the current trend toward lower \textit{Helicobacter pylori} infection rates in Japan may result in lower EV rates and advanced EV rates in the future, and examination for CLE may benefit alcoholics with advanced liver disease by identifying their risk for the development or  

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**Table 6  Multivariate analyses to predict the presence of esophageal varices in Japanese alcoholic men with liver cirrhosis**

| Independent variables | All forms of EVs | Advanced forms of EVs |
|-----------------------|------------------|-----------------------|
|                       | OR (95%CI)       | P value               | OR (95%CI)       | P value               |
| Age, per +10 yr       | 0.88 (0.67-1.16) | 0.35                  | 0.90 (0.64-1.26) | 0.55                  |
| Usual alcohol consumption, per +22 g ethanol | 1.00 (0.94-1.06) | 0.97                  | 1.02 (0.95-1.10) | 0.52                  |
| Ever smoker vs never smoker | 1.04 (0.59-2.16) | 0.93                  | 2.13 (1.09-4.57) | 0.19                  |
| Columnar-lined esophagus,  \( \geq 5 \text{ mm} \) vs 0-4 mm | 0.46 (0.23-0.93) | 0.030                 | 0.24 (0.08-0.74)  | 0.013                 |
| Hiatal hernia  \( \geq 10 \text{ mm} \), presence vs absence | 1.10 (0.54-2.21) | 0.80                  | 0.97 (0.38-2.49)  | 0.95                  |
| Child-Pugh class      |                  |                       |                      |                       |
| A                     | 1.00 Referent    |                       | 1.00 Referent        |                       |
| B                     | 1.18 (0.70-1.98) | 0.53                  | 1.06 (0.55-2.03)    | 0.87                  |
| C                     | 1.56 (0.64-3.82) | 0.33                  | 1.85 (0.67-5.16)    | 0.24                  |
| Gastric varices, presence vs absence | 1.94 (0.96-3.91) | 0.065                 | 2.89 (1.29-6.47)    | 0.010                 |
| Portal hypertensive gastropathy | 1.00 Referent                      |                       |                      |                       |
| Absent                |                  |                       |                      |                       |
| Grade 1               | 2.24 (1.32-3.80) | 0.003                 | 1.92 (0.97-3.77)    | 0.060                 |
| Grade 2.3             | 4.40 (2.11-9.15) | <0.0001               | 5.29 (2.18-12.81)   | 0.0002                |
| Anti-HCV antibody, positive vs negative | 1.09 (0.41-2.93) | 0.87                  | 1.54 (0.49-4.88)    | 0.46                  |
| HBs antigen, positive vs negative | 1.16 (0.26-5.16) | 0.85                  | 0.61 (0.06-6.36)    | 0.68                  |
| \textit{ADH1B} genotype, *1/*1 vs *1/*2 | 1.02 (0.47-2.30) | 0.96                  | 1.00 (0.38-2.60)    | 1.00                  |
| \textit{ADH1B} genotype, *2 carrier vs *1/*1 | 1.10 (0.61-1.99) | 0.76                  | 1.59 (0.72-3.51)    | 0.25                  |

\textsuperscript{1}Advanced forms of EVs vs no EVs, EVs: Esophageal varices; \textit{ADH1B}: Alcohol dehydrogenase-1B; \textit{ALDH2}: Aldehyde dehydrogenase-2; OR: Multivariate odds ratio; ORs and CIs were calculated by using a multiple logistic regression model; Advanced forms of EVs were F2-F3 varices, red-color-sign positive varices, or post-treatment varices.
progression of EVs.

In conclusion, this cross-sectional observational study revealed a negative association between the presence of CLE and the presence of EVs in Japanese alcoholic men. Further studies should be conducted prospectively in a longitudinal fashion to confirm this finding.

ARTICLE HIGHLIGHTS

Research background
Esophageal varices (EVs) develop as a result of portal hypertension, which is mainly due to liver cirrhosis (LC) in alcoholics. Excessive alcohol consumption has been reported to be associated with the presence of a short-segmental circumferential-lined esophagus (CLE) in East-Asian studies. It has not been evaluated whether associations exist between the presence of EVs and the presence of CLE in alcoholics.

Research motivation
Our empirical impression based on the results of endoscopic screening examinations of Japanese alcoholic men is that EVs are less common among men with short-segmental CLE. The development of CLE is accompanied by several histological changes around the palisade vessels at the lower end of the esophagus. Some of the histological changes accompanying the development of CLE may protect against the development of EVs.

Research objectives
To determine whether and to what extent associations exist between the presence of EVs and the presence of CLE in Japanese alcoholic men based on the results of endoscopic screening examinations.

Research methods
The subjects were 1614 Japanese alcohol-dependent men (≥ 40 years of age) who had undergone upper gastrointestinal endoscopic screening. Digitalized records of high-quality endoscopic images that included the squamocolumnar junction and esophagogastric junction were retrospectively jointly reviewed by four expert endoscopists for the purpose of diagnosing CLE. The authors investigated whether and to what extent there were associations between the presence of CLE and the presence of EVs, especially in the group with LC.

Research results
CLE ≥ 5 mm in length was found in 355 subjects, LC without EVs in 152 subjects, LC with EVs in 174 subjects, and EVs without LC in 6 subjects. The incidence of CLE ≥ 5 mm decreased in the following order (P < 0.0001): 23.3% in the group with EVs, 17.4% in the group with small and straight EVs, and 5.7% in the group with LC without EVs [0.46 (0.23-0.93) vs 0.24 (0.08-0.74), respectively, vs 0.4 mm CLE]. To clarify the pathological backgrounds of the negative association between the presence of CLE and the presence of EVs, the further pathological studies of autopspied citholic subjects may be warranted.

Research conclusions
The presence of CLE was negatively associated with the presence of EVs, and even more negatively associated with the presence of advanced forms of EVs. Since the first resistance vessels to EVs are the mucosal palisade vessels and submucosal veins at the lower end of the esophagus, the development of CLE may impede the development of EVs. Helicobacter pylori infection and chronic atrophic gastritis protect against the development of GERD and CLE. If the observed associations between CLE and EVs and advanced EVs reflected causal relationships, the current trend toward lower Helicobacter pylori infection rates in Japan may influence EV rates and advanced EV rates in the future, and examination for CLE may benefit alcoholics with advanced liver disease by identifying their risk for the development or progression of EVs. The further studies should be conducted prospectively in the longitudinal fashion to test this finding.

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