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# Outcomes and Recurrence Rate of Esophageal Varices after Endoscopic Treatment in Patients with Alcoholic Cirrhosis and Viral Cirrhosis

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**Background:** The incidence of alcoholic liver cirrhosis (ALC) is increasing. However, few reports have focused on ALC-derived esophageal varices (EV). We retrospectively examined differences in overall survival (OS) and EV recurrence rate in patients after endoscopic injection sclerotherapy (EIS) for ALC and hepatic B/C virus liver cirrhosis (B/C-LC).

**Methods:** We analyzed data from 215 patients (B/C-LC, 147; ALC, 68) who underwent EIS. The primary endpoints were OS and EV recurrence in patients with unsuccessful abstinence ALC and those with uncontrolled B/C-LC, before and after propensity score matching (PSM) to unify the patients' background. The secondary endpoints were predictors associated with these factors, as determined by multivariate analysis.

**Results:** The observation period was 1,430 ± 1,363 days. In the analysis of all patients, OS was significantly higher in the ALC group than in the B/C-LC group ($p = 0.039$); however, there was no difference in EV recurrence rate ($p = 0.502$). Ascites and history of hepatocellular carcinoma (HCC) ($p = 0.019$ and $p < 0.001$, respectively) predicted OS, whereas age and EV size predicted recurrence ($p = 0.011$ and 0.024, respectively). In total, 96 patients without an HCC history were matched by PSM, and there was no significant difference in OS or EV recurrence rate ($p = 0.508$ and 0.246, respectively).

**Conclusion:** When limited to patients without a history of HCC, OS and the EV recurrence rate were comparable in patients with ALC who continued to consume alcohol and those with B/C-LC without viral control. (J Nippon Med Sch 2024; 91: 180–189)

**Key words:** alcoholic liver cirrhosis, esophageal varices, hepatocellular carcinoma, endoscopic injection sclerotherapy, overall survival

## Introduction

Direct-acting antivirals against hepatitis C virus (HCV) are reported to be highly effective[1,2]. Although cases of HCV-related liver cirrhosis (LC) have decreased, worldwide rates of alcoholic hepatitis (ASH) and non-alcoholic fatty liver disease are rapidly increasing with the occurrence of various stressors[3]. Of particular concern is the rapid increase in portal venous pressure seen in ASH, which often causes fatal bleeding from esophagogastric varices (EGV)[4]. An analysis of data from the national rehospitalization database in the United States found that the incidence of bleeding from esophageal varices (EV) associated with alcoholic LC (ALC) is increasing every year[5]. However, EGV bleeding even can recur after treatment, as patients find abstaining from alcohol and adhering to a healthier diet difficult because of mental health challenges such as stress. We previously reported that between 2014 and 2020 the 1-year and 3-year cumulative EV recurrence rates after endoscopic injection sclerotherapy (EIS) were extremely high (48.2% and 73.1%)[6]. Because EGV continue to recur in the presence of LC, a radical treatment such as liver transplantation may be

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the only option. However, in Japan, opportunities for liver transplantation are limited because of the small number of donors. An alternative endoscopic treatment that is designed to decrease EGV recurrence by using an image-enhanced function has been developed[7,8]. The rapid increase in ALC is a serious problem in Japan. Therefore, clarifying the characteristics of EV recurrence and outcomes in patients with ALC is necessary. One study reported that survival of ALC patients at 1 year after the occurrence of EV was worse than that of patients without ALC[9]. A study of 273 cases of EV bleeding found that bleeding episodes were more frequent in patients with ALC (51.28%) than in those with B virus cirrhosis (7.69%) or C virus cirrhosis (25.27%)[10]. These findings suggest that patients with EV who develop ALC may have a worse prognosis and recurrence rate than patients with viral cirrhosis. Because no studies have focused on these factors, we retrospectively investigated differences in survival and EV recurrence rate after EIS in patients with ALC and hepatic B/C virus-related LC (B/C-LC).

## Patients and Methods

### Study Design

The primary endpoints of this retrospective study were overall survival (OS) and EV recurrence in patients with unsuccessful abstinence ALC and those with uncontrolled B/C-LC, before and after propensity score matching to unify patient background factors. The secondary endpoints were factors that predicted OS, liver-related death, and EV recurrence in multivariate analysis.

The study protocol was approved by the Clinical Research Ethics Committee of Tokyo Women's Medical University (study approval no. 2022-0050) and conforms to the principles of the Declaration of Helsinki. As the opt-out, a public announcement of this study was posted at our hospital before starting the research.

### Patient Selection

The inclusion criteria were as follows: (1) age >20 years; (2) EIS treatment between January 2001 and March 2016; (3) ALC with unsuccessful abstinence; (4) hepatic B virus-related or HCV-related LC in which viral control was impossible; and (5) patients with high-risk EV (F2, F3, or any form that is red color sign [RCS]-positive) who were treated with EIS. The exclusion criteria were as follows: (1) emergency cases with EV rupture; (2) presence of gastric varices (Lg-cf and Lg-f); (3) incidence of portal vein tumor thrombosis; (4) presence of portal vein thrombosis >10% of the lumen; (5) elevated bilirubin level (>5 mg/dL); (6) uncontrolled hepatocellular carcinoma (HCC); (7) treatment with hypotensive medication, and (8) overlapping ALC and B/C-LC. Diagnosis of ALC was based on a self-reported past or current history of alcohol misuse (>60 g/day) in the absence of other causes of liver insult such as viral or autoimmune hepatitis, Wilson's disease, and idiopathic portal hypertension. The reasons for the above exclusions are as follows. Emergency EV rupture is associated with poor liver function. Isolated gastric varices were treated with n-butyl-2-cyanoacrylate injection or balloon-occluded retrograde transvenous obliteration, and the recurrence rate is thought differ from that for EV. The rate of EV recurrence for patients with portal vein tumor thrombosis and portal venous thrombosis is higher than that for patients without these complications. OS and the EV recurrence rate are worse for patients with liver failure and uncontrolled HCC than for those without these conditions.

This study included 339 patients with high-risk EV. Patients with emergency bleeding (44 patients), high bilirubin levels (4 patients), and uncontrolled HCC (25 patients), and those receiving antihypertensive medication (20 patients) and those with overlapping ALC and B/C-LC (31 patients) were excluded. Cases of isolated gastric varices were not included. Data from the remaining 215 patients (B/C-LC group, 147 patients; ALC group, 68 patients) who met the inclusion criteria were analyzed (**Table 1**, **Fig. 1**). When evaluating OS, we performed a supplementary analysis that excluded patients with a treatment history of HCC (73 patients), to account for bleeding-related deaths, including death due to hepatic failure (B/C-LC group, 84 patients; ALC group, 58 patients; **Table 1**).

For these 142 patients, propensity score matching was performed using the SPSS 28.0.1 software (SPSS Inc. Chicago, IL, USA) to unify the following background factors in both groups: age, presence of ascites, hemoglobin level, platelet count, number of endoscopic treatment sessions, and liver function values (aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, ammonia, prothrombin time-international normalized ratio, and Child-Pugh score).

### Endoscopic Devices

The endoscopes used were the GIF-Q240, Q260, H260, and HQ290 (Olympus Medical Systems, Japan). The EVIS 240 and LUCERA series were used as the light-source devices (Olympus Medical Systems, Japan). Endoscopic findings of EV (L: location, F: form, and C: color) and RCS were classified according to the general rules for EV in Japan[11].

Table 1 Comparison between viral and alcoholic cirrhosis patients

| | All patients | | | Without HCC history | | |
|---|---|---|---|---|---|---|
| | B/C-LC (n=147) | ALC (n=68) | p value | B/C-LC (n=84) | ALC (n=58) | p value |
| Age, yrs (±SD) | 65.1±10.2 | 61.0±12.7 | 0.014 | 63.4±10.9 | 60.0±12.8 | 0.092 |
| Men, n (%) | 97 (66.0) | 60 (88.2) | 0.001 | 55 (65.4) | 50 (86.2) | 0.006 |
| Virus (HBV/HCV) | 26/121 | N/A | N/A | | N/A | N/A |
| Ascites (presence/absence) | 52/95 | 22/46 | 0.665 | 30/54 | 17/41 | 0.425 |
| History of HCC (presence/absence) | 63/84 | 10/58 | <0.001 | 0/84 | 0/58 | 1.000 |
| Previous history of EVs treatment (presence/absence) | 5/142 | 1/67 | 0.424 | 1/83 | 1/57 | 0.791 |
| Esophageal varices classification | | | | | | |
| Ls/Lm/Li | 53/66/28 | 26/25/17 | 0.455 | 31/35/18 | 22/20/16 | 0.603 |
| F0/F1/F2/F3 | 6/41/84/16 | 1/17/40/10 | 0.637 | 1/22/50/11 | 1/15/34/8 | 0.993 |
| Cw/Cb | 0/147 | 0/68 | 1.000 | 0/84 | 0/58 | 1.000 |
| RC0/RC1/RC2/RC3 | 3/106/31/7 | 0/45/16/7 | 0.269 | 0/58/20/6 | 0/40/11/7 | 0.528 |
| Observation period (days) | 1,461±1,373 | 1,364±1,347 | 0.629 | 1,790±1,451 | 1,414±1,398 | 0.125 |
| Endoscopic treatment session | 3.5±1.2 | 3.6±1.2 | 0.412 | 3.6±1.3 | 3.6±1.2 | 0.974 |
| EIS | 2.9±1.1 | 2.8±1.2 | 0.709 | 2.9±1.2 | 2.8±1.2 | 0.808 |
| EVL | 0.2±0.4 | 0.3±0.5 | 0.187 | 0.2±0.4 | 0.2±0.5 | 0.487 |
| APC | 0.5±0.5 | 0.6±0.5 | 0.087 | 0.5±0.5 | 0.6±0.5 | 0.962 |
| Hemoglobin (g/dL) | 11.8±2.2 | 11.1±2.6 | 0.033 | 11.8±2.2 | 11.0±2.5 | 0.035 |
| Platelet ($\times 10^4/\mu L$) | 8.2±3.6 | 10.6±4.9 | 0.001 | 8.0±3.9 | 10.0±4.3 | 0.005 |
| PT-INR | 1.1±0.1 | 1.2±0.2 | 0.204 | 1.2±0.1 | 1.2±0.2 | 0.452 |
| AST (U/L) | 57.9±31.0 | 74.9±212.7 | 0.513 | 56.5±32.5 | 75.4±227.0 | 0.454 |
| ALT (U/L) | 42.6±30.2 | 31.5±34.3 | 0.017 | 41.2±32.4 | 32.3±36.9 | 0.131 |
| Total bilirubin (mg/dL) | 1.4±0.6 | 1.5±0.8 | 0.472 | 1.4±0.6 | 1.5±0.9 | 0.310 |
| Albumin (g/dL) | 3.3±0.6 | 3.3±0.7 | 0.554 | 3.3±0.6 | 3.3±0.6 | 0.402 |
| Ammonia (μg/dL) | 85.3±44.7 | 87.0±35.0 | 0.777 | 88.5±43.5 | 86.6±35.4 | 0.787 |
| Child-Pugh score | 6.1±1.0 | 6.2±1.3 | 0.639 | 6.2±1.1 | 6.2±1.3 | 0.982 |
| Prognosis (living/deceased) | 104/43 | 59/9 | 0.011 | 68/16 | 51/7 | 0.267 |
| Cause of death (HCC/EVs bleeding/ hepatic failure/other) | 27/1/7/8 | 2/1/3/3 | 0.134 | 0/1/7/8 | 0/1/3/3 | 0.813 |
| EVs recurrence (presence/absence) | 65/82 | 25/43 | 0.303 | 36/48 | 23/35 | 0.704 |
| Adverse events, n (%) | | | | | | |
| Abdominal pain | 78 (53.1) | 27 (39.7) | 0.062 | 46 (54.8) | 22 (37.9) | 0.041 |
| Hypertension | 97 (66.0) | 51 (75.0) | 0.185 | 57 (67.9) | 44 (75.9) | 0.301 |
| Hematuria | 23 (15.6) | 10 (14.7) | 0.859 | 14 (16.7) | 7 (12.1) | 0.448 |
| Esophageal stenosis | 3 (2.0) | 2 (2.9) | 0.684 | 3 (3.6) | 1 (1.7) | 0.513 |
| Pleural effusion | 3 (2.0) | 2 (2.9) | 0.684 | 2 (2.4) | 1 (1.7) | 0.789 |
| Ascites | 6 (4.1) | 3 (4.4) | 0.911 | 3 (3.6) | 2 (3.4) | 0.969 |
| Portal venous thrombosis | 1 (0.7) | 0 (0.0) | 0.495 | 0 (0.0) | 0 (0.0) | 1.000 |
| Oxygen desaturation | 7 (4.8) | 9 (13.2) | 0.028 | 4 (4.8) | 7 (12.1) | 0.109 |

Data are expressed as mean±standard deviation (SD). The Student t-test was used to compare continuous values. Categorical variables were evaluated by the chi-square test. A p-value of less than 0.05 was considered to indicate a significant difference between groups.

B/C-LC, hepatic B/C virus related liver cirrhosis; ALC, alcoholic liver cirrhosis; yrs, years; n, number; HBV, hepatic B virus; HCV, hepatic C virus; HCC, hepatocellular carcinoma; EVs, esophageal varices; Ls, locus superior; Lm, locus medialis; Li, locus inferior; F1, straight, small-caliber varices; F2, moderately enlarged, beady varices; F3, markedly enlarged, nodular or tumor-shaped varices; Cw, white varices; Cb, blue varices; RC0, absent; RC1, small in number and localized; RC2, intermediate between RC1 and RC3; RC3, large in number and circumferential; EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; APC, argon plasma coagulation; PT-INR, prothrombin time-international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase

**Endoscopic Treatment Protocol**

The EIS procedures were performed by 17 endoscopists with more than 8 years of experience each. The EIS puncture was performed several times with a 23-gauge

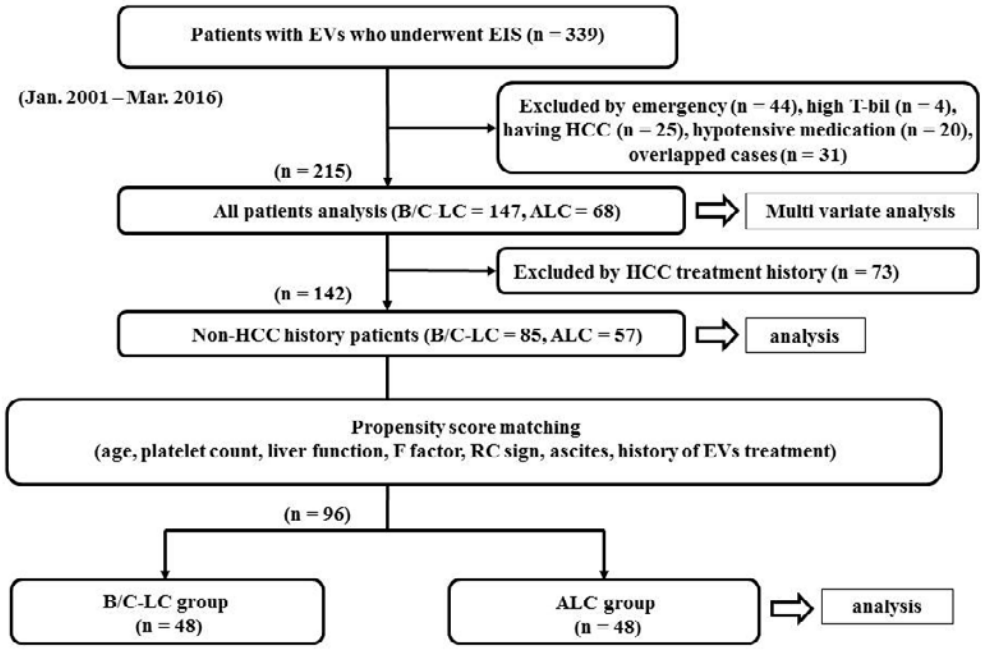


Fig. 1 Flow diagram of patient selection

Of 308 patients with esophageal varices (EV) who underwent endoscopic injection sclerotherapy (EIS), 93 were excluded. Ultimately, predictors associated with overall survival (OS) and EV recurrence rate were investigated using univariate and multivariate analyses of 215 patients after EIS. After the analysis, 73 patients with a history of hepatocellular carcinoma treatment were excluded. OS and EV recurrence rate were compared between patients with hepatic B/C virus liver cirrhosis (B/C-LC) and those with alcoholic liver cirrhosis (ALC) (142 patients). Propensity score matching was performed, and 48 patients were matched. OS and rate of recurrence were compared between the two groups.

needle (upper limit, eight times). A 5% ethanolamine oleate iopamidol mixture was the sclerosant used. Intravariceal and paravariceal injections were confirmed by fluoroscopy. At 1 week after the first session comprising several punctures, if EVs were eradicated, the patient was discharged from hospital. If not, an additional session of EIS was performed. However, all patients were discharged after three sessions of EIS. When intravariceal injection was not performed at the first (or second) session, endoscopic ligation was performed in the second (or third) session. The sedative dose was adjusted so that patients did not awaken or move during EIS.

All patients were strongly recommended to receive additional consolidation treatment with argon plasma coagulation (APC). For those who consented, APC was performed within 3 months after the EIS procedure. Follow-up endoscopy was performed at 3 to 6 months after treatment with EIS and APC, and we recommended that all patients undergo a yearly endoscopy. Presence of F1 or larger EV or RCS positivity was defined as a recurrence, and EIS was recommended.

**Statistical Analyses**

Statistical analyses were performed using the SPSS 28.0.1 software. Continuous values are presented as mean ±SD. Because all clinical data had a normal distribution, Student's t-test was used for comparing values between two groups. The chi-square test was used to compare sex, cause of LC, ascites, history of EV and HCC treatment, and variceal classification. Each background factor with a significant difference ($p < 0.05$) in univariate analysis was included in multivariate analysis (Cox proportional hazards model) to identify predictive factors associated with OS. Logistic regression analysis was performed to extract predictors of EV recurrence in univariate and multivariate analyses. A propensity score was calculated by using logistic regression, and one-to-one caliper matching and nearest neighbors caliper matching were performed. The strict caliper value was set to 0.055 to obtain an exact match. A p-value of less than 0.05 was considered to indicate a significant difference between groups.

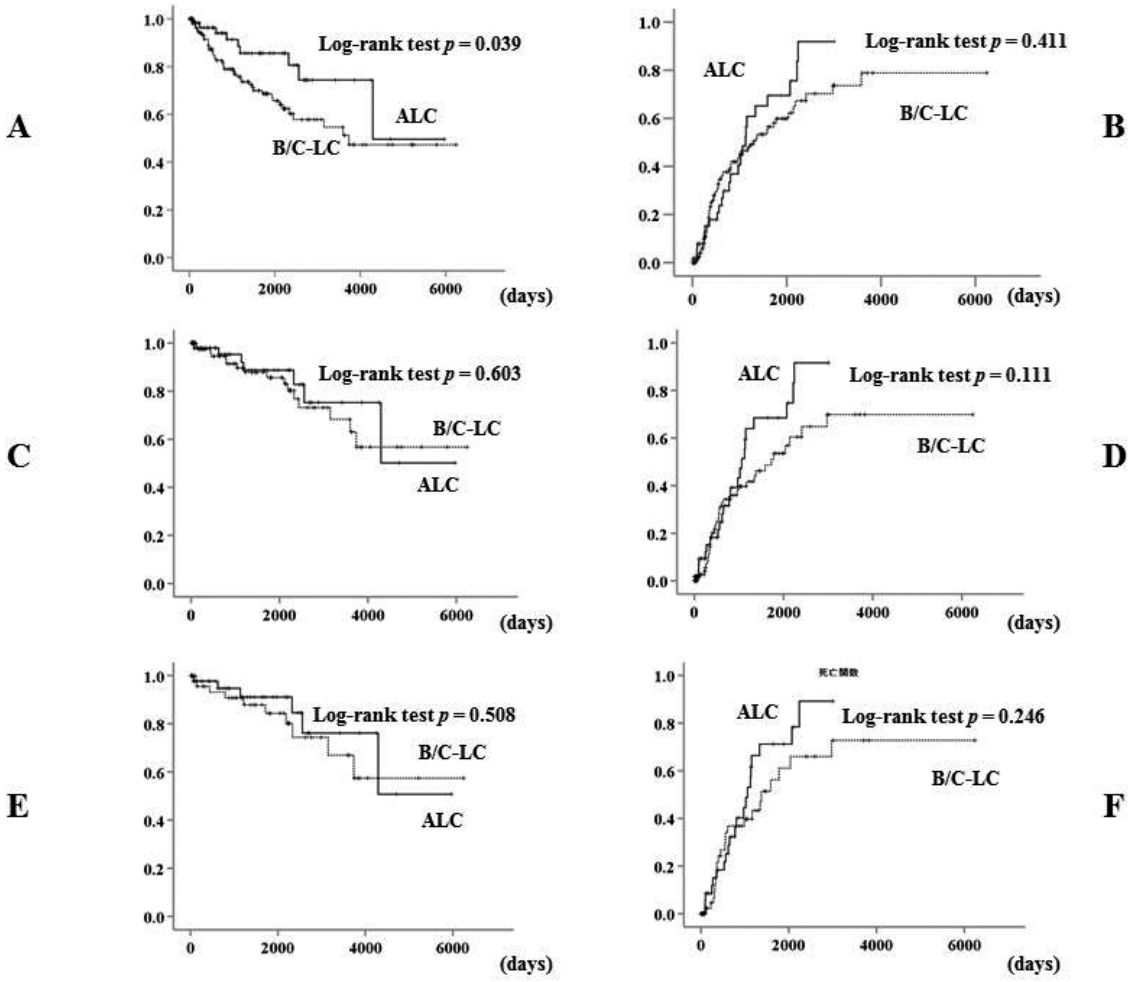


Fig. 2 Overall survival (OS) and recurrence of esophageal varices (EV)

A. In an analysis of all patients, OS was compared between patients with hepatic B/C virus-related liver cirrhosis (B/C-LC) and those with alcoholic liver cirrhosis (ALC).

B. The EV recurrence rate was compared between the B/C-LC and ALC groups in all patients.

C. OS was compared between the B/C-LC and ALC groups in patients without a history of HCC treatment.

D. The recurrence rate of EV was compared between the B/C-LC and ALC groups in patients without a history of HCC treatment.

E. OS was compared between the B/C-LC and ALC groups after propensity score matching.

F. The recurrence rate of EV was compared between the B/C-LC and ALC groups after propensity score matching.

## Results

**OS and EV Recurrence Rate after Treatment in All Patients**

In the analysis of all patients (**Table 1**), OS was significantly higher in the ALC group than in the B/C-LC group (p = 0.039; **Fig. 2A**). However, there was no significant difference in the rate of EV recurrence (p = 0.411; **Fig. 2B**).

**Comparison of Survivors and Nonsurvivors and Predictors of OS and Liver-Related Death**

In total, 52 patients died during the observation period. The background factors of survivors and nonsurvivors were compared. Significant differences were observed in ALC cause, ascites, history of HCC, number of endoscopic treatment sessions, additional APC, and ammonia levels (data not shown). Univariate analysis using a Cox proportional hazards model that was performed on these factors showed that ascites, history of HCC, EV classification, number of endoscopic treatment sessions, additional APC, and ALC cause were significantly associated with OS (**Table 2**). After multivariate analysis using a Cox proportional hazards model, ascites and history of HCC were identified as independent predictors of OS (p = 0.019 and p < 0.001, respectively). EV classification (F2 or F3) tended to predict OS (p = 0.053).

Predictors of liver-related death were also investigated.

Table 2 Predictors associated with overall survival (liver-related death) and recurrence of esophageal varices

| Factors | Cut-off value | n | AUC | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|---|
| | | | | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value |
| Predictors associated with overall survival | | | | | | | |
| Ascites | presence | 74 | 0.577 | 2.07 (1.20-3.58) | 0.009 | 1.93 (1.11-3.35) | 0.019 |
| | absence | 141 | | 1.00 | | 1.00 | |
| History of HCC | presence | 73 | 0.644 | 3.78 (2.17-6.59) | <0.001 | 3.32 (1.85-5.97) | <0.001 |
| | absence | 142 | | 1.00 | | 1.00 | |
| EVs classification (F0/F1/F2/F3) | F0/F1 | 65 | 0.592 | 1.00 | | 1.00 | |
| | F2/F3 | 150 | | 0.51 (0.30-0.89) | 0.017 | 0.56 (0.31-1.00) | 0.053 |
| Endoscopic treatment session | <3.5 | 101 | 0.616 | 1.00 | | 1.00 | |
| | ≥3.5 | 114 | | 0.53 (0.31-0.93) | 0.027 | 0.69 (0.38-1.26) | 0.226 |
| APC | presence | 108 | 0.590 | 0.57 (0.32-1.00) | 0.049 | 0.68 (0.38-1.24) | 0.213 |
| | absence | 107 | | 1.00 | | 1.00 | |
| Ammonia | <87.5 | 125 | 0.552 | 1.00 | | 1.00 | |
| | ≥87.5 | 90 | | 0.94 (0.53-1.66) | 0.834 | Not performed | |
| Etiology | B/C-LC | 147 | 0.594 | 1.00 | | 1.00 | |
| | ALC | 68 | | 0.48 (0.23-0.98) | 0.043 | 0.76 (0.36-1.64) | 0.489 |
| Predictors associated with liver-related death | | | | | | | |
| Ascites | presence | 74 | 0.634 | 2.96 (1.59-5.50) | 0.001 | 1.97 (1.03-3.78) | 0.040 |
| | absence | 141 | | 1.00 | | 1.00 | |
| History of HCC | presence | 73 | 0.727 | 6.79 (3.44-13.41) | <0.001 | 6.46 (3.13-13.09) | <0.001 |
| | absence | 142 | | 1.00 | | 1.00 | |
| Endoscopic treatment session | <3.5 | 101 | 0.571 | 1.00 | | 1.00 | |
| | ≥3.5 | 114 | | 0.58 (0.31-1.07) | 0.083 | Not performed | |
| APC | presence | 108 | 0.599 | 0.50 (0.26-0.96) | 0.036 | 0.77 (0.38-1.56) | 0.468 |
| | absence | 107 | | 1.00 | | 1.00 | |
| Child-Pugh score | <5.5 | 68 | 0.571 | 1.00 | | 1.00 | |
| | ≥5.5 | 147 | | 3.28 (1.38-7.80) | 0.007 | 2.98 (1.18-7.55) | 0.021 |
| Etiology | B/C-LC | 147 | 0.605 | 1.00 | | 1.00 | |
| | ALC | 68 | | 0.39 (0.16-0.92) | 0.032 | 0.68 (0.27-1.73) | 0.420 |
| Predictors associated with EV recurrence | | | | | | | |
| Age | <64.5 | 102 | 0.585 | 1.00 | | 1.00 | |
| | ≥64.5 | 113 | | 0.49 (0.28-0.85) | 0.010 | 0.48 (0.27-0.84) | 0.011 |
| EVs classification (F0/F1/F2/F3) | F0/F1/F2 | 189 | 0.558 | 1.00 | | 1.00 | |
| | F3 | 26 | | 3.00 (1.27-7.09) | 0.012 | 2.82 (1.15-6.93) | 0.024 |
| EIS | <5 | 196 | 0.571 | 1.00 | | 1.00 | |
| | ≥5 | 19 | | 2.59 (0.98-6.88) | 0.055 | 1.95 (0.69-5.48) | 0.206 |

Data were analyzed using the Cox proportional hazards model for overall survival, and logistic regression analysis for the occurrence of esophageal varices after endoscopic injection sclerotherapy. A *p*-value of less than 0.05 was considered to indicate a significant difference between groups.

OR, odds ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve

Abbreviations are as explained in the legend in Table 1.

Significant differences were observed in ALC cause (p = 0.009), ascites (p = 0.003), history of HCC (p < 0.001), number of endoscopic treatment sessions (p = 0.018), additional APC (p = 0.021), and Child-Pugh score (p = 0.006) in a comparison of background factors (data not shown). Univariate analysis showed that ALC cause (p = 0.032), ascites (p = 0.001), history of HCC (p < 0.001), additional APC (p = 0.036), and a Child-Pugh score ≥5.5 (p = 0.007) were significantly associated with liver-related death (**Table 2**). In multivariate analysis, ascites, history of HCC, and a Child-Pugh score ≥5.5 were identified as independent predictors of liver-related death (p = 0.040, p < 0.001, and p = 0.021, respectively).

**Comparison of EV Recurrence and Non-Recurrence Groups and Predictors of Recurrence**

Ninety patients experienced EV recurrence during the

observation period. Background factors were compared between those who did and did not develop recurrence. Significant differences were observed in age, EV classification, and number of EIS sessions (p = 0.048, 0.037, and 0.044, respectively; data not shown). Univariate and multivariate analyses showed that age ≥64.5 years was a negative predictor associated with EV recurrence, and an EV classification of F3 was a positive predictor (p = 0.011 and 0.024, respectively; **Table 2**). In patients aged ≥64.5 years, the EV recurrence rate was lower.

We investigated Pearson correlations between recurrence of EV bleeding and background factors obtained from univariate analyses in all patients. There was a significant negative correlation between age and bleeding recurrence (r = −0.243, p = 0.004; data not shown).

**OS and EV Recurrence Rate in Patients with No History of HCC**

After excluding patients with a history of HCC (**Table 1**), there was no significant difference in OS between the two groups (p = 0.603; **Fig. 2C**). However, there was a tendency for a higher EV recurrence rate in the ALC group than in the B/C-LC group (p = 0.111; **Fig. 2D**). In multivariate analysis, factors associated with OS were a history of HCC and ascites (**Table 2**). Among the 142 patients without a history of HCC treatment, 47 had ascites. Analysis of OS and EV recurrence rates in 95 patients without a history of HCC treatment or ascites showed no significant difference between the ALC and B/C-LC groups (**Supplementary Fig.: https://doi.org/10.1272/jnms.JNMS.2024_91-209**).

**OS and EV Recurrence Rate after Propensity Score Matching**

Among the 142 patients without a history of HCC treatment, propensity score matching was performed because there were significant differences in gender and hemoglobin and platelet values (**Table 1**). Ultimately, 96 patients met the criteria (B/C-LC group, 48 patients; ALC group, 48 patients; **Table 3**). There was no significant difference in OS or EV recurrence rate between the two groups (p = 0.508 and 0.246, respectively; **Fig. 2E and F**).

**Adverse Events**

In a comparison of the B/C-LC and ALC groups after propensity score matching, the incidence of abdominal pain was higher in the B/C-LC group (p = 0.041), and the incidences of intraoperative hypertension and oxygen desaturation were higher in the ALC group (p = 0.033 and 0.025, respectively; **Table 3**).

## Discussion

In the present study, patients with LC who did not abstain from alcohol consumption had an OS and EV recurrence rate that were comparable to those of patients with unsuccessful viral elimination of HBV and HCV. The predictors associated with OS were ascites and history of HCC, and the predictors of liver-related death were ascites, history of HCC, and a Child-Pugh score ≥5.5. Although we had hypothesized that OS and the EV recurrence rate would be worse in the ALC group than in the B/C-LC group, the rates were comparable. The factor that affected OS seemed to be treatment of EV before bleeding to death, as described below. In a previous study of 5,138 patients with LC, Jain et al. showed that survival at 1 year was significantly worse in patients with ALC than in those without ALC (42.3% vs. 27.3%, respectively)[9]. They showed that the incidence of acute variceal bleeding was significantly higher in patients with ALC than in those without ALC (32.0% vs. 23.7%, respectively). In contrast, Thörn et al.[12] found no significant differences in OS between ALC and HCV-LC groups after treatment for bleeding from EV or gastric varices. In their report, OS after varices treatment was significantly worse for patients with both ALC and HCV-LC than for those with either of these conditions. These studies suggest that OS for patients with ALC is associated with a higher EV bleeding rate, as compared to patients with B/C-LC. However, after treatment of EV, the outcomes for patients with ALC and B/C-LC may be comparable. In our study, ALC was not a predictor of OS in multivariate analysis (**Table 2**) because EVs were eliminated by EIS with APC (or EVL) before bleeding.

A history of treatment for HCC and ascites was a predictor of OS. A history of HCC is associated with increased risk of HCC recurrence, even after treatment with direct-acting antiviral agents for HCV[1]. In our study, HCC-related complications were the most common cause of death (**Table 2**). The presence of ascites is associated with a poor prognosis in patients with LC[13], as indicated in previous studies. However, large (F2 and F3) EV, but not small EV, tended to be associated with improved OS (**Table 2**). Beppu et al.[14] reported that the rate of bleeding of EV in the F2 and F3 groups was higher than in the F1 group (31.8% or 67.6% vs. 15.0%, respectively). In our study, 14 patients developed recurrence of EV bleeding after EIS treatment, but there was no correlation between EV form (F0-3) and recurrence of EV bleeding (r = 0.115, Pearson correlation coefficient, p = 0.790; data not shown). Moreover, there was no correlation between the

Table 3 Comparison after propensity score matching

| | B/C-LC (n=48) | ALC (n=48) | p value |
|---|---|---|---|
| Age, yrs (±SD) | 59.2±11.2 | 61.5±11.7 | 0.329 |
| Men, n (%) | 36 (75) | 43 (89.6) | 0.061 |
| Ascites (presence/absence) | 19/29 | 14/34 | 0.283 |
| History of HCC treatment | none | none | none |
| Previous history of EVs treatment (presence/absence) | 0/48 | 1/47 | 0.315 |
| Esophageal varices classification | | | |
| Ls/Lm/Li | 22/18/8 | 19/18/11 | 0.707 |
| F0/F1/F2/F3 | 0/13/29/6 | 1/11/28/8 | 0.689 |
| Cw/Cb | 0/48 | 0/48 | 1.000 |
| RC0/RC1/RC2/RC3 | 0/29/16/3 | 0/32/9/7 | 0.157 |
| Observation period (days) | 1,933±1,417 | 1,550±1,435 | 0.192 |
| Endoscopic treatment session | 3.6±1.2 | 3.6±1.2 | 0.931 |
| EIS | 2.8±1.1 | 2.9±1.1 | 0.927 |
| EVL | 0.2±0.4 | 0.2±0.5 | 0.818 |
| APC | 0.5±0.5 | 0.6±0.5 | 0.839 |
| Hemoglobin (g/dL) | 11.5±2.5 | 11.2±2.5 | 0.571 |
| Platelet ($\times 10^4/\mu L$) | 9.1±4.6 | 9.2±3.7 | 0.907 |
| PT-INR | 1.1±0.1 | 1.2±0.2 | 0.785 |
| AST (U/L) | 49.4±25.3 | 48.3±26.2 | 0.828 |
| ALT (U/L) | 32.0±15.1 | 30.4±15.2 | 0.609 |
| Total bilirubin (mg/dL) | 1.5±0.6 | 1.5±0.8 | 0.787 |
| Albumin (g/dL) | 3.3±0.6 | 3.3±0.6 | 0.647 |
| Ammonia (μg/dL) | 82.0±31.8 | 84.7±32.8 | 0.687 |
| Child-Pugh score | 6.3±1.2 | 6.2±1.1 | 0.722 |
| Prognosis (living/deceased) | 38/10 | 42/6 | 0.243 |
| Cause of death (HCC/EVs bleeding/hepatic failure/other) | 0/1/6/3 | 0/1/3/2 | 0.899 |
| EVs recurrence (presence/absence) | 23/25 | 21/27 | 0.682 |
| Adverse events, n (%) | | | |
| Abdominal pain | 27 (56.3) | 17 (35.4) | 0.041 |
| Hypertension | 26 (54.2) | 36 (75.0) | 0.033 |
| Hematuria | 10 (20.8) | 5 (10.4) | 0.160 |
| Esophageal stenosis | 2 (4.2) | 0 (0.0) | 0.153 |
| Pleural effusion | 2 (4.2) | 1 (2.1) | 0.557 |
| Ascites | 2 (4.2) | 2 (4.2) | 1.000 |
| Portal venous thrombosis | 0 (0.0) | 0 (0.0) | 1.000 |
| Oxygen desaturation | 1 (2.1) | 7 (14.9) | 0.025 |

Abbreviations are as explained in the legend in Table 1.

incidence of death and bleeding recurrence ($r = -0.17$, $p = 0.839$). In patients with ALC, the complete disappearance of EV appears to be the most important factor associated with OS. Large EV have a wide lumen diameter, which facilitates intravariceal injection of the sclerosant in EIS. Thus, EV eradication is more likely for large EV than for small EV. Unfortunately, the rate of intravariceal injection was unknown in this study.

Regarding the comparable rates of EV recurrence in the groups, the recurrence rate is mainly associated with the success rate of EIS. Krige et al.[15] showed that repeat EIS treatment with eradication of EV, even in ALC patients, decreases the rate of bleeding recurrence of EV. Therefore, we believe that the factor related to EV recurrence is not the cause of LC but the intravariceal success rate of EIS, as we previously reported[16].

In the present study, predictors of EV recurrence were age <64.5 and EV classified as F3. Patients with LC presenting with F3 EV had very high portal pressure[14,17], which may have contributed to the higher recurrence rate. The high recurrence rate of EV in young patients may be related to the amount of alcohol consumed. In a previous report, alcohol consumption significantly increased the risk of infection after EV bleeding, even in low-risk patients[18]. Regarding recurrence of EV bleeding, there was a negative correlation between EV bleeding

rate and age (data not shown). Higher bleeding rates in younger people may also be related to the amount of alcohol consumed.

Regarding adverse events after propensity score matching, the incidences of abdominal pain and intraoperative hypertension were higher in the B/C-LC group, and the incidence of oxygen desaturation was higher in the ALC group. We believe that these differences are related to the sedative dose. In patients with ALC, sedation is less effective and the dose must be increased, which tends to produce oversedation. However, there is no record of sedative dose, so this is only speculation.

This study had some limitations. First, it was carried out retrospectively, and the number of patients was small (especially those with ALC). Second, since 17 operators were involved, the success rate of intravariceal injection likely varied. Third, because of the use of old patient records, the intravariceal injection success rate and dose of ethanolamine oleate are unknown. Fourth, blood testing was limited to before and after EIS. However, we demonstrated that OS and the rate of EV recurrence were comparable in patients with ALC and those with B/C-LC after EIS. Future studies should recruit a larger number of participants at multiple centers.

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