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ORIGINAL ARTICLE

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Factors involved in gastroesophageal varix-related events in patients with hepatitis C virus-related compensated and decompensated cirrhosis after direct-acting antiviral therapy

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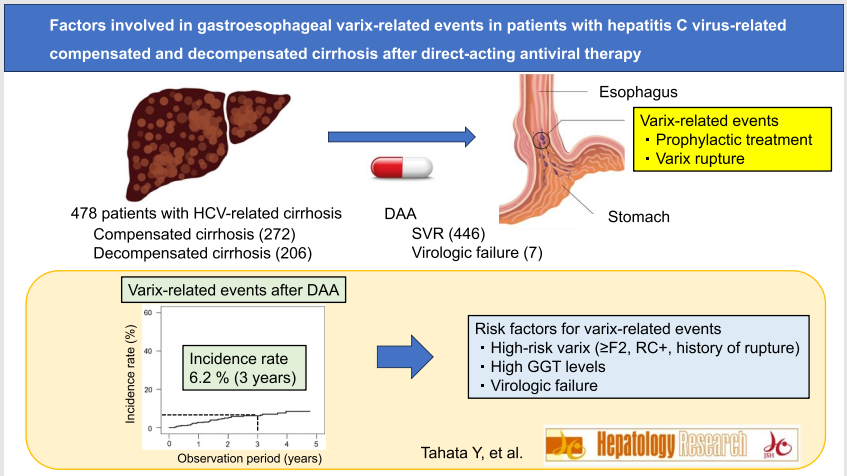
Graphical Abstract



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; EBR, elbasvir; EOT, end of therapy; GGT, gamma-glutamyl transpeptidase; GLE, glecaprevir; GZR, grazoprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LDV, ledipasvir; LSM, liver stiffness measurement; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

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The 3-year incidence rate of gastroesophageal varix-related events defined as varix rupture or prophylactic treatment for varix after direct-acting antiviral therapy in hepatitis C virus-related cirrhosis was 6.2%. High-risk varix, high baseline gamma-glutamyl transpeptidase levels, and virologic failure were related to varix-related events after direct-acting antiviral therapy.

Abstract

Aim: The incidence of and factors involved in gastroesophageal varix-related events in hepatitis C virus-related cirrhosis patients, including decompensated cirrhosis, after direct-acting antiviral therapy are unclear.

Methods: We conducted a multicenter study using prospective data from 478 hepatitis C virus-related cirrhosis patients treated with direct-acting antiviral therapy from February 2019 to December 2021 at 33 Japanese hospitals. Gastroesophageal varices were classified as F1 (small-caliber), F2 (moderately enlarged), or F3 (markedly enlarged) according to the Japanese criteria. Patients without varix or with F1 without red color signs were defined as low-risk varix, and patients with ≥F2 or red color signs or a history of rupture were defined as high-risk varix. Varix-related events were defined as prophylactic treatment or rupture of gastroesophageal varix.

Results: The median age was 70 years, 43% of patients had decompensated cirrhosis, and 16% had high-risk varices (13% in compensated and 33% in decompensated, $p < 0.001$). Sustained virologic response rates were 94.9% for compensated cirrhosis and 91.3% for decompensated cirrhosis ($p = 0.120$). Across 35.7 months, 25 patients received prophylactic treatment, and four experienced varix rupture. The 3-year incidence rate of varix-related events was 6.2% (3.5% in compensated and 9.9% in decompensated, $p = 0.001$). In the multivariate analysis, high-risk varix ($p < 0.001$), high baseline gamma-glutamyl transpeptidase levels ($p < 0.001$), and virologic failure ($p = 0.004$) were significantly involved in varix-related events.

Conclusions: The cumulative incidence rate of varix-related events was significantly higher in decompensated cirrhosis than in compensated cirrhosis. Baseline varix status, baseline gamma-glutamyl transpeptidase levels, and virologic response were related to varix-related events after direct-acting antiviral therapy.

KEYWORDS

DAA, esophagogastric varix, HCV, sustained virologic response, varix aggravation, varix rupture

INTRODUCTION

The development of direct-acting antiviral (DAA) therapy has made it possible to eliminate hepatitis C virus (HCV) in almost all patients with chronic HCV infection, including cirrhosis patients, who are difficult to treat in the era of interferon therapy.[1–6] In patients with HCV-related cirrhosis, including those in the decompensated phase, it has been reported that DAA therapy improves liver function reserve, mainly serum albumin levels, and may improve prognosis.[7–11]

Gastroesophageal varices due to portal hypertension are among the most serious complications in cirrhosis patients. In patients with compensated cirrhosis, the de novo gastroesophageal varix occurrence rate is 5%–7% per year, and the progression rate from a small varix to a large varix is approximately 10% per year.[12,13] D'Amico et al. reported that variceal bleeding rates were 4% per year in patients with compensated cirrhosis, and 7.6% per year in patients with decompensated cirrhosis.[13] Thabut et al. reported that the de novo gastroesophageal varix occurrence rate was 4.1% at 3 years, and the progression rate from a small varix to a large varix was 15.7% at 3 years in patients with hepatitis B virus or HCV-related compensated cirrhosis under viral suppression.[14] Thus, varix-related events are observed in some cirrhotic patients after DAA therapy, and several reports have examined the factors involved in varix-related events after DAA therapy.[15–19] However, these studies

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were conducted mainly on patients with compensated cirrhosis, and the frequency of and factors involved in varix-related events after DAA therapy in patients with cirrhosis, including those in the decompensated phase, are unclear.

The purpose of the present study was to determine the incidence of gastroesophageal varix-related events after DAA therapy, and the factors involved in gastroesophageal varix-related events in patients with HCV-related cirrhosis, including those in the decompensated phase.

METHODS

Study patients

The present multicenter study was retrospectively analyzed using a prospectively registered cohort of 478 patients with HCV-related cirrhosis who started DAA therapy between February 2019 and December 2021 at 33 Japanese institutions. There were no exclusion criteria.

This study was designed in line with the ethical principles of the Declaration of Helsinki as amended in 2013, and was approved by the institutional review board at Osaka University Hospitals (18431) and all other institutions. Informed consent was obtained from the study patients through an opt-out method. This study was registered with the University Hospital Medical Information Network (36150).

Antiviral treatment

Patients with compensated cirrhosis were treated with one of the following regimens: a 12-week course of sofosbuvir plus ribavirin (SOF + RBV), SOF plus ledipasvir (SOF/LDV), elbasvir plus grazoprevir (EBR/GZR) or glecaprevir plus pibrentasvir (GLE/PIB), or a 24-week course of SOF plus velpatasvir plus RBV (SOF/VEL + RBV). All patients with decompensated cirrhosis were treated for 12 weeks with SOF/VEL. Decompensated cirrhosis was defined as any of the following according to our previous reports[6,20,21]: patients with Child–Pugh class B or C when considering DAA therapy, or patients with Child–Pugh class A and a history of decompensation events when considering DAA therapy ($n = 20$). When we examined the criteria for decompensation, ascites ($n = 14$), hepatic encephalopathy ($n = 1$), and rupture or prophylactic treatment for varix ($n = 5$) were included in decompensation events.

We treated all study patients in line with Japanese guidelines.[22] A sustained virologic response (SVR) was defined as an undetectable serum HCV RNA level at 12 or 24 weeks after the end of therapy (EOT).

Clinical data collection

Clinical data, including laboratory data, imaging test results, and physical examination results, were examined at baseline, at the EOT, 12 weeks after the EOT, 24 weeks after the EOT, and every 6 months thereafter. Liver stiffness measurement (LSM) was taken by vibration-controlled transient elastography (FibroScan; Echosens). The clinical data of the study patients were registered on the Research Electronic Data Capture system, which is a web-based data collection and management system.[23,24]

Classification and aggravation of gastroesophageal varix

Gastroesophageal varices were classified according to Japanese criteria: F1 was a straight, small-caliber varix; F2 was a moderately enlarged, beady varix; and F3 was a markedly enlarged, nodular, or tumor-shaped varix.[25] Patients with no varices before DAA therapy and those with F1 varix without red color signs were considered to have low-risk varix, and patients with F2 varix or more, those with red color signs, or those with a history of varix rupture were considered to have high-risk varix. Varix rupture or prophylactic treatment for varix was defined as varix-related events. These events were considered grade 3 or 4 adverse events according to the Common Terminology Criteria for Adverse Events, version 5.0. In addition, among patients whose gastroesophageal varix was evaluated before DAA, varix rupture, prophylactic treatment for varix, or progression from low-risk varix to high-risk varix was defined as varix aggravation. The criteria for the indication of prophylactic treatment for varix was determined by the attending physician.

Statistical analysis

Categorical values were described as numbers, and continuous values were described as medians and interquartile ranges. The differences in the percentages of patients whose gastroesophageal varices were evaluated before DAA therapy and the baseline gastroesophageal varix classification between patients with compensated cirrhosis and those with decompensated cirrhosis were analyzed by the χ^2-test. For the analysis of varix-related events, the start date of the observation period was set at the date when DAA therapy was started, and the last observation date was defined as the date of the first event to varix rupture or prophylactic treatment for the varix, or the last visit, whichever came first. For the analysis of varix aggravation, the last observation date was defined as the date of the first event to varix rupture or prophylactic treatment for the varix, the date of progression from low-risk varix to high-risk varix, or the last visit, whichever came first. For patients who developed hepatocellular carcinoma (HCC) after DAA, patients who developed HCC before the incidence of varix-related events or varix aggravation were considered to the event of HCC development after DAA. As HCC development after DAA was a time-varying covariate, we performed time-dependent analysis. The cumulative incidence rates were estimated by the Kaplan–Meier method, and log-rank tests were used to analyze the differences in the cumulative incidence rates. In patients whose baseline LSM and platelet counts were evaluated, we examined the cumulative aggravation rates of varix according to the Baveno VI criteria.[26] Patients

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with a baseline LSM <20 kPa and platelet counts >150 000/mm^3 were considered as the favorable Baveno group, and patients with a baseline LSM ≥20 kPa and/or platelet counts ≤150 000/mm^3 were considered as the unfavorable Baveno group. Among patients with SVR and whose LSM were evaluated before and after DAA, the distributions of the Baveno VI criteria before and after DAA was analyzed by the McNemar test. Factors involved in varix-related events and varix aggravation were examined by Cox proportional hazard analysis with time-dependent covariates. Multivariate analysis was conducted by the stepwise backward selection method. We excluded factors, such as ascites, encephalopathy, platelet count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, international normalization ratio, and albumin, from the multivariate analysis, because these factors were associated with cirrhosis status and Fibrosis-4 index. The cutoff values for baseline gamma-glutamyl transpeptidase (GGT) levels to predict varix-related events were determined by the Youden index. We set the cutoff value of alcohol intake as 20 g/day according to previous studies.[27,28] Correlations between baseline GGT levels and other biomarkers were examined by Pearson's product moment correlation coefficient, and differences in baseline GGT levels between patients with and without diabetes mellitus were examined by the Mann–Whitney *U*-test. Baseline GGT levels according to alcohol intake were compared by the Jonckheere–Terpstra test.

All the statistical analyses were conducted by using SPSS ver. 24 (IBM) or EZR version 1.37 (Saitama Medical Center, Jichi Medical University).[29] We defined a two-tailed *p*-value < 0.05 as statistically significant. In the analysis of the cumulative incidence rates of varix-related events according to various factors, the Bonferroni method was used for multiple comparisons.

RESULTS

Baseline characteristics

The median age was 70 years, 53% of the patients were men, 43% of the patients had decompensated cirrhosis, and 35% of patients had a history of HCC (Table 1). The percentages of patients with Child–Pugh class A, B, or C were 57%, 37%, or 6%, respectively, and the worst Child–Pugh score was 13. For gastroesophageal varix classification, 136 patients had no varices before DAA therapy, and the number of patients with F1 varix without red color signs, with F2 varix or more or with red color signs, or with a history of varix rupture were 113, 60, or 17, respectively. Gastroesophageal varix classification was not determined before DAA therapy in 152 patients. The SVR rate was 94.9% (258/272) in patients with compensated cirrhosis, and 91.3% (188/206) in patients with decompensated cirrhosis, and no significant differences were observed ($p = 0.120$). In total, 446 patients were SVR, seven had virologic failure (VF), and seven were missing HCV RNA data. A total of 11 patients were lost to follow-up, and seven died before SVR confirmation. Among 169 patients with a history of HCC before DAA, portal vein tumor thrombosis was observed in 12 patients during follow-up.

Evaluation of gastroesophageal varix before DAA therapy

Evaluation of varix before DAA therapy was performed in 54.4% (148/272) of patients with compensated cirrhosis, and in 86.4% (178/206) of patients with decompensated cirrhosis. The percentage of patients whose varix were evaluated before DAA therapy was significantly higher in patients with decompensated cirrhosis than in those with compensated cirrhosis ($p < 0.001$). Among patients whose varices were evaluated before DAA therapy, the proportion of patients with high-risk varix was significantly higher in decompensated cirrhosis (33%) than in compensated cirrhosis (13%; $p < 0.001$; Figure S1).

Incidence of and factors involved in gastroesophageal varix-related events after DAA therapy

Across 35.7 months (20.8–46.1 months) after DAA initiation, 25 patients received prophylactic treatment for varix, and four patients experienced rupture of varix. The cumulative incidence rate of varix-related events at 3 years was 6.2% (Figure 1a). When we compared the rates of varix-related events between compensated and decompensated cirrhosis, the cumulative incidence rate of varix-related events at 3 years were 3.5% in patients with compensated cirrhosis and 9.9% in patients with decompensated cirrhosis ($p = 0.001$; Figure 1b). Factors involved in varix-related events after DAA therapy were examined by Cox proportional hazard analysis with time-dependent covariate using baseline data, virologic response data, and HCC development after DAA (Table 2). In the multivariate analysis, high-risk varix (hazard ratio [HR] 8.649, 95% CI 3.611–20.710, $p < 0.001$), high baseline GGT levels (HR 1.005, 95% CI 1.002–1.008, $p < 0.001$), and VF (HR 8.852, 95% CI 1.970–39.780, $p = 0.004$) were significantly involved in varix-related events.

Next, the cumulative incidence rates of varix-related events were examined according to the baseline varix status, baseline GGT levels, or virologic response. Regarding the baseline varix status, the cumulative incidence rates at 3 years were 22.8% in patients with high-risk varix, 3.9% in those with low-risk varix, and 2.3% in those with unknown varix status, respectively, and the cumulative incidence rates were significantly higher in patients with high-risk varix than in those with low-risk varix or with unknown varix status ($p < 0.001$; Figure 1c). The cutoff value for the baseline GGT level to predict varix-related events was 75 U/L according to the Youden index. The cumulative incidence rates at 3 years were 11.3% in patients with baseline GGT levels of ≥75 U/L and 4.5% in those with baseline GGT levels <75 U/L, and the cumulative incidence rates were significantly higher in patients with high baseline GGT levels than in those with low baseline GGT levels ($p = 0.006$; Figure 1d). For virologic response, the cumulative incidence rates at 3 years were 46.7% in patients with VF and 5.9% in those with SVR, and the cumulative incidence rates were significantly higher in patients with VF than in those with SVR ($p < 0.001$; Figure 1e).

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TABLE 1 Patient characteristics.

Factor	*N* = 478	Missing
Age (years)	70 (61–77)	0
Sex (male/female)	254/224	0
BMI (kg/m^2)	23.4 (21.2–25.9)	11
Diabetes mellitus (yes/no)	127/351	0
Alcohol intake, 0/<20/20–59/≥60 (g/day)	296/68/55/40	19
Genotype (1/2/3/4/1 + 2)	296/164/10/1/1	6
Antiviral treatment (naïve/IFN-based/IFN-free)	382/61/33	2
Child–Pugh score (5/6/7/8/9/10/11/12/13)	157/116/91/53/31/19/7/3/1	0
Gastroesophageal varix (absent/F1 without red color signs/≥F2 or red color signs/history of rupture)	136/113/60/17	152
Cirrhosis (compensated/decompensated)	272/206	0
History of HCC treatment (yes/no)	169/309	0
LSM (kPa)	22.3 (12.3–27.0)	352
HCV-RNA ($\log_{10}$ IU/mL)	5.9 (5.3–6.4)	0
Platelet count ($\times 10^4/\mu L$)	9.6 (6.7–12.9)	0
Total bilirubin (mg/dL)	0.9 (0.6–1.4)	0
AST (U/L)	53 (38–77)	0
ALT (U/L)	39 (26–69)	0
GGT (U/L)	36 (23–74)	0
Creatinine (mg/dL)	0.8 (0.6–1.0)	0
Albumin (g/dL)	3.4 (3.0–3.8)	0
INR[a]	1.11 (1.04–1.21)	33
FIB4-index	6.16 (4.15–9.02)	0
MELD score[a]	9 (7–11)	33
Ascites (no/mild/severe)	317/136/25	0
Encephalopathy (no/mild/severe)	444/34/0	0
AFP (ng/mL)	7.6 (4.0–18.4)	5

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4 index, fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; INR, international normalization ratio; LSM, liver stiffness measurement; MELD score, model for end-stage liver disease score.

[a]The INR and MELD score were missing for 33 patients who were taking warfarin.

Cumulative incidence rate of gastroesophageal varix-related events after DAA therapy according to the Baveno VI criteria

In the present study, both baseline LSM and platelet counts were examined in 126 patients. We examined the cumulative incidence rates of varix-related events according to the Baveno VI criteria (Figure S2). Among the 126 patients, 13 patients were included in the favorable Baveno group (i.e. LSM <20 kPa and platelet counts >150 000/mm^3), and 113 patients were included in the unfavorable Baveno group (i.e. LSM ≥20 kPa and or platelet counts ≤150 000/mm^3). Among the 113 patients in the unfavorable Baveno group, six experienced varix-related events, and the cumulative incidence rate of varix-related events at 3 years was 6.3%. In contrast, among the 13 patients in the favorable Baveno group, no patients experienced varix-related events ($p = 0.365$).

Distribution of the Baveno VI criteria before and after DAA therapy

We examined the distribution of the Baveno VI criteria before and after DAA among 40 patients who achieved SVR and whose LSM were evaluated before and after DAA. The percentage of patients in the favorable Baveno group were 17.5% according to the Baveno VI criteria at baseline, and 25% according to the Baveno VI criteria at

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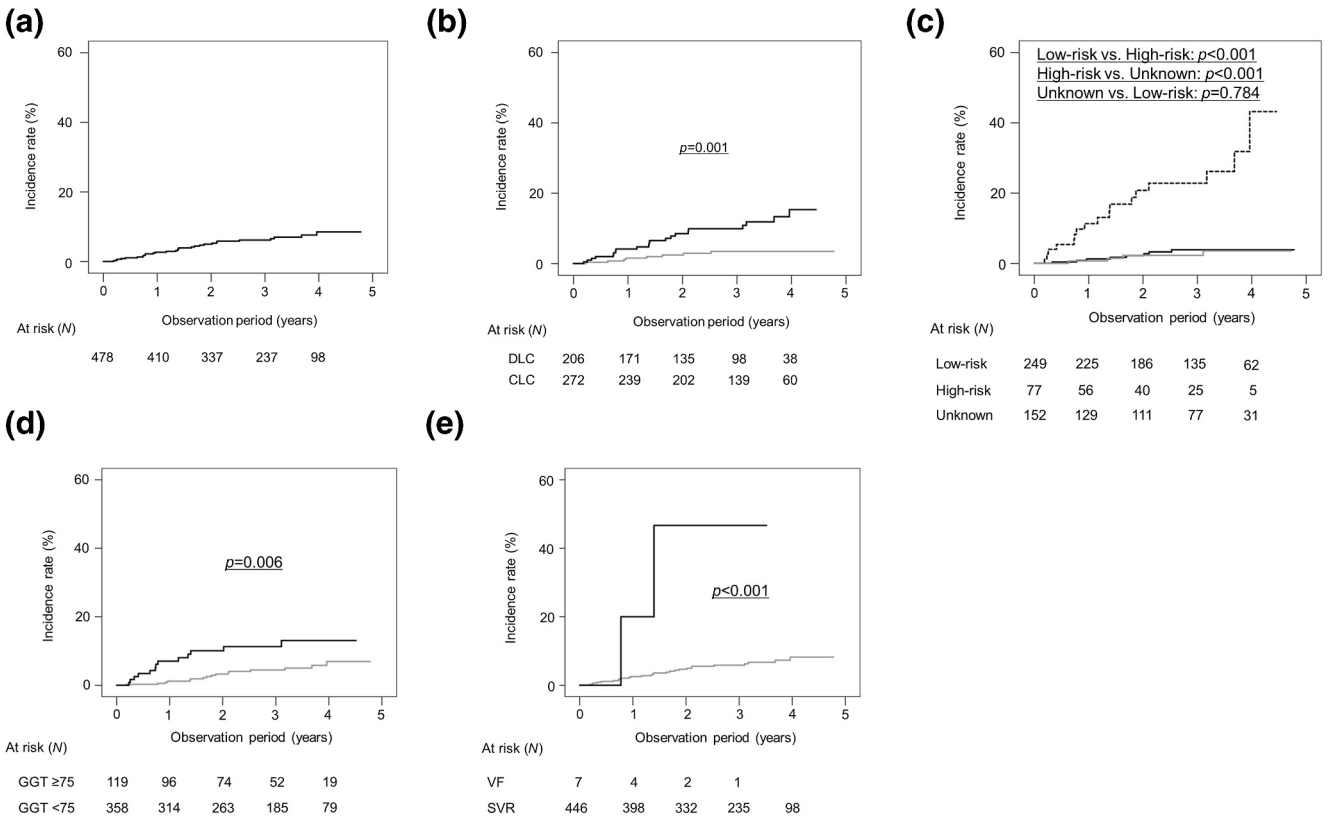

FIGURE 1 Cumulative incidence rates of gastroesophageal varix-related events after direct-acting antiviral (DAA) therapy. (a) All patients. (b) Cumulative incidence rates of varix-related events after DAA therapy between patients with compensated and decompensated cirrhosis. The black line indicates patients with decompensated cirrhosis; the gray line indicates patients with compensated cirrhosis. (c) Cumulative incidence rates of varix-related events after DAA therapy according to the baseline form of gastroesophageal varix. Black solid line, patients with low-risk varices; black dotted line, patients with high-risk varices; gray solid line, patients with unknown varix data. (d) Cumulative incidence rates of varix-related events after DAA therapy according to baseline GGT levels. Black line, patients with GGT levels of 75 U/L or more; gray line, patients with GGT levels <75 U/L. (e) Cumulative incidence rates of varix-related events after DAA therapy according to virologic response. Black line, patients with VF; gray line, patients with SVR. We used the log-rank test and Kaplan–Meier estimation to analyze the difference in cumulative incidence rates. We used the Bonferroni method for multiple comparisons, and described the unadjusted *p*-value. CLC, compensated cirrhosis; DLC, decompensated cirrhosis; GGT, gamma-glutamyl transpeptidase; SVR, sustained virologic response; VF, virologic failure.

12 weeks after the EOT (Figure S3). There was no significant difference in the distribution between baseline and post-treatment Baveno VI criteria ($p = 0.375$).

Factors involved in gastroesophageal varix-related events after DAA therapy and the association between baseline GGT levels and other biomarkers in patients without alcohol intake

As baseline GGT levels increased according to the amount of alcohol consumed (Figure S4), the factors involved in varix-related events after DAA therapy in 296 patients without alcohol intake were examined by Cox proportional hazard analysis with time-dependent covariates using baseline data, virologic response data, and HCC development after DAA (Table 3). In the multivariate analysis, high-risk varix (HR 25.790, 95% CI 5.676–117.10, $p < 0.001$) and high baseline GGT levels (HR 1.005, 95% CI 1.002–1.009, $p = 0.001$) were significantly involved in varix-related events.

Next, we examined the associations between baseline GGT levels and other biomarkers. GGT levels were correlated with aspartate aminotransferase and alanine aminotransferase levels, but not with albumin or total bilirubin levels (Figure 2a–d). Little correlation was observed between GGT levels and the Fibrosis-4 index (Figure 2e). GGT levels in patients with diabetes mellitus were significantly higher than those in patients without diabetes mellitus (Figure 2f).

Incidence of and factors involved in the aggravation of gastroesophageal varix after DAA therapy

Among the 326 patients whose gastroesophageal varix could be evaluated before DAA therapy, 44 experienced varix aggravation.

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TABLE 2 Factors involved in the incidence of varix-related events after DAA therapy.

		Univariate analysis			Multivariate analysis		
Factor	**Category**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age	Per 1 year	0.974	0.943–1.007	0.118			
Sex	Male	1					
	Female	0.412	0.183–0.931	0.033			
BMI	Per 1 kg/m^2	1.015	0.926–1.113	0.748			
Diabetes mellitus	Absent	1					
	Present	1.785	0.843–3.781	0.130			
Alcohol intake	<20 g/day	1					
	≥20 g/day	0.901	0.341–2.380	0.834			
Gastroesophageal varix	Low-risk	1			1		
	High-risk	9.398	4.037–21.880	<0.001	8.649	3.611–20.710	<0.001
	Unknown	0.852	0.256–2.828	0.793	0.891	0.267–2.980	0.852
History of HCC	Absent	1					
	Present	1.470	0.707–3.056	0.302			
FIB-4 index	Per 1	1.049	0.988–1.115	0.119			
Ascites[a]	1	1					
	2 or 3	2.575	1.238–5.354	0.011			
Encephalopathy[a]	1	1					
	2 or 3	1.915	0.579–6.337	0.287			
Liver cirrhosis	Compensated	1					
	Decompensated	3.775	1.672–8.525	0.001			
Platelet count	Per 1 × 10^4/μL	0.973	0.899–1.053	0.495			
AST	Per 1 U/L	1.007	0.999–1.015	0.109			
ALT	Per 1 U/L	1.001	0.992–1.010	0.904			
GGT	Per 1 U/L	1.005	1.002–1.008	0.002	1.005	1.002–1.008	<0.001
Total bilirubin	Per 1 mg/dL	1.133	0.814–1.577	0.460			
INR	Per 1	3.102	0.584–16.480	0.184			
Albumin	Per 1 g/dL	0.345	0.182–0.655	0.001			
Creatinine	Per 1 g/dL	0.738	0.392–1.393	0.349			
Virologic response	SVR	1			1		
	VF	8.856	2.081–37.690	0.003	8.852	1.970–39.780	0.004
HCC development after DAA	No	1					
	Yes	1.526	0.659–3.549	0.327			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral; FIB-4 index, fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalization ratio; SVR, sustained virologic response; VF, virologic failure.

[a]Ascites and encephalopathy scores were based on the Child–Pugh scores.

The cumulative varix aggravation rate at 3 years was 13.3% (Figure 3). Factors involved in varix aggravation after DAA therapy were examined by Cox proportional hazards analysis with time-dependent covariate using baseline data, virologic response data, and HCC development after DAA (Table 4). In the multivariate analysis, female sex (HR 0.330, 95% CI 0.165–0.660, $p = 0.002$) and decompensated cirrhosis (HR 2.958, 95% CI 1.480–5.911, $p = 0.002$) were significantly involved in varix aggravation.

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TABLE 3 Factors involved in the incidence of varix-related events after direct-acting antiviral therapy in patients without alcohol intake.

		Univariate analysis			Multivariate analysis		
Factor	**Category**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age	Per 1 year	0.995	0.950–1.042	0.824			
Sex	Male	1					
	Female	0.348	0.129–0.942	0.038			
BMI	Per 1 kg/m^2	0.975	0.858–1.106	0.690			
Diabetes mellitus	Absent	1					
	Present	1.029	0.335–3.160	0.960			
Gastroesophageal varix	Low-risk	1			1		
	High-risk	25.500	5.660–114.900	<0.001	25.790	5.676–117.10	<0.001
	Unknown	2.584	0.431–15.480	0.299	2.362	0.393–14.180	0.347
History of HCC	Absent	1					
	Present	1.649	0.636–4.276	0.303			
FIB-4 index	Per 1	1.093	1.026–1.164	0.006			
Ascites[a]	1	1					
	2 or 3	1.908	0.736–4.949	0.184			
Encephalopathy[a]	1	1					
	2 or 3	1.997	0.455–8.766	0.360			
Liver cirrhosis	Compensated	1					
	Decompensated	3.395	1.196–9.637	0.022			
Platelet count	Per 1 × 10^4/μL	0.922	0.822–1.033	0.162			
AST	Per 1 U/L	1.011	0.999–1.023	0.065			
ALT	Per 1 U/L	1.002	0.990–1.014	0.748			
GGT	Per 1 U/L	1.006	1.003–1.010	<0.001	1.005	1.003–1.009	0.001
Total bilirubin	Per 1 mg/dL	1.576	1.000–2.486	0.050			
INR	Per 1	3.612	0.584–22.320	0.167			
Albumin	Per 1 g/dL	0.347	0.153–0.788	0.011			
Creatinine	Per 1 g/dL	0.728	0.342–1.551	0.411			
Virologic response	SVR	1					
	VF	6.215	0.810–47.710	0.079			
HCC development after DAA	No	1					
	Yes	1.602	0.543–4.725	0.393			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral; GGT, gamma-glutamyl transpeptidase; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalization ratio; SVR, sustained virologic response; VF, virologic failure.

[a]Ascites and encephalopathy scores were based on the Child–Pugh scores.

DISCUSSION

In the present study, we examined the cumulative incidence of and clinical factors involved in gastroesophageal varix-related events in patients with HCV-related compensated or decompensated cirrhosis treated with DAA. This study revealed that cumulative rates of varix-related events were significantly higher in patients with decompensated cirrhosis (9.9% at 3 years) than in those with compensated cirrhosis (3.5% at 3 years). High-risk varices at baseline, high GGT levels at baseline, and VF were identified as risk factors for varix-related events in patients with HCV-related cirrhosis treated with DAA.

GGT is a liver enzyme found mainly in hepatocytes, and is an indicator of hepatobiliary disorders and alcohol consumption.[30] Serum GGT levels are included in the formula for the fatty liver index, a noninvasive indicator of steatotic liver disease,[31] and have been

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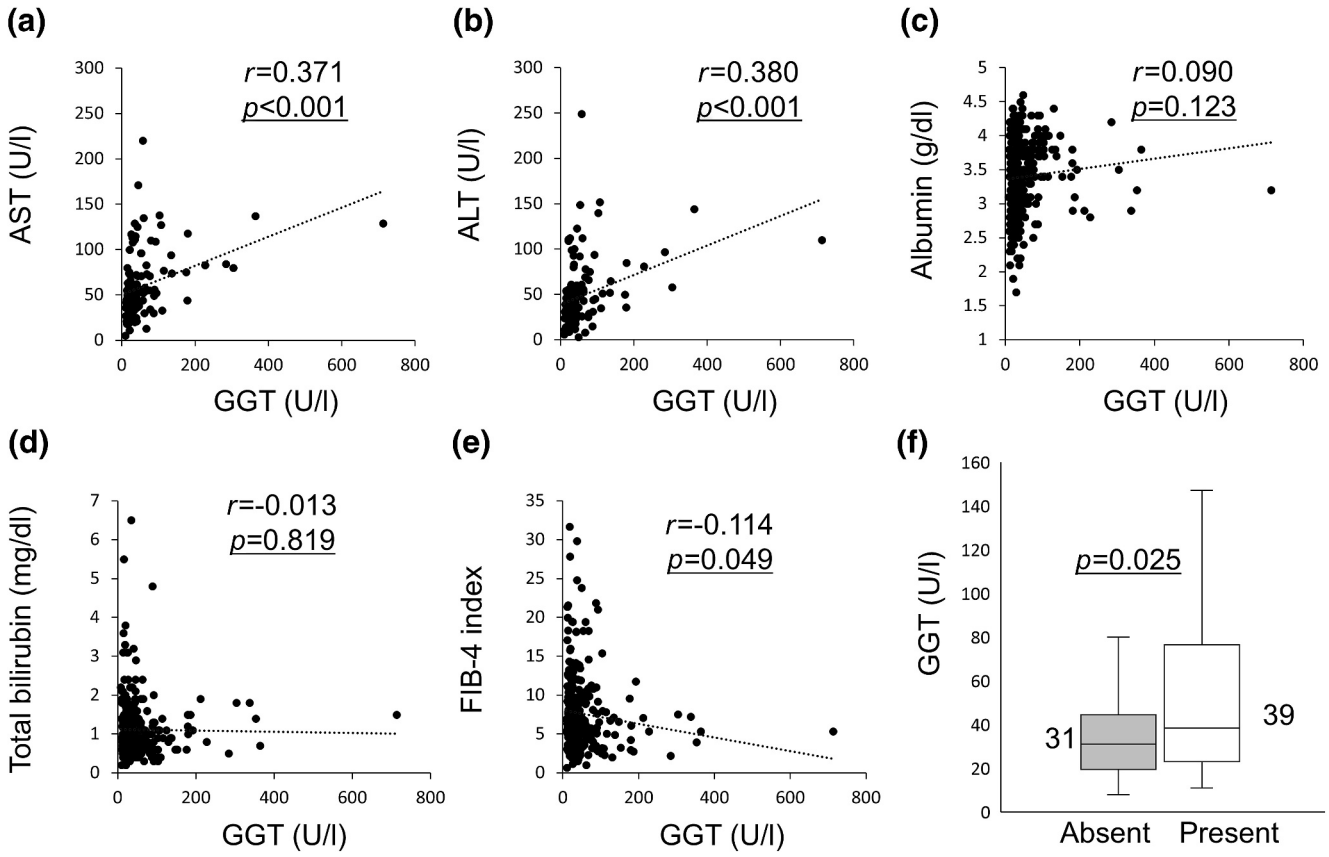

FIGURE 2 Correlations between baseline gamma-glutamyl transpeptidase (GGT) levels and other biomarkers. (a) Correlations between baseline GGT levels and aspartate aminotransferase (AST) levels. (b) Correlations between baseline GGT levels and alanine aminotransferase (ALT) levels. (c) Correlations between baseline GGT levels and albumin levels. (d) Correlations between baseline GGT levels and total bilirubin levels. (e) Correlations between baseline GGT levels and the Fibrosis-4 (FIB-4) index. (f) Baseline GGT levels according to diabetes mellitus status. Gray box, patients without diabetes mellitus; white box, patients with diabetes mellitus. Boxes show the 25th to 75th percentiles. Lines within the boxes show the median values. We evaluated the correlation between baseline GGT levels and other biomarkers by Pearson's product moment correlation coefficient, and compared baseline GGT levels according to diabetes mellitus status by the Mann–Whitney *U*-test.

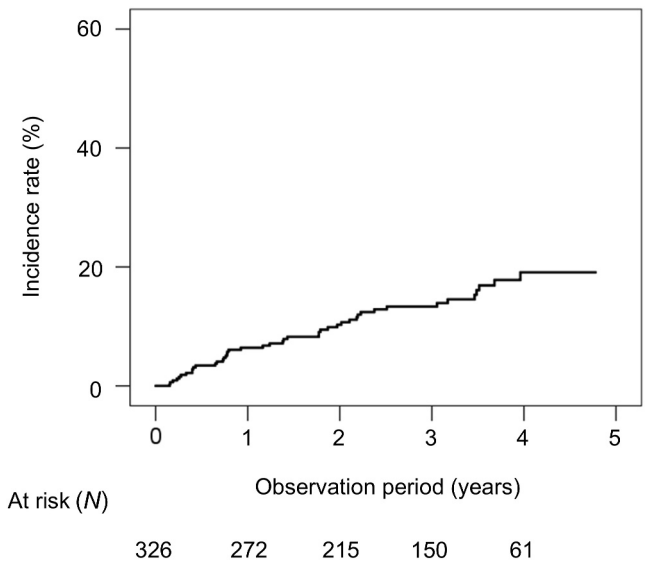

FIGURE 3 Cumulative gastroesophageal varix aggravation rates after direct-acting antiviral therapy.

reported to be associated with liver-related mortality.[32] In the present study, serum GGT levels were identified as factors involved in varix-related events after DAA therapy in patients with HCV-related cirrhosis (Tables 2 and 3; Figure 1d). As baseline GGT levels increased according to the amount of alcohol consumed (Figure S4), we examined the associations between baseline GGT levels and other biomarkers in patients without alcohol intake. Among patients without alcohol intake, serum GGT levels were correlated with serum aspartate aminotransferase and alanine aminotransferase levels, but not with liver function indicators, such as serum albumin and total bilirubin levels, or liver fibrosis indicators, such as the Fibrosis-4 index (Figure 2). In addition, serum GGT levels in patients with diabetes mellitus were significantly higher than those in patients without diabetes mellitus. Although we did not have data regarding the degree of liver steatosis, such as controlled attenuation parameter, serum GGT levels might be associated with liver injury due to metabolic dysfunction, such as diabetes mellitus.

In the present study, the baseline degree of varix was involved in varix-related events after DAA therapy (Tables 2 and 3; Figure 1c).

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TABLE 4 Factors involved in the aggravation of gastroesophageal varix after direct-acting antiviral therapy.

		Univariate analysis			Multivariate analysis		
Factor	**Category**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age	Per 1 year	0.961	0.935–0.988	0.004			
Sex	Male	1			1		
	Female	0.394	0.203–0.765	0.006	0.330	0.165–0.660	0.002
BMI	Per 1 kg/m^2	1.009	0.937–1.086	0.818			
Diabetes mellitus	Absent	1					
	Present	1.262	0.659–2.415	0.483			
Alcohol intake	<20 g/day	1					
	≥20 g/day	0.872	0.387–1.966	0.741			
Gastroesophageal varix	Low-risk	1					
	High-risk	2.572	1.398–4.731	0.002			
History of HCC	Absent	1					
	Present	0.860	0.466–1.590	0.631			
FIB-4 index	Per 1	1.010	0.956–1.067	0.718			
Ascites[a]	1	1					
	2 or 3	1.620	0.897–2.926	0.110			
Encephalopathy[a]	1	1					
	2 or 3	1.602	0.630–4.073	0.322			
Liver cirrhosis	Compensated	1			1		
	Decompensated	2.822	1.426–5.586	0.003	2.958	1.480–5.911	0.002
Platelet count	Per 1 × 10^4/μL	1.000	0.942–1.060	0.987			
AST	Per 1 U/L	1.006	0.998–1.014	0.136			
ALT	Per 1 U/L	1.001	0.993–1.009	0.840			
GGT	Per 1 U/L	1.003	1.000–1.006	0.023			
Total bilirubin	Per 1 mg/dL	1.152	0.889–1.495	0.285			
INR	Per 1	2.399	0.586–9.825	0.224			
Albumin	Per 1 g/dL	0.385	0.220–0.673	<0.001			
Creatinine	Per 1 g/dL	0.720	0.393–1.317	0.286			
Virologic response	SVR	1					
	VF	3.932	0.946–16.350	0.060			
HCC development after DAA	No	1					
	Yes	0.773	0.351–1.705	0.524			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral; GGT, gamma-glutamyl transpeptidase; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalization ratio; SVR, sustained virologic response; VF, virologic failure.

[a]Ascites and encephalopathy scores were based on the Child–Pugh scores.

Moon et al. reported an HR of 3.09 for variceal bleeding in patients with varices without previous bleeding, and 9.39 in patients with varices with previous bleeding compared with patients without varices among patients with HCV-related cirrhosis treated with DAA, indicating that the risk of variceal bleeding increases with the progression of varices.[17] Patients with high-risk varix before DAA therapy require regular variceal surveillance even after DAA therapy. In contrast, in the present study, no difference in varix-related events after DAA therapy was observed between patients with an unknown varix status before DAA therapy and those with low-risk varix (Tables 2 and 3). In patients with an unknown varix status before DAA therapy, the varix might not have been evaluated before DAA therapy, because the attending physician thought that the probability of having a high-risk varix was low based on the patient's clinical data.

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In the present study, the cumulative rates of varix-related events at 3 years were 46.7% in patients with VF and 5.9% in those with SVR, and the cumulative incidence rates of varix-related events were significantly higher in patients with VF than in those with SVR ($p < 0.001$; Table 2; Figure 1e). We examined the cumulative incidence rates of varix-related events between compensated and decompensated patients with SVR and VF. In the present study, VF was not observed in patients with compensated cirrhosis. Among patients with compensated cirrhosis, the cumulative incidence rate of varix-related events at 3 years was 3.6% in patients with SVR. Among patients with decompensated cirrhosis, the cumulative incidence rates of varix-related events at 3 years were 46.7% in patients with VF and 10.1% in those with SVR, and the cumulative incidence rates of varix-related events were significantly higher in patients with VF than in those with SVR ($p = 0.013$; Figure S5). A previous study reported that the incidence of variceal bleeding after DAA therapy was significantly lower in cirrhotic patients who achieved SVR (1.55 per 100 patient-years) than in those who did not achieve SVR (2.96 per 100 patient-years).[17] Although the number of patients with VF in the present study was small, viral eradication might reduce the risk of varix-related events in cirrhotic patients, including those in the decompensated phase.

The Baveno VI criteria state that endoscopic surveillance can be avoided in patients with compensated cirrhosis with LSM <20 kPa and platelet counts >150 000/mm^3, because these patients are unlikely to have gastroesophageal varices that require treatment.[26] Thabut et al. reported that the de novo gastroesophageal varix occurrence rate could be stratified by the Baveno VI criteria in patients with compensated cirrhosis due to chronic viral hepatitis under viral suppression. Puigvehi et al. reported that the progression rate of gastroesophageal varices could be stratified by using LSM in patients with SVR.[18] In the present study, no patients in the favorable Baveno group (LSM <20 kPa and platelet counts >150 000/mm^3) experienced varix-related events, but only approximately 10% of patients were included in the favorable Baveno group (Figure S2). In addition, LSM was performed in approximately 25% of study patients. Examining clinical biomarkers to predict varix-related events is important, as not all hospitals can measure LSM.

In the natural history of cirrhotic patients, Child–Pugh B or C were reported to be significantly involved in the varix progression compared with Child–Pugh A.[12] In the present study, the cumulative rates of varix-related events were significantly higher in patients with decompensated cirrhosis than in those with compensated cirrhosis in univariate analysis, but not in multivariate analysis (Tables 2 and 3). Among patients whose varices were evaluated before DAA therapy, the proportion of patients with high-risk varix was significantly higher in decompensated cirrhosis (33%) than in compensated cirrhosis (13%; $p < 0.001$; Figure S1). These factors were confounded, and decompensated cirrhosis might not have been identified as a risk factor for varix-related events in multivariate analysis in the present study.

There were some limitations in the present study. First, gastroesophageal varices were not evaluated before DAA therapy in all of the patients. Second, LSM was performed in only approximately 25% of the patients. Third, data on nonselective beta-blocker administration were lacking. Unlike the European and USA guidelines, the Japanese guidelines do not strongly recommend nonselective beta-blocker administration for bleeding prophylaxis in patients with high-risk varix.[33–36] Fourth, the interval for follow-up endoscopy and the criteria for the indication of prophylactic treatment were determined by the attending physician.

In conclusion, the cumulative rates of varix-related events at 3 years were 9.9% in patients with decompensated cirrhosis and 3.5% in patients with compensated cirrhosis, and these rates were significantly higher in patients with decompensated cirrhosis than in those with compensated cirrhosis. The baseline status of the varix, baseline GGT levels, and virologic response were identified as risk factors for varix-related events in patients with HCV-related cirrhosis treated with DAA.

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CONFLICT OF INTEREST STATEMENT

Hayato Hikita received lecture fees from Gilead Sciences. Satoshi Mochida received research funding from MSD, Intellim Corporation, Abbvie, Eisai, and Sumitomo Pharma, and received lecture fees from Abbvie, Gilead Sciences, Otsuka Pharmaceutical, Toray Industries, Eisai, ASKA Pharmaceutical, and Chugai Pharmaceutical. Norifumi Kawada received research funding from AstraZeneca, Bristol Myers Squibb, Glaxo Smithkline, MSD, NovoNordisk Pharma, and Eisai, and received lecture fees from AbbVie GK, Gilead Sciences, and MSD. Masayuki Kurosaki received lecture fees from Gilead Sciences and AbbVie. Hitoshi Yoshiji received lecture fees from Otsuka Pharmaceutical, Asuka Pharmaceutical, Gilead Sciences, Novel Pharmaceutical, Taisho Pharmaceutical, and AbbVie Inc, and research funding from Otsuka Pharmaceutical, Asuka Pharmaceutical, and AbbVie. Yoichi Hiasa received lecture fees from AstraZeneca, Gilead Sciences, Otsuka Pharmaceutical, Aska Pharmaceutical, and Taisho Pharmaceutical, and research funding from Otsuka Pharmaceutical and Sumitomo Pharma. Naoya Kato received research funding from AbbVie and MSD, and received lecture fees from AbbVie. and Gilead Sciences. Yoshiyuki Ueno received lecture fees from Eisai and AbbVie, and research funding from AbbVie, Gilead Sciences, and Eisai. Yoshito Itoh received research funding from AbbVie, and received lecture fees from Gilead Sciences and AbbVie. Taro Takami belonged to a donation-funded department funded by SHIBUYA, and received lecture fees from Gilead Sciences, AbbVie, Otsuka Pharmaceutical, and Chugai Pharmaceutical. Yasuhiro Asahina belongs to a donation-funded department funded by Abbott Japan and Fujirebio. Norio Akuta received lecture fees from AbbVie. Shuji Terai received research funding from Rohto, Interstem, Aska, Mochida, Fujifilm Wako, Stemrim, Abbott, Tsumura, Kowa, Tosoh, JBP, and Shionogi, and lecture fees from Otsuka, Abbvie, Daiichisankyo, Chiome, Takeda, and Gilead. Takahiro Kodama received lecture fees from Chugai Pharmaceutical, AstraZeneca, and Gilead Sciences. Tetsuo Takehara received research funding from Gilead Sciences and Chugai Pharmaceutical, and received lecture fees from Gilead Sciences and AbbVie GK. Hayato Hikita, Hidekatsu Kuroda, Goki Suda, Taro Takami, Yasuhiro Asahina and Tomohide Tatsumi are the editorial board members of Hepatology

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Research and coauthors of this article. Hitoshi Yoshiji, Naoya Kato and Yasunari Nakamoto are the Deputy-Editors-in-Chief of Hepatology Research and coauthors of this article. Masayuki Kurosaki is the Editor-in-Chief of Hepatology Research and a coauthor of this article. All other authors declare no Conflict of Interests for this article.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENTS

Approval of the research protocol by an Institutional Reviewer Board: This study was approved by the institutional review board of Osaka University Hospital (18431) and all other institutions.

Informed Consent: Informed consent was obtained from the study patients through an opt-out method.

Registry and the Registration No. of the study/trial: This study was registered with the University Hospital Medical Information Network (36150).

Animal Studies: N/A.

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SUPPORTING INFORMATION

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