Risk factors for liver-related and non-liver-related mortality following a sustained virological response after direct-acting antiviral treatment for hepatitis C virus infection in a real-world cohort

Risk Factors for Liver-Related and Non-Liver-Related Mortality following a Sustained Virological Response after Direct-Acting Antiviral Treatment for Hepatitis C Virus Infection in a Real-World Cohort

Short title: Mortality after DAA-induced SVR

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Abbreviations: AFP, α-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; EOT, end of treatment; FIB-4, Fibrosis-4; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; SVR, sustained virological response.

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Abstract

A direct-acting antiviral (DAA)-induced sustained virological response (SVR) reduces the risk of mortality. However, the risk factors associated with liver-related and non-liver-related mortality following a SVR after DAA treatment are unclear. We assessed the incidence and risk factors of liver-related and non-liver-related mortality in 1,180 patients who achieved a SVR after DAA treatment. During the follow-up period after DAA treatment (median duration, 1,099 [range: 84–2,345] days), 53 (4.5%) patients died: 15 due to liver-related mortality, 25 due to non-liver-related mortality, and 13 due to unknown causes. The all-cause, liver-related, and non-liver-related mortality rates were 14.9, 4.2, and 7.0/1,000 person-years, respectively. In a multivariate analysis, the development of hepatocellular carcinoma (HCC) after DAA treatment ($p = 0.009$; hazard ratio [HR], 31.484), an estimated glomerular filtration rate (eGFR) at baseline ≤ 61.68 mL/min/1.73 m^2 ($p = 0.015$; HR, 6.607), and an α-fetoprotein level post-treatment ≥ 7.6 ng/mL ($p = 0.041$; HR, 18.490) were significantly associated with liver-related mortality. Furthermore, eGFR ≤ 67.94 mL/min/1.73 m^2 at baseline ($p = 0.012$; HR, 3.407) and albumin–bilirubin (ALBI) grade ≥ 2 at SVR ($p = 0.024$; HR, 3.449) were significantly associated with non-liver-related mortality. Early diagnosis and therapeutic interventions for HCC development after DAA treatment are important to reduce liver-related mortality. The ALBI grade, which reflects the hepatic functional reserve, is a useful predictor of non-liver-related mortality after a SVR induced by DAA treatment. Furthermore, the renal dysfunction caused by metabolic syndrome may affect prognosis even after eliminating hepatitis C virus.

Key words: direct-acting antiviral, hepatitis C virus, liver-related mortality**,** non-liver-related mortality, sustained virological response

Introduction

An estimated 58 million people were chronically infected with hepatitis C virus (HCV) worldwide in 2019,[1] and 10–20% of HCV-infected individuals develop liver complications, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[2] Thus, the ultimate goal of anti-HCV treatment is to prevent the development of cirrhosis and HCC and reduce mortality.

An all-oral direct-acting antiviral (DAA) regimen was approved in Japan in 2014. This regimen is used for a large number of patients with chronic HCV infection, and it results in a rapid elimination of the HCV RNA level and remission of liver inflammation in most patients without any adverse effects. This interferon (IFN)-free DAA treatment achieves a sustained virological response (SVR) in nearly 100% of patients with chronic HCV infection.[3–6]

PEG-IFN and ribavirin had been the standard treatments for patients with chronic hepatitis C. Although SVR rates are lower in patients who received an IFN-based treatment compared with IFN-free DAA treatment, several long-term follow-up studies of patients who received IFN-based treatment showed that the HCC incidence and all-cause, liver-related, and non-liver-related mortality rates were significantly lower in patients who achieved a SVR than in those who did not.[7–9]

Although the follow-up periods in studies of patients who received DAA treatment have been relatively short, several studies have reported that the HCC incidence[10–14] as well as all-cause, liver-related, and non-liver-related mortality rates[13–19] were significantly lower in patients who achieved a SVR than in those who did not or in untreated patients. Janjua, *et al.* evaluated the effect of a DAA-induced SVR on mortality risk in a large population-based cohort after more than 5 years of follow-up and found that achieving an SVR was associated with 81% and 78% reductions in all-cause and liver-related mortality rates, respectively, compared with no treatment. Achieving a SVR was associated with 81% and 87% reductions in all-cause and liver-related mortality rates, respectively, compared with not achieving a

SVR.[19] Furthermore, there was no significant effect of achieving a SVR induced by IFN-based or DAA treatment on HCC risk or mortality.[20, 21]

In addition, a DAA-induced SVR results in hepatic benefits, such as improved or reduced hepatic fibrosis,[22, 23] portal hypertension,[24, 25] hepatic decompensation,[13, 15, 26] and extrahepatic benefits, such as reduced risks of non-HCC malignancy,[27] diabetes mellitus,[28] and cardiovascular disease.[18, 29]

A DAA-induced SVR reduces the risk of mortality. However, the risk factors associated with liver-related and non-liver-related mortality in patients with SVR following DAA treatment are unclear. Therefore, this study aimed to assess the incidence and risk factors of liver-related and non-liver-related mortality in patients who achieved SVR after DAA treatment in a real-world cohort.

Patients and Methods

Patients

Among the 1,322 patients with chronic HCV infection who were treated with IFN-free DAAs between September 2014 and December 2020 at Osaka Metropolitan University Hospital, 1,180 who had a SVR at 12 weeks post-treatment (SVR_{12}) were included in this prospective study (**Fig. 1**). Patients with hepatitis B virus co-infection, autoimmune liver diseases, alcoholic liver injury, or uncontrolled HCC were excluded. This study was conducted according to the guidelines of the 1975 Declaration of Helsinki (2013 version). Written informed consent was obtained from all patients before treatment. This study protocol was approved by the Ethics Committee of Osaka Metropolitan University Hospital (nos. 2905, 3131, 3212, 3303, 3619, 3898, 4292, 4312, and 2021-268).

Study design

Among the 1,180 patients who achieved SVR_{12}, 145 were treated with 200 mg asunaprevir plus 60 mg daclatasvir for 24 weeks, 197 were treated with 400 mg sofosbuvir plus 600–1,000 mg (based on weight) ribavirin for 12 weeks, 459 were treated with 400 mg sofosbuvir plus 90 mg ledipasvir for 12 weeks, 24 were treated with 150 mg paritaprevir plus 25 mg ombitasvir plus 100 mg ritonavir for 12 weeks, 113 were treated with 100 mg grazoprevir plus 50 mg elbasvir for 12 weeks, 216 were treated with 300 mg glecaprevir plus 120 mg pibrentasvir for 8–12 weeks, 19 were treated with 400 mg sofosbuvir plus 100 mg velpatasvir for 12 weeks, and 7 were treated with 400 mg sofosbuvir plus 100 mg velpatasvir plus 600–1,000 mg (based on weight) ribavirin for 24 weeks according to the Japanese Society of Hepatology guidelines[3] (**Table 1**). SVR_{12} was defined as undetectable HCV RNA in serum at the end of treatment (EOT) and 12 weeks post-treatment. During the follow-up period, clinical, biochemical, and quantitative serum HCV RNA assessments were evaluated at 3–6-month intervals. Cirrhosis was defined as a METAVIR score of F4 on histological examination[30] or > 14.5 kPa on transient elastography.[31]

Evaluations

The study endpoint was all-cause mortality, including liver-related and non-liver-related mortality, after the end of DAA treatment. Survival time was calculated from the EOT. Patients were followed up until a confirmed diagnosis of liver-related or non-liver-related mortality or the last visit in June 2021. All patients underwent ultrasonography or dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) every 3–6 months for HCC surveillance. HCC was diagnosed based on the presence of arterial hypervascularization and delayed washout on dynamic CT and/or MRI. Liver-related mortality was defined as death due to liver-related events, such as gastroesophageal varices/bleeding, HCC, and decompensated cirrhosis. Non-liver-related mortality was defined as death due to clinical events, such as cardiovascular disease (coronary vascular disease, heart failure, or arrhythmia), stroke (cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage),

and extrahepatic cancers. All liver-related or non-liver-related events were collected using data from the patient's electronic medical records, and the date and cause of all deaths were recorded. If the date or details of an event were uncertain, the principal investigator inspected the records and made corrections, as appropriate.

Routine laboratory examinations

Blood cell counts and biochemical tests were performed using standard procedures. HCV RNA was assessed using the TaqMan HCV assay (COBAS TaqMan HCV assay, Roche Molecular Diagnostics, Tokyo, Japan) with a lower limit of quantification of 15 IU/mL and an upper limit of quantification of 6.9×10^7 IU/mL (1.2–7.8 log IU/mL). The HCV genotype was determined using an HCV genotype primer kit (Institute of Immunology Co., Ltd., Tokyo, Japan). Serum α-fetoprotein (AFP) levels were measured by chemiluminescence enzyme immunoassay. The albumin–bilirubin (ALBI) score was calculated as $-0.085 \times$ (albumin g/L) $+ 0.66 \times$ log (bilirubin μmol/L), and patients were stratified into three grades according to previously reported ALBI score cut-offs: grade 1 (ALBI score ≤ -2.60), grade 2 (> -2.60 to -1.39), and grade 3 (> -1.39).[32] The fibrosis (FIB)-4 index was calculated using Sterling's formula: age (years) × aspartate aminotransferase (U/L)/platelet count ($\times 10^9$/L) × $\sqrt{}$ alanine aminotransferase (ALT) (U/L).[33]

Statistical analysis

Statistical analyses were performed using JMP software (ver. 12.0; SAS Institute, Cary, NC, USA). Continuous variables were compared using the Mann–Whitney *U*-test, and discontinuous variables were compared using Fisher's exact test. Receiver operating characteristic curves were generated to obtain the optimal cut-off values for distinguishing between patients with and those without mortality. Kaplan–Meier analysis and the log-rank test were used to analyze cumulative rates of mortality after the end of DAA treatment. Cox proportional hazards models were used to identify factors associated with mortality. Variables

with a p-value < 0.05 in the univariate Cox regression analyses were subjected to multivariate Cox regression analysis. Spearman's rank analysis was performed to evaluate correlations. A two-tailed p-value < 0.05 was considered significant.

Results

Baseline characteristics of the patients

The baseline characteristics of the patients are shown in **Table 1**. The median age was 68 (range, 21–93) years. Among the 1,180 patients, 226 (19.2%) had cirrhosis and 954 (80.8%) no cirrhosis; 142 (12.0%) had a history of HCC and 1,038 (88.0%) no history. In this cohort, 231 (19.6%) patients had diabetes mellitus, and 599 (50.8%) had hypertension.

Cumulative rates of mortality after DAA treatment

During the follow-up period after DAA treatment (median duration, 1,099 [range: 84–2,345] days), 53 (4.5%) patients died: 15 due to liver-related mortality, 25 due to non-liver-related mortality, and 13 due to unknown causes. The causes of mortality are shown in **Supplementary Table 1**. Among the patients with liver-related mortality, 14 died from HCC. Among the patients with non-liver-related mortality, 14 died from non-HCC malignancy and 6 from cerebral-cardiovascular events, but none died from coronavirus disease 2019. The all-cause, liver-related, and non-liver-related mortality rates were 14.9, 4.2, and 7.0/1,000 person-years, respectively. The 1-, 3-, and 5-year cumulative rates of all-cause mortality were 1.0%, 4.3%, and 8.0% (**Fig. 2A**), those of liver-related mortality were 0.2%, 0.7%, and 2.9% (**Fig. 2B**), and those of non-liver-related mortality were 0.4%, 2.4%, and 3.5% (**Fig. 2C**), respectively. In addition, 144 patients developed HCC during the follow-up period (median duration, 350 [range, 0–2,104] days). Among the patients who developed HCC, 89 had a history of HCC and 55 no history.

Cumulative rates of mortality after DAA treatment by the platelet count and ALT level at baseline

The cumulative rates of all-cause mortality by the platelet count are shown in **Supplementary Figure 1A**. The rates at 1, 3, and 5 years were 1.6, 6.4, and 14.2% respectively in patients with platelet counts ≤ 131 $\times 10^3/mm^3$ (n = 357); and 0.7, 3.2, and 4.2% respectively in those with platelet counts > 131 $\times 10^3/mm^3$ (n = 823) ($p < 0.001$).

The cumulative rates of liver-related mortality by the platelet count are shown in **Supplementary Figure 1B**. The rates at 1, 3, and 5 years were 0.9, 1.4, and 9.0% respectively in patients with platelet counts ≤ 111 $\times 10^3/mm^3$ (n = 242) and 0, 0.5, and 0.5% respectively in those with platelet counts > 111 $\times 10^3/mm^3$ (n = 938) ($p < 0.001$).

The cumulative rates of non-liver-related mortality by the platelet count are shown in **Supplementary Figure 1C**. The rates at 1, 3, and 5 years were 1.0, 4.6, and 5.9% respectively in patients with platelet counts ≤ 126 $\times 10^3/mm^3$ (n = 330); and 0.1, 1.4, and 2.4% respectively in those with platelet counts > 126 $\times 10^3/mm^3$ (n = 850) ($p = 0.012$).

There was no significant association between any of all-cause, liver-related, or non-liver-related mortality and the ALT level at baseline (**Supplementary Fig. 2**).

Risk factors associated with all-cause mortality after DAA treatment

Age, body mass index, cirrhosis, HCC history, hypertension, white blood cell count, hemoglobin level, platelet count, albumin level, ALBI grade, estimated glomerular filtration rate (eGFR), and FIB-4 index at baseline, ALBI grade and FIB-4 index at EOT and SVR_{12}, and HCC development post-treatment were associated with all-cause mortality after DAA treatment in the univariate analyses. In the multivariate analysis, HCC development post-treatment ($p = 0.011$; hazard ratio [HR], 2.502; 95% confidence interval [CI], 1.229–5.094), a baseline eGFR ≤ 68.52 mL/min/1.73 m^2 ($p = 0.021$; HR, 2.035; 95% CI, 1.112–3.725), and an ALBI grade at $SVR_{12} \geq 2$ ($p = 0.021$; HR, 2.413; 95% CI, 1.142–5.098) were

independently and significantly associated with all-cause mortality after DAA treatment (**Table 2**).

Risk factors associated with liver-related mortality after DAA treatment

Age, cirrhosis, HCC history, diabetes mellitus, white blood cell count, hemoglobin level, platelet count, albumin level, ALBI grade, eGFR, FIB-4 index, and AFP level at baseline; the ALBI grade, FIB-4 index, and AFP level at EOT and SVR_{12}; and HCC development post-treatment were associated with liver-related mortality after DAA treatment in the univariate analysis.

In the multivariate analysis, HCC development post-treatment ($p = 0.009$; HR, 31.484; 95% CI, 2.411–411.207), a baseline eGFR ≤ 61.68 mL/min/1.73 m^2 ($p = 0.015$; HR, 6.607; 95% CI, 1.436–30.395), and an AFP level ≥ 7.6 ng/mL at EOT ($p = 0.041$; HR, 18.490; 95% CI, 1.130–302.667) were independently and significantly associated with liver-related mortality after DAA treatment (**Table 3**).

Risk factors associated with non-liver-related mortality after DAA treatment

Cirrhosis, white blood cell count, hemoglobin level, platelet count, albumin level, ALBI grade, and eGFR at baseline; ALBI grade and FIB-4 index at EOT; ALBI grade at SVR_{12}; and HCC development post-treatment were associated with non-liver-related mortality after DAA treatment in the univariate analyses.

In the multivariate analysis, a baseline eGFR ≤ 67.94 mL/min/1.73 m^2 ($p = 0.012$; HR, 3.407; 95% CI, 1.315–8.825) and ALBI grade ≥ 2 at SVR_{12} ($p = 0.024$; HR, 3.449; 95% CI, 1.181–10.072) were independently and significantly associated with non-liver-related mortality after DAA treatment (**Table 4**).

Association between the baseline eGFR and metabolic factors

The eGFR was significantly lower in patients with diabetes mellitus ($p = 0.010$; **Supplementary Fig. 3A**) or hypertension ($p < 0.001$; **Supplementary Fig. 3B**) compared with those without diabetes mellitus or hypertension, respectively, and was negatively correlated with age ($p < 0.001$, $r = -0.41$; **Supplementary Fig. 4A**) but was not correlated with body mass index ($p = 0.78$, $r = -0.008$; **Supplementary Fig. 4B**).

Changes in the ALBI grade at baseline, EOT, and SVR_{12}

The proportions of patients with each ALBI grade at baseline, EOT, and SVR_{12} among the patients who survived or suffered all-cause mortality, liver-related mortality, or non-liver-related mortality are shown in **Supplementary Figure 5**. The frequency of an ALBI grade at $SVR_{12} \geq 2$ was higher in patients with all-cause mortality (50.0%), liver-related mortality (60.0%), or non-liver-related mortality (52.0%) than in those who survived (17.8%).

Supplementary Figure 6 shows the rate of change in the ALBI grade at SVR_{12} among patients with a baseline ALBI grade ≥ 2 at baseline. Among the patients with a baseline ALBI grade ≥ 2 (n = 443), 60.2%, 32.4%, 33.3%, or 26.7% of the patients who survived (n = 382), suffered all-cause mortality (n = 34), suffered liver-related mortality (n = 12), or suffered non-liver-related mortality (n = 15), respectively, improved to ALBI grade 1 at SVR_{12}. Furthermore, the rate of improvement to ALBI grade 1 at SVR_{12} among the patients who survived was significantly higher compared with the patients with all-cause mortality ($p = 0.002$) or non-liver-related mortality ($p = 0.010$) and non-significantly higher compared with those with liver-related mortality ($p = 0.060$).

In contrast, among the patients with ALBI grade 1 at baseline, there was no significant difference in the rate of worsening to ALBI grade at $SVR_{12} \geq 2$ according to mortality (**Supplementary Fig. 7**).

Discussion

To the best of our knowledge, few studies have assessed the risk factors associated with liver-related and non-liver-related mortality in patients who achieved a SVR after DAA treatment in a real-world cohort. Our results indicated that HCC development post-treatment, a low baseline eGFR, and a high AFP level at EOT were independently associated with an increased risk of liver-related mortality (**Table 3**), and a low eGFR at baseline and ALBI grade ≥ 2 at SVR_{12} were independently associated with an increased risk of non-liver-related mortality (**Table 4**).

DAA treatment is effective for eliminating HCV, achieving a sustained histological improvement, and reducing the risks of mortality and hepatocarcinogenesis after SVR following DAA treatment. The reported all-cause and liver-related mortality rates in patients who achieved a SVR after DAA treatment were 19.9 and 5.9/1,000 person-years in a large population-based cohort, respectively,[19] and the all-cause mortality rate was 11.8–16.7/1,000 person-years in patients without cirrhosis[16, 19] and 26.0–45.9/1,000 person-years in those with cirrhosis.[17, 19] Similar to those reports, our study showed all-cause and liver-related mortality rates of 14.9 and 4.2/1,000 person-years, respectively, and an all-cause mortality rate of 8.6/1,000 person-years in patients without cirrhosis and 37.9/1,000 person-years in those with cirrhosis (data not shown).

In the era of IFN-based treatment, metabolic risk factors, particularly diabetes mellitus[34, 35] and hypertension,[34] are significantly associated with all-cause and liver-related mortality in patients who achieve a SVR. Benhammou *et al.* reported that diabetes mellitus significantly increases the risks of mortality, cirrhosis, and decompensated cirrhosis,[36] and Backus *et al.* reported that hypertension is associated with an increased risk of all-cause mortality after achieving a SVR following DAA treatment.[17] In our study, a significant association was observed between liver-related mortality and diabetes mellitus in the univariate analysis but not in the multivariate analysis (**Table 3**). Although significant associations between mortality and metabolic risk factors were not observed directly, a low eGFR at baseline was an independent risk factor associated with liver-related and non-liver-

related mortality after DAA treatment (**Tables 3 and 4**). Furthermore, the eGFR was significantly lower in patients with diabetes mellitus or hypertension compared with those without diabetes mellitus or hypertension (**Supplementary Fig. 3**). Therefore, these results suggest that the renal dysfunction caused by metabolic syndrome, such as diabetes mellitus and hypertension, is associated with liver-related and non-liver-related mortality after DAA treatment.

In our study, among 15 patients with liver-related mortality, 14 died from HCC (**Supplementary Table 1**), and HCC development after DAA treatment was detected as a risk factor associated with liver-related mortality after achieving a SVR following DAA treatment. According to previous reports, a DAA-induced SVR results in a reduced HCC incidence and risks of all-cause and liver-related mortality.[10–19] However, the benefits of a DAA-induced SVR for recurrent HCC are controversial.[37] Interestingly, we found that a history of HCC before DAA treatment was not associated with liver-related mortality, as prognosis was poor regardless of having *de novo* (n = 2) or recurrent (n = 12) HCC after DAA treatment. The association between a history of HCC and liver-related mortality after a SVR following DAA treatment has not been fully discussed. D'Ambrosio *et al*. reported that a significant association between liver-related mortality and history of HCC was observed on univariate analysis, but not multivariate analysis, in patients with cirrhosis who achieved a SVR after DAA treatment,[38] which is consistent with our results (**Table 3**). Therefore, it is important that HCC surveillance is continued after achieving HCV clearance, and that it leads to an early diagnosis and therapeutic interventions for HCC to reduce liver-related mortality, regardless of a history of HCC.

In addition, a high AFP level at EOT was a risk factor associated with liver-related mortality. Previous studies reported that a high post-treatment AFP level was an independent predictor of *de novo* and recurrent HCC after DAA treatment.[20, 39] AFP is a surrogate marker that reflects the liver disease condition, such as inflammation, fibrosis, liver regeneration, and hepatocarcinogenesis. In most cases, the AFP level started to decrease in response to DAA

treatment. In contrast, maintenance of a high AFP level at EOT indicates a potential risk of HCC before the initiation of carcinogenesis. Hence, a high AFP level at EOT may be a predictor of liver-related mortality and hepatocarcinogenesis because most patients with liver-related mortality (93.3%) died from HCC in our study (**Supplementary Table 1**).

The ALBI grade at SVR_{12} was a significant risk factor associated with non-liver-related mortality after DAA treatment in this study (**Table 4**). The ALBI grade, a new non-invasive marker to evaluate the hepatic functional reserve and predict survival in HCC patients,[32] provides a better estimate of hepatic function compared with the Child–Pugh classification.[40] The ALBI grade is calculated based on only the albumin and total bilirubin levels. The frequency of an ALBI grade at $SVR_{12} \geq 2$ was higher in patients with non-liver-related mortality than in those who survived (**Supplementary Fig. 5**), and the rate of improvement to ALBI grade 1 at SVR_{12} was significantly lower in patients with non-liver-related mortality than in those who survived ($p = 0.010$) (**Supplementary Fig. 6**). Thus, these results indicate that the hepatic functional reserve does not often improve even after DAA treatment in patients with non-liver-related mortality. In addition, more than half of the patients (14/25 [56%]; **Supplementary Table 1**) with non-liver-related mortality died from a non-HCC malignancy in our study, and the relationship between the ALBI grade and prognosis in patients with non-HCC malignancies, such as pancreatic cancer and lung cancer, has been investigated. Several studies reported that a higher pretreatment ALBI grade (≥ 2) is related to worse overall survival and progression-free survival in patients with pancreatic cancer treated with chemotherapy[41] or surgical resection[42] and in those with lung cancer treated with chemotherapy[43] or surgical resection.[44] In addition, many patients with a non-HCC malignancy did not receive adequate chemotherapy due to pancytopenia or did not undergo surgical resection due to a poor hepatic functional reserve in our study. Therefore, these results suggest that patients with an ALBI grade ≥ 2 after DAA treatment should undergo systemic screening regularly, as they represent a population potentially at higher risk

of non-liver-related mortality, particularly from non-HCC malignancy, because of a poor hepatic functional reserve.

An important finding of our study was that risk factors associated with mortality were detected only in the analysis limited to patients who achieved a SVR after DAA treatment. DAAs are widely administered to a large number of patients with chronic HCV infection and can lead to a SVR in most patients, including patients of older age or with various complications such as metabolic syndrome; therefore, understanding the risk factors for liver-related and non-liver-related mortality before commencing DAA treatment may help improve prognosis in patients who achieve a SVR.

Our study had some limitations. First, it was a single-center study involving only Japanese patients. Second, there were no comparable control groups, i.e., untreated or non-SVR patients. Third, the median follow-up period after DAA treatment in this study was 3.0 years, which may be relatively short for monitoring patient mortality. Further studies with longer follow-up periods are required.

In conclusion, our study showed that early diagnosis of, and therapeutic interventions for, HCC development after DAA treatment are important to reduce liver-related mortality. The ALBI grade, which reflects the hepatic functional reserve, was a useful predictor of non-liver-related mortality following a SVR after DAA treatment. Furthermore, the renal dysfunction caused by metabolic syndrome may affect prognosis even after eliminating HCV.

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Figure Legends

Figure 1. Study flowchart. Among the 1,322 patients with chronic hepatitis C virus (HCV) infection who were treated with interferon-free direct-acting antivirals (DAAs), 1,180 who achieved a sustained virological response for 12 weeks after treatment $(SVR)_{12}$ were enrolled; 22 patients with hepatitis B virus (HBV) co-infection, 85 with an unknown SVR_{12} status, and 35 who did not achieve a SVR_{12} were excluded.

Figure 2. Cumulative rates of all-cause mortality (A), liver-related mortality (B), and non-liver-related mortality (C) after DAA treatment. A total of 53 patients died after DAA treatment: 15 due to liver-related mortality, 25 due to non-liver-related mortality, and 13 due to unknown causes.

Supplementary Figure Legends

Supplementary Figure 1. Cumulative rates of all-cause mortality (A), liver-related mortality (B), and non-liver-related mortality (C) after direct-acting antiviral (DAA) treatment by the platelet count level at baseline.

Supplementary Figure 2. Cumulative rates of all-cause mortality (A), liver-related mortality (B), and non-liver-related mortality (C) after DAA treatment by the alanine aminotransferase level at baseline.

Supplementary Figure 3. Differences in the estimated glomerular filtration rate (eGFR) with respect to diabetes mellitus (A) and hypertension (B). Medians are shown as horizontal bars. Boxes cover the interquartile range, and tails show minimum and maximum values.

Supplementary Figure 4. Correlations of the eGFR with age (A) and body mass index (B).

Supplementary Figure 5. Changes in the albumin–bilirubin (ALBI) grade at baseline, end of DAA treatment (EOT), and a sustained virological response lasting 12 weeks $(SVR)_{12}$ among patients who survived (A) and those who suffered all-cause mortality (B), liver-related mortality (C), and non-liver-related mortality (D).

Supplementary Figure 6. The proportion of patients with each ALBI grade at SVR_{12} among patients with a baseline ALBI grade ≥ 2.

Supplementary Figure 7. Changes in the ALBI grade at SVR_{12} among patients with ALBI grade 1 at baseline. Among the patients with ALBI grade 1 at baseline (n = 754), 6.2%, 16.7%, 33.3%, and 22.2% of patients who survived (n = 724), suffered all-cause mortality (n = 18), suffered liver-related mortality (n = 3), and suffered non-liver-related mortality (n = 9),

respectively, worsened to ALBI grade ≥ 2 at SVR_{12}. The rate of worsening to ALBI grade at SVR_{12} > 2 was not significantly lower in patients who survived than in those with all-cause mortality (p = 0.105), liver-related mortality (p = 0.178), or non-liver-related mortality (p = 0.109).

Table 1. Characteristics of the patients at baseline, EOT, and SVR_{12}.

	Total (n = 1,180)
Age (years)	68 (21–93)
Sex (male)	554 (46.9%)
Body mass index (kg/m^2)	22.8 (11.7–40.0)
Cirrhosis	226 (19.2%)
HCC history (+)	142 (12.0%)
DAA treatment (AD/Sr/SL/POR/GE/GP/SV/SVr)	145/197/459/24/113/216/19/7
Alcohol consumption (+)	344 (29.2%)
Cigarette smoking (+)	446 (37.8%)
Diabetes mellitus (+)	231 (19.6%)
Hypertension (+)	599 (50.8%)
Baseline	
White blood cells (/μL)	4,800 (1,400–11,700)
Hemoglobin (g/dL)	13.4 (7.5–18.2)
Platelet count (×10^3/mm^3)	165 (13–438)
Aspartate aminotransferase (U/L)	42 (4–275)
Alanine aminotransferase (U/L)	37 (3–610)
γ-Glutamyltransferase (U/L)	33 (4–827)
Total bilirubin (mg/dL)	0.6 (0.1–3.4)
Albumin (g/dL)	4.0 (2.0–5.0)
Albumin–bilirubin grade (1/2/3)	754/417/9
Estimated glomerular filtration rate (mL/min/1.73 m^2)	73.0 (4.2–166.5)
Fibrosis-4 index	2.81 (0.18–49.75)
α-Fetoprotein (ng/mL)	4.5 (<2.0–661.9)
HCV genotype (1/2/3)	819/358/3
HCV RNA (log IU/mL)	6.2 (1.4–7.7)
EOT	
Albumin–bilirubin grade (1/2/3)	773/389/4
Fibrosis-4 index	2.20 (0.13–24.77)
α-Fetoprotein (ng/mL)	3.6 (<2.0–2,955.4)
SVR_{12}	
Albumin–bilirubin grade (1/2/3)	935/218/5
Fibrosis-4 index	2.26 (0.27–54.60)
α-Fetoprotein (ng/mL)	3.3 (<2.0–188.1)
After the end of DAA treatment	
Observation period (days)	1,099 (84–2,345)
HCC development (+)	144 (12.2%)

The values are medians (with ranges) or numbers (with percentages). EOT, end of treatment; SVR, sustained virological response; HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; AD, asunaprevir plus daclatasvir; Sr, sofosbuvir plus ribavirin; SL, sofosbuvir plus ledipasvir; POR, paritaprevir plus ombitasvir plus ritonavir; GE, grazoprevir plus elbasvir;

GP, glecaprevir plus pibrentasvir; SV, sofosbuvir plus velpatasvir; SVr, sofosbuvir plus velpatasvir plus ribavirin; HCV, hepatitis C virus.

Table 2. Predictive factors associated with all-cause mortality after DAA treatment.

Factor	Category	Univariate analysis					Multivariate analysis				
		HR	95 % CI		p-value		HR	95 % CI		p-value	
Age (years)	≥ 71	2.187	1.255	3.813	**0.006**	*	0.918	0.472	1.785	0.80	
Sex	male	1.512	0.880	2.598	0.134						
Body mass index (kg/m^2)	≥ 23.0	1.763	1.011	3.072	**0.046**	*	1.358	0.746	2.472	0.32	
Cirrhosis	(+)	4.284	2.491	7.367	**<0.001**	*	1.219	0.523	2.841	0.65	
HCC history	(+)	4.135	2.371	7.211	**<0.001**	*	1.566	0.771	3.180	0.22	
Alcohol consumption	(+)	0.552	0.270	1.132	0.105						
Cigarette smoking	(+)	1.482	0.858	2.561	0.159						
Diabetes mellitus	(+)	1.442	0.783	2.656	0.24						
Hypertension	(+)	1.965	1.104	3.499	**0.022**	*	1.411	0.764	2.606	0.27	
Baseline											
White blood cells (/μL)	≤ 4,200	2.566	1.480	4.450	**<0.001**	*	1.858	0.967	3.570	0.063	
Hemoglobin (g/dL)	≤ 12.7	2.202	1.281	3.785	**0.004**	*	1.357	0.739	2.491	0.32	
Platelet count (×10^3/mm^3)	≤ 131	2.823	1.625	4.907	**<0.001**	*	1.208	0.451	3.234	0.71	
Aspartate aminotransferase (U/L)	≤ 44	1.353	0.780	2.347	0.28						
Alanine aminotransferase (U/L)	≤ 36	1.559	0.902	2.693	0.112						
γ-Glutamyltransferase (U/L)	≤ 33	1.289	0.744	2.235	0.37						
Total bilirubin (mg/dL)	≥ 0.7	1.048	0.610	1.801	0.87						
Albumin (g/dL)	≤ 3.8	2.775	1.581	4.870	**<0.001**	*	0.726	0.268	1.964	0.53	
Albumin–bilirubin grade	≥ 2	3.016	1.706	5.331	**<0.001**	*	1.397	0.514	3.798	0.51	
Estimated glomerular filtration rate (mL/min/1.73 m^2)	≤ 68.52	2.908	1.633	5.177	**<0.001**	*	2.035	1.112	3.725	**0.021**	*
Fibrosis-4 index	≥ 3.25	2.361	1.335	4.174	**0.003**	*	0.549	0.200	1.506	0.24	
α-Fetoprotein (ng/mL)	≥ 5.4	1.125	0.656	1.930	0.67						
HCV RNA (log IU/mL)	≤ 6.3	1.762	0.969	3.205	0.063						
EOT											
Albumin–bilirubin grade	≥ 2	2.699	1.562	4.662	**<0.001**	*	0.980	0.459	2.092	0.96	
Fibrosis-4 index	≥ 3.25	3.275	1.893	5.665	**<0.001**	*	1.673	0.524	5.337	0.38	
α-Fetoprotein (ng/mL)	≥ 4.6	1.241	0.703	2.190	0.46						
SVR_{12}											
Albumin–bilirubin grade	≥ 2	4.078	2.367	7.024	**<0.001**	*	2.413	1.142	5.098	**0.021**	*
Fibrosis-4 index	≥ 3.25	2.664	1.552	4.574	**<0.001**	*	0.790	0.287	2.174	0.65	
α-Fetoprotein (ng/mL)	≥ 4.7	1.515	0.873	2.627	0.140						
After the end of DAA treatment											
HCC development	(+)	4.955	2.882	8.519	**<0.001**	*	2.502	1.229	5.094	**0.011**	*

*$p < 0.05$ indicates statistical significance. DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; EOT, end of treatment; SVR, sustained virological response.

Table 3. Predictive factors associated with liver-related mortality after DAA treatment.

Factor	Category	Univariate analysis					Multivariate analysis				
		HR	95 % CI		p-value		HR	95 % CI		p-value	
Age (years)	≥ 74	4.450	1.521	13.022	**0.006**	*	1.767	0.351	8.898	0.49	
Sex	male	1.467	0.532	4.047	0.46						
Body mass index (kg/m^2)	≥ 23.3	2.592	0.886	7.585	0.082						
Cirrhosis	(+)	13.373	3.761	47.548	**<0.001**	*	0.989	0.125	7.854	0.99	
HCC history	(+)	26.707	7.519	94.859	**<0.001**	*	3.887	0.735	20.560	0.110	
Alcohol consumption	(+)	0.430	0.097	1.907	0.27						
Cigarette smoking	(+)	1.471	0.523	4.140	0.46						
Diabetes mellitus	(+)	3.504	1.269	9.674	**0.016**	*	2.146	0.614	7.503	0.23	
Hypertension	(+)	2.509	0.799	7.882	0.115						
Baseline											
White blood cells (/μL)	≤ 4,000	8.587	2.423	30.437	**<0.001**	*	3.253	0.566	18.710	0.186	
Hemoglobin (g/dL)	≤ 12.4	3.849	1.367	10.835	**0.011**	*	1.559	0.443	5.487	0.49	
Platelet count (×10^3/mm^3)	≤ 111	11.521	3.238	40.997	**<0.001**	*	2.235	0.159	31.349	0.55	
Aspartate aminotransferase (U/L)	≥ 39	2.009	0.639	6.314	0.23						
Alanine aminotransferase (U/L)	≥ 53	1.722	0.624	4.752	0.29						
γ-Glutamyltransferase (U/L)	≥ 40	1.551	0.562	4.278	0.40						
Total bilirubin (mg/dL)	≥ 0.7	1.659	0.587	4.691	0.34						
Albumin (g/dL)	≤ 3.7	4.293	1.460	12.623	**0.008**	*	0.813	0.097	6.808	0.85	
Albumin–bilirubin grade	≥ 2	5.897	1.658	20.974	**0.006**	*	0.962	0.078	11.871	0.98	
Estimated glomerular filtration rate (mL/min/1.73 m^2)	≤ 61.68	3.929	1.397	11.049	**0.009**	*	6.607	1.436	30.395	**0.015**	*
Fibrosis-4 index	≥ 3.25	7.372	1.658	32.778	**0.009**	*	0.058	0.001	2.278	0.128	
α-Fetoprotein (ng/mL)	≥ 7.2	2.911	1.033	8.198	**0.043**	*	0.060	0.002	1.612	0.094	
HCV RNA (log IU/mL)	≤ 6.3	2.645	0.746	9.382	0.132						
EOT											
Albumin–bilirubin grade	≥ 2	5.245	1.668	16.488	**0.005**	*	0.696	0.106	4.569	0.71	
Fibrosis-4 index	≥ 3.25	14.259	3.207	63.408	**<0.001**	*	2.459	0.047	128.327	0.66	
α-Fetoprotein (ng/mL)	≥ 7.6	6.394	2.211	18.492	**<0.001**	*	18.490	1.130	302.667	**0.041**	*
SVR_{12}											
Albumin–bilirubin grade	≥ 2	6.272	2.230	17.637	**<0.001**	*	0.713	0.078	6.544	0.77	
Fibrosis-4 index	≥ 3.25	14.589	3.285	64.803	**<0.001**	*	5.702	0.115	281.768	0.38	
α-Fetoprotein (ng/mL)	≥ 5.7	5.131	1.825	14.429	**0.002**	*	1.993	0.207	19.155	0.55	
After the end of DAA treatment											
HCC development	(+)	71.957	9.433	548.907	**<0.001**	*	31.484	2.411	411.207	**0.009**	*

*$p < 0.05$ indicates statistical significance. DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; EOT, end of treatment; SVR, sustained virological response.

Table 4. Predictive factors associated with non-liver-related mortality after DAA treatment.

Factor	Category	Univariate analysis					Multivariate analysis				
		HR	95 % CI		p-value		HR	95 % CI		p-value	
Age (years)	≥ 71	1.997	0.897	4.446	0.090						
Sex	male	1.147	0.523	2.515	0.73						
Body mass index (kg/m^2)	≤ 21.7	1.409	0.639	3.104	0.40						
Cirrhosis	(+)	3.889	1.772	8.535	**<0.001**	*	1.477	0.435	5.009	0.53	
HCC history	(+)	2.167	0.865	5.427	0.099						
Alcohol consumption	(+)	0.364	0.109	1.218	0.101						
Cigarette smoking	(+)	1.154	0.510	2.612	0.73						
Diabetes mellitus	(+)	0.551	0.165	1.843	0.33						
Hypertension	(+)	1.401	0.629	3.118	0.41						
Baseline											
White blood cells (/μL)	≤ 4,200	2.536	1.139	5.646	**0.023**	*	1.765	0.693	4.498	0.23	
Hemoglobin (g/dL)	≤ 12.7	3.198	1.412	7.242	**0.005**	*	2.073	0.849	5.062	0.110	
Platelet count (×10^3/mm^3)	≤ 126	2.668	1.208	5.890	**0.015**	*	1.028	0.290	3.648	0.97	
Aspartate aminotransferase (U/L)	≥ 40	1.243	0.558	2.768	0.59						
Alanine aminotransferase (U/L)	≤ 33	1.457	0.665	3.196	0.35						
γ-Glutamyltransferase (U/L)	≤ 33	1.892	0.810	4.422	0.141						
Total bilirubin (mg/dL)	≤ 0.5	1.827	0.832	4.014	0.133						
Albumin (g/dL)	≤ 3.8	3.308	1.426	7.669	**0.005**	*	1.378	0.331	5.741	0.66	
Albumin–bilirubin grade	≥ 2	2.787	1.230	6.314	**0.014**	*	0.835	0.212	3.287	0.80	
Estimated glomerular filtration rate (mL/min/1.73 m^2)	≤ 67.94	4.590	1.833	11.494	**0.001**	*	3.407	1.315	8.825	**0.012**	*
Fibrosis-4 index	≥ 3.25	2.204	0.973	4.994	0.058						
α-Fetoprotein (ng/mL)	≥ 5.8	1.715	0.777	3.783	0.182						
HCV RNA (log IU/mL)	≤ 6.0	2.107	0.956	4.641	0.064						
EOT											
Albumin–bilirubin grade	≥ 2	2.436	1.106	5.367	**0.027**	*	0.617	0.211	1.803	0.38	
Fibrosis-4 index	≥ 3.25	3.003	1.361	6.625	**0.006**	*	0.842	0.254	2.793	0.78	
α-Fetoprotein (ng/mL)	≥ 4.9	1.418	0.612	3.285	0.42						
SVR$_{12}$											
Albumin–bilirubin grade	≥ 2	4.746	2.125	10.598	**<0.001**	*	3.449	1.181	10.072	**0.024**	*
Fibrosis-4 index	≥ 3.25	1.898	0.861	4.187	0.112						
α-Fetoprotein (ng/mL)	≥ 4.1	1.379	0.619	3.073	0.43						
After the end of DAA treatment											
HCC development	(+)	3.797	1.702	8.469	**0.001**	*	2.077	0.823	5.241	0.122	

*$p < 0.05$ indicates statistical significance. DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; EOT, end of treatment; SVR, sustained virological response.

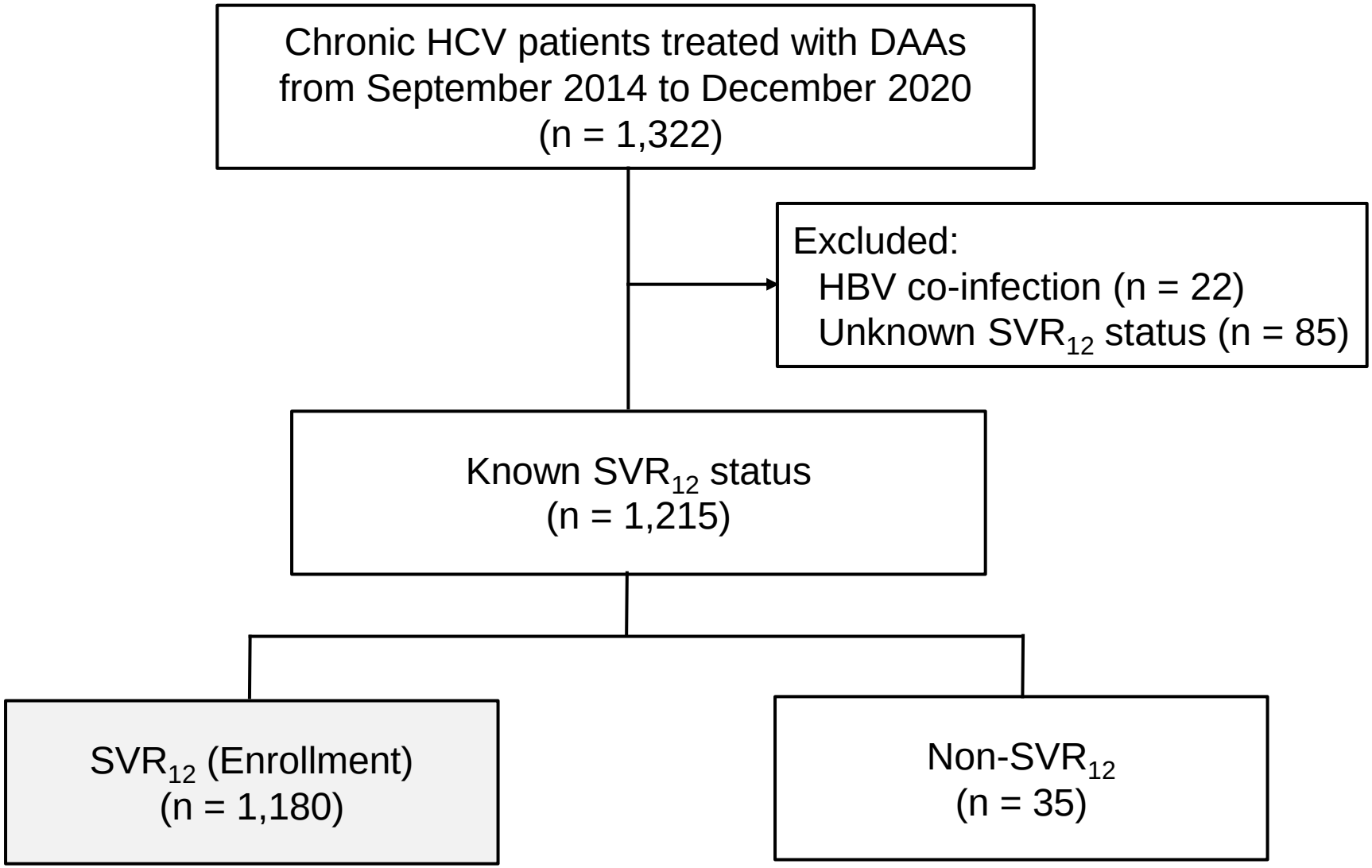
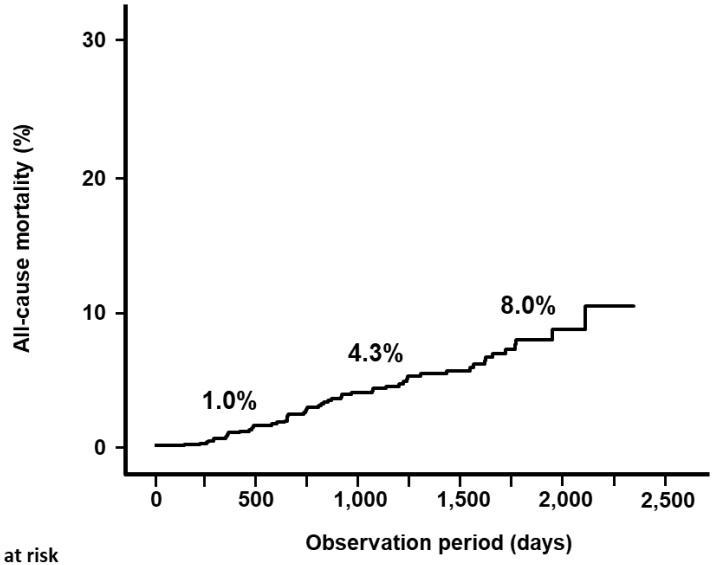

Chronic HCV patients treated with DAAs
from September 2014 to December 2020
(n = 1,322)
Excluded:
HBV co-infection (n = 22)
Unknown SVR12 status (n = 85)
Known SVR12 status
(n = 1,215)
SVR12 (Enrollment)
(n = 1,180)
Non-SVR12
(n = 35)

Figure 1

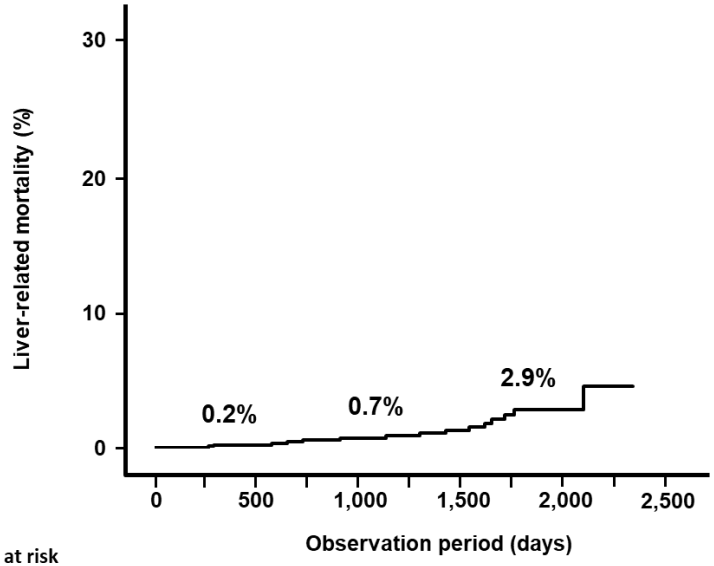
(A) All-cause mortality (n = 53)



Number at risk

Observation period (yr)	0	1	3	5
Patients	1,180	975	595	213

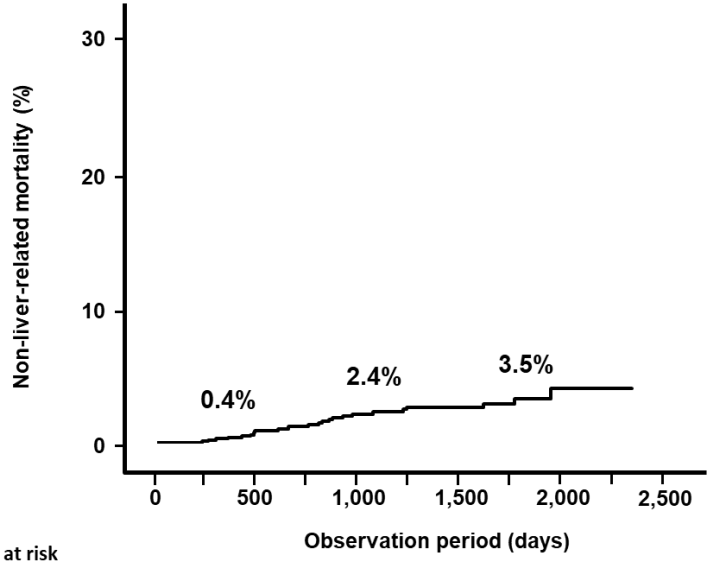
(B) Liver-related mortality (n = 15)



Number at risk

Observation period (yr)	0	1	3	5
Patients	1,180	975	595	213

(C) Non-liver-related mortality (n = 25)



Number at risk

Observation period (yr)	0	1	3	5
Patients	1,180	975	595	213

Figure 2