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ORIGINAL RESEARCH—CLINICAL

# The Impact of Cirrhosis and History of Hepatocellular Carcinoma on All-Cause Mortality After Eradication of Hepatitis C Virus in Patients With Chronic Hepatitis C

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**BACKGROUNDS AND AIMS:** Cirrhosis and hepatocellular carcinoma (HCC) are potentially fatal complications of chronic hepatitis C virus (HCV) infection. We investigated how compensated cirrhosis and a history of curatively treated HCC influenced patient mortality after HCV eradication, that is, sustained virologic response (SVR). **METHODS:** We studied 5458 patients with confirmed SVR who were prospectively followed up for more than 1 year after SVR achieved with direct-acting antivirals. Mortality and the incidence of HCC development after SVR were analyzed based on the presence or absence of compensated cirrhosis or a history of curatively treated HCC before the start of therapy. **RESULTS:** Mortality and the incidence of post-SVR HCC were significantly higher in patients with compensated cirrhosis and those with a history of curatively treated HCC than in those without these complications. Multivariate analysis showed that a history of HCC was associated with high mortality after SVR. In patients with no history of HCC, cirrhosis was associated with high mortality. Although both liver-related and nonliver-related mortality rates were significantly higher in patients with a history of HCC or cirrhosis, nonliver-related mortality did not differ based on HCC history, and liver-related and nonliver-related mortality were comparable regardless of cirrhosis after propensity score matching with age, gender, alcohol intake, and comorbidities. **CONCLUSION:** Mortality after SVR was significantly higher in patients with compensated cirrhosis or a history of HCC. While a history of HCC significantly increased mortality after SVR, even following curative treatment, the impact of pre-SVR compensated cirrhosis on post-SVR mortality was modest.

*Keywords:* Hepatitis C Virus; Sustained Virologic Response; Hepatocellular Carcinoma; Mortality; Cirrhosis

***Abbreviations used in this paper:*** **CI, confidence interval; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PSM, propensity score matching; SVR, sustained virologic response.**

**Most current article**



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## Introduction

Cirrhosis and hepatocellular carcinoma (HCC) are 2 main complications of chronic hepatitis C virus (HCV) infection. A primary reason to eradicate HCV is to

prevent these conditions because both increase mortality. The recent use of oral direct-acting antivirals (DAAs) to eradicate HCV has dramatically improved antiviral efficacy and tolerability, and the proportion of patients who achieve sustained virologic response (SVR) has markedly increased. Of note, regimens using DAAs also show high tolerability in elderly patients, those with cirrhosis or HCC, and those with other comorbidities such as diabetes or hypertension. Studies of DAA regimens have demonstrated comparable SVR rates in patients with and without compensated cirrhosis, indicating the high virological efficacy of these drugs in patients with compensated cirrhosis.[1,2] Although one previous study reported reduced SVR rates in patients with HCC,[3] several recent studies showed comparable virological efficacy in patients with and without HCC when HCC was treated curatively and was inactive.[4,5] Thus, both compensated cirrhosis and inactive HCC seem to have little impact on the ability of DAA therapy to eradicate HCV.

However, cirrhosis or HCC may unfavorably influence the survival of patients who achieve SVR, even when cirrhosis is in a compensated stage and HCC is treated curatively. Furthermore, when these complications are present before the start of DAA therapy, it is unclear how they, among the other comorbidities, impact the mortality of post-SVR patients with HCV infection. In Japan in particular, where most patients with SVR are elderly and the majority have several comorbidities, it is unclear whether these liver-related complications still influence mortality after SVR. In this large, multicenter cohort of patients in Japan who achieved HCV eradication by DAA therapy, we sought to elucidate the impact of compensated cirrhosis or a history of curatively treated HCC on mortality after SVR.

## Patients and Methods

### Patients

A total of 6201 patients underwent interferon-free DAA-based anti-HCV therapy between October 2012 and December 2018 at one of the following 16 institutions across Japan: Asai General Hospital, Ehime Prefectural Central Hospital, Jikei University Katsushika Hospital, Kagawa Prefectural Central Hospital, Kikkoman General Hospital, Kitasato University Hospital, Nagoya City University Hospital, Nippon Medical School Hospital, Nippon Medical School Chiba Hokusoh Hospital, Ogaki Municipal Hospital, Otakanomori Hospital, Saiseikai Niigata Hospital, Shinmatsudo Central General Hospital, St. Marianna University Hospital, Teine Keijinkai Hospital, and Yokohama City University Medical Center. Some patients underwent DAA therapy in the context of clinical trials. SVR was confirmed by the absence of serum HCV RNA at 12 weeks after the end of DAA therapy (ie, SVR12) in 5794 patients, and 5458 patients were continuously followed up for more than 1 year. We excluded 336 patients whose follow-up period after SVR was $<1$ year because post-SVR HCC within 1 year after SVR might have existed before SVR. We enrolled these 5458 patients in this study (Figure A1). The presence of compensated cirrhosis was clinically determined by attending hepatologists based on the results of imaging and endoscopic studies, including the presence of esophageal/gastric varices, collateral veins due to portal hypertension, and splenomegaly. Laboratory liver fibrosis markers such as the FIB-4 index[6] or aspartate aminotransferase platelet ratio index[7] and liver stiffness determined by ultrasonographic or magnetic resonance elastography were also taken into consideration. Patients with decompensated cirrhosis were not included in this study because the use of DAAs was not allowed in this population in Japan during the study period. Curatively treated HCC was defined as HCC treated by resection or locoregional ablation, and patients were confirmed to have no residual intrahepatic or extrahepatic liver tumors on computed tomography or magnetic resonance imaging scans before the start of DAA therapy. Patients with active HCC were not included in this study because the use of DAAs is not permitted in this population in Japan.

The study protocol was approved by the institutional review board of each participating hospital. Written informed consent was waived for this descriptive, observational study.

### Post-SVR Follow-Up and Outcomes

All patients were followed up after SVR; they regularly underwent ultrasonography and laboratory testing, including measurements of tumor markers, and computed tomography or magnetic resonance imaging was planned if necessary. Principally, patients with a history of curatively treated HCC were followed up every 3 months with laboratory tests and every 6 months with imaging studies for the first 5 years after treatment of HCC and every 6 months thereafter. Patients with no history of HCC were followed up every 6 months with laboratory tests and imaging studies. When a liver nodule was detected, further imaging and laboratory examinations for the diagnosis of HCC were conducted. Diagnosis and treatment of HCC were based on Japanese guidelines.[8]

Patients were followed up from the time of SVR confirmation by negative serum HCV RNA at SVR12 until the last visit before the end of October 2020, and their outcomes were measured. Causes of death during the study were categorized as liver related or nonliver related.

### Statistical Analysis

For comparisons of baseline characteristics between patient groups, differences in distribution were analyzed using the chi-square test, and differences in quantitative values were analyzed using the Mann–Whitney U test. Multivariate analyses with the Cox proportional hazard model were performed for factors associated with the development of HCC or death after SVR. Factors potentially associated with the post-SVR HCC development or mortality,

including patient age, gender, hepatitis B virus (HBV) coinfection, regular alcohol intake, presence of diabetes, presence of hypertension, compensated cirrhosis, and history of curatively treated HCC, were included in the multivariate analysis. To compare the incidences of HCC development and mortality after SVR, the Kaplan–Meier method and log-rank test were used. Actuarial analysis of cumulative mortality from cause of death category (liver-related mortality and nonliver-related mortality) was performed using cumulative incidence with the competing risks method, and differences across groups were tested using the Gray test. The date of the definition of SVR (SVR12, 12 weeks after the end of DAA therapy) was defined as time 0 for calculations of the incidence of HCC development or mortality. In the analysis of the incidence of HCC after SVR, patients who developed HCC after SVR were not censored, whereas those with no HCC development were censored. The observation period ended on the date of HCC development in noncensored cases and the date of the last visit in censored cases. In the analysis of mortality incidence, patients who died after SVR were not censored, whereas those who survived were censored. The observation period ended on the date of death in noncensored cases and the date of the last visit in censored cases. Propensity score matching (PSM) involving one-to-one pairing of patients was performed with propensity scores matched at 2 decimal places. PSM was conducted based on age, gender, HBV coinfection, regular alcohol intake, presence of diabetes, and presence of hypertension with calibration of 0.2. Statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). All *P* values were derived from 2-tailed tests, with $P < .05$ accepted as statistically significant.

**Table 1.** Baseline Characteristics of the Study Patients (N = 5458)

| | |
|---|---|
| Age (y) | 68 (59–75) |
| Gender (male/female) | 2603 (47.7)/2855 (52.3) |
| Compensated cirrhosis[a] (absent/present) | 3945 (72.3)/1513 (27.7) |
| History of curatively treated hepatocellular carcinoma (no/yes) | 4854 (88.9)/604 (11.1) |
| Coinfection with hepatitis B virus (no/yes) | 5146 (99.2)/42 (0.8) |
| Regular alcohol intake (no/yes) | 4266 (78.2)/1192 (21.8) |
| Diabetes (no/yes) | 4373 (80.1)/1085 (19.9) |
| Hypertension (no/yes) | 3495 (64.0)/1963 (36.0) |
| HCV genotype (1/2/other, mix[b]) | 3904 (71.5)/1539 (28.2)/14 (0.3) |
| Platelet count ($10^3/\mu L$) | 156 (113–199) |
| Alanine aminotransferase (IU/L) | 37 (24–62) |
| Aspartate aminotransferase (IU/L) | 40 (28–61) |
| FIB-4 index | 2.98 (1.89–4.99) |
| APRI | 0.78 (0.45–1.50) |
| Treatment regimen (DCV-ASV/LDV-SOF/OMV-PRV-Rit/EBR-GPR/DCV-ASV-BCV/SOF-RBV/OMV-PRV-Rit-RBV/GLE-PIB) | 1382 (25.3)/1641 (30.1)/359 (6.6)/318 (5.8)/29 (0.5)/1237 (22.7)/83 (1.5)/409 (7.5) |

Values in parentheses are interquartile ranges or percentages.
APRI, aspartate aminotransferase–platelet ratio index; DCV, daclatasvir; ASV, asunaprevir; LDV, ledipasvir; SOF, sofosbuvir; OMV; ombitasvir; PRV, paritaprevir; Rit, ritonavir; EBR, elbasvir; GPR, grazoprevir; BCV, beclabuvir; GLE, glecaprevir; PIB, pibrentasvir.
[a]Compensated cirrhosis was defined clinically by imaging and endoscopic study findings, including the presence of esophageal/gastric varices, collateral veins due to portal hypertension, and splenomegaly. Patients with decompensated cirrhosis were not included in this study because the use of DAAs was not allowed in patients with decompensated cirrhosis in Japan during the study period.
[b]Including HCV genotype 3 (n = 8), genotypes 1 and 2 (n = 3), and genotypes 1 and 3 (n = 1).

## Results

### Background Characteristics of Study Patients

Table 1 lists the background characteristics of study patients at the start of DAA therapy. Patients consisted of 2603 (47.7%) males and 2855 (52.3%) females, with a median age of 68 years (interquartile range [IQR], 59–75) years. Among the 5458 total patients, 1513 (27.7%) had compensated cirrhosis and 604 (11.1%) had a history of curative treatment of HCC (441 patients had both compensated cirrhosis and a history of curatively treated HCC). Patients were followed up after SVR for a median of 2.9 years (IQR, 2.0–3.4 years). During follow-up, 481 patients (8.8%) were lost to follow-up, with median 1.9 years (IQR, 1.4–2.6 years) after SVR. There were no differences in patient background characteristics between patients who continued follow-up and those who dropped out (data not shown). HCC was developed in 525 patients (344 recurrences in patients with a history of curatively treated HCC and 181 cases of de novo HCC after SVR), and 189 patients died during the study period. The causes of death in the overall population were HCC in 53 patients, liver-related causes excluding HCC in 17 patients, and nonliver-related causes in 119 patients. In patients who died due to nonliver-related causes, 29 (24.4%) died of non-HCC gastroenterological cancer, 2 (1.7%) died of benign gastroenterological diseases, 10 (8.4%) died of lung malignancy, 12 (10.1%) died of benign lung diseases, 8 (6.7%) died of hematological malignancy, 14 (11.8%) died of cardiovascular diseases, 8 (6.7%) died of cerebrovascular diseases, 5

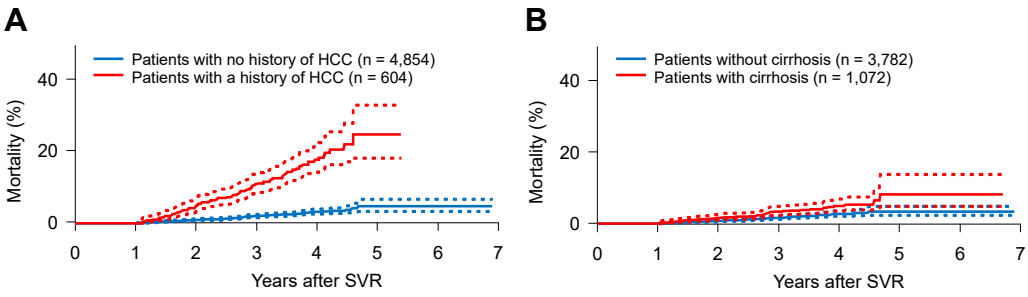


**Figure 1.** Comparisons of the all-cause mortality after sustained virologic response (SVR) based on the history of curatively treated hepatocellular carcinoma (HCC) in the entire study patients (A) and the presence of compensated cirrhosis in patients with no history of HCC (B). Dotted line, 95% confidence intervals.

died (4.2%) of renal diseases, 11 (9.2%) died of other diseases, and 20 (16.8%) died of unknown causes (Table A1).

## *Impact of a History of Curatively Treated HCC and Compensated Cirrhosis on Mortality After SVR*

Mortality after SVR was significantly higher in patients with a history of curatively treated HCC (hazard ratio [HR] 6.30, 95% confidence interval [CI], 4.51–8.03; Figure 1A) and in those with compensated cirrhosis (HR 2.57, 95% CI 1.93–3.43) before SVR than in patients without these complications. Multivariate analysis identified higher age, male gender, and a history of curative treatment of HCC (adjusted HR 3.76, 95% CI 2.71–5.21) as independent factors correlated with higher likelihood of mortality (Table 2). Cirrhosis was not significantly associated with high mortality in multivariate analysis (adjusted HR 1.27, 95% CI 0.93–1.75).

Among 4854 patients with no history of HCC, mortality after SVR remained significantly higher in patients with compensated cirrhosis before SVR than in those without cirrhosis (HR 1.95, 95% CI 1.30–2.88; Figure 1B). In multivariate analysis, cirrhosis before SVR was significantly associated with high mortality (adjusted HR 1.53, 95% CI 1.02-2.26) as were older age, male gender, and alcohol intake (Table 3).

## *Impact of a History of Curatively Treated HCC and Compensated Cirrhosis on Liver-Related and Nonliver-Related Mortality After SVR*

Competing risks analysis was performed to compare liver-related and nonliver-related mortality based on a history of curatively treated HCC and the presence of compensated cirrhosis. Liver-related mortality was significantly higher in patients with a history of HCC

**Table 2.** Multivariate Analyses of Baseline Factors Associated With All-Cause Mortality After SVR (N = 5458)

| Factors | Parameter estimate | Standard error | Likelihood ratio | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|---|
| Age (y) | | | | | |
| Per 1 y | 0.0645 | 0.0091 | 57.527 | 1.07 (1.05–1.09) | <.0001 |
| Gender | | | | | |
| Male | 0.2686 | 0.0811 | 11.095 | Reference | |
| Female | | | | 0.58 (0.42–0.80) | .0009 |
| HBV coinfection | | | | | |
| No | 10.516 | 13,725 | 3.592 | Reference | |
| Yes | | | | 7.34e-10 (0–1.07) | .0581 |
| Regular alcohol intake | | | | | |
| No | −0.1836 | 0.0875 | 4.243 | Reference | |
| Yes | | | | 1.44 (1.02–2.03) | .0394 |
| Diabetes | | | | | |
| Absent | −0.0763 | 0.0821 | 0.844 | Reference | |
| Present | | | | 1.16 (0.84–1.60) | .3581 |
| Hypertension | | | | | |
| Absent | 0.0514 | 0.0751 | 0.471 | Reference | |
| Present | | | | 0.90 (0.67–1.21) | .4926 |
| Cirrhosis | | | | | |
| Absent | −0.1202 | 0.0810 | 2.204 | Reference | |
| Present | | | | 1.27 (0.93–1.75) | .1377 |
| History of HCC | | | | | |
| No | −0.6625 | 0.0831 | 60.531 | Reference | |
| Yes | | | | 3.76 (2.71–5.21) | <.0001 |

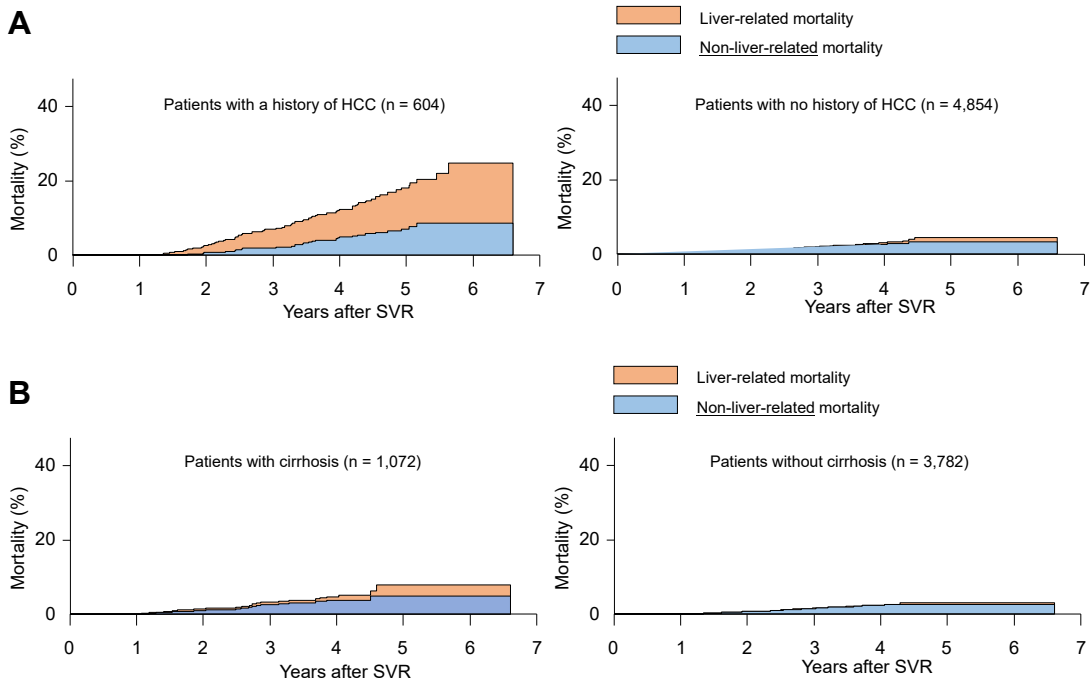


**Figure 2.** Comparisons of liver-related and liver-unrelated mortality after sustained virologic response (SVR) based on the history of curatively treated hepatocellular carcinoma (HCC) in the entire study patients (A) and the presence of compensated cirrhosis in patients with no history of HCC (B).

before SVR than in those without it (HR 32.27, 95% CI 17.22–60.50). A history of HCC had a similar impact on nonliver-related mortality (HR 2.58, 95% CI 1.72–3.87) but to a lesser degree (Figure 2A). When patient backgrounds were adjusted using PSM by patient age, gender, HBV coinfection, alcohol intake, and comorbidities (diabetes and hypertension), liver-related mortality in patients with a history of HCC remained higher than in those with no history of HCC (HR 49.39, 95% CI 6.83–357.2). By contrast, nonliver-related mortality did not differ between the 2 groups ($P = .3430$, HR 1.34, 95% CI 0.77–2.33; Figure A2A).

In patients without a history of HCC, both liver-related and nonliver-related mortality rates were significantly

**Table 3.** Multivariate Analyses of Baseline Factors Associated With All-Cause Mortality After SVR in Patients With No History of HCC Before SVR (N = 4854)

| Factors | Parameter estimate | Standard error | Likelihood ratio | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|---|
| Age (y) | | | | | |
| Per 1 y | 0.0831 | 0.0117 | 60.620 | 1.09 (1.06–1.11) | <.0001 |
| Gender | | | | | |
| Male | 0.4462 | 0.1083 | 17.432 | Reference | |
| Female | | | | 0.41 (0.27–0.62) | <.0001 |
| HBV coinfection | | | | | |
| No | 9.9480 | 13,457 | 1.202 | Reference | |
| Yes | | | | 2.29e-9 (0–3.23) | .2729 |
| Regular alcohol intake | | | | | |
| No | −0.2656 | 0.1151 | 5.041 | Reference | |
| Yes | | | | 1.70 (1.07–2.65) | .0248 |
| Diabetes | | | | | |
| Absent | −0.0808 | 0.1151 | 0.480 | Reference | |
| Present | | | | 1.18 (0.74–1.82) | .4884 |
| Hypertension | | | | | |
| Absent | 0.1229 | 0.1012 | 1.492 | Reference | |
| Present | | | | 0.78 (0.52–1.16) | .2217 |
| Cirrhosis | | | | | |
| Absent | −0.2117 | 0.1017 | 4.169 | Reference | |
| Present | | | | 1.53 (1.02–2.26) | .00412 |

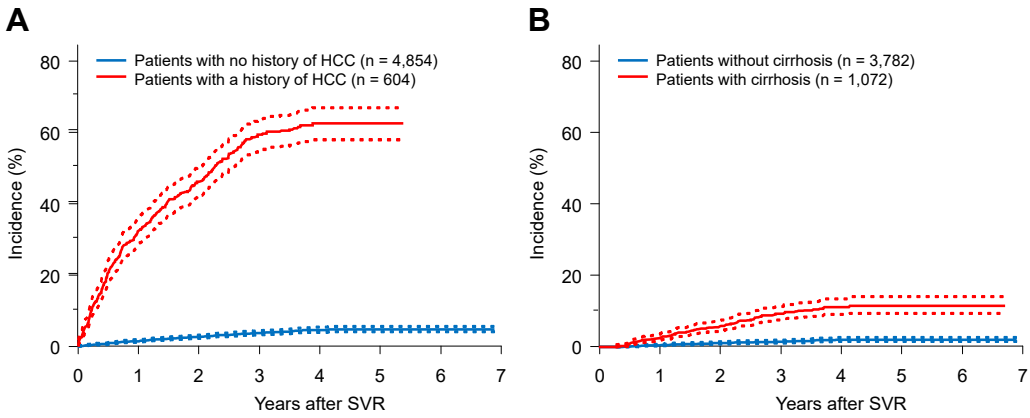


**Figure 3.** Comparisons of the incidence of the development of hepatocellular carcinoma (HCC) after sustained virologic response (SVR) based on the history of curatively treated HCC in the entire study patients (A) and the presence of compensated cirrhosis in patients with no history of HCC (B). Dotted line, 95% confidence intervals.

higher in patients with compensated cirrhosis before SVR than in those without it, but the difference was less significant for nonliver-related mortality (liver-related mortality, HR 10.24, 95% CI 2.70–38.83; nonliver-related mortality, HR 1.80, 95% CI 1.16–2.79; Figure 2B). When patient backgrounds were adjusted using PSM, there was no significant difference in liver-related and nonliver-related mortality rates based on the presence of cirrhosis before SVR (liver-related mortality, HR 2.03, 95% CI 0.82–4.63, nonliver-related mortality, HR 1.50, 95% CI 0.85–2.64; Figure A2B).

### *Impact of a History of Curatively Treated HCC and Compensated Cirrhosis on the Development of HCC After SVR*

The incidence of post-SVR HCC was significantly higher in patients with a history of curatively treated HCC (HR 22.20, 95% CI 18.51–26.71; Figure 3A) and in those with pre-SVR compensated cirrhosis than in those without these complications (HR 7.31, 95% CI 6.05–8.89). Multivariate analysis identified higher age, male gender, hypertension, presence of compensated cirrhosis (adjusted HR 2.70, 95% CI 2.19–3.35), and a history of curatively treated HCC (adjusted HR 11.62, 95% CI 9.46–14.33) as factors independently associated with a higher likelihood of HCC development after SVR (Table A2).

When patients with a history of curatively treated HCC before SVR were excluded, the incidence of HCC remained higher in patients with compensated cirrhosis than those without cirrhosis (HR 6.09, 95% CI 4.40–8.50; Figure 3B), and cirrhosis was associated with HCC development after SVR in multivariate analysis (adjusted HR 5.20, 95% CI 3.74–7.29; Table A3).

### *Effects of de Novo and Recurrent HCC After SVR on Post-SVR Mortality*

Among patients with a history of curatively treated HCC before SVR, the mortality in patients in whom HCC developed (ie, recurred) after SVR was significantly higher than that in patients with no post-SVR HCC (HR 2.25, 95% CI 1.38–3.86; Figure A3A). By contrast, among patients with no history of HCC before SVR, there was no difference in post-SVR mortality between patients who experienced HCC after SVR (ie, de novo HCC) and in those who did not (HR 1.83, 95% CI 0.86–3.42; Figure A3B).

## Discussion

Recent studies reported the beneficial effect of eradicating HCV (ie, achieving SVR) using DAA therapy in patients with HCV. Patients who achieved SVR showed higher survival rates than untreated patients with HCV; this was the case both in those with no history of HCC[9,10] and in those with HCC.[11,12] Current anti-HCV DAA regimens are tolerable even in patients with cirrhosis or HCC, leading to high rates of HCV eradication. However, it is unclear whether patient outcomes after SVR are affected by progression to compensated cirrhosis or by the development of HCC when these occur before DAA therapy; it is therefore unknown if the eradication of HCV can overcome these pre-SVR complications.

This prospective, observational study consisted of a large cohort of Japanese HCV patients who achieved SVR by DAA therapy. A previous study showed that Japanese HCV patients treated with DAA therapy are characterized by older age and a high prevalence of cirrhosis,[13] both of which are risk factors for HCC. In the present study, more than 25% of patients had compensated cirrhosis, and more than 10% had a history of HCC at baseline.

The findings of this study clearly showed that progression to compensated cirrhosis or a history of curatively treated HCC, both occurring before the start of DAA-based anti-HCV therapy, strongly influenced the outcomes of patients with HCV after SVR. The incidence of HCC development after SVR was significantly higher in patients with a history of curatively treated HCC than in those with no history of HCC before SVR. It has been reported that the

incidence of HCC recurrence after SVR is higher than that of de novo HCC, which is consistent with the findings of this study. The incidence of post-SVR HCC was also significantly higher in the overall study patients who had compensated cirrhosis at baseline than in those without cirrhosis. The percentage of patients with a history of curatively treated HCC was higher among those with cirrhosis (29.6%, 426/1440 patients) than among those without (4.2%, 160/3778 patients; $P < .0001$), which contributed to the higher incidence of HCC development after SVR in patients with cirrhosis. However, in an analysis limited to patients with no history of HCC, the incidence of post-SVR HCC in patients with compensated cirrhosis remained higher than that in patients without cirrhosis. This is not surprising because cirrhosis is a strong risk factor for HCC in patients with HCV, even after SVR.

The higher mortality of patients with a history of curatively treated HCC is considered to be primarily because of these patients' higher rate of post-SVR HCC. Indeed, patients with a history of HCC who experienced post-SVR HCC, ie, HCC recurrence, had significantly higher mortality than those who did not experience recurrence after SVR. Consequently, patients with a history of HCC had markedly higher liver-related mortality. By contrast, nonliver-related mortality was comparable between patients with and without a history of HCC when PSM was used to adjust for background characteristics.

Unlike post-SVR HCC recurrence in patients with a history of HCC, post-SVR HCC in patients with no history of HCC, ie, de novo HCC, only modestly increased mortality after SVR. The survival rate of patients with de novo HCC after SVR was significantly higher than that of patients with HCC that developed during persistent HCV infection,[14] which was associated with a decreased unfavorable influence of post-SVR HCC on mortality in patients with no history of HCC. Consequently, patients with compensated cirrhosis and those without cirrhosis showed no difference in either liver-related or nonliver-related mortality after PSM. Thus, in patients with no history of HCC, a negative influence of compensated cirrhosis on mortality may be overcome by HCV eradication.

There are several limitations to this study. First, the study patients with cirrhosis were limited to those who had compensated cirrhosis because DAA-based anti-HCV therapy for patients with decompensated cirrhosis had not yet been approved by the Japanese government at the time of patient enrollment. Although we did not find a difference in mortality between patients with compensated cirrhosis and those without cirrhosis after PSM, these results may differ when patients with decompensated cirrhosis are included. Further studies are needed to determine how decompensated cirrhosis before DAA therapy impacts post-SVR survival. In addition, patients with active HCC that was treated noncuratively were not included in this study, because anti-HCV therapy with DAAs was not approved by the Japanese government for patients with active HCC. Second, the assessment of cirrhosis was not standardized throughout the study population and instead was determined on an institutional or individual basis by attending hepatologists using several methods. In current clinical practice, cirrhosis is not frequently evaluated by liver biopsy because of the risk of complications.[15] Transient elastography, an established alternative for measuring liver fibrosis and cirrhosis, is not available at all institutions. However, all attending hepatologists who participated in this study were experienced in the diagnosis of cirrhosis, and determination of the presence of compensated cirrhosis should have been consistent. Third, surveillance intensity differed some patients with a history of curatively treated HCC, in whom surveillance was more intensive. This might have increased the incidence of post-SVR HCC development, although they were minor population. Finally, the observation period was relatively short, and longer observation will be necessary to confirm the current findings and, in particular, to determine whether a higher incidence of post-SVR HCC in patients with compensated cirrhosis than in those without cirrhosis really does not result in a mortality difference between the 2 groups. In addition, this study included a high proportion of elderly patients, which may have contributed to the high rate of nonliver-related death. Longer follow-up of younger SVR patients may reveal a different distribution of causes of death after SVR.

In summary, this prospective, observational study of a large cohort of patients with SVR revealed that compensated cirrhosis existing before anti-HCV therapy with DAAs did not influence the survival of patients with HCV after SVR, despite the higher incidence of HCC. In contrast, a history of HCC before DAA therapy strongly influenced survival after SVR, even when HCC was treated curatively.

## Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.02.018.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

**Data Transparency Statement:**
Data, analytic methods, and study materials will be available to other researchers on request to corresponding author.