Effects of Achieving SVR on Clinical Characteristics and Surgical Outcomes in Patients Who Developed Early-Stage HCV-Related Hepatocellular Carcinoma and Received Curative Resection: Preoperative versus Postoperative SVR

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Abstract: The high accessibility to healthcare and increasing awareness of hepatocellular carcinoma (HCC) surveillance after sustained virologic response (SVR) to HCV treatment allow early detection of operable HCC in Taiwan. However, the effects of achieving SVR on patient characteristics and surgical outcomes after curative resection remain elusive. We aimed to compare the clinical presentation and postoperative prognosis among patients with early-stage HCV-related HCC and different viral status. We retrospectively analyzed 208 patients with BCLC stage 0 or A-HCC, including 44 patients who remained HCV viremic, 90 patients who developed HCC after achieving SVR (post-SVR HCC), and 74 patients who subsequently achieved SVR after resection. Patients with post-SVR HCC had a lower degree of hepatitis and better liver function than those who achieved SVR or remained viremic after resection. Notably, 75.6% of patients with post-SVR HCC did not have cirrhosis. Patients with post-SVR HCC and those achieving SVR after resection exhibited comparable recurrence rates and recurrence-free survival, while patients with persistent viremia had the worst surgical outcomes. We concluded that patients with post-SVR HCC had a better liver function but similar surgical outcomes compared with patients who achieved SVR after resection. The low prevalence of cirrhosis in patients with post-SVR HCC highlights the importance of regular surveillance after SVR.

Keywords: chronic hepatitis C; viremia; sustained virologic response; hepatocellular carcinoma; recurrence

1. Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death and ranks sixth in terms of incident cases globally [1]. The majority of HCC arises from underlying liver diseases, such as hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, alcohol abuse, and nonalcoholic fatty liver disease. Taiwan is an epidemic region for HCV, with a much higher prevalence (3.28% [1.8–5.5%]) than other regions of the world, leading to a high incidence rate of HCC [2–4].

Although interferon (IFN)-based regimens have demonstrated their beneficial effects on recurrence and mortality in patients with HCV-related HCC who underwent curative resection.
treatment [5–7], ineligibility and treatment-related adverse events often limit the applicability of IFN-based treatment and cause a large gap between clinical efficacy and community effectiveness [2]. Fortunately, these dilemmas have been resolved with the introduction of novel IFN-free, direct-acting antiviral (DAA) agents, which have excellent safety and effectiveness and require a shorter treatment duration. While some previous studies reported unexpectedly high rates of HCC occurrence and recurrence with DAA treatment [8–10], subsequent prospective cohort studies and meta-analyses refuted these findings [11–13].

To eliminate HCV, the National Health Insurance of Taiwan has reimbursed IFN-based therapy since 2003 and DAA therapy since 2017. While more and more HCV-infected patients achieved sustained virologic response (SVR) and gained benefits from HCV eradication, the risk of HCC development persists, especially for those with HCC-related risk factors, such as diabetes, cirrhosis, and high alpha-fetoprotein (AFP) [14–16]. With the high accessibility of healthcare in Taiwan, regular surveillance after SVR allows early detection and curative treatment for HCC. However, little is known about the clinical presentation and treatment outcomes after curative therapies in patients who developed early-stage HCC after achieving SVR. It is also unclear if there are different patient and tumor features, recurrence rates after surgical intervention, and recurrence-free survival between patients who developed HCC after SVR and those who achieved SVR after HCC occurrence. Because patient and tumor characteristics play vital roles in the long-term outcomes of HCC after resection, it is essential to characterize these factors in these patient populations [17–20]. The current study aimed to evaluate and compare the clinical characteristics and surgical outcomes among patients with Barcelona Clinic Liver Cancer (BCLC) stage 0 or A-HCC and different viral status.

2. Materials and Methods

2.1. Study Population

This retrospective cohort study reviewed patients with HCC between March 2005 and July 2020 at Kaohsiung Medical University Hospital. The diagnosis of HCC was made based on the criteria of the American Association for the Study of Liver Diseases [21]. The diagnosis was also confirmed by an HCC expert group for each patient. The inclusion criteria were as follows: (1) patients diagnosed with only HCV infection based on the presence of hepatitis C antibody and negative hepatitis B surface antigen (HBsAg); (2) HCC in BCLC stage 0 or A; (3) receiving curative liver resection. We excluded patients who had positive surgical margins, human immunodeficiency virus (HIV) infection, or were concurrent with other cancers. Informed consent was obtained from all individual participants included in the study.

All patients enrolled in this study were categorized into three groups according to the presence of HCV viremia at the time of HCC occurrence and the presence of SVR to HCV treatment: HCC with persistent viremia (patients who had positive HCV RNA at HCC diagnosis and were untreated or failed to achieve SVR), Post-SVR HCC (patients with negative HCV RNA at HCC diagnosis), and viremic HCC with subsequent SVR (patients who achieved HCV SVR after surgical resection). SVR was defined as persistent undetectable serum HCV RNA (24 weeks for patients treated with IFN-based therapy or 12 weeks for patients treated with DAA therapy after the end of treatment).

2.2. Data Collection

All data were obtained retrospectively from the medical record, including age, sex, body mass index (BMI), presence of type 2 diabetes mellitus, hypertension, alcohol drinking, smoking history, serum biochemistry, and AFP. The histological features of the resected tumor, including tumor differentiation, number and size of the tumors, microvascular invasion, capsule invasion, and satellite nodules, were recorded. The presence of hepatic steatosis, Ishak fibrosis score, and Scheuer score were assessed and recorded from non-tumorous liver parts [22,23]. Hepatic steatosis was defined as the presence of ≥5% steatotic
hepatocytes in histology specimen. Liver cirrhosis was defined as Ishak fibrosis score 5–6 or Scheuer score 4.

2.3. Surgical Outcome Assessment

All the patients were under regular surveillance for tumor recurrence by sonography, dynamic computed tomography, and/or magnetic resonance imaging every 3–4 months. Recurrence of the tumor was defined as the appearance of new HCC nodules, local tumor progression, or both. Recurrence rates were calculated as the time from surgical resection to recurrence events. Recurrence-free survival (RFS) was defined as the time from surgical resection to HCC recurrence or death from any cause. The census of survival and recurrence status was checked by the end of August 2022. We compared the recurrence rates and RFS between patients in different groups.

2.4. Statistical Analysis

Continuous variables were expressed as means ± standard deviations, and categorical variables were presented as number (percentage). The one-way ANOVA was used to compare continuous variables, and the chi square test or Fisher’s exact test was used to compare categorical variables of different groups. The Kaplan–Meier method and the log-rank test were used to analyze recurrence and survival rates. Multivariate analysis with Cox proportional hazard analysis was used to identify the independent prognostic factors. Variables with a potential relationship (p < 0.1) identified in the univariate analyses were included in the multivariate analysis. All p values are two-sided, and p < 0.05 is determined as statistically significant difference. All database processing and analyses were conducted with SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Baseline Patient Characteristics

Between March 2005 and July 2020, 256 patients with BCLC stage 0 or A-HCC who received primary curative hepatectomy were reviewed. We excluded 29 patients with positive HBsAg, three patients who had positive surgical margins, fifteen patients who possessed concurrent cancers other than HCC, and 1 patient who had HIV infection. A total of 208 patients were enrolled in the current study. Forty-four patients had HCC with persistent HCV viremia, 90 patients possessed post-SVR HCC, and 74 patients had viremic HCC and subsequently achieved SVR to antiviral therapies (Figure 1). Their baseline patient characteristics are presented in Table 1. Patients with post-SVR HCC had significantly lower aspartate aminotransferase (AST) levels, lower alanine aminotransferase (ALT) levels, and a higher prevalence of albumin-bilirubin (ALBI) grade I compared to those who had viremic HCC. AFP levels and the presence of histological features, including tumor differentiation, number and size of the tumors, microvascular invasion, capsule invasion, satellite nodules, hepatic steatosis, and cirrhosis, were similar among the three groups.

Table 1. Baseline characteristics of the 208 patients with early-stage HCV-related HCC.

| Variable                          | All Patients (n = 208) | HCC with Persistent Viremia (n = 44) | Post-SVR HCC (n = 90) | Viremic HCC with Subsequent SVR (n = 74) | p Value |
|-----------------------------------|------------------------|--------------------------------------|-----------------------|-----------------------------------------|---------|
| Age (years), mean ± SD            | 64.6 ± 8.6             | 67.5 ± 8.2                           | 64.7 ± 8.1            | 62.8 ± 8.9†                            | 0.016   |
| Male gender, n (%)                | 136 (65.4)             | 25 (56.8)                            | 65 (72.2)             | 46 (62.2)                               | 0.163   |
| BMI (kg/m²), mean ± SD           | 24.6 ± 3.8             | 24.2 ± 3.5                           | 25.4 ± 4.1            | 23.9 ± 3.3‡                            | 0.032   |
| Diabetes mellitus, n (%)          | 68 (32.7)              | 17 (38.6)                            | 32 (35.6)             | 19 (25.7)                               | 0.260   |
| Hypertension, n (%)               | 104 (50.0)             | 25 (56.8)                            | 54 (60.0)             | 25 (33.8)†                              | 0.002   |
| Alcohol drinking, n (%)           | 44 (21.2)              | 8 (18.2)                             | 22 (24.4)             | 14 (18.9)                               | 0.595   |
| Smoking, n (%)                    | 61 (29.3)              | 9 (20.5)                             | 29 (32.2)             | 23 (31.1)                               | 0.342   |
| AST (IU/L), mean ± SD             | 53.6 ± 44.2            | 68.3 ± 28.8                          | 37.9 ± 52.1†          | 64.0 ± 34.6‡                           | <0.001  |
Table 1. Baseline characteristics of the 208 patients with early-stage HCV-related HCC.

| Variable                                      | All Patients (n = 208) | HCC with Persistent Viremia (n = 44) | Post-SVR HCC (n = 90) | Viremic HCC with Subsequent SVR (n = 74) | p Value |
|------------------------------------------------|------------------------|--------------------------------------|-----------------------|----------------------------------------|---------|
| ALT (IU/L), mean ± SD                          | 55.2 ± 42.5            | 68.7 ± 39.3                          | 34.7 ± 32.2†          | 72.1 ± 44.9‡                          | <0.001  |
| Platelet count (10^3/μL), mean ± SD            | 166.9 ± 71.1           | 148.0 ± 54.5                         | 181.2 ± 62.9†         | 160.8 ± 85.3                         | 0.025   |
| ALBI grade I/II/III                            |                        |                                      |                       |                                        |         |
| Grade I, n (%)                                 | 147 (70.7)             | 19 (43.2)                            | 78 (86.7)†            | 50 (67.6)†                            | <0.001  |
| Grade II, n (%)                                | 59 (28.4)              | 24 (54.5)                            | 11 (12.2)†            | 24 (32.4)‡                           |         |
| Grade III, n (%)                               | 2 (1.0)                | 1 (2.3)                              | 1 (1.1)               | 0 (0)                                 |         |
| AFP ≥ 20 ng/mL, n (%)                          | 80 (38.5)              | 25 (56.8)                            | 26 (28.9)†            | 29 (39.2)                             | 0.008   |
| AFP ≥ 200 ng/mL, n (%)                         | 32 (15.4)              | 11 (25.0)                            | 12 (13.3)             | 9 (12.2)                              | 0.135   |
| BCLC stage 0/A, n (%)                          | 71/137 (34.1/65.9)     | (29.5/70.5)                          | (34.4/65.6)           | (36.5/63.5)                           | 0.742   |
| Histological grade                             |                        |                                      |                       |                                        |         |
| Well-differentiated, n (%)                     | 27 (13.0)              | 7 (15.9)                             | 7 (7.8)               | 13 (17.6)                             | 0.168   |
| Moderately differentiated, n (%)               | 144 (69.2)             | 33 (75.0)                            | 64 (71.1)             | 47 (63.5)                             |         |
| Poorly differentiated, n (%)                   | 37 (17.8)              | 4 (9.1)                              | 19 (21.1)             | 14 (18.9)                             |         |
| Multiple tumors, n (%)                         | 19 (9.1)               | 3 (6.8)                              | 8 (9.8)               | 8 (10.8)                              | 0.822   |
| Largest tumor size (cm), mean ± SD             | 2.6 ± 1.1              | 2.5 ± 1.1                            | 2.5 ± 1.0             | 2.6 ± 1.2                             | 0.832   |
| Microvascular invasion, n (%)                  | 43 (20.7)              | 9 (20.5)                             | 20 (22.2)             | 14 (18.9)                             | 0.873   |
| Capsule invasion, n (%)                        | 75 (36.1)              | 13 (29.5)                            | 32 (35.6)             | 30 (40.5)                             | 0.481   |
| Satellite nodules, n (%)                       | 52 (25.0)              | 14 (31.8)                            | 19 (21.1)             | 19 (25.7)                             | 0.400   |
| Hepatic steatosis, n (%)                       | 100 (48.1)             | 26 (59.1)                            | 46 (51.1)             | 28 (37.8)                             | 0.061   |
| Liver cirrhosis, n (%)                         | 65 (31.3)              | 19 (43.2)                            | 22 (24.4)             | 24 (32.4)                             | 0.186   |
| Follow-up (months), mean ± SD                  | 70.7 ± 43.3            | 50.5 ± 37.6                          | 67.0 ± 40.4           | 87.3 ± 44.2 †‡                        | <0.001  |

Abbreviations: BMI, body mass index; SVR, sustained virologic response; IFN, interferon; DAA, direct-acting antiviral; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALBI, Albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer. Continuous data were presented as mean ± standard deviation; Categorical data were presented as number (%). † p < 0.05 vs. HCC with persistent viremia; ‡ p < 0.05 vs. post-SVR HCC; ¶ Liver cirrhosis was defined as Ishak fibrosis score 5–6 or Scheuer score 4 from non-tumor part.

Figure 1. Flow chart of the study.
3.2. Surgical Outcomes of HCC with Different Viral Status

Of the 208 patients with HCC after curative resection, 126 patients (60.6%) developed recurrence during a mean follow-up time of 70.7 months. The cumulative recurrence rates of HCC at the end of the first, third, and fifth year were 35%, 50%, and 61%, respectively (Table 2). Recurrence rates were compared among the three groups: one-year recurrence rates were 60%, 25%, and 32%, three-year recurrence rates were 76%, 45%, and 42%, and five-year recurrence rates were 89%, 51%, and 59% in the HCC with the persistent viremia group, post-SVR HCC group, and viremic HCC with subsequent SVR group, respectively. The recurrence rates of patients achieving SVR either before or after HCC occurrence were significantly lower than that in patients who remained viremic, while the recurrence rates were similar between patients with post-SVR HCC and those achieving SVR after surgical intervention \((p = 0.638, \text{Figure 2A})\). During a mean follow-up duration of 70.7 months, the median RFS was 39.5 months (95% CI, 23.1–55.9). The median RFS of the HCC with persistent viremia group, post-SVR HCC group, and viremic HCC with subsequent SVR group were 11.6 months (95% CI, 9.5–13.7), 56.7 months (95% CI, 11.8–101.6), and 56.7 months (95% CI, 43.3–70.0), respectively (Table 2). Patients achieving SVR showed significantly longer RFS than those with persistent viremia \((p < 0.001)\), while subjects with post-SVR HCC and those with HCC and subsequent SVR showed comparable RFS \((p = 0.616, \text{Figure 2B})\). In subgroup analyses based on various clinical characteristics, similar findings were observed for recurrence rates and RFS (Figures 3A–D and 4A–D).

![Figure 2](image_url1)  
(A) Cumulative recurrence rates and (B) recurrence-free survival of HCV-related HCC based on viral status.

| All Patients (n = 208) | HCC with Persistent Viremia (n = 44) | Post-SVR HCC (n = 90) | Viremic HCC with Subsequent SVR (n = 74) | HCC with Persistent Viremia vs. Post-SVR HCC p Value | HCC with Persistent Viremia vs. Viremic HCC with Subsequent SVR p Value | Post-SVR HCC vs. Viremic HCC with Subsequent SVR p Value |
|-----------------------|-------------------------------------|-----------------------|----------------------------------------|------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------|
| Cumulative recurrence rates | <0.001 | <0.001 | 0.638 |
| 1-year recurrence rate | 35% | 60% | 25% | 32% |
| 3-year recurrence rate | 50% | 76% | 45% | 42% |
| 5-year recurrence rate | 62% | 89% | 51% | 59% |
| Recurrence-free survival, months (95% CI) | 39.5 (23.1–55.9) | 11.6 (9.5–13.7) | 56.7 (11.8–101.6) | 56.7 (43.3–70.0) | <0.001 | <0.001 | 0.616 |
Table 2. Prognosis of the 208 patients with HCV-related early-stage HCC based on HCV status

|                                | All Patients (n = 208) | HCC with Persistent Viremia (n = 44) | Post-SVR HCC (n = 90) | Viremic HCC with Subsequent SVR (n = 74) | HCC with Persistent Viremia vs. Viremic HCC with Subsequent SVR p Value | HCC with Persistent Viremia vs. Post-SVR HCC p Value | Post-SVR HCC vs. Viremic HCC with Subsequent SVR p Value |
|--------------------------------|------------------------|--------------------------------------|-----------------------|------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------|
| 1-year RFS                     | 63%                    | 33%                                  | 73%                   | 68%                                      | <0.001                                                                | <0.001                                              | 0.616                                                   |
| 3-year RFS                     | 47%                    | 16%                                  | 53%                   | 58%                                      | 0.638                                                                 |                                                      |                                                        |
| 5-year RFS                     | 36%                    | 8%                                   | 48%                   | 40%                                      |                                                                       |                                                      |                                                        |

Abbreviations: SVR, sustained virologic response; CI, confidence interval; RFS, recurrence-free survival.

Figure 3. Comparisons of recurrence rates of HCC based on viral status in patients with (A) ALBI grade I, (B) ALBI grade II/III, (C) non-LC, and (D) LC.
Figure 3. Comparisons of recurrence rates of HCC based on viral status in patients with (A) ALBI grade I, (B) ALBI grade II/III, (C) non-LC, and (D) LC.

3.3. Prognostic Factors

We evaluated the prognostic factors associated with HCC recurrence and RFS. By multivariate analysis, post-SVR HCC (HR, 0.42; p < 0.001) and viremic HCC with subsequent SVR (HR, 0.41; p < 0.001) were independent factors predictive of lower recurrence rates (vs. HCC with persistent viremia [Table 3]). Post-SVR HCC (vs. HCC with persistent viremia, HR, 0.35; p < 0.001), viremic HCC with subsequent SVR (vs. HCC with persistent viremia, HR, 0.34; p < 0.001) were independent factors related to longer RFS (Table 4).

Table 3. Factors predictive of HCC recurrence.

| Predictor                        | Univariate       |         | Multivariate     |         |
|----------------------------------|------------------|---------|------------------|---------|
|                                  | HR (95% CI)      | p Value | HR (95% CI)      | p Value |
| Age ≥ 60 (years)                 | 1.38 (0.92–2.07) | 0.126   |                  |         |
| Male                             | 1.11 (0.77–1.61) | 0.569   |                  |         |
| Diabetes mellitus                | 1.25 (0.86–1.80) | 0.243   |                  |         |
| Hypertension                     | 0.84 (0.59–1.19) | 0.332   |                  |         |
| Alcohol drinking                 | 0.90 (0.58–1.39) | 0.619   |                  |         |
| Smoking                          | 0.79 (0.53–1.18) | 0.244   |                  |         |
| AST ≥ 40 (IU/L)                  | 1.31 (0.92–1.86) | 0.138   |                  |         |
| ALT ≥ 40 (IU/L)                  | 1.36 (0.96–1.94) | 0.085   | 1.21 (0.81–1.80) | 0.358   |
Table 3. Cont.

| Predictor | Univariate | Multivariate |
|-----------|------------|--------------|
|           | HR (95% CI) | p Value      | HR (95% CI) | p Value      |
| Platelet ≥ 150 (10^3/µL) | 0.72 (0.50–1.02) | 0.064 | 0.72 (0.50–1.05) | 0.089 |
| ALBI grade II/III (vs. grade I) | 1.26 (0.86–1.83) | 0.233 |                |                |
| AFP ≥ 200 ng/mL | 1.44 (0.90–2.31) | 0.127 |                |                |
| HCV status |                |                |                |                |
| HCC with persistent viremia |                |                | 0.37 (0.24–0.58) | <0.001 |
| Viremic HCC with subsequent SVR | 0.41 (0.26–0.65) | <0.001 | 0.41 (0.26–0.66) | <0.001 |
| BCLC stage A (vs. stage 0) | 1.41 (0.96–2.06) | 0.079 | 1.25 (0.74–2.11) | 0.413 |
| Multiple tumors | 1.04 (0.59–1.85) | 0.886 |                |                |
| Largest tumor size (cm) | 1.16 (0.99–1.37) | 0.065 | 1.11 (0.89–1.38) | 0.377 |
| Histological grade: poor/moderate (vs. well) | 1.40 (0.81–2.45) | 0.232 |                |                |
| Microvascular invasion | 1.14 (0.74–1.77) | 0.548 |                |                |
| Capsule invasion | 1.12 (0.78–1.61) | 0.538 |                |                |
| Satellite nodules | 1.53 (1.04–2.26) | 0.031 | 1.59 (1.06–2.38) | 0.025 |
| Hepatic steatosis | 1.38 (0.97–1.96) | 0.072 | 1.41 (0.97–2.04) | 0.070 |
| Liver cirrhosis † | 1.30 (0.90–1.87) | 0.159 |                |                |

Abbreviations: HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; SVR, sustained virologic response; BCLC, Barcelona Clinic Liver Cancer. † Liver cirrhosis was defined as Ishak fibrosis score 5–6 or Scheuer score 4 from non-tumor part.

Table 4. Factors predictive of recurrence-free survival.

| Predictor | Univariate | Multivariate |
|-----------|------------|--------------|
|           | HR (95% CI) | p Value      | HR (95% CI) | p Value      |
| Age ≥ 60 (years) | 1.40 (0.95–2.08) | 0.093 | 1.31 (0.86–1.99) | 0.214 |
| Male | 1.06 (0.74–1.50) | 0.756 |                |                |
| Diabetes mellitus | 1.23 (0.86–1.76) | 0.257 |                |                |
| Hypertension | 0.83 (0.59–1.16) | 0.263 |                |                |
| Alcohol drinking | 0.89 (0.59–1.36) | 0.601 |                |                |
| Smoking | 0.77 (0.52–1.13) | 0.184 |                |                |
| AST ≥ 40 (IU/L) | 1.33 (0.94–1.86) | 0.104 |                |                |
| ALT ≥ 40 (IU/L) | 1.35 (0.96–1.89) | 0.085 | 1.25 (0.84–1.85) | 0.275 |
| Platelet ≥ 150 (10^3/µL) | 0.71 (0.51–0.99) | 0.049 | 0.71 (0.49–1.04) | 0.077 |
| ALBI grade II/III (vs. grade I) | 1.38 (0.97–1.96) | 0.077 | 0.88 (0.58–1.34) | 0.560 |
| AFP ≥ 200 ng/mL | 1.48 (0.94–2.32) | 0.091 | 1.59 (1.00–2.54) | 0.051 |
| HCV status |                |                |                |                |
| HCC with persistent viremia |                |                | 0.32 (0.21–0.49) | <0.001 |
| Viremic HCC with subsequent SVR | 0.36 (0.23–0.56) | <0.001 | 0.34 (0.21–0.54) | <0.001 |
| BCLC stage A (vs. stage 0) | 1.46 (1.01–2.11) | 0.046 | 1.25 (0.75–2.08) | 0.392 |
| Multiple tumors | 1.05 (0.60–1.82) | 0.877 |                |                |
| Largest tumor size (cm) | 1.17 (1.00–1.37) | 0.046 | 1.10 (0.89–1.37) | 0.370 |
| Histological grade: poor/moderate (vs. well) | 1.42 (0.83–2.42) | 0.204 |                |                |
| Microvascular invasion | 1.25 (0.83–1.89) | 0.286 |                |                |
| Capsule invasion | 1.09 (0.77–1.55) | 0.616 |                |                |
| Satellite nodules | 1.48 (1.02–2.16) | 0.040 | 1.43 (0.97–2.11) | 0.069 |
| Hepatic steatosis | 1.29 (0.92–1.81) | 0.141 |                |                |
| Liver cirrhosis † | 1.20 (0.84–1.71) | 0.318 |                |                |

Abbreviations: HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; SVR, sustained virologic response; BCLC, Barcelona Clinic Liver Cancer. † Liver cirrhosis was defined as Ishak fibrosis score 5–6 or Scheuer score 4 from non-tumor part.
4. Discussion

The current study demonstrated that viral status at the time of and after HCC diagnosis is the most important factor influencing patient characteristics and postoperative prognosis. Patients with post-SVR HCC had a lower degree of hepatitis and better liver function than those who had subsequent SVR or remained viremic after HCC diagnosis. Patients with post-SVR HCC and those achieving SVR after resection exhibited comparable recurrence rates and RFS, which were markedly better than those in patients who remained viremic after resection. In multivariate analyses, achieving SVR both before and after HCC occurrence was a substantial factor predictive of lower HCC recurrence and longer RFS compared with constant HCV viremia.

In our study, lower levels of liver enzymes, a higher proportion of ALBI grade I, higher platelet counts, and a numerically lower incidence of liver cirrhosis in patients achieving SVR before HCC diagnosis indicated that HCV clearance improved hepatitis, leading to a lower degree of liver fibrosis and incidence of cirrhosis as well as a better liver function. These findings were consistent with the results of prior studies [24–27]. Notably, as many as 75.6% of patients who developed HCC after achieving SVR did not have cirrhosis. This phenomenon might be ascribed to the epigenetic alterations caused by HCV infection, which induce long-term oncogenic effects even after viral eradication [28,29]. Our result highlights the importance of post-SVR surveillance, regardless of the presence of cirrhosis.

Previous studies mainly focused on the effect of anti-HCV therapy after HCC developed and showed improved liver-related and overall survival [30–32]. However, there were limited data regarding the clinical outcomes of patients who developed HCC after achieving SVR. Our prior large multinational study demonstrated that patients with post-SVR HCC had better overall survival (OS) than patients with viremic HCC, while eradicating hepatitis C after HCC occurrence also improved survival. The subgroup analysis for patients with BCLC stage 0/A showed a comparable OS between the post-SVR HCC and the viremic HCC with subsequent SVR groups [25]. With many efforts in managing HCV, including outreach screening and treatment programs for people in hyperendemic areas, patients undergoing dialysis, people who inject drugs, and prisoners, as well as the increasing awareness of HCC surveillance after SVR in Taiwan [33–35], we can expect a growing number of patients with operable HCC. The current study expands on the clinical characteristics and surgical outcomes in this population. The current study investigated the recurrence rates and RFS after resection of HCC with various viral status. Similar recurrence rates and RFS were observed between subjects with post-SVR HCC and those with viremic HCC and subsequent SVR. At the same time, patients with persistent viremia had worse surgical outcomes. One multicenter study including 504 Japanese patients who had HCV-related HCC and underwent curative resection exhibited significantly better survival outcomes in patients achieving SVR either before or after hepatectomy than those without SVR [27]. Another study from Japan showed that achieving SVR before HCC development allowed a superior clinical outcome after curative ablation in HCV-related HCC patients [36]. Our results were in line with these studies and further demonstrated similar surgical outcomes between patients with preoperative SVR and those with postoperative SVR.

Considering the potential impact of cirrhosis and liver functional reserve on the surgical outcomes of early-stage HCC, we compared the recurrence rates and RFS in various subgroups. Similar patterns of recurrent rates and RFS were found in all subgroups, including patients with/without cirrhosis and people with different ALBI grades. The similar surgical outcomes and better hepatic functional reserve observed in patients with post-SVR HCC compared with those achieving SVR after resection suggested that achieving SVR might be a stronger factor predictive of lower recurrence rates and longer RFS than liver function. This perspective was supported by the results of multivariate analyses, which exhibited that achieving SVR either before or after HCC was an independent factor associated with recurrence and RFS, while ALBI grade was not significantly associated with surgical outcomes. Previous studies have demonstrated a suboptimal reduction in the risk of disease progression after achieving HCV SVR in patients with decompensated
cirrhosis [37,38]. It is unclear if different HCV viral status can result in different prognoses after resection in this population. As only two patients (0.96%) had decompensated cirrhosis (Child–Pugh class B) in this study, it is impossible to address this issue with our data. Further investigation is warranted.

The current study has some limitations. First, owing to the single-center and retrospective design, a relatively small number of patients, possible selection bias, and unknown confounders that influence surgical outcomes may exist, limiting the applicability of our study’s results to a broader population. Because this is the first study to compare the surgical outcomes after curative resection between post-SVR HCC and viremic HCC with subsequent SVR, more investigations are needed to verify our findings. Second, we failed to exclude patients with occult or past HBV infection due to a lack of data on anti-HBc antibody and HBV-DNA. Occult or past HBV infection can be prevalent in an HBV-endemic country such as Taiwan [39]. An increasing number of studies have reported more advanced tumor histological grades in patients with HCV and occult HBV infection (OBI) compared with patients without OBI, potentially influencing the postoperative prognosis [40]. Additionally, we did not analyze the interval between achieving SVR and hepatectomy. Previous studies have shown that a longer interval between achieving SVR and curative therapies was associated with better surgical outcomes [36,41].

5. Conclusions

In conclusion, our results demonstrated that patients with post-SVR HCC had a better liver function but similar clinical outcomes after curative resection compared with patients who achieved SVR after resection. Achievement of SVR both before and after HCC occurrence, in comparison to persistent HCV viremia, was the most important factor associated with lower recurrence rates and longer RFS. Our data highlight the beneficial impact on liver function and clinical outcomes as well as the necessity of timely antiviral treatment for HCV-infected patients. In addition, given that 75.6% of patients with post-SVR HCC did not have cirrhosis, HCC surveillance after SVR should be individualized based on the degrees of liver fibrosis and the presence of HCC-related risk factors instead of restricted to cirrhotic patients [42].

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [C.-Y.D.] upon reasonable request.

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PharmaEssentia. Chia-Yen Dai has served as a speaker for AbbVie, Bristol-Myers Squibb, Gilead, Merck, Sysmex, Roche, a consultant for AbbVie, Bristol-Myers Squibb, Gilead, Merck.

References

1. International Agency for Research on Cancer, World Health Organization. Cancer Today. Available online: https://gco.iarc.fr/ today/home (accessed on 31 August 2022).

2. Yu, M.L.; Yeh, M.L.; Tsai, P.C.; Huang, C.I.; Huang, J.F.; Huang, C.F.; Hsieh, M.H.; Liang, P.C.; Lin, Y.H.; Hsieh, M.Y.; et al. Huge gap between clinical efficacy and community effectiveness in the treatment of chronic hepatitis C: A nationwide survey in Taiwan. Medicine 2015, 94, e690. [CrossRef] [PubMed]

3. Bennett, H.; Waser, N.; Johnston, K.; Kao, J.H.; Lim, Y.S.; Duan, Z.P.; Lee, Y.J.; Wei, L.; Chen, C.J.; Sievert, W.; et al. A review of the burden of hepatitis C virus infection in China, Japan, South Korea and Taiwan. Hepatol. Int. 2015, 9, 378–390. [CrossRef] [PubMed]

4. Chen, D.S. Hepatocellular carcinoma in Taiwan. Hepatol. Res. 2007, 37 (Suppl. S2), S101–S105. [CrossRef] [PubMed]

5. Shen, Y.C.; Hsu, C.; Chen, L.T.; Cheng, C.C.; Hu, F.C.; Cheng, A.L. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): A meta-regression approach. J. Hepatol. 2010, 52, 889–894. [CrossRef]

6. Miyake, Y.; Takaki, A.; Iwasaki, Y.; Yamamoto, K. Meta-analysis: Interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. J. Viral Hepat. 2010, 17, 287–292. [CrossRef]

7. Breitenstein, S.; Dimitroulis, D.; Petrowsky, H.; Puhan, M.A.; Müllhaupt, B.; Clavien, P.-A. Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. Br. J. Surg. 2009, 96, 975–981. [CrossRef]

8. Ravi, S.; Axley, P.; Jones, D.; Kodali, S.; Simpson, H.; McGuire, B.M.; Singal, A.K. Unusually High Rates of Hepatocellular Carcinoma After Treatment With Direct-Acting Antiviral Therapy for Hepatitis C Related Cirrhosis. Gastroenterology 2017, 152, 911–912. [CrossRef]

9. Reig, M.; Mariño, Z.; Perelló, C.; Íñarrairaegui, M.; Ribeiro, A.; Lens, S.; Díaz, A.; Vilana, R.; Darnell, A.; Varela, M.; et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J. Hepatol. 2016, 65, 719–726. [CrossRef]

10. Conti, F.; Buonfiglioli, F.; Scuteri, A.; Crespi, C.; Bolondi, L.; Caraceni, P.; Foschi, F.G.; Lenzi, M.; Mazzella, G.; Verucchi, G.; et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J. Hepatol. 2016, 65, 727–733. [CrossRef]

11. Frazzoni, L.; Sikandar, U.; Metelli, F.; Sadalla, S.; Mazzella, G.; Bazzoli, F.; Fuccio, L.; Azzaroli, F. Hepatocellular Carcinoma Recurrence after Hepatitis C Virus Therapy with Direct-Acting Antivirals. A Systematic Review and Meta-Analysis. J. Clin. Med. 2021, 10, 1694. [CrossRef]

12. Carrat, F.; Fontaine, H.; Derival, C.; Simony, M.; Diallo, A.; Hezode, C.; De Ledinghen, V.; Larrey, D.; Haour, G.; Bronowicki, J.P.; et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: A prospective cohort study. Lancet 2019, 393, 1453–1464. [CrossRef]

13. The ANRS Collaborative Study Group on Hepatocellular Carcinoma. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J. Hepatol. 2016, 65, 734–740. [CrossRef] [PubMed]

14. Hung, C.H.; Lee, C.M.; Wang, J.H.; Hu, T.H.; Chen, C.H.; Lin, C.Y.; Lu, S.N. Impact of diabetes mellitus on incidence of hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy. Int. J. Cancer 2011, 128, 2344–2352. [CrossRef] [PubMed]

15. Ooka, Y.; Miho, K.; Shuntaro, O.; Nakamura, M.; Ogasawara, S.; Suzuki, E.; Yasui, S.; Chiba, T.; Arai, M.; Kanda, T.; et al. Prediction of the very early occurrence of HCC right after DAA therapy for HCV infection. Hepatol. Int. 2015, 9, 122–129. [CrossRef] [PubMed]

16. Asahina, Y.; Tsuchiya, K.; Nishimura, T.; Muraoka, M.; Suzuki, Y.; Tamaki, N.; Yasui, Y.; Hosokawa, T.; Ueda, K.; Nakanishi, H.; et al. α-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. Hepatology 2013, 58, 1253–1262. [CrossRef] [PubMed]

17. Dai, C.Y.; Lin, C.Y.; Tsai, P.C.; Lin, P.Y.; Yeh, M.L.; Huang, C.F.; Chang, W.T.; Huang, J.F.; Yu, M.L.; Chen, Y.L. Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection. J. Chin. Med. Assoc. 2018, 81, 155–163. [CrossRef]

18. Tabrizian, P.; Jibara, G.; Shragar, B.; Schwartz, M.; Roayaie, S. Recurrence of hepatocellular cancer after resection: Patterns, treatments, and prognosis. Am. Surg. 2015, 61, 497–505. [CrossRef]

19. Chan, A.W.H.; Zhong, J.; Berhane, S.; Toyoda, H.; Cucchetti, A.; Shi, K.; Tada, T.; Chong, C.C.N.; Xiang, B.D.; Li, L.Q.; et al. Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J. Hepatol. 2018, 69, 120–129. [CrossRef]

20. Andreana, L.; Burroughs, A.K. Treatment of early hepatocellular carcinoma: How to predict and prevent recurrence. Dig. Liver Dis. 2010, 42 (Suppl. S3), S249–S257. [CrossRef]

21. Marrero, J.A.; Kulik, L.M.; Sirlin, C.B.; Zhu, A.X.; Finn, R.S.; Abecassiss, M.M.; Roberts, L.R.; Heimbach, J.K. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018, 68, 723–750. [CrossRef]
22. Ishak, K.; Baptista, A.; Bianchi, L.; Callea, F.; De Groote, J.; Gudat, F.; Denk, H.; Desmet, V.; Korb, G.; MacSween, R.N.; et al. Histological grading and staging of chronic hepatitis. J. Hepatol. 1995, 22, 696–699. [CrossRef]
23. Scheuer, P.J. Classification of chronic viral hepatitis: A need for reassessment. J. Hepatol. 1991, 13, 372–374. [CrossRef]
24. Sou, F.M.; Wu, C.K.; Chang, K.C.; Lu, S.N.; Wang, J.H.; Hung, C.H.; Chen, C.H.; Kee, K.M.; Yen, Y.H.; Lin, M.T.; et al. Clinical characteristics and prognosis of HCC occurrence after antiviral therapy for HCV patients between sustained and non-sustained. J. Formos. Med. Assoc. 2019, 118, 504–513. [CrossRef]
25. Yeh, M.L.; Liang, P.C.; Tsai, P.C.; Wang, S.C.; Leong, J.; Ogawa, E.; Jun, D.W.; Tseng, C.H.; Landis, C.; Tanaka, Y.; et al. Characteristics and Survival Outcomes of Hepatocellular Carcinoma Developed after HCV SVR. Cancers 2021, 13, 3455. [CrossRef]
26. Calvaruso, V.; Craxi, A. Hepatic benefits of HCV cure. J. Hepatol. 2020, 73, 1548–1556. [CrossRef]
27. Nakajima, M.; Kobayashi, S.; Wada, H.; Tomokuni, A.; Takahashi, H.; Noda, T.; Matsui, H.; Matsukuma, S.; Kanekiyos, S.; Shindo, Y.; et al. Viral elimination is essential for improving surgical outcomes of hepatitis C virus-related hepatocellular carcinoma: Multicenter retrospective analysis. Ann. Gastroenterol. Surg. 2020, 4, 710–720. [CrossRef]
28. Perez, S.; Kaspi, A.; Domovitz, T.; Davidovich, A.; Lavi-Itzkovitz, A.; Meirson, T.; Alison Holmes, J.; Dai, C.Y.; Huang, C.E.; Chung, R.T.; et al. Hepatitis C virus leaves an epigenetic signature post cure of infection by direct-acting antivirals. PLoS Genet. 2019, 15, e1008181. [CrossRef]
29. Hamdane, N.; Jühlung, F.; Crouchet, E.; El Saghire, H.; Thumann, C.; Oudot, M.A.; Bandiera, S.; Saviano, A.; Ponsolles, C.; Roca Suarez, A.A.; et al. HCV-Induced Epigenetic Changes Associated With Liver Cancer Risk Persist after Sustained Virologic Response. Gastroenterology 2019, 156, 2313–2329.e7. [CrossRef]
30. Singal, A.G.; Rich, N.E.; Mehta, N.; Branch, A.; Pillai, A.; Hoteit, M.; Volk, M.; Odedele, M.; Scaglione, S.; Guy, J.; et al. Direct-Acting Antiviral Therapy Not Associated With Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study. Gastroenterology 2019, 156, 1683–1692.e1. [CrossRef]
31. Dang, H.; Yeo, Y.H.; Yasuda, S.; Huang, C.F.; Iio, E.; Landis, C.; Jun, D.W.; Enomoto, M.; Ogawa, E.; Tsai, P.C.; et al. Cure With Interferon-Free Direct-Acting Antiviral Is Associated With Increased Survival in Patients With Hepatitis C Virus-Related Hepatocellular Carcinoma From Both East and West. Hepatology 2020, 71, 1910–1922. [CrossRef]
32. Koda, M.; Tanaka, S.; Takemura, S.; Shinkawa, H.; Kinoshita, M.; Hamano, G.; Ito, T.; Kawada, N.; Shibata, T.; Kubo, S. Long-Term Prognostic Factors after Hepatocellular Antigen after Hepatitis C Virus-Related Hepatocellular Carcinoma, with a Special Reference to Viral Status. Liver Cancer 2018, 7, 261–276. [CrossRef]
33. Yang, T.H.; Fang, Y.J.; Hsu, S.J.; Lee, J.Y.; Chiu, M.C.; Yu, J.J.; Kuo, C.C.; Chen, C.H. Microelimation of Chronic Hepatitis C by Universal Screening Plus Direct-Acting Antivirals for Inarcerated Persons in Taiwan. Open Forum Infect. Dis. 2020, 7, ofaa301. [CrossRef]
34. Tsai, P.C.; Huang, C.I.; Ye, M.L.; Huang, C.F.; Hsieh, M.H.; Yang, J.F.; Hsu, P.Y.; Liang, P.C.; Lin, Y.H.; Jang, T.Y.; et al. Significant amelioration of hepatitis C virus infection in a hyperendemic area: Longitudinal evidence from the COMPACT Study in Taiwan. BMJ Open 2021, 11, e042861. [CrossRef]
35. Ryu, T.; Takami, Y.; Wada, Y.; Tateishi, M.; Matsushima, H.; Yoshitomi, M.; Mikagi, K.; Saitsu, H. Effect of achieving sustained virological response before hepatitis C virus-related hepatocellular carcinoma occurrence on survival and recurrence after curative surgical microwave ablation. Hepatol. Int. 2018, 12, 149–157. [CrossRef]
36. Krassenburg, L.A.P.; Maan, R.; Ramji, A.; Manns, M.P.; Cornberg, M.; Wedemeyer, H.; de Knecht, R.J.; Hansen, B.E.; Janssen, H.L.A.; de Man, R.A.; et al. Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J. Hepatol. 2021, 74, 1053–1063. [CrossRef]
37. Calvaruso, V.; Cabibbo, G.; Cacciola, I.; Petta, S.; Madonia, S.; Bellia, A.; Tiné, F.; Distefano, M.; Licata, A.; Giannitrapani, L.; et al. Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. Gastroenterology 2018, 155, 411–421.e141. [CrossRef]
38. Mu, S.C.; Lin, Y.M.; Jow, G.M.; Chen, B.F. Occult hepatitis B virus infection in hepatitis B vaccinated children in Taiwan. J. Hepatol. 2009, 50, 264–272. [CrossRef]
39. Mak, L.Y.; Wong, D.K.; Pollicino, T.; Raimondo, G.; Hollinger, F.B.; Yuen, M.F. Occult hepatitis B infection and hepatocellular carcinoma: Epidemiology, virology, hepatocarcinogenesis and clinical significance. J. Hepatol. 2020, 73, 952–964. [CrossRef]
40. Okimoto, S.; Kobayashi, T.; Kuroda, S.; Ishiyama, K.; Ide, K.; Ohira, M.; Tahara, H.; Shimizu, S.; Iwako, H.; Hamaoka, M.; et al. Prediction of recurrence following hepectomy in patients with hepatitis C virus infection-related hepatocellular carcinoma who achieved a sustained virological response. Hepatol. Res. 2017, 47, 1186–1195. [CrossRef]
41. Yu, M.L.; Chen, P.J.; Dai, C.Y.; Hu, T.H.; Huang, C.F.; Huang, Y.H.; Hung, C.H.; Lin, C.Y.; Liu, C.H.; Liu, C.J.; et al. 2020 Taiwan consensus statement on the management of hepatitis C: Part (I) general population. J. Formos. Med. Assoc. 2020, 119, 1019–1040. [CrossRef] [PubMed]