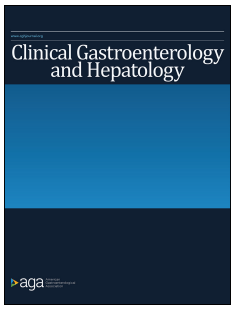

Regional differences in clinical presentation and prognosis of patients with post-sustained virologic response (SVR) hepatocellular carcinoma

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Regional differences in clinical presentation and prognosis of patients with post-sustained virologic response (SVR) hepatocellular carcinoma

Short title: Regional differences of post-SVR HCC

Hidenori Toyoda[1], Mounika Kanneganti[2], Jonathan Melendez-Torres[2], Neehar D. Parikh[3], Prasun K. Jalal[4], Federico Piñero[5], Manuel Mendizabal[5], Ezequiel Ridruejo[6], Hugo Cheinquer[7], Andrea Casadei-Gardini[8], Arndt Weinmann[9], Markus Peck-Radosavljevic[10], Jean-Francois Dufour[11], Pompilia Radu[11], Gamal Shiha[12], Riham Soliman[13], Shiv K. Sarin[14], Manoj Kumar[14], Jing-Houng Wang[15], Pisit Tangkijvanich[16], Wattana Sukeepaisarnjaroen[17], Masanori Atsukawa[18], Haruki Uojima[19], Akito Nozaki[20], Makoto Nakamuta[21], Koichi Takaguchi[22], Atsushi Hiraoka[23], Hiroshi Abe[24], Kentaro Matsuura[25], Tsunamasa Watanabe[26], Noritomo Shimada[27], Kunihiko Tsuji[28], Toru Ishikawa[29], Shigeru Mikami[30], Ei Itobayashi[31], Amit G. Singal[2], Philip J. Johnson[32].

* Amit G. Singal and Philip J. Johnson are co-senior authors.

Affiliations

[1]Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan,
[2]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA,
[3]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA,
[4] Division of Abdominal Transplantation, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA,
[5]Hospital Universitario Austral, School of Medicine, Austral University, Buenos Aires, Argentina,
[6]CEMIC, Centro de Educación Medica e Investigaciones Clinicas, Norberto Quirno, Buenos Aires, Argentina,
[7]Gastroenterology and Hepatology Division, Universidad de Federal do Rio Grande do Sul, Porto Alegre, Brazil,
[8]Department of Medical Oncology, Vita-Salute San Raffaele University, Milan, Italy,
[9]Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University, Mainz, Germany,
[10]Innere Medizin und Gastroenterologie, Klinikum Klagenfurt am Worthersee, Klagenfurt, Austria,

[11]Hepatology-Department of Biomedical Research, University of Bern, Bern, Switzerland,
[12]Hepatology and Gastroenterology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University and Egyptian Liver Research Institute and Hospital (ELRIAH), El Mansoura, Egypt,
[13]Tropical Medicine Department, Faculty of Medicine, Port Said University, Egypt
[14]Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India,
[15]Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan,
[16] Center of Excellence in Hepatitis and Liver Cancer, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand,
[17]Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand,
[18]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Nippon Medical School, Tokyo, Japan,
[19]Department of Gastroenterology, Internal Medicine, Kitasato University School of Medicine, Sagamihara, Japan,
[20]Gastroenterology Center, Yokohama City University Medical Center, Yokohama, Japan,
[21]National Hospital Organization Kyushu Medical Center, Fukuoka, Japan,
[22]Department of Hepatology, Kagawa Prefectural Central Hospital, Takamatsu, Japan,
[23]Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Japan,
[24]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Shinmatusdo Central General Hospital, Matsudo, Japan,
[25]Department of Gastroenterology and Metabolism, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan,
[26]Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan,
[27]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Otakanomori Hospital, Kashiwa, Japan,
[28]Center for Gastroenterology, Teine Keijinkai Hospital, Sapporo, Japan,
[29]Department of Hepatology, Saiseikai Niigata Hospital, Niigata, Japan,
[30]Department of Internal Medicine, Division of Gastroenterology, Kikkoman General Hospital, Noda, Japan,
[31]Department of Gastroenterology, Asahi General Hospital, Asahi, Japan,

[32]Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK.

Corresponding author:

Hidenori Toyoda, MD, PhD

Department of Gastroenterology, Ogaki Municipal Hospital, 4-86 Minaminokawa, Ogaki, Gifu, 503-8502 JAPAN, telephone: +81-584-81-3341, facsimile: +81-584-75-5715, email: hmtoyoda@spice.ocn.ne.jp

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List of Abbreviations

DAA, direct-acting antiviral; HCV, hepatitis C virus; HCC, hepatocellular carcinoma;

SVR, sustained virologic response; HR, hazard ratio; BCLC, Barcelona Clinic Liver Cancer; NAFLD, nonalcoholic fatty liver disease; USA, United States of America; HBV, hepatitis B virus; HIV, human immunodeficiency virus; AFP, alpha-fetoprotein; IQR, interquartile range;

ABSTRACT

Background & Amis: Widespread use of direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection has resulted in increased numbers of patients with hepatocellular carcinoma (HCC) after achieving sustained virologic response ('post-SVR HCC') worldwide. Few data compare regional differences in presentation and prognosis of patients with post-SVR HCC.

Methods*:* We identified patients with advanced fibrosis (F3/F4) who developed incident post-SVR HCC between March, 2015 and October, 2021 from 30 sites in Europe, North America, South America, Middle East, South Asia, East Asia, and Southeast Asia. We compared patient demographics, liver dysfunction, and tumor burden by region. We compared overall survival by region using Kaplan-Meier analysis and identified factors associated with survival using multivariable Cox regression analysis.

Results: Among 8,796 patients with advanced fibrosis or cirrhosis who achieved SVR, 583 (6.6%) developed incident HCC. There was marked regional variation in the proportion of detection by surveillance (range: 59.5–100%), median maximum tumor diameter (range: 1.8–5.0 cm), and proportion with multinodular HCC (range: 15.4–60.8%). Prognosis of patients highly varied by region (HR range: 1.82–9.92), with the highest survival in East Asia, North America, and South America, and lowest in the Middle East and South Asia. After adjusting for geographic region, HCC surveillance was associated with early-stage detection (BCLC stage 0/A: 71.0% vs. 21.3%, $p<0.0001$) and lower mortality (adjusted HR 0.29, 95%CI 0.18–0.46).

Conclusions*:* Clinical characteristics, including early-stage detection, and prognosis of post-SVR HCC significantly differed across geographic regions. Surveillance utilization appears to be a high-yield intervention target to improve prognosis among patients with

post-SVR HCC globally.

Keywords: hepatocellular carcinoma, hepatitis C virus infection, sustained virologic response, surveillance, prognosis

Introduction

Hepatitis C virus (HCV) infection has been the most common underlying etiological risk factor for hepatocellular carcinoma (HCC) in Europe, the United States, and Japan for decades. Sustained virological response (SVR) significantly reduces HCC risk and is one of the most effective methods of primary HCC prevention [1,2]; however, many patients went untreated or failed to achieve SVR prior to availability of direct-acting antivirals (DAAs). Although there has been a marked increase in the number of patients with successful HCV eradication, HCC can still develop in a subset of patients after SVR (i.e., 'post-SVR HCC') [1]. Risk of HCC can persist for several years beyond SVR, so HCC surveillance in post-SVR patients is recommended by many professional society guidelines [3]. HCC surveillance has been associated with significant improvement in early tumor detection and reduced HCC-related mortality [4], although a recent meta-analysis identified few data specifically in post-SVR population. Recent studies suggest SVR may portend better prognosis in patients with HCC compared to those who develop HCC in the setting of persistent HCV infection, likely related to better preserved liver function [5-8].

However, most studies are derived from a single geographic region, so it is unclear if characteristics and prognosis of post-SVR HCC differ globally. HCC presentation and prognosis may differ by region based on several factors including differences in biological factors and co-existent liver diseases (e.g., NAFLD or alcohol abuse) or how patients are managed after SVR, including adherence and quality of post-SVR surveillance [9,10]. Herein, we compared clinical characteristics and prognosis of patients with post-SVR HCC across geographic regions in a multi-center international cohort. We examined differences in surveillance patterns, and its

association with clinical outcomes, to explore differences in HCC prognosis across region.

Patients and Methods

Study Patients

We conducted an international multicenter study at 30 centers from Europe (Italy, Germany, Austria, and Switzerland), North America (USA), South America (Brazil and Argentine), Middle East (Egypt), South Asia (India), East Asia (Taiwan and Japan), and Southeast Asia (Thailand) (**Supplementary Figure 1**). We included adults (age ≥18 years) with advanced fibrosis (F3 or F4 fibrosis) who underwent DAA therapy and had confirmed SVR (i.e., absence of serum HCV RNA at least 12 weeks after end of DAA therapy). Advanced fibrosis was defined as FIB-4 ≥3.25, whereas cirrhosis was determined by non-invasive markers of fibrosis (e.g., transient elastography or Fibrosure), biopsy or imaging showing a cirrhotic-appearing liver and signs of portal hypertension (e.g., gastroesophageal varices, collateral veins on imaging, or splenomegaly). Exclusion criteria included presence of HCC or suspicious liver nodules on imaging prior to DAA initiation or coinfection with hepatitis B virus (HBV) or HIV. The study protocol was approved by the institutional review board of each participating hospital, with waiver of written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

Diagnosis of HCC and Follow-up for Prognosis

HCC diagnosis was based on guidelines of academic societies for each participating country, typically consisting of histological confirmation or characteristic

radiological imaging features (i.e., arterial phase hyperenhancement and delayed phase washout). Data were collected from medical records on patient demographics, degree of liver dysfunction (Child-Pugh class), tumor burden (number of lesions, maximum diameter, presence of portal vein invasion, and extrahepatic metastases), serum AFP levels, HCC-directed treatments, and overall survival. Patients were followed from the time of the initial HCC diagnosis to the last visit, or end of the study period on December 31, 2021.

We compared clinical presentation (e.g., tumor burden and stage), initial treatment, and overall survival between regions and by receipt of HCC surveillance. Patients with continued HCC surveillance at least every 7 months (i.e., one month window around semi-annual surveillance) after SVR were defined as adherent with surveillance whereas others were defined as being without guideline-concordant surveillance.

Statistical Analysis

Categorical and continuous variables were compared between groups using chi-square test and Mann-Whitney U test, respectively. Time zero was defined as date of initial HCC diagnosis for survival analysis and date of curative treatment for time-to-HCC recurrence. For both analyses, patients without death or recurrence, respectively, were censored at last follow-up prior to study completion in December 2021. Kaplan-Meier method was used to calculate survival and recurrence rates, and the log-rank test was used to analyze differences.

Cox proportional hazards models were used for multivariable analyses of factors associated with survival and adjustment for patient background factors. Variables

included patient age, gender, presence of cirrhosis, geographic regions, and surveillance status. Data analysis was performed using JMP statistical software, version 11.0.0 (Macintosh version; SAS Institute, Cary, NC, USA). All *P* values were derived from 2-tailed tests, with $P < 0.05$ accepted as statistically significant.

Results

Regional Differences in Patient Characteristics

Among 8,796 patients with advanced fibrosis or cirrhosis who achieved SVR, 583 (6.6%) developed incident HCC during a median follow-up of 2.65 (IQR, 1.70–3.55) years after SVR. There were variations in the incidence of HCC across regions, from 2.11% in South America to 11.18% in South Asia (**Supplementary Table 1**). **Table 1** describes patient characteristics stratified by region. There were regional differences in patient age, gender, HCV genotype, history of interferon-based therapy, DAA-regimen (non-pangenotypic vs. pangenotypic), FIB-4 index, and proportion of patients with cirrhosis, although the majority of patients had Child-Pugh class A liver function in all regions. There were also regional differences in surveillance recommendations among patients after SVR (**Supplementary Table 2**).

There were significant differences in the proportion of patients whose HCC was detected by surveillance. Post-SVR HCC was detected by surveillance in around 60% of patients from the Middle East and South Asia, compared to ~90% in the other regions. We noted variations in maximum tumor diameter, ranging from 1.8 cm (East Asia) to 5.0 cm (South Asia), as well as proportions with multinodular HCC (15.4–60.8%), portal vein invasion (2.4–48.7%), and HCC with extrahepatic spread (0.4–30.8%). Consequently, the proportion of patients who underwent curative treatment (hepatic

resection, local ablative therapies, or transplantation) varied from 9.4% (Middle East) to 78.8% (East Asia).

Regional Differences in Survival Rates of Post-SVR HCC

During the study period, 130 (22.3%) of the 583 patients with post-SVR HCC died. All but two patients died from HCC or liver-related causes. Whereas 16 patients underwent liver transplantation as an initial treatment of HCC, no patient underwent transplantation after an initial treatment. **Figure 1** and **Table 2** show the survival rates of patients with post-SVR HCC by regions. The survival rate varied widely, being highest in East Asia (95.5% and 90.1% at 1 and 3 years), followed by North America (87.8% and 75.0%), South America (63.7% and 63.7%), Southeast Asia (91.4% and 61.9%), Europe (85.8% and 59.8%), and lowest in Middle East (85.1% and 20.7%) and South Asia (52.5% and 22.5%). Compared to East Asia, the hazard of mortality after diagnosis was 2.05 (95% C.I. 1.05–3.82) in North America, 9.58 (95% C.I. 3.36–24.02) in South America, 3.70 (95% C.I. 1.76–7.26) in Southeast Asia, 3.40 (95% C.I. 1.83–6.12) in Europe, 9.64 (95% C.I. 4.72–18.95) in Middle East, and 14.05 (95% C.I. 7.89–25.56) in South Asia in crude comparisons. When adjusting for patient age, gender, and presence of cirrhosis, aHR were 2.44 (95% C.I. 1.18–4.89) in North America, 11.46 (95% C.I. 3.36–31.52) in South America, 4.90 (95% C.I. 2.03–11.72) in Southeast Asia, 3.85 (95% C.I. 2.01–7.18) in Europe, 9.45 (95% C.I. 4.52–19.06) in Middle East, and 12.61 (95% C.I. 6.35–25.53) in South Asia.

Among 337 patients whose initial HCC that was treated curatively, HCC recurred in 110 patients (32.6%). **Supplementary Figure 2** compares recurrence-free survival rates of HCC after the treatment for initial HCC. The recurrence-free survival rate was

higher in Europe and East Asia than other regions; however, differences in the recurrence-free survival rates were modest between regions.

Survival Rates of Post-SVR HCC after Diagnosis by Surveillance Status

Among 583 patients with post-SVR HCC, 504 patients (86.4%) were under surveillance and 78 patients were not (surveillance status was unknown in one patient). **Table 3** compares characteristics between patients in whom HCC was detected under surveillance and those without surveillance. Patients with surveillance were significantly older than those without surveillance, but there were no differences in patient gender, presence of cirrhosis, or Child-Pugh class. HCC tumor burden was significantly larger in patients who did not undergo surveillance, with larger tumor size and higher percentage of multinodular tumor, portal vein invasion, and extrahepatic spread. Serum AFP levels at diagnosis was significantly higher in patients without surveillance. Whereas HCC stage was BCLC class 0 or A in more than 70% of patients with surveillance, it was BCLC class C in more than 70% of patients without surveillance. Consequently, there was a large difference in the percentage of patients who were treated curatively between patients with and without surveillance after SVR (68.0% versus 26.9%).

Survival of patients, stratified by surveillance receipt after SVR, is described in **Figure 2** and **Supplementary Table 3**. The survival of patients without HCC surveillance was significantly lower than that of patients in whom HCC was detected under surveillance ($p<0.0001$). Lack of surveillance receipt was associated with increased mortality in unadjusted (HR 5.96; 95% C.I. 3.99–8.75) and adjusted (aHR 5.82; 95% C.I. 3.79–8.81) models.

When multivariable analysis was conducted including regions, lack of surveillance receipt remained associated with increased mortality (aHR 3.44, 95% C.I. 2.16–5.46), although there continued to be geographic disparities in prognosis (HR range: 1.82–9.92 between regions) (**Table 4**).

Regional Differences in Clinical Presentations and Survival Rates of Post-SVR HCC among Patients under Surveillance

In patients whose post-SVR HCC was detected by surveillance (**Supplementary Table 4**), regional differences in HCC burden were mitigated; however, areas with low surveillance detection, such as South Asia, continued to have larger tumor burden and lower curative treatment receipt. Accordingly, differences in survival by region also persisted in this subgroup of patients (**Supplementary Figure 3**).

Discussion

Our international multi-center cohort study demonstrated clear variation in the clinical presentation and prognosis of post-SVR HCC across regions. Specifically, we found differences in the proportion of patients detected by HCC surveillance, tumor burden, and receipt of curative therapy. As expected, these differences in clinical presentation translated into significant disparities in overall survival after HCC diagnosis.

Recently, several models for predicting post-SVR HCC have been reported from several regions of the world [11-15]. These studies reported the high predictability of post-SVR HCC of their own model in their own cohort. Given the large difference in the progression of HCC at detection, however, the best predictive model may differ

based on regions. The later detection of advanced HCC after SVR will result in the longer interval between SVR and HCC development. In contrast, early detection of post-SVR HCC will make the interval between SVR and HCC shorter. These differences in intervals between SVR and HCC, reflected by the progression of HCC at detection, would strongly influence the performance of predictive models. The best predictive model for post-SVR HCC that can be applicable universally for global post-SVR patients is being determined. Further, it is unclear whether the universal predictive model can exist or not [16].

The large variations in tumor burden of post-SVR HCC at detection resulted in the large variation of survival rates after HCC diagnosis by regions. Previous studies reported improved prognosis of patients with post-SVR HCC in comparison to patients with HCC during persistent HCV infection [5-7]. However, the results of this study indicated that the benefit of SVR, i.e., the eradication of HCV, on the outcome of HCC patients may differ by regions.

The variations of post-SVR HCC with prognosis is mainly due to the differences in surveillance practice after SVR. This is particular in cases of Middle East and South Asia. In such regions, the percentages of patients who continued undergoing surveillance for HCC were lower than other regions, despite all patients having cirrhosis or advanced liver fibrosis. Consequently, HCC was more progressed at the detection and diagnosis and the survival rates after the diagnosis of HCC were significantly low in comparison to other regions. Prior studies have shown underuse of surveillance in clinical practice, related to provider and patient barriers, although much of these data are derived from the United States [17-19]. It is unclear if these barriers would be observed in other regions [20], particularly given differences in healthcare coverage,

patient and provider awareness of HCC risk, and HCC surveillance guidelines for post-SVR patients [21-23], including the concept, candidates, and quality [9]. In contrast to survival rates, recurrence rates in patients who had undergone curative treatment showed modest variations. Because patients who developed HCC and received curative treatment usually undergo surveillance after treatment, variations by regions might have mitigated in this comparison.

The difference of HCC characteristics and prognosis between patients who continued surveillance after SVR and who did not was shown obviously in this study. The size and percentages of multinodular tumor, portal vein invasion, and extrahepatic spread were significantly higher in patients without surveillance after SVR. Whereas patients in whom HCC was detected under surveillance mainly had HCC of BCLC stage 0 or A, patients who were not surveyed before the diagnosis of HCC mainly had HCC of BCLC stage C. In contrast, the number of patients with HCC of BCLC stage B, i.e., intermediate stage, was small in both groups. This result indicated that there are two distinct patterns of patients with post-SVR HCC, i.e., surveyed patients with early-stage HCC and unsurveyed patients with advanced HCC, with obviously different prognosis. The results strongly suggested the importance of surveillance to enhance the benefit of SVR for improving patient survivals.

In a subgroup analysis of patients with surveillance-detected HCC, we continued to observe regional differences in tumor burden at diagnosis, curative treatment receipt, and overall survival. These may have been due to the differences in surveillance practice including modalities and interval, as well as surveillance quality [9]. For example, semi-annual surveillance has been shown to have improved early detection compared to annual surveillance and data suggest tumor marker may have incremental

benefit for early HCC detection compared to ultrasound alone [24,25]. Further, differences in patient characteristics, such as obesity, and operator experience could have led to difference in ultrasound effectiveness [26,27]. Finally, there were marked differences in curative treatment receipt, so underuse of curative treatment among patients detected at an early stage could have amplified differences in survival. Further studies will be necessary to investigate the association of the style of post-SVR surveillance with the characteristics of post-SVR HCC and prognosis.

There are several limitations to this study. First, this study is an international comparison of post-SVR HCC across regions, but the data for study patients were not based on the national data of respective regions. Therefore, the characteristics and prognosis of post-SVR HCC from respective regions could not represent ones of the entire countries/regions, although every participating institution was high-volume academic liver center that represented the highest standard in respective regions. In addition, there may be variations by countries even in the same regions of the world. Further studies are necessary to confirm the variations of characteristics of post-SVR HCC with prognosis between regions. Second, we focused on patients with post-SVR HCC who have had cirrhosis or advanced liver fibrosis as study patients of this study. Therefore, patients with post-SVR HCC that developed in the absence of advanced liver fibrosis or cirrhosis was not included in this study. Patients with cirrhosis or advanced fibrosis are usually recommended for continuing surveillance for HCC after SVR worldwide. In contrast, all SVR patients, regardless of the degree of liver fibrosis, are recommended to undergo post-SVR surveillance in some countries like Japan [28], and post-SVR HCC developed in some patients even in the absence of cirrhosis or advanced fibrosis [7]. We excluded these patients from the study in order to make study patients

homogenous, because only patients with cirrhosis or advanced liver fibrosis are recommended to undergo post-SVR surveillance in most guidelines worldwide including Western guidelines [21,22]. Further, the style of surveillance after SVR might differ by regions based on guidelines of respective region. Although we defined the adherence to surveillance as interval of hospital visits for surveillance, the rigorousness of surveillance at hospital visit might vary, which affected the characteristics and prognosis of post-SVR HCC.

In conclusion, we observed marked variations in the characteristics and prognosis of post-SVR HCC across regions, which were strongly associated with the post-SVR surveillance practice of regions. Continuation of rigorous surveillance for HCC is necessary in patients with cirrhosis who achieved SVR for HCV infection to optimize the prognosis of patients in whom HCC develops after SVR.

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Figure Legends

Figure 1. Survival rates after the diagnosis of post-SVR de novo HCC by regions.

Figure 2. Survival rates after the diagnosis of post-SVR de novo HCC by surveillance after SVR.

Table 1. Characteristics of patients with post-SVR de novo HCC by regions

	Europe (Italy, Germany, Austria, Switzerland)	North America (USA)	South America (Argentine, Brazil)	Middle East (Egypt)	South Asia (India)	East Asia (Japan, Taiwan)	Southeast Asia (Thailand)
Number of patients	50	55	42	35	74	288	39
Age (years)	62 (57–72)	62 (58-67)	65 (58-71)	59 (56-62)	52 (46-61)	71 (64–77)	60 (57-64)
Gender-male	32 (64.0)	38 (69.1)	19 (45.2)	28 (80.0)	62 (83.8)	154 (53.5)	25 (64.1)
HCV genotype (1/ 2/ 3/ 4/ 6/ others)	30 (61.2)/ 2 (4.1)/ 9 (18.4)/ 8 (16.3)/ 0/ 0	44 (80.0)/ 2 (3.6)/ 6 (10.9)/ 2 (3.6)/ 0/ 1 (1.8)*	35 (83.3)/ 2 (4.8)/ 5 (11.9)/ 0/ 0/ 0	0/ 0/ 0/ 35 (100)/ 0/ 0	30 (40.5)/ 2 (2.7)/ 42 (56.8)/ 0/ 0/ 0	237 (82.3)/ 51 (17.7)/ 0/ 0/ 0/ 0	13 (33.3)/ 0/ 21 (53.9)/ 0/ 5 (12.8)/ 0
History of IFN–based therapy	25 (51.0)	12 (22.2)	1 (2.4)	7 (20.0)	7 (9.5)	92 (37.3)	29 (74.4)
DAA regimen (non-pangenotypic/ pangenotypic)	40 (80.0)/ 5 (10.0)	38 (69.1)/ 17 (30.9)	Not available	34 (97.1)/ 1 (2.9)	36 (48.6)/ 38 (51.4)	276 (95.8)/ 12 (4.2)	21 (53.8)/ 18 (46.2)
FIB4 index	6.80 (3.72–11.55)	3.33 (2.42–6.39)	Not available	5.28 (3.01–9.36)	8.94 (5.61–14.23)	5.41 (3.71–7.97)	4.73 (2.25–6.34)
Cirrhosis	42 (85.7)	48 (87.3)	24 (57.1)	26 (74.3)	71 (96.0)	220 (76.4)	39 (100)
Child-Pugh class A	35	44	31	17	Not available	253	24

	(77.8)	(80.0)	(73.8)	(77.3)		(94.1)	(61.5)
ABLI score	-2.59	-2.42	-2.72	-2.64	-2.00	-2.57	-2.56
	(-2/84–-2.28)	(-2.73–-1.96)	(-3.06–-2.22)	(-2.93–-2.35)	(-2.42–-1.61)	(-2.99–-2.28)	(-3.12–-2.30)
Detection by	43	48	42	23	44	268	36
surveillance	(86.0)	(87.3)	(100)	(65.7)	(59.5)	(93.4)	(92.3)
Maximal tumor	3.2	2.5	2.5	2.6	5.0	1.8	2.9
size (cm)	(2.2–5.1)	(1.6-3.7)	(2.0-4.3)	(2.0-5.0)	(2.1-9.2)	(1.3–2.5)	(1.4-5.9)
Multinodular	26	13	18	15	45	44	13
tumors	(57.8)	(23.6)	(42.9)	(46.9)	(60.8)	(15.4)	(33.3)
Portal vein	11	7	1	6	36	11	18
invasion	(23.4)	(12.7)	(2.4)	(18.8)	(48.7)	(3.9)	(46.2)
Extrahepatic	8	3	1	3	12	1	12
spread	(17.0)	(5.5)	(2.4)	(9.7)	(16.2)	(0.4)	(30.8)
AFP (ng/mL)	45.0	18.0	12.9	53.2	175.5	6.7	15.1
	(6.1–263.0)	(4.4-68.9)	(3.8-213.8)	(10.0-262.5)	(14.2-1120.3)	(4–37.0)	(4.0-181.5)
Treatment			Not available				
Hepatic resection	10 (37.0)	9 (17.3)		2 (6.3)	2 (2.8)	72 (25.6)	3 (8.1)
Transplantation	5 (18.5)	4 (7.7)		0	0	5 (1.8)	0
LAT	10 (37.0)	20 (38.5)		1 (3.1)	29 (40.3)	150 (53.4)	9 (24.3)
TACE	1 (3.7)	4 (7.7)		14 (43.8)	24 (33.3)	39 (13.9)	22 (59.5)
Systemic therapy	0	13 (25.0)		7 (21.9)	12 (16.7)	6 (2.1)	1 (2.7)
BSC	1 (3.7)	2 (3.9)		8 (25.0)	5 (6.9)	9 (3.2)	2 (5.4)

Curative treatment**	27 (58.7)	33 (60.0)	Not available	3 (9.4)	32 (43.2)	227 (78.8)	13 (34.2)

AFP, alpha-fetoprotein; BSC, best supportive care; LAT, local ablative therapies; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; SVR, sustained virologic response; TACE, transarterial chemoembolization.

*genotype 1+2

**Hepatic resection, transplantation, or local ablative therapies including microwave thermocoagulation and radiofrequency ablation

Table 2. Survival rates of patients with post-SVR de novo HCC after diagnosis by regions

	Number	MST (years)	1-year (%)	2-year (%)	3-year (%)	4-year (%)	5-year (%)	6-year (%)
Europe	50	4.84	85.8	73.3	59.8	59.8	26.2	
North America	55	Not reached	87.8	83.2	75.0	59.2	59.2	
South America	42	Not reached	63.7	63.7				
Middle East	35	1.74	85.1	49.6	20.7	0		
South Asia	74	1.09	52.5	42.1	22.5	0		
East Asia	288	Not reached	95.5	93.3	90.1	77.1	74.1	74.1
Southeast Asia	39	4.43	91.4	68.7	61.9	61.9	30.9	

MST, median survival time

Table 3. Characteristics of patients with post-SVR de novo HCC by surveillance status after SVR

	HCC detected under surveillance	HCC detected without surveillance	*P* value
Number of patients	504	78	
Age (years)	66 (59–74)	58 (52-66)	< 0.0001
Gender (male/ female)	304 (60.3)/ 200 (39.7).0)	54 (69.2)/ 24 (30.8)	0.1686
Cirrhosis	408 (81.0)/ 96 (19.1)	61 (79.2)/ 16 (20.8)	0.7565
Child-Pugh class (A/ B/ C)*	375 (86.4)/ 50 (11.5)/ 9 (2.1)	29 (76.3)/ 9 (23.7)/ 0	0.0693
Maximal tumor size (cm)	2.0 (1.4–3.0)	7.9 (3.6-10.0)	< 0.0001
Number of tumors (single/ multiple)	368 (74.2)/ 128 (25.8)	30 (39.5)/ (60.5)	< 0.0001
Portal vein invasion (no/ yes)	442 (88.8)/ 56 (11.2)	40 (54.1)/ 34 (46.0)	< 0.0001
Extrahepatic spread (no/ yes)	474 (95.2)/ 24 (4.8)	57 (78.1)/ 16 (21.9)	< 0.0001
AFP (ng/mL)	9.1 (4.1–74.9)	88.9 (12.7-1582.1)	< 0.0001
BCLC (0/ A/ B/ C/ D)	147 (32.7)/ 172 (38.3)/ 15 (3.3)/ 104 (23.2)/ 11 (2.5)	1 (1.6)/ 12 (19.7)/ 3 (4.9)/ 43 (70.5)/ 2 (3.3)	< 0.0001
Milan criteria (in/ out)	410 (82.7)/ 86 (17.3)	16 (21.1)/ 60 (79.0)	< 0.0001
Treatment (curative**/ non-curative)	316 (68.0)/ 149 (32.0)	21 (26.9)/ 57 (73.1)	< 0.0001

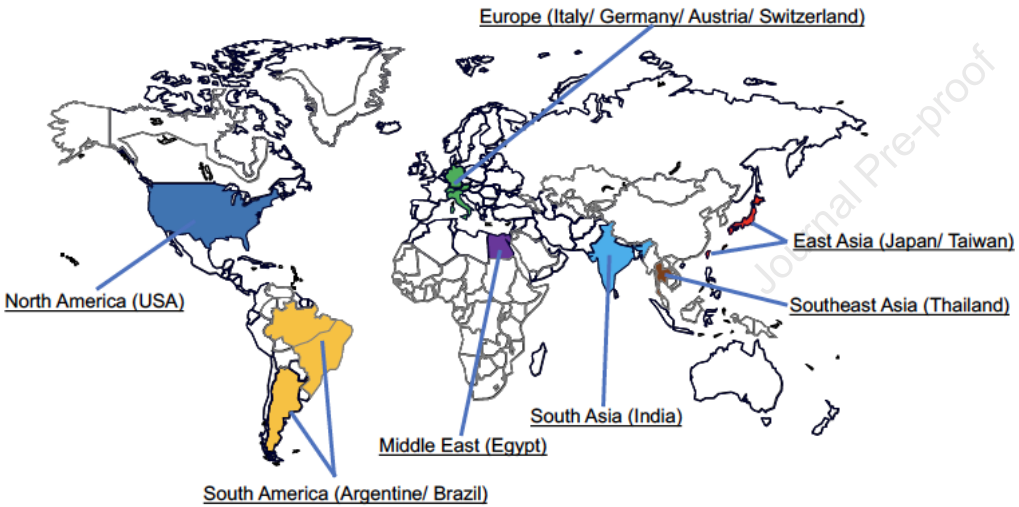
*Child-Pugh class was not known in 110 patients.

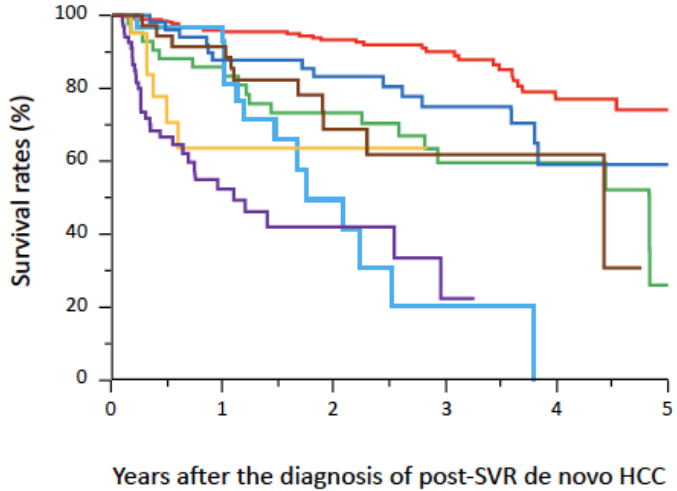
**Hepatic resection, transplantation, or locoregional ablative therapies including microwave thermocoagulation and radiofrequency ablation

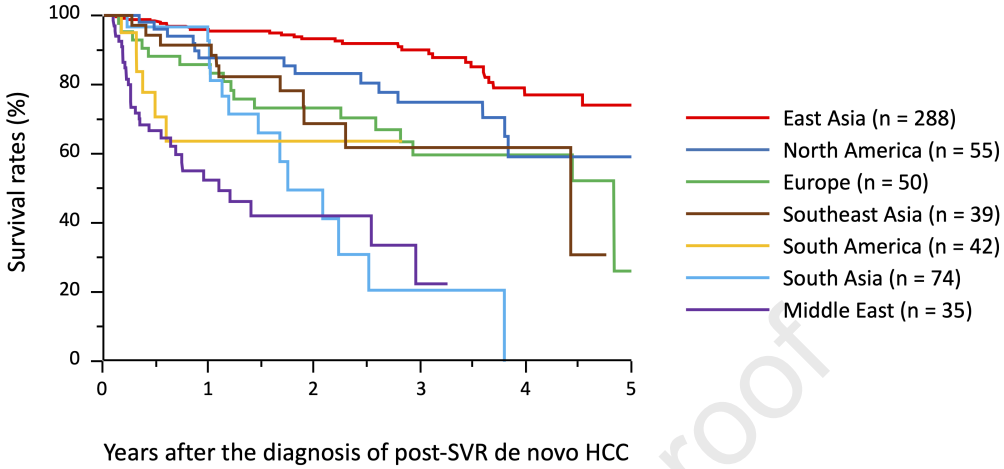
Table 4. Multivariate analysis for factors associated mortality after the diagnosis of post-SVR de novo HCC.

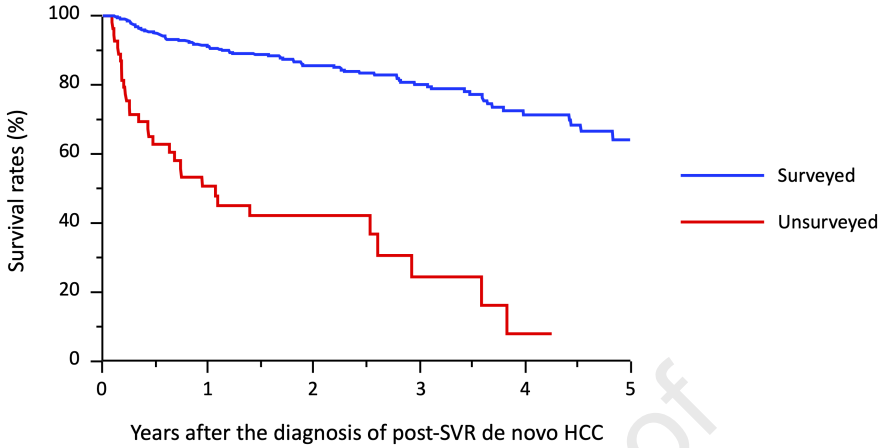
		HR (95% C.I.)	P value
Age	per 1 year	1.01 (0.99–1.03)	0.3501
Gender	Female	Reference	
	Male	1.01 (0.68–1.51)	0.9753
Cirrhosis	No	Reference	
	Yes	1.31 (0.74–2.51)	0.3607
Surveillance	Yes	Reference	
	No	3.44 (2.16–5.46)	<0.0001
Regions	East Asia	Reference	
	North America	1.82 (0.91–3.50)	0.0894
	South America	8.83 (2.92–21.80)	0.0005
	Southeast Asia	3.59 (1.65–7.34)	0.0019
	Europe	2.93 (1.53–5.44)	0.0015
	Middle East	4.47 (2.11–9.11)	0.0002
	South Asia	9.92 (5.17–19.09)	<0.0001

Survival of post-SVR HCC by regions.









Patients at risk						
Surveyed	458	331	229	132	60	20
Unsurveyed	67	29	15	6	2	

What You Need to Know

Background:

Due to the increase in patients with cured-HCV by DAA-based antiviral therapy, the number of patients with post-SVR HCC is increasing rapidly. Understanding regional differences among these patients can help inform interventions to improve prognosis of patients after SVR.

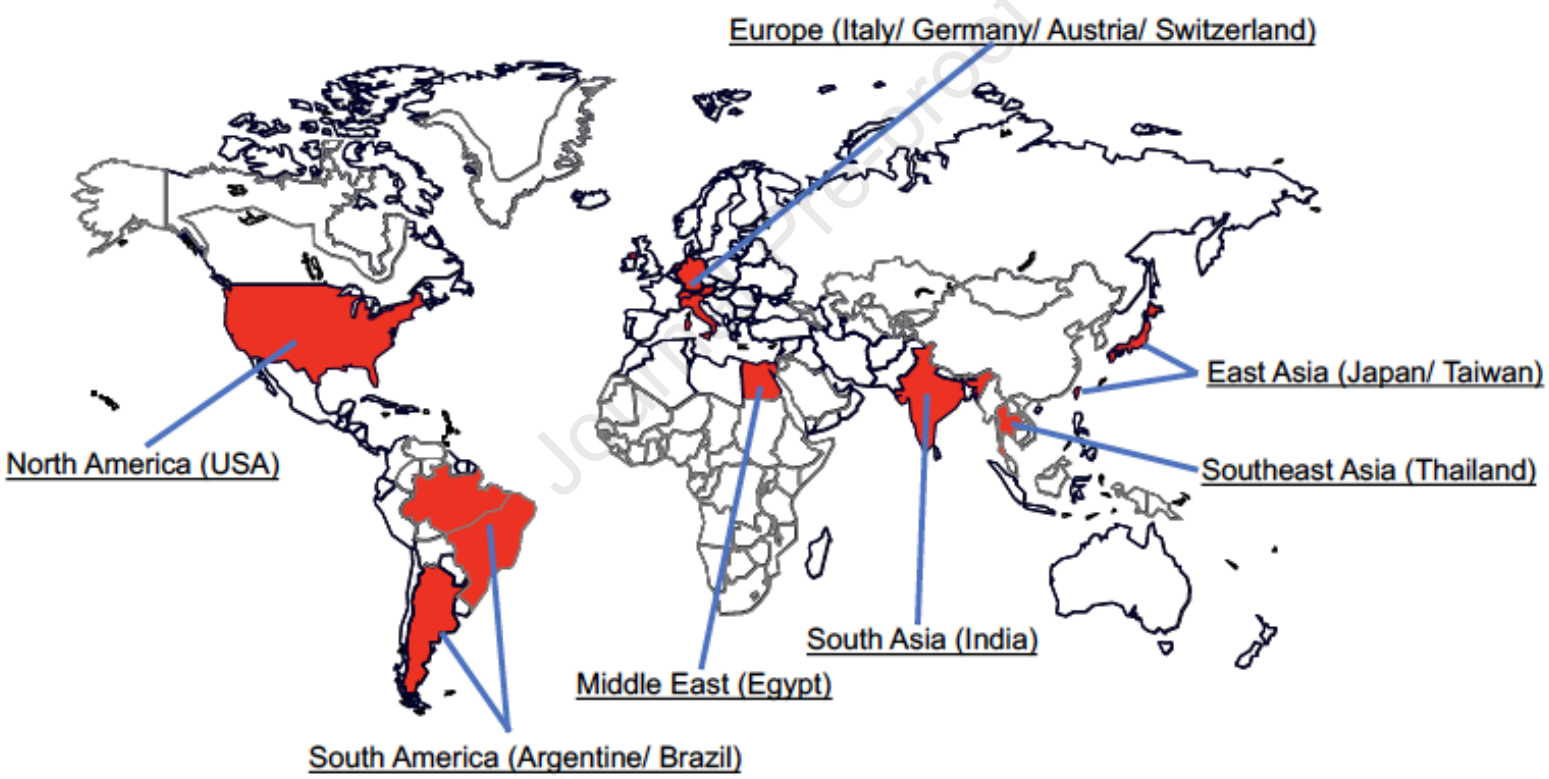
Findings:

There were marked regional differences in clinical presentations and prognosis of patients with post-SVR HCC. Differences in prognosis were likely related to variation in HCC surveillance programs for patients after SVR and treatment practice patterns in patients with HCC.

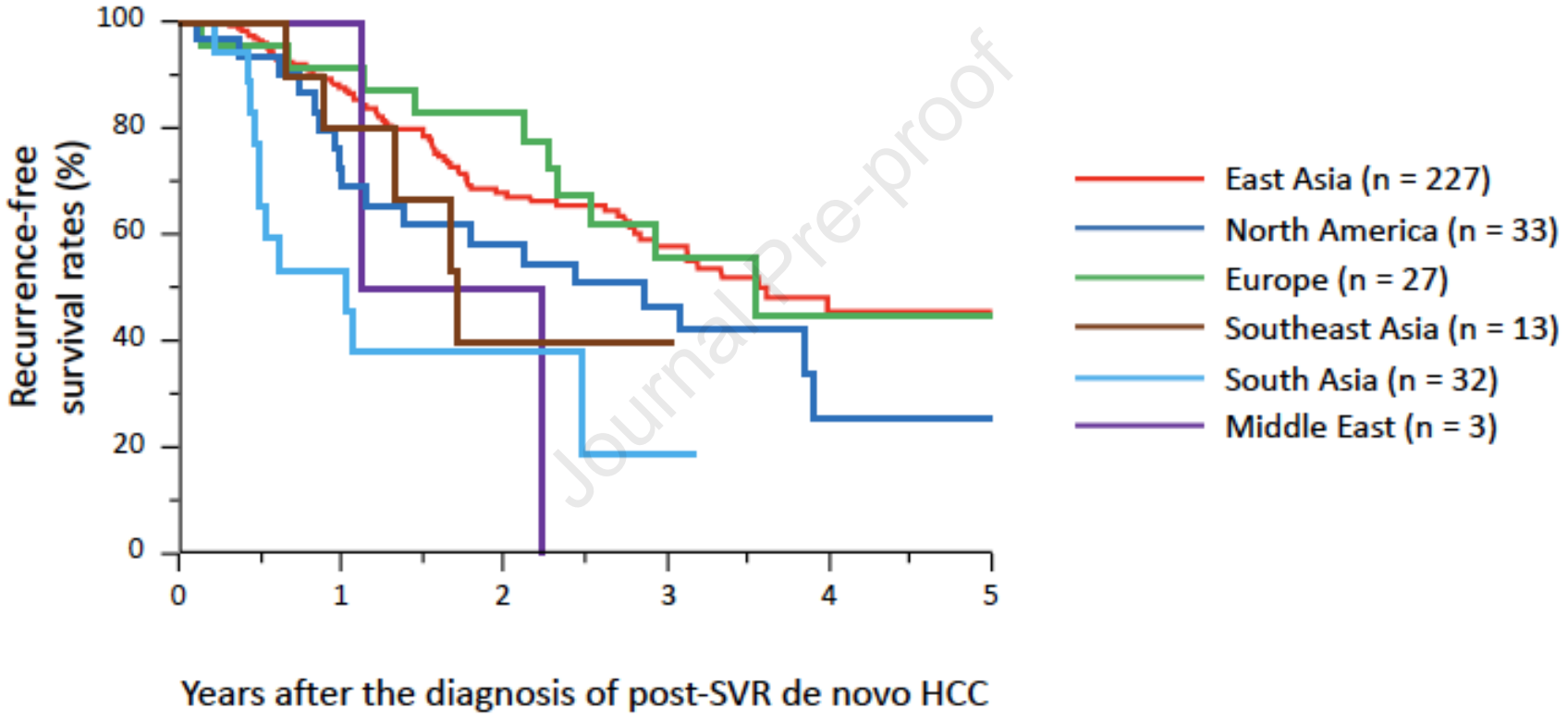
Implications:

Efforts to improve surveillance and treatment practice patterns for post-SVR HCC are necessary to improve the survival benefit of HCV eradication.

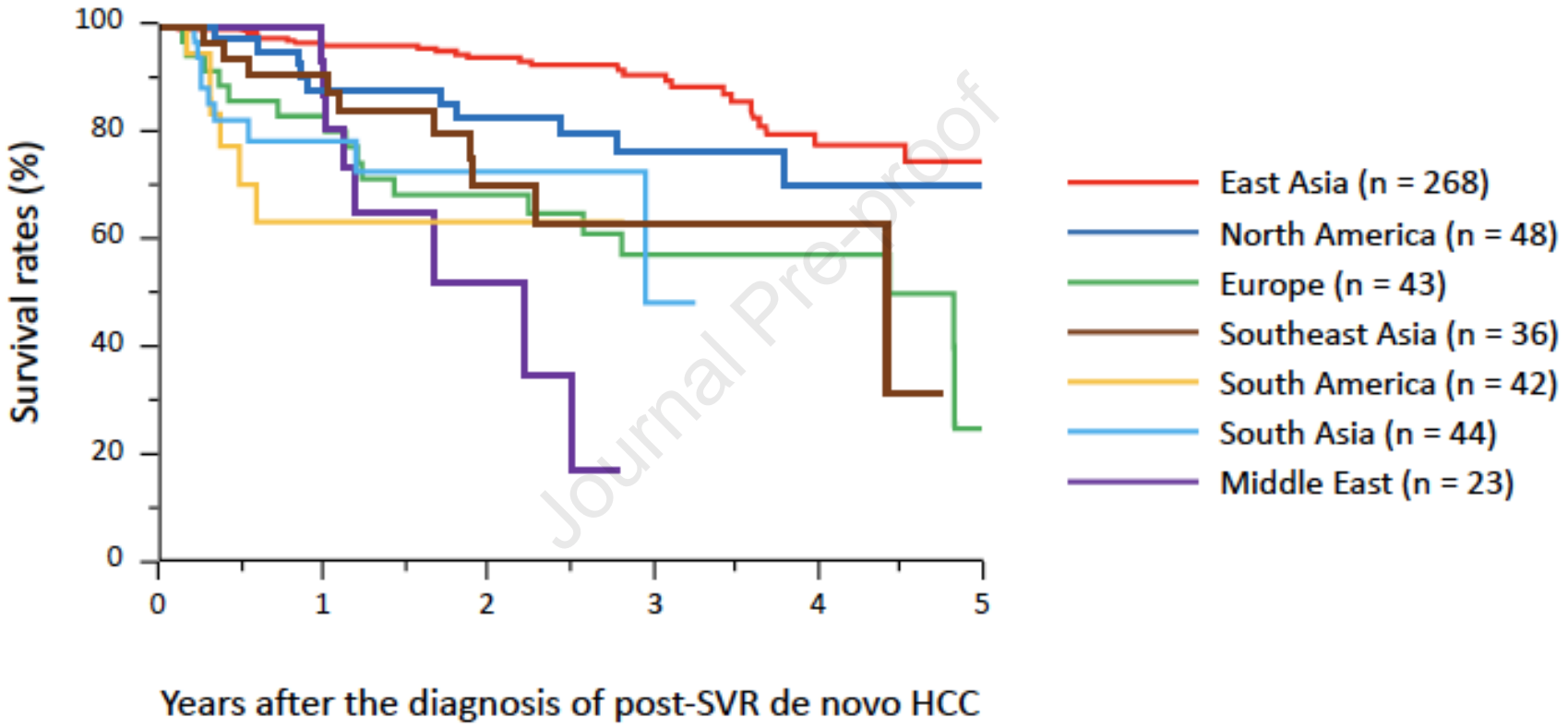
Supplementary Figure 1: Participating regions for international comparison of post-SVR HCC (HAVE study). Only patients with cirrhosis of advanced liver fibrosis (F3 or F4 fibrosis) and with no previous history of HCC could be enrolled.



Supplementary Figure 2: Recurrence-free survival rates after the diagnosis of post-SVR de novo HCC treated by curative treatment by regions.



Supplementary Figure 3: Survival rates after the diagnosis of post-SVR de novo HCC detected under surveillance by regions.



Supplementary Table 1. Incidence of HCC by regions

	Number of SVR patients	Follow-up period (years)	HCC (%)
Europe (Italy/ Germany/ Austria/ Switzerland)	838	2.62 (1.72–2.91)	50 (5.97)
North America (USA)	1144	3.24 (1.59–4.78)	55 (4.81)
South America (Argentine/ Brazil)	1990	1.96 (1.08–2.92)	42 (2.11)
Middle East (Egypt)	1041	2.61 (2.21–2.91)	35 (3.36)
South Asia (India)	662	2.18 (1.27–2.86)	74 (11.18)
East Asia (Japan/ Taiwan)	3026	3.32 (2.26–4.78)	288 (9.52)
Southeast Asia (Thailand)*	---	3.00 (1.41–3.59)	39 (---)

SVR, sustained virologic response; HCC, hepatocellular carcinoma.

*The number of total SVR patients in which post-SVR HCC enrolled to this study was unknown.

Supplementary Table 2. Surveillance practices by regions.

	Europe (Italy, Germany, Austria, Switzerland)	North America (USA)	South America (Argentine, Brazil)	Middle East (Egypt)	South Asia (India)	East Asia (Japan*, Taiwan)	Southeast Asia (Thailand)
Surveillance modalities	Ultrasound	Ultrasound ± AFP	Ultrasound ± AFP	Ultrasound + AFP	Ultrasound + AFP	Ultrasound + AFP	Ultrasound + AFP
Surveillance interval	6 months	6 months	6 months	6 months	6 months	3–6 months	6–12 months**

AFP, alpha-fetoprotein.

*In addition to ultrasound + AFP, additional HCC tumor markers including des-gamma-carboxy prothrombin and lens culinaris agglutinin-reactive AFP are measured in Japan.

**Patients whose surveillance interval above 7 months were categorized to unsurveyed cases in this study.

Supplementary Table 3. Survival rates of patients with post-SVR de novo HCC after diagnosis by surveillance status after SVR

	Number	MST (years)	1-year (%)	2-year (%)	3-year (%)	4-year (%)	5-year (%)	6-year (%)
Surveillance	458	Not reached	91.1	84.5	78.4	69.8	62.8	62.8
No surveillance	67	1.39	56.2	43.8	25.7	6.4		

MST, median survival time

Supplementary Table 4. Characteristics of patients with post-SVR de novo HCC detected under surveillance by regions

	Europe (Italy, Germany, Austria, Switzerland)	North America (USA)	South America (Argentine, Brazil)	Middle East (Egypt)	South Asia (India)	East Asia (Japan, Taiwan)	Southeast Asia (Thailand)
Number of patients	43	48	42	23	44	268	36
Maximal tumor size (cm)	3.1 (2.0–4.9)	2.2 (1.6-3.3)	2.5 (2.0-4.3)	2.5 (2.0-3.5)	3.1 (1.7-5.6)	1.7 (1.3–2.4)	3.0 (1.4-5.8)
Multinodular tumors	22 (57.8)	11 (22.9)	18 (42.9)	10 (50.0)	18 (40.9)	38 (14.2)	11 (30.6)
Portal vein invasion	9 (22.5)	4 (8.3)	1 (2.4)	2 (18.8)	17 (38.6)	6 (2.2)	17 (47.2)
Extrahepatic spread	8 (20.0)	0	1 (2.4)	0	3 (6.8)	0	12 (33.3)
AFP (ng/mL)	46.0 (5.9–312.0)	18.0 (5.0-63.0)	12.9 (3.8-213.8)	129.7 (28.8-312.3)	31.4 (5.2-502.5)	6.7 (4–26.8)	13.1 (4.0-176.0)
Curative treatment*	22 (56.4)	31 (64.6)	Not available	2 (10.0)	24 (54.6)	222 (82.8)	13 (37.1)

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

*Hepatic resection, transplantation, or local ablative therapies including microwave thermocoagulation and radiofrequency ablation.