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ORIGINAL ARTICLE

Long-term outcomes after curative resection of HCV-positive versus non-hepatitis related hepatocellular carcinoma: an international multi-institutional analysis

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Abstract

Background: To define the chronological changes of long-term survival among patients with non-hepatitis-related hepatocellular carcinoma (Non-Hep-HCC) versus hepatitis C-related HCC (HCV-HCC) over the last two decades.

Methods: Patients who underwent curative-intent resection for HCC between 2000 and 2017 were identified from an international multi-institutional database. Overall (OS) and recurrence-free survival (RFS) were analyzed and compared among Non-Hep-HCC versus HCV-HCC patients. Propensity score matching (PSM) was utilized to mitigate residual bias.

Results: Among 617 patients, 196 (31.8%) patients had HCV-HCC, whereas 421 (68.2%) patients had Non-Hep-HCC. While patients with HCV-HCC had an improvement in OS over time (5-year OS, 2000–2009 55% vs. 2010–2017 67%, $p = 0.034$), OS among patients with Non-Hep-HCC remain unchanged (5-year OS, 2000–2009 53% vs. 2010–2017 52%, $p = 0.905$). In the matched cohort, patients with HCV-HCC had a worse OS versus patients with Non-Hep-HCC during 2000 and 2009 (5-year OS, 12% vs. 63%, $p = 0.029$), but significantly better OS from 2010 to 2017 than patients with Non-Hep-HCC (5-year OS, 86% vs. 73%, $p = 0.035$). The recurrence timing, patterns and re-treatments were comparable among Non-Hep-HCC and HCV-HCC patients.

Conclusion: While OS of patients with HCV-HCC improved over time, the long-term survival of patients with Non-Hep-HCC patients remained unchanged and was more unfavorable.

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death with a 5-year survival of only 15–20%.[1,2] Liver transplantation may be the best therapeutic approach for HCC, yet this option is largely limited to patients with tumors confined to the Milan criteria.[3] In addition, due to the shortage of donor organs, transplantation is often not feasible for many patients with early stage disease.[4] As such, surgical resection is employed as the major curative treatment option for many patients with HCC.[5] The incidence of recurrence following resection of HCC can, however, be as high as 50–70% and recurrence has been strongly associated with worse long-term survival.[6,7]

HCC frequently occurs in patients with underlying liver disease related to hepatitis. Implementation of new treatment approaches for hepatitis infection has decreased the incidence of HCC, and has prolonged the long-term survival of patients with hepatitis-associated HCC.[8–10] Over the last decade, the treatment of hepatitis C (HCV) has been revolutionized by the introduction of anti-viral therapies.[11–13] In particular, new, short-duration therapies can result in high sustained viral response rates for HCV-infected patients. The Centers for Disease Control and Prevention guidelines recommend increased screening for HCV as the availability of new therapies may lead to the treatment of many more people with chronic HCV infection.[13] Despite treatments for HCV, the incidence of HCC in Western countries has continued to increase.[12,14] In particular, non-hepatitis HCC (Non-Hep-HCC) has been on the rise.[2,15] The etiology of Non-Hep-HCC is multi-factorial, being linked to non-alcoholic steatohepatitis (NASH), metabolic syndrome related factors, as well as obesity, diabetes mellitus, and insulin resistance.[16–19] In fact, while the peak of HCV was estimated to have occurred in 2010, the incidence of NASH or alcoholic liver disease has remained high over time.[17,20]

HCC associated with varied backgrounds of chronic liver damage may have unique genetic and epigenetic aberrations, perhaps leading to different biological behaviors.[21,22] Data on possible differences in disease course, recurrence patterns, and prognosis among HCC patients with distinct etiologies are scarce. In fact, most studies comparing patients with HCV-HCC versus Non-Hep-HCC were based on single center case series or involved multi-center data from a single country.[23–27] In particular, no study has investigated outcomes among patients with Non-Hep-HCC versus HCV-HCC patients over time. Therefore, the objective of the current study was to define the clinical presentation and long-term outcomes among patients with HCV-HCC versus Non-Hep-HCC, as well as characterize changes over the last two decades using a large international multi-institutional study.

Methods

Study population and patient inclusion criteria

Patients who underwent curative-intent surgical resection for pathological confirmed HCC between 2000 and 2017 were identified from an international multi-institutional database. Patients were treated at one of ten institutions: The Ohio State University Wesner Medical Center, Columbus, OH, USA (n = 145); University of Verona, Verona, Italy (n = 111); Ospedale San Raffaele, Milan, Italy (n = 37); Curry Cabral Hospital, Lisbon, Portugal (n = 191); APHP, Beaujon Hospital, Clichy, France (n = 101); Westmead Hospital, Sydney, Australia (n = 100); Stanford University, Stanford, CA, USA (n = 98); Fundeni Clinical Institute, Bucharest, Romania (n = 97); University of Ottawa, Ottawa, Canada (n = 64); The University of Sydney, School of Medicine, Sydney, Australia (n = 32). Patients were followed and outcomes were recorded in a multi-institutional database. The study was approved by the Institutional Review Boards of each participating institution.

Clinicopathological variables

Demographic factors including age, gender, American Society of Anesthesiologists (ASA) performance score, alcohol intake and smoking, diabetes mellitus, body mass index (BMI), and HCV infection were assessed. Data included platelet (PLT) count, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), and α-fetoprotein (AFP). Perioperative variables include Child-Pugh classification, Barcelona Clinic Liver Cancer (BCLC) staging, surgical approach (open or laparoscopic), extent (major or minor) and type (anatomic or non-anatomic) of hepatectomy, maximum tumor size, tumor number and location, differentiation grade, presence of cirrhosis and microvascular invasion, underlying liver disease, liver capsule involvement, and width of resection margin. Fibrosis and NASH were defined in the liver parenchyma based on the NASH Clinical Research Network criteria.[28]

Patients with HCV infection were defined as seropositive for HCV antibody or HCV RNA, respectively. Protocols of HCV treatments included interferon, ribavirin, interferon + ribavirin, direct-acting antivirals, or interferon/ribavirin + direct-acting antivirals. Sustained virologic response (SVR) indicates aviremia 24 weeks after completion of antiviral therapy for HCV infection. Postoperative morbidity was graded as I–V according to the Clavien-Dindo classification.[29] Long-term outcomes included overall survival (OS) and recurrence-free survival (RFS).

Statistical analysis

Clinicopathological variables were summarized using frequencies plus percentages for categorical variables, while medians and interquartile range (IQR) were reported for

continuous covariates. Categorical covariates were compared using chi-square test or Fisher's exact test, and continuous variables with Mann–Whitney U test or the Kruskal–Wallis test as appropriate. OS and RFS were calculated using the Kaplan–Meier method and differences were compared using the log-rank test. Univariate analyses were performed to identify risk factors associated with OS and RFS, and *P* values less than 0.1 were included as independent predictors using multivariate Cox regression model with a forward stepwise method. To reduce the effect of selection bias and confounding factors, a propensity score matching analysis between HCV-HCC and Non-Hep-HCC was performed using the nearest neighbor matching method without replacement. The propensity score was estimated using logistic regression, and one-to-one patient matching was performed. The variables included in the propensity score model were age, sex, Child-Pugh grade, ASA score, cirrhosis, the largest tumor diameter, tumor number, and AFP. All statistical analyses were conducted using SPSS version 23.0 (IBM SPSS, Chicago, IL, USA). A 2-tailed P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 976 patients were identified; patients with inadequate follow-up or incomplete medical records (n = 212, 21.7%) and patients who died within 30 days (n = 21, 2.2%) after surgery were excluded. In addition, patients with HBV infection (n = 60, 6.1%), HBV and HCV coinfection (n = 5, 0.5%), as well as those individuals with no information of hepatitis virus infection (n = 61, 6.3%) were also excluded. A total of 617 (63.2%) patients with Non-Hep-HCC or HCV-HCC who underwent curative-intent resection were included in the analytic cohort. The baseline clinicopathologic characteristics and surgical details of the whole cohort, as well as of patients with Non-Hep-HCC versus HCV-HCC were summarized (Supplementary Table 1).

Long-term outcomes of Non-Hep-HCC versus HCV-HCC

Median, 1-, 3-, 5-year OS were 74 months, 83%, 66%, and 53% among Non-Hep-HCC patients compared with 141 months, 91%, 71% and 62% among HCV-HCC patients (HR 1.4, 95% CI 1.0–2.0, $p = 0.043$) (Fig. 1a). RFS was comparable among Non-Hep-HCC versus HCV-HCC patients (5-year RFS, Non-Hep-HCC 39% vs. HCV-HCC 32%; $p = 0.962$) (Fig. 1b). Of note, OS was different over the time periods examined (2000–2009 versus 2010–2017) (Supplementary Table 2). In particular, among patients with HCV-HCC, OS improved over time (5-year OS, 2000–2009 55% vs. 2010–2017 67%, $p = 0.034$) (Fig. 2a), yet RFS remained unchanged (5-year RFS, 30% vs. 34%, $p = 0.186$) (Fig. 2b). In contrast, both OS (5-year OS, 2000–2009 53% vs. 2010–2017 52%, $p = 0.905$) and RFS (5-year RFS, 42% vs. 30%, $p = 0.362$) remained the same among patients with Non-Hep-HCC across the time periods examined (Fig. 2c–d). In turn, while patients with HCV-HCC and Non-Hep-HCC had comparable OS between 2000 and 2009 (5-year OS, HCV 55% vs. Non-Hep-HCC 53%, $p = 0.694$) (Fig. 2e), patients with HCV-HCC had a more favorable OS in later years (2010–2017: 5-year OS, HCV 67% vs. Non-Hep-HCC 52%, $p = 0.015$) (Fig. 2f). As baseline characteristics among HCV-HCC and Non-Hep-HCC patients were different (Supplementary Table 1), propensity score matching analysis was performed (Table 1). In the matched cohort, patients with HCV-HCC had a roughly comparable OS with Non-Hep-HCC patients during the study period (5-year OS, HCV 49% vs. Non-Hep-HCC 64%, $p = 0.489$) (Fig. 3a). Of note, when stratified by time period, patients with HCV-HCC had a worse OS versus patients with Non-Hep-HCC during 2000 and 2009 (5-year OS, HCV 12% vs. Non-Hep-HCC 63%, $p = 0.029$) (Fig. 3b), but a better OS from 2010 to 2017 versus

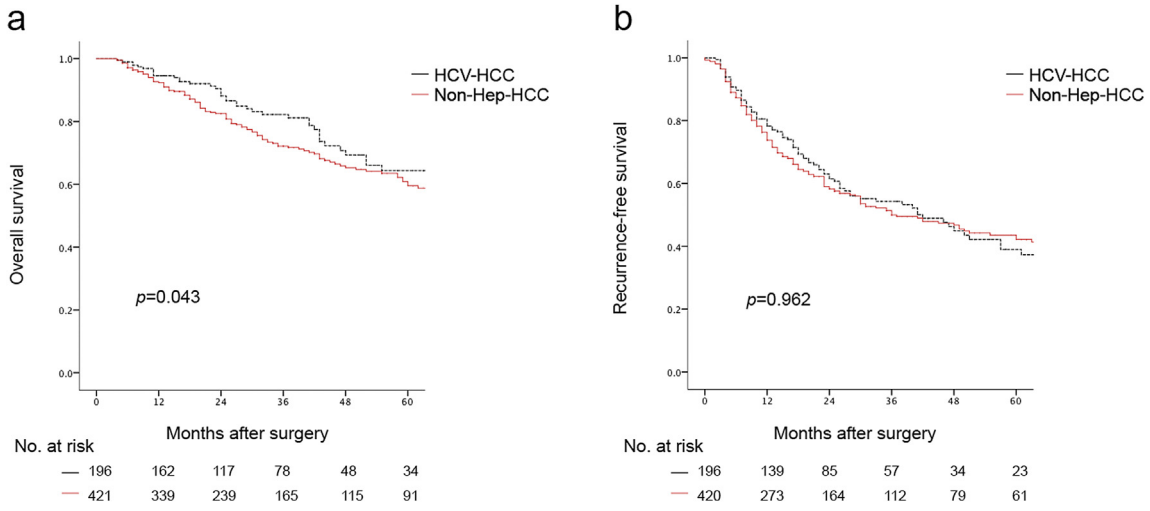

Figure 1 **(a)** Overall (OS) and **(b)** recurrence-free survival (RFS) curves after surgical resection of Non-Hep-HCC and HCV-HCC

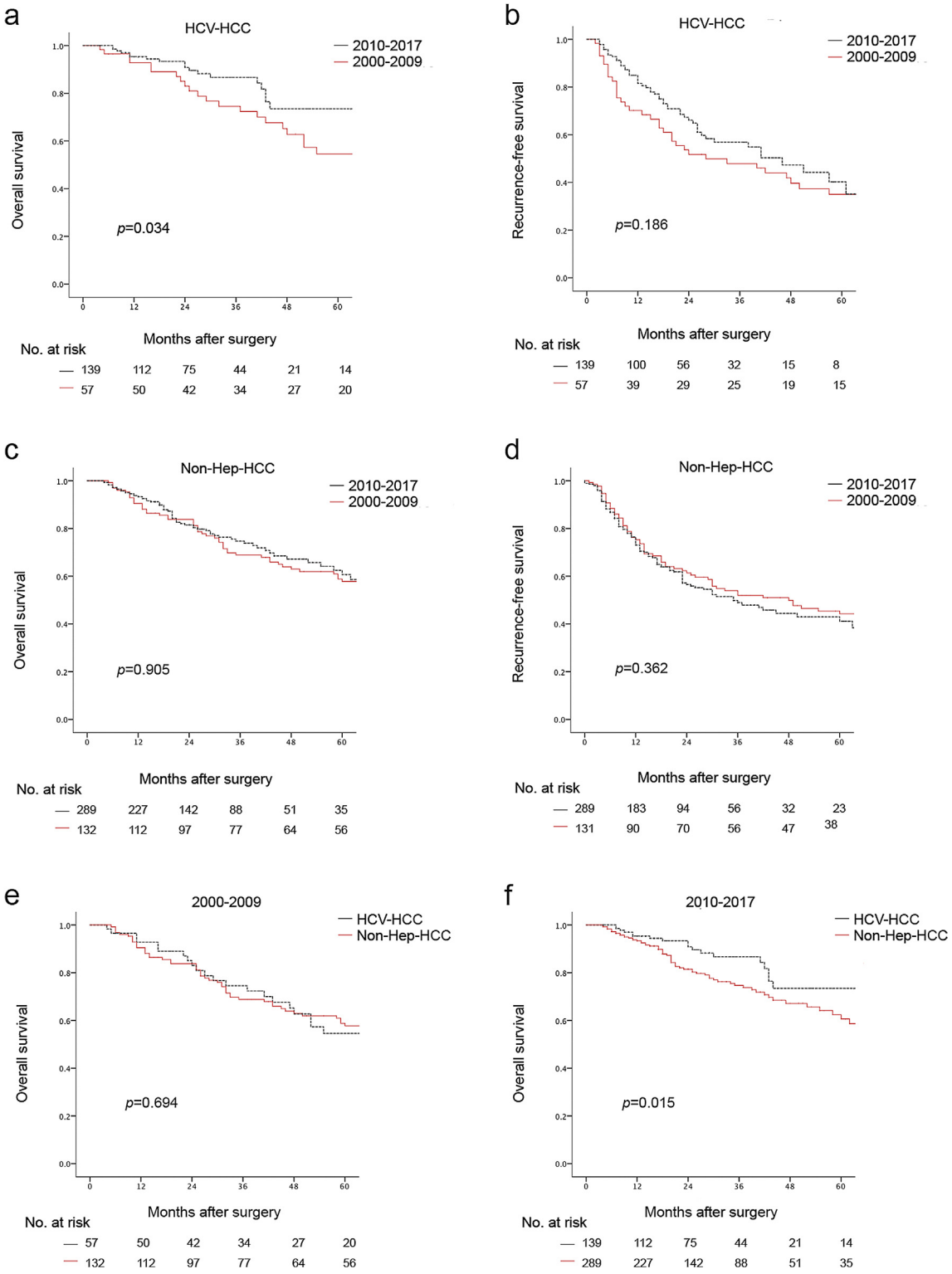

Figure 2 **(a)** Overall (OS) and **(b)** recurrence-free survival (RFS) curves of patients with HCV-HCC surgically treated in 2000–2009 versus 2010–2017; **(c)** OS and **(d)** RFS for patients with Non-Hep-HCC surgically treated in 2000–2009 versus 2010–2017; Comparison of OS among patients with Non-Hep-HCC or HCV-HCC who were surgically treated during time period of 2000–2009 **(e)** and 2010–2017 **(f)**

Table 1 Baseline demographics and clinicopathologic variables of patients with Non-Hep-HCC versus HCV-HCC after propensity score matching

Variables	Overall (n = 176)	Non-Hep-HCC (n = 88, 50%)	HCV-HCC (n = 88, 50%)	*P*
Age, years				0.629
≤60	57 (32%)	27 (31%)	30 (34%)	
>60	119 (68%)	61 (69%)	58 (66%)	
Gender				0.744
Male	122 (69%)	62 (71%)	60 (68%)	
Female	54 (31%)	26 (30%)	28 (32%)	
Diabetes mellitus	69 (40%)	46 (52%)	23 (27%)	0.001
Chronic alcohol intake	47 (27%)	30 (35%)	17 (20%)	0.023
Baseline liver disease				<0.001
Fibrosis	67 (44%)	23 (31%)	44 (57%)	
NASH	20 (13.2%)	19 (26%)	1 (1%)	
PSC	3 (2%)	3 (4%)	0 (0%)	
None	61 (40%)	29 (39%)	32 (42%)	
AFP > 400, ng/ml	30 (17%)	14 (16%)	16 (18%)	0.668
Child-Pugh classification				0.799
A	159 (90%)	80 (91%)	79 (90%)	
B	17 (10%)	8 (9%)	9 (10%)	
Surgery types				0.697
Minimally invasive	77 (44%)	37 (43%)	40 (46%)	
Open	98 (56%)	50 (58%)	37 (43%)	
Maximum tumor size > 5, cm	55 (31%)	30 (34%)	25 (28%)	0.416
Tumor number				0.434
Single	144 (82%)	70 (80%)	74 (84%)	
Multiple	32 (18%)	18 (21%)	14 (16%)	
Tumor location, bilobar	8 (5%)	5 (6%)	3 (3%)	0.479
BCLC staging				0.880
0/A	138 (80%)	69 (79%)	69 (80%)	
B/C	35 (20%)	18 (21%)	17 (20%)	
Liver cirrhosis	105 (60%)	51 (58%)	54 (61%)	0.645
Microvascular invasion	59 (36%)	31 (37%)	28 (35%)	0.711
Capsule involvement	29 (24%)	16 (26%)	13 (21%)	0.557
Margin status				0.517
R0	151 (86%)	74 (84%)	77 (88%)	
R1	25 (14%)	14 (16%)	11 (13%)	
Postoperative complications	75 (44%)	35 (41%)	40 (48%)	0.364
Postoperative liver failure	7 (4%)	3 (3%)	4 (5%)	0.688

BMI: body mass index; ASA: American Society of Anesthesiologists; NASH: non-alcoholic steatohepatitis; PSC: primary sclerosing cholangitis; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: α-fetoprotein; BCLC: Barcelona Clinic Liver Cancer.

patients with Non-Hep-HCC (5-year OS, HCV 86% vs. Non-Hep-HCC 73%, $p = 0.035$) (Fig. 3c).

Among 196 HCV-HCC patients, 137 had available information on anti-HCV treatment, among which 77 patients (56%) had received preoperative anti-HCV treatments. OS was better among patients who received preoperative anti-HCV treatments versus patients who did not (5-year OS, 69% vs. 54%, $p = 0.016$) (Supplementary Fig. 1a). In addition, among 79 patients who received preoperative anti-HCV treatment, patients who achieved SVR (n = 29, 37%) had a much improved OS versus patients in whom SVR was not achieved (5-year OS, 64% vs. 46%, $p = 0.042$) (Supplementary Fig. 1b).

With a median follow-up of 28 months, 192 (46%) patients with Non-Hep-HCC and 94 (48%) patients with HCV-HCC experienced recurrence ($p = 0.585$). Patients with Non-Hep-HCC had a higher incidence of extrahepatic ± intrahepatic recurrence compared with HCV-HCC patients (33% vs. 17%, $p = 0.024$) (Table 2). In addition, among patients who recurred, the recurrence patients tended to occur within 24 months more often among Non-Hep-HCC versus HCV-HCC patients (79% vs. 70%, $p = 0.088$). In general, similar curative-intent treatment options were offered to Non-Hep-HCC versus HCV-HCC patients who experienced a recurrence (Table 2). However, in the matched cohort, the recurrence timing, patterns, as well as re-treatments were not significantly different among patients with Non-Hep-HCC versus HCV-HCC (Table 2).

Discussion

As the incidence of hepatitis-related HCC has decreased, Non-Hep-HCC has been on the rise becoming the dominant HCC subtype in many geographic regions.[2,30] Data on the clinical and long-term outcomes of patients with hepatitis versus Non-Hep-CC have not, however, been well defined, especially in the era of antiviral therapies. As such, by utilizing a large international cohort of patients with HCC from a multi-institutional database, the current study was important because we were able to specifically delineate distinct clinicopathologic characteristics, as

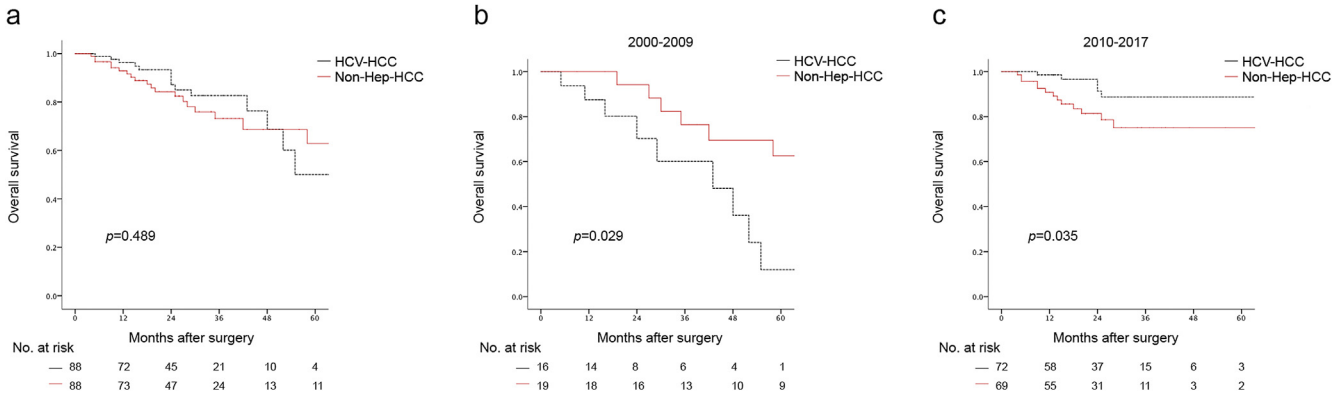

Figure 3 Overall survival (OS) curves of patients with HCV-HCC or Non-Hep-HCC in the matched cohort during the whole study period **(a)**, from the year of 2000–2009 **(b)**, or from the year of 2010–2017 **(c)**

well as chronological changes in long-term survival, among patients with Non-Hep-HCC versus HCV-HCC over the last two decades. Interestingly, OS among HCV-HCC patients increased over the study periods examined, likely as a result of the introduction of more effective anti-viral treatments.[2] In contrast, patients with Non-Hep-HCC did not have any improvement in survival over time. In fact, patients with Non-Hep-HCC were more likely to experience an early recurrence, as well as experience extrahepatic recurrence compared with patients who had HCV-HCC, although these were not significantly different in the matched cohort. Collectively, these data serve to highlight that Non-Hep-HCC was an aggressive disease process with outcomes as grave as – or worse – than patients with the previously more common HCV-HCC.

Perhaps not surprisingly, liver cirrhosis and chronic liver injury were more common among HCV-HCC versus Non-Hep-HCC patients. Chronic HCV typically progresses to cirrhosis within 20 years in an estimated 20–30% of patients.[31] Certain HCV proteins, such as core and NS5A, can induce derangement of lipid metabolism or alter signal transduction of infected hepatocytes which leads to the production of reactive oxygen radicals and profibrogenic mediators.[32] Importantly, the year 2011 marked the dawn of a new era of Direct-Acting Antivirals (DAA) for hepatitis C. In turn, usage of DAA resulted in more effective treatment of patients with much higher probability of SVR and, in turn, improvements and avoidance of liver fibrosis and cirrhosis among patients with HCV.[2,33] In the current study, among patients with HCV-HCC, OS was noted to improve over time, with a markedly better OS in the latter periods correlating with the introduction of DAA for HCV (Fig. 2a). OS was better among patients who received preoperative anti-HCV treatments and, in particular, those individuals who had a SVR had much

Table 2 Recurrence patterns of patients with Non-Hep-HCC versus HCV-HCC before and after propensity score matching

Variables	Before propensity score matching				After propensity score matching			
	Total (n = 617)	Non-Hep-HCC (n = 421, 67%)	HCV-HCC (n = 196, 32%)	P	Total (n = 176)	Non-Hep-HCC (n = 88, 50%)	HCV-HCC (n = 88, 50%)	P
Any recurrence	286 (46%)	192 (46%)	94 (48%)	0.585	74 (42%)	38 (43%)	36 (41%)	0.760
Local recurrence	25 (10%)	17 (10%)	8 (10%)	0.905	9 (14%)	5 (16%)	4 (12%)	0.645
Recurrence site				0.024				0.123
Intrahepatic	186 (73%)	116 (67%)	70 (83%)		47 (73%)	20 (65%)	27 (82%)	
Extrahepatic	45 (18%)	37 (22%)	8 (10%)		12 (19%)	9 (29%)	3 (9%)	
Both	25 (10%)	19 (11%)	6 (7%)		5 (8%)	2 (7%)	3 (9%)	
Time to recurrence				0.088				0.257
≤24 months	216 (76%)	150 (79%)	66 (70%)		56 (78%)	30 (83%)	26 (72%)	
>24 months	67 (24%)	39 (21%)	28 (30%)		16 (22%)	6 (17%)	10 (28%)	
Treatment for recurrence				0.153				0.537
Curative	78 (32%)	48 (29%)	30 (39%)		26 (41%)	12 (38%)	14 (45%)	
Non-curative	164 (68%)	116 (71%)	48 (62%)		37 (59%)	20 (63%)	17 (55%)	

improved OS (Supplementary Fig. 1a, b). These data were consistent with previous data that demonstrated that patients with HCV-HCC who had a SVR exhibited a much better prognosis – even better than Non-Hep-HCC patients.[34]

The outcomes of patients following resection of Non-Hep-HCC relative to HCV-HCC have been inconsistent, and somewhat controversial.[18–20,27,35–38] One study from Japan reported that patients with Non-Hep-HCC had better long-term outcomes versus patients who had HCV-HCC.[27] However, the majority of patients with HCV in this study had undergone resection prior to 2005 and the introduction of DAA for HCV.[27] As noted above, the clinical use of anti-HCV treatments such as DAA have dramatically changed the clinical course of patients with HCV over the last decade.[2,33] To this point, the current study included patients from ten institutions and seven Western countries and noted improvement in OS among patients with HCV-HCC over time. While there was a noted improvement in outcomes among patients with HCV-HCC, the OS of patients with Non-Hep-HCC remained the same over time. As such, in more recent periods, patients with Non-Hep-HCC actually had a worse prognosis than patients with HCV-HCC. Related to this finding, early and extrahepatic recurrence were more common among patients with Non-Hep-HCC versus HCV-HCC. In turn, postoperative recurrence has been associated with a worse prognosis as timing and patterns of recurrence strongly correlate with long-term outcomes.[27] Taken together, the findings suggested that different postoperative monitoring strategies may be need to optimize surveillance among patients with Non-Hep-HCC versus HCV-HCC.

The current study should be interpreted in light of several limitations. While the use of an international multi-institutional study provided increased sample size and more generalizability, the incorporation of patients from multiple different centers likely contributed to potential heterogeneity with respect to treatment strategy, follow-up protocols, and identification of recurrence. In addition, detailed information on possible etiologies of Non-Hep-HCC was not available in the current database.

In conclusion, Non-Hep-HCC represented a dominant subtype of HCC in the current era. While OS of patients with HCV-HCC improved over time, the long-term survival of patients with Non-Hep-HCC patients remained unchanged and was more unfavorable than HCV-HCC in the more recently time period examined. The improvement in HCV-HCC was likely related to the introduction of anti-viral therapy, as patients with SVR had a much better prognosis. In contrast, patients with Non-Hep-HCC were more likely to recur early and at an extrahepatic site following surgical resection. In sum, data from the current study highlight important differences in clinical, pathologic, as well as long-term outcomes among patients with Non-Hep-HCC versus HCV-HCC that can help inform the treatment of patients with this challenging disease.

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Conflict of interest

None declared.

References

1. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B *et al*. (2017) Annual report to the nation on the status of cancer, 1975–2014, featuring survival. *J Natl Cancer Inst* 109.
2. Villanueva A. (2019) Hepatocellular carcinoma. *N Engl J Med* 380: 1450–1462.
3. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F *et al*. (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334:693–699.
4. Fan ST, Mau Lo C, Poon RT, Yeung C, Leung Liu C, Yuen WK *et al*. (2011) Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. *Ann Surg* 253: 745–758.
5. Rahbari NN, Mehrabi A, Mollberg NM, Muller SA, Koch M, Buchler MW *et al*. (2011) Hepatocellular carcinoma: current management and perspectives for the future. *Ann Surg* 253:453–469.
6. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S *et al*. (2003) Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 38:200–207.
7. Xu XF, Xing H, Han J, Li ZL, Lau WY, Zhou YH *et al*. (2019) Risk factors, patterns, and outcomes of late recurrence after liver resection for hepatocellular carcinoma: a multicenter study from China. *JAMA Surg* 154:209–217.
8. Chang MH, You SL, Chen CJ, Liu CJ, Lai MW, Wu TC *et al*. (2016) Long-term effects of hepatitis B immunization of infants in preventing liver cancer. *Gastroenterology* 151:472–480 e471.
9. Huang G, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F *et al*. (2015) Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. *Ann Surg* 261: 56–66.
10. Singal AG, Rich NE, Mehta N, Branch AD, Pillai A, Hoteit M *et al*. (2019) Direct-acting antiviral therapy for hepatitis C virus infection is associated with increased survival in patients with a history of hepatocellular carcinoma. *Gastroenterology* 157:1253–1263.
11. Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z *et al*. (2011) Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Ann Intern Med* 154:85–93.
12. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. (2004) Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. *Gastroenterology* 127: 1372–1380.
13. Kohli A, Shaffer A, Sherman A, Kottilil S. (2014) Treatment of hepatitis C: a systematic review. *J Am Med Assoc* 312:631–640.

14. El-Serag HB. (2011) Hepatocellular carcinoma. *N Engl J Med* 365: 1118–1127.
15. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A *et al*. (2019) Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol* 17:748–755. e743.
16. Starley BQ, Calcagno CJ, Harrison SA. (2010) Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 51:1820–1832.
17. Siegel AB, Zhu AX. (2009) Metabolic syndrome and hepatocellular carcinoma: two growing epidemics with a potential link. *Cancer* 115: 5651–5661.
18. Cauchy F, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L *et al*. (2013) Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. *Br J Surg* 100:113–121.
19. Nishio T, Hatano E, Sakurai T, Taura K, Okuno M, Kasai Y *et al*. (2015) Impact of hepatic steatosis on disease-free survival in patients with non-B non-C hepatocellular carcinoma undergoing hepatic resection. *Ann Surg Oncol* 22:2226–2234.
20. Vigano L, Conci S, Cescon M, Fava C, Capelli P, D'Errico A *et al*. (2015) Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: a multicenter matched analysis with HCV-related HCC. *J Hepatol* 63:93–101.
21. Schulze K, Nault JC, Villanueva A. (2016) Genetic profiling of hepatocellular carcinoma using next-generation sequencing. *J Hepatol* 65: 1031–1042.
22. Kuramoto J, Arai E, Tian Y, Funahashi N, Hiramoto M, Nammo T *et al*. (2017) Genome-wide DNA methylation analysis during non-alcoholic steatohepatitis-related multistage hepatocarcinogenesis: comparison with hepatitis virus-related carcinogenesis. *Carcinogenesis* 38: 261–270.
23. Tanaka K, Shimada H, Matsuo K, Nagano Y, Endo I, Togo S. (2007) Clinical characteristics and surgical outcome in hepatocellular carcinoma without hepatitis B virus surface antigen or hepatitis C virus antibody. *Ann Surg Oncol* 14:1170–1181.
24. Nanashima A, Abo T, Sumida Y, Takeshita H, Hidaka S, Furukawa K *et al*. (2007) Clinicopathological characteristics of patients with hepatocellular carcinoma after hepatectomy: relationship with status of viral hepatitis. *J Surg Oncol* 96:487–492.
25. Cescon M, Cucchetti A, Grazi GL, Ferrero A, Vigano L, Ercolani G *et al*. (2009) Role of hepatitis B virus infection in the prognosis after hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a Western dual-center experience. *Arch Surg* 144:906–913.
26. Li T, Qin LX, Gong X, Zhou J, Sun HC, Qiu SJ *et al*. (2013) Hepatitis B virus surface antigen-negative and hepatitis C virus antibody-negative hepatocellular carcinoma: clinical characteristics, outcome, and risk factors for early and late intrahepatic recurrence after resection. *Cancer* 119:126–135.
27. Utsunomiya T, Shimada M, Kudo M, Ichida T, Matsui O, Izumi N *et al*. (2015) A comparison of the surgical outcomes among patients with HBV-positive, HCV-positive, and non-B non-C hepatocellular carcinoma: a nationwide study of 11,950 patients. *Ann Surg* 261:513–520.
28. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW *et al*. (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 41: 1313–1321.
29. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al*. (2009) The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 250:187–196.
30. Tateishi R, Uchino K, Fujiwara N, Takehara T, Okanoue T, Seike M *et al*. (2019) A nationwide survey on non-B, non-C hepatocellular carcinoma in Japan: 2011–2015 update. *J Gastroenterol* 54:367–376.
31. Powell EE, Edwards-Smith CJ, Hay JL, Clouston AD, Crawford DH, Shorthouse C *et al*. (2000) Host genetic factors influence disease progression in chronic hepatitis C. *Hepatology* 31:828–833.
32. Schuppan D, Krebs A, Bauer M, Hahn EG. (2003) Hepatitis C and liver fibrosis. *Cell Death Differ* 10(Suppl 1):S59–S67.
33. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. (2017) Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology* 153:996–1005. e1001.
34. Shinkawa H, Tanaka S, Takemura S, Ito T, Aota T, Miyazaki T *et al*. (2019) Outcomes of non-B non-C hepatocellular carcinoma with reference to patients with interferon-induced hepatitis C virus eradication. *J Gastrointest Surg*. https://doi.org/10.1007/s11605-019-04339-1.
35. Wakai T, Shirai Y, Sakata J, Korita PV, Ajioka Y, Hatakeyama K. (2011) Surgical outcomes for hepatocellular carcinoma in nonalcoholic fatty liver disease. *J Gastrointest Surg* 15:1450–1458.
36. Reddy SK, Steel JL, Chen HW, DeMateo DJ, Cardinal J, Behari J *et al*. (2012) Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. *Hepatology* 55:1809–1819.
37. Pawlik TM, Poon RT, Abdalla EK, Sarmiento JM, Ikai I, Curley SA *et al*. (2004) Hepatitis serology predicts tumor and liver-disease characteristics but not prognosis after resection of hepatocellular carcinoma. *J Gastrointest Surg* 8:794–804. discussion 804–795.
38. Mgaieth S, Kemp W, Gow P, Fink M, Lubel J, Nicoll A *et al*. (2017) Impact of viral hepatitis aetiology on survival outcomes in hepatocellular carcinoma: a large multicentre cohort study. *J Viral Hepat* 24:982–989.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.01.003.