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# Hepatitis B- and C-related hepatocellular carcinomas yield different clinical features and prognosis

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## ARTICLE INFO

### Article history:

Received 9 May 2006

Accepted 12 June 2006

Available online 22 August 2006

### Keywords:

Hepatocellular carcinoma

Hepatitis B virus

Hepatitis C virus

Survival

## ABSTRACT

The purpose of this study was to compare the clinical features and survival in patients with hepatitis B virus-related hepatocellular carcinoma (HBV-HCC) and hepatitis C virus-related hepatocellular carcinoma (HCV-HCC). A total of 2820 HCC patients were included. The mean age of HBV-HCC patients was  $52.5 \pm 13.4$  years, while it was  $64.8 \pm 8.7$  years in HCV-HCC patients. The male/female ratio was 7.8 in HBV-HCC, while it was 1.7 in HCV-HCC. The mean  $\alpha$ -fetoprotein level in HBV-HCC was  $11,661 \pm 22,805$  ng/mL, while it was  $5079 \pm 15,005$  ng/mL in HCV-HCC. The mean tumour size was  $6.4 \pm 4.1$  cm in HBV-HCC, while it was  $4.6 \pm 3.1$  cm in HCV-HCC. The median survival was 11.1 months in HBV-HCC, while it was 23.9 months in HCV-HCC. Compared with HBV-HCC patients, HCV-HCC patients were older, had a lower male/female ratio, lower white blood cell count, lower serum albumin level, higher serum ALT level, lower serum  $\alpha$ -fetoprotein level, smaller tumour size and survived longer.

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## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, especially in sub-Saharan Africa and Southeast Asia. Since 1984, it has been the leading cause of cancer death in Taiwan.<sup>1</sup> Around 7000 people die of HCC annually and around 8000 new HCC cases are found every year in Taiwan.<sup>2</sup> The high risk groups of HCC in Taiwan include patients chronically infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), liver cirrhosis, or family history of HCC. Among them, HBV and HCV chronic infections are the two major aetiologies for HCCs in Taiwan.<sup>3</sup>

Several studies have examined the differences among HBV-related HCC (HBV-HCC) and HCV-related HCC (HCV-HCC).<sup>4–17</sup> However, there were still some limitations in the previous studies. Most investigations focused on surgical patients only.<sup>4–6,8–10,13–15</sup> The surgical patients represented the better prognosis groups out of all HCC patients. Thus, the results might not be generalised to the whole HBV-HCC and HCV-HCC patients. Furthermore, the case numbers were small and the follow-up period was not long enough. Only a few studies explored HCC patients receiving different treatment modalities.<sup>7,11,12</sup> However, these studies were from the areas where the HCV was the predominant aetiology for HCC.

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doi:10.1016/j.ejca.2006.06.007

Whether such conclusions can also be applied in the HBV-endemic area, like Taiwan, is still unclear. Thus, the purpose of this study is to compare the clinical features and survival in patients with HBV-HCC and HCV-HCC in Taiwan.

## 2. Patients and methods

### 2.1. Patients and data collection

The medical records with the diagnosis of HCC in National Taiwan University Hospital from 1981 to 2000 June were retrospectively reviewed. Those who received their initial treatments for HCC at other hospitals were excluded. The diagnosis of HCC was based on either histologic examination of tumour tissues or typical radiological image pictures. The following data were collected at diagnosis: name, chart number, national citizen identification number, sex, birthday, date of HCC diagnosis, date of death and date of last follow-up, diagnostic criteria for HCC, modality of first treatment, presence of liver cirrhosis, Child–Pugh stage and its constitutive variables (albumin, bilirubin, prothrombin time, ascites and encephalopathy), hepatitis B surface antigen (HBsAg) and antibody for hepatitis C virus (anti-HCV) status, WBC, haemoglobin, platelet, AST, ALT, alkaline phosphatase (ALP), BUN, creatinine, serum  $\alpha$ -fetoprotein (AFP), tumour size, tumour number, evidence of portal vein invasion, bile duct invasion or distant metastases. Only patients with both HBsAg and anti-HCV available data were enrolled in this study.

### 2.2. Aetiology of HCC

HBV-HCC was defined as HCC with a positive HBsAg status and a negative anti-HCV status. HCV-HCC was defined as HCC with a negative HBsAg status and a positive anti-HCV status. The HBV plus HCV-related HCC (HBV+HCV-HCC) was defined as HCC with a positive status for both HBsAg and anti-HCV. The non-HBV and non-HCV-related HCC (NBNC-HCC) was defined as HCC with a negative status for both HBsAg and anti-HCV.

### 2.3. Searching for fatalities

To verify patients' deaths, we used the national citizen identification (ID) number of patients with HCC to search the mortality data bank established by the Statistics Office, Department of Health, Taiwan. The mortality data bank includes data from the certificate of death, which contains the demographic data of the patient; the time, place, and cause of death; and the name of the person who issued the document. The mortality data bank included patients who had expired before 31st December 2001. Thus, cases that still survived after 31st December 2001 were right censored. Since the mortality data bank did not contain the original ID number before 1985, a verification and re-insertion of ID was completed using the database of Internal Revenue Service.<sup>18</sup>

### 2.4. Statistical analysis

Statistical analysis of differences among the four groups was done using Pearson's  $\chi^2$  test. Survival curves were estimated

using the Kaplan–Meier method and the differences in the survival rates between the groups were compared by the log-rank test. All statistical analyses were performed using the SAS software, Version 8 (Statistical Analysis System, Cary, NC, United States). The statistical significance was defined as  $p < 0.05$ .

## 3. Results

A total of 4968 Taiwanese HCC patients were collected. Medical records in which details pertaining to any of the following three items, HBsAg, anti-HCV and initial treatment method, were missing were excluded. Most of the excluded records were due to missing anti-HCV data. Thus, a total of 2820 patients were analysed in this study, including 1698 HBV-HCC (60.2%), 613 HCV-HCC (21.7%), 214 HBV+HCV-HCC (7.6%) and 295 NBNC-HCC (10.5%).

### 3.1. Age and sex of HCC patients

As shown in Table 1, the mean age of HCV-HCC patients was 4 years older than those of HBV+HCV-HCC or NBNC-HCC patients, and 12 years older than that of HBV-HCC patients. The male/female ratio (7.8) was highest in HBV-HCC, while it was lowest in HCV-HCC (1.7).

### 3.2. Biochemistry in HCC patients

The HCV-HCC patients had lower WBC and platelet counts. The serum albumin levels were lower in the HCV-HCC and HBV+HCV-HCC patients compared with those in the HBV-HCC or NBNC-HCC patients. The mean ALT level was lowest in the NBNC-HCC patients. Though the ALT level was slightly higher in the HCV-HCC patients, there was no statistically significant difference in the mean ALT level between HBV-HCC and HCV-HCC patients. The mean bilirubin levels, prolongation of prothrombin time, presence of ascites or encephalopathy were similar among all four groups.

### 3.3. Tumour characteristics and staging of HCCs

The HBV-HCC group had higher AFP levels than other groups. The mean tumour size was largest in the NBNC-HCC group, followed by the HBV-HCC, HBV+HCV-HCC and HCV-HCC groups ( $7.6 \pm 4.5$  cm,  $6.4 \pm 4.1$  cm,  $5.7 \pm 3.8$  cm, and  $4.6 \pm 3.1$  cm, respectively). There were no statistically significant differences in the tumour numbers between different groups. The HCV-HCC group had a higher percentage of patients in the earlier stages, while the NBNC-HCC group had the lowest percentage of patients in the earlier stage. The resectable rate was similar among all four groups (42.3% in HBV-HCC, 40.5% in HCV-HCC, 40.7% in HBV+HCV-HCC, and 44.1% in NBNC-HCC) (Fig. 1).

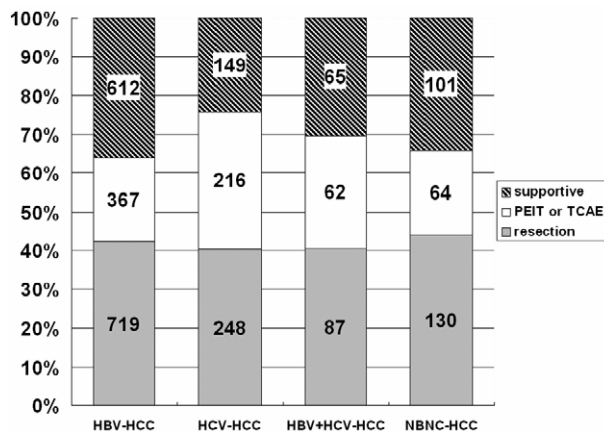
### 3.4. Survival

As shown in Table 2 and Fig. 2, the patients with HCV-HCC had the best overall survival. However, it was interesting to find that the better survival of HCV-HCC patients happened in the initial 5 years, while the survival of HCV-HCC patients

**Table 1 – Clinical features of HCC patients**

Aetiology	HBV (N = 1698)	HCV (N = 613)	HBV+HCV (N = 214)	NBNC (N = 295)	p
Age (years)	52.5 ± 13.4	64.8 ± 8.7	60.7 ± 10.4	60.4 ± 14.5	<0.0001
Male/female (ratio)	1505/193 (7.8)	384/229 (1.7)	161/53 (3.0)	218/77 (2.8)	<0.0001
White blood cell (/μL)	6473 ± 3064	5639 ± 3318	6008 ± 2832	7656 ± 4772	<0.0001
Haemoglobin (g/dL)	12.9 ± 2.3	12.2 ± 2.1	12.3 ± 2.2	12.2 ± 2.3	<0.0001
Platelet (K/μL)	188 ± 113.7	128 ± 77.6	158 ± 113.3	226 ± 109.8	<0.0001
PT prolonged (s)	2.0 ± 2.5	2.1 ± 2.1	2.0 ± 2.5	1.6 ± 2.5	0.094
Albumin (g/dL)	3.6 ± 0.6	3.5 ± 0.6	3.5 ± 0.5	3.6 ± 0.6	<0.0001
Bilirubin (mg/dL)	2.0 ± 3.9	1.7 ± 3.0	2.0 ± 4.4	2.4 ± 4.6	0.128
Ascites (+/-)	302/1287	95/482	41/164	51/220	0.536
Encephalopathy(+/-)	10/1627	5/585	2/207	2/281	0.903
ALT (U/L)	65.8 ± 100.8	75.9 ± 79.5	69.8 ± 53.0	44.9 ± 46.7	<0.0001
Child–Pugh stage (A/B/C)	1097/248/46	401/96/11	138/31/3	180/38/9	0.716
AFP (ng/mL)	11,661 ± 22,805	5079 ± 15,005	5852 ± 15,966	7639 ± 18,603	<0.0001
Tumour number (1/2/3/≥4)	970/251/101/197	363/93/44/83	128/34/14/16	172/41/15/26	0.585
Mean tumour size (cm)	6.4 ± 4.1	4.6 ± 3.1	5.7 ± 3.8	7.6 ± 4.5	<0.0001
CLIP stage 0/1/2/3/4–6	258/343/266/129/77	144/157/96/37/13	37/52/35/15/4	57/39/37/22/10	<0.0001

HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time.

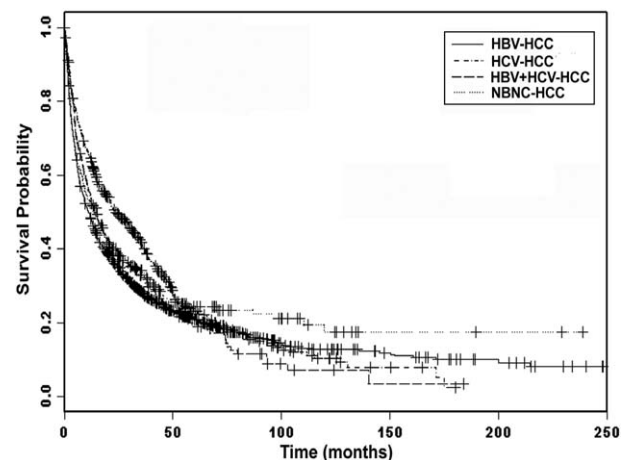


**Fig. 1 – Distributions of treatment modalities in HCCs. The numbers within the bar indicate case numbers. TACE, transarterial chemoembolisation; PEIT, percutaneous ethanol injection therapy.**

**Table 2 – Cumulative survival rates and median survival of the 2820 HCC patients as a whole**

Aetiology	HBV	HCV	HBV+HCV	NBNC
Median survival (months)	11.1	23.9	14.0	15.0
1 year	48.6%	64.6%	54.6%	52.6%
3 year	28.3%	40.8%	32.9%	33.6%
5 year	21.0%	23.1%	19.1%	24.3%
10 year	12.8%	10.5%	7.2%	17.5%

was worse than NBNC-HCC patients at 10 years. In patients who received resection as the initial treatment, though the survival was better in the NBNC-HCC groups in the 10 years, there were no statistically significant differences between different groups (Table 3, Fig. 3). There were no statistically significant differences in the disease-free survival between different groups in surgical patients. In patients who received transarterial chemoembolisation (TACE) or percutaneous ethanol injection therapy (PEIT) as the initial treatment, the HCV-HCC patients had the best survival. However, the advantage of better survival in HCV-HCC patients disappeared after 5 years (Table 4, Fig. 4). In patients who received supportive care or

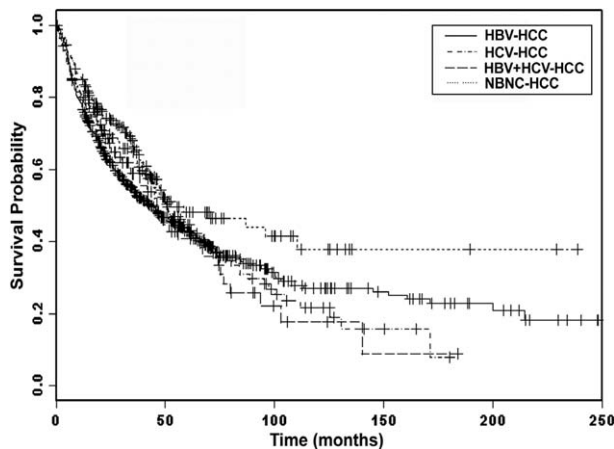


**Fig. 2 – Kaplan-Meier estimated survival curves of HCC patients as a whole. The HCV-HCC group showed a better survival than the HBV-HCC ( $p < 0.05$ ) or NBNC-HCC ( $p < 0.05$ ) groups. HBV-HCC, HBV-related HCC; HCV-HCC, HCV-related HCC; HBV+HCV-HCC, HBV plus HCV-related HCC; NBNC-HCC: non-HBV-non-HCV-related HCC.**

**Table 3 – Cumulative survival rates and median survival of the 1184 HCC patients who received surgical resection as the initial treatment**

Aetiology	HBV	HCV	HBV+HCV	NBNC
Median survival (months)	44.2	50.6	46.2	53.2
1 year	77.0%	85.0%	78.1%	80.8%
3 year	54.2%	65.3%	58.8%	63.8%
5 year	42.7%	44.7%	40.7%	48.3%
10 year	27.2%	21.8%	17.7%	37.7%

anol injection therapy (PEIT) as the initial treatment, the HCV-HCC patients had the best survival. However, the advantage of better survival in HCV-HCC patients disappeared after 5 years (Table 4, Fig. 4). In patients who received supportive care or

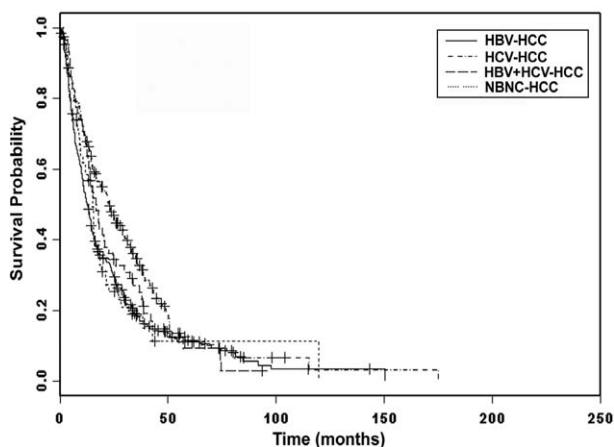


**Fig. 3 – Kaplan–Meier estimated survival curves of HCC patients underwent surgical resection. There were no statistically significant differences in the survival among groups ( $p = 0.188$ ). HBV-HCC, HBV-related HCC; HCV-HCC, HCV-related HCC; HBV+HCV-HCC, HBV plus HCV-related HCC, NBNC-HCC: non-HBV-non-HCV-related HCC.**

**Table 4 – Cumulative survival rates of the 709 HCC patients who received TACE or PEIT as the initial treatment**

Aetiology	HBV	HCV	HBV+HCV	NBNC
Median survival (months)	12.6	22.8	16.7	15.0
1 year	53.0%	70.6%	67.7%	58.4%
3 year	19.5%	35.2%	28.4%	19.0%
5 year	12.1%	12.3%	9.0%	11.4%
10 year	3.7%	3.1%	3.0%	0%

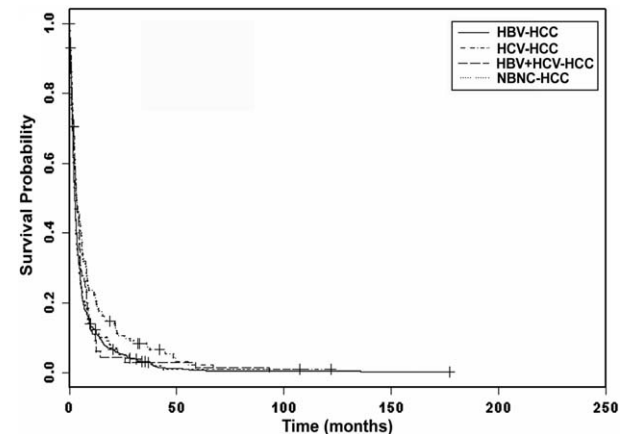
TACE, transarterial chemoembolisation; PEIT, percutaneous ethanol injection therapy.



**Fig. 4 – Kaplan–Meier estimated survival curves of HCC patients who underwent TACE or PEIT. The HCV-HCC group showed a better survival than the HBV-HCC ( $p < 0.001$ ) or NBNC-HCC ( $p < 0.05$ ) groups. HBV-HCC, HBV-related HCC; HCV-HCC, HCV-related HCC; HBV+HCV-HCC, HBV plus HCV-related HCC, NBNC-HCC: non-HBV-non-HCV-related HCC. TACE, transarterial chemoembolisation; PEIT, percutaneous ethanol injection therapy.**

**Table 5 – Cumulative survival rates of the 927 HCC patients who received supportive care or chemotherapy as the initial treatment**

Aetiology	HBV	HCV	HBV+HCV	NBNC
Median survival (months)	2.5	3.4	3.4	2.6
1 year	12.4%	21.7%	10.8%	11.2%
3 year	3.4%	8.5%	3.1%	3.1%
5 year	0.8%	2.2%	1.5%	1.0%
10 year	0.5%	1.1%	0%	1.0%



**Fig. 5 – Kaplan–Meier estimated survival curves of HCC patients who underwent chemotherapy or supportive care. The HCV-HCC group showed a better survival than the HBV-HCC ( $p < 0.001$ ) or NBNC-HCC ( $p < 0.05$ ) groups. HBV-HCC, HBV-related HCC; HCV-HCC, HCV-related HCC; HBV+HCV-HCC, HBV plus HCV-related HCC, NBNC-HCC: non-HBV-non-HCV-related HCC.**

chemotherapy as the initial treatment, the HCV-HCC patients had the best survival (Table 5, Fig. 5).

#### 4. Discussion

Our data showed that HCV-HCC patients had the best overall survival. However, the better survival of HCV-HCC patients was found only in the non-surgical patients. This point was important because the treatment modality was a strong factor influencing survival. Our result was consistent with a recent observation that in the whole population, patients with HBV-HCC tended to have a poorer prognosis than those with HCV-HCC, and this difference became statistically significant among the patients with an advanced HCC.<sup>19</sup> The previous conflicting results of comparing the prognosis of HBV-HCC versus HCV-HCC were probably due to the different inclusion criteria. Some investigators included only the surgical patients,<sup>4–6,8–10,13–15,17</sup> while the others included all HCC patients.<sup>7,11,12,19,20</sup>

It was interesting to note that the better survival in the HCV-HCC patients was not uniform over the course of time. Actually, the HCV-HCC patients had better prognosis in the initial 5 years. Then, the HCV-HCC patients lost their survival advantage at a longer follow-up period. The survival of HCV-HCC patients was worse than that in NBNC-HCC and HBV-HCC at



10 years. A previous study did not find such paradox because the follow-up period was not long enough. The exact explanation for the paradox of survival advantage of HCV-HCC patients was not clear. One of the possibilities was that HCV-HCC, as compared with HBV-HCC, had a higher cumulated recurrence.<sup>21</sup> An alternative explanation was that more HCV-HCC patients might die of non-liver-related disease since the HCV-HCC patients were 12 years older than HBV-HCC patients.

The mean age of HCV-HCC patients was 12 years older than that of the HBV-HCC patients. The male/female ratio in HBV-HCC was 7.8, which was much higher than that found in the HCV-HCC group (1.7). These findings were the same as were reported in our previous multi-centre study.<sup>22</sup> The lower WBC and platelet counts, and lower serum albumin levels in HCV-HCC patients might reflect the underlying higher percentage of liver cirrhosis in HCV-HCCs. However, the mean total bilirubin levels, the prolonged prothrombin time, and presence of ascites or encephalopathy, and Child–Pugh scores were similar among all four groups.

The mean tumour size was largest in the NBNC-HCC group. This was probably due to fewer NBNC-HCC patients receiving regular follow-up for the liver diseases since the two major risk factors for HCC, HBsAg and anti-HCV, were negative. The hepatic tumours might be detected only after symptoms occurred in the NBNC-HCC patients. Thus, the mean tumour size was larger. Though we defined HBsAg-negative, anti-HCV-negative HCC as NBNC-HCC, previous studies have demonstrated that some of these NBNC-HCC are caused by an occult HBV infection.<sup>23,24</sup> Alcoholism may be one of the aetiologies of the NBNC-HCC.<sup>25</sup> However, because this was a retrospective study, it was difficult to verify alcoholism among the NBNC-HCC patients. It was also interesting to note that the mean AFP levels were higher in the HBV-HCC groups than those in other groups. The higher AFP level in HBV-HCC might not be directly related to tumour size since the mean tumour size was larger in the NBNC-HCC group while the highest mean AFP level was in the HBV-HCC group, not in the NBNC-HCC group.

## 5. Conclusion

In conclusion, we found that HBV-HCC patients were characterised by younger ages, higher male/female ratio, higher serum AFP levels and larger tumour sizes. HCV-HCC patients were characterised by older ages, lower male/female ratio, lower WBC and platelet counts, lower serum albumin levels, higher percentage of liver cirrhosis, smaller tumour sizes. The HCV-HCC patients had best overall survival. However, the better survival in HCV-HCC patients was found only in the non-surgical patients and in the initial 5 years.

## Conflict of interest statement

None declared.

## Acknowledgements

This study was financially supported by the grants from the Department of Health, Taiwan (DOH90-HP-1002), the National

Health Research Institute, Taiwan (NHRI-EX94-9204PP), and the Liver Disease Prevention & Treatment Research Foundation, Taiwan. We are indebted to our colleagues at the Cancer Registry, Office of Medical Record, NTUH, for their excellent work in the cancer registry system and to the physicians for their care of the patients.

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