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More advanced disease and worse survival in cryptogenic compared to viral hepatocellular carcinoma

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Abbreviations:

AFP: Alpha-fetoprotein

ALT: Alanine transaminase

AST: Aspartate aminotransferase

BCLC stage: Barcelona clinic liver cancer stage

BMI: Body mass index

CAD: Coronary artery disease

CT: Computed tomography

HBV: Hepatitis B virus

HBV-HCC: HBV-related HCC

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

HCV-HCC: HCV-related HCC

HR: Hazard ratio

IQR: Interquartile range

MELD: Model for end-stage liver disease

MRI: Magnetic resonance imaging

NAFLD: Non-alcoholic fatty liver disease

NAFLD-HCC: NAFLD-related HCC

NASH: Non-alcoholic steatohepatitis

RE: Radioembolization

RFA: Radiofrequency ablation

TACE: Transcatheter arterial chemoembolization

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Abstract

Background & Aims: Although hepatitis B virus (HBV) and hepatitis C virus (HCV) infections remain major risk factors for hepatocellular carcinoma (HCC), non-viral causes of HCC, particularly non-alcoholic fatty liver disease, are becoming increasingly prevalent. The aim of this study was to compare the clinical characteristics and survival of cryptogenic and viral HCC.
Methods: We conducted a retrospective cohort study involving 3,878 consecutive HCC patients seen at two tertiary centers in the United States and one in Taiwan from 2004-2014. We compared the clinical characteristics, treatment and survival of patients by underlying etiology: cryptogenic (n=696), HBV (n=1,304), or HCV (n=1,878).
Results: Cirrhosis was present in 66.8% of the cryptogenic HCC patients, compared with 74.7% of HBV-HCC (p=0.001) and 85.9% of HCV-HCC (p<0.001). Compared to viral HCC, cryptogenic HCC patients presented with larger tumors and at later stages of disease. Five-year overall survival was 16.3% among cryptogenic HCC patients compared with 31.9% among HBV-HCC patients and 27.7% among HCV-HCC patients (p<0.001 for both by the log-rank test). HCC etiology was not an independent predictor of survival, though ethnicity, cirrhosis status, meeting Milan criteria and treatment allocation were.
Conclusions: Compared with viral HCC patients, those with cryptogenic HCC had lower prevalence of cirrhosis, were diagnosed with larger tumors at more advanced stages of disease, and had poorer overall survival. Additional efforts are needed to identify patients at risk of cryptogenic HCC and to identify cryptogenic HCC at earlier stages of disease.
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Key Points

1. One third of cryptogenic HCC patients were non-cirrhotic, significantly more than viral HCC patients
2. Cryptogenic HCC patients presented with larger tumors and at more advanced stages of disease than viral HCC patients
3. Compared to viral HCC patients, those with cryptogenic HCC had worse overall survival despite often receiving treatments with curative intent
4. Cryptogenic etiology of HCC was not an independent predictor of survival after adjusting for factors such as stage of disease and treatment strategy

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer mortality worldwide and was the fourth leading cause of death with 800,000 deaths in 2015.[1] In the United States and Taiwan, where we practice, 5-year survival for liver cancer is 18% and 28.9%, respectively.[2,3]

While chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the major HCC risk factors globally (53% and 25%, respectively), other chronic liver diseases are also associated with HCC, such as non-alcoholic fatty liver disease (NAFLD).[4] NAFLD is an increasingly important cause of HCC with an estimated global prevalence of 25% and rising.[5–8]

Current HCC surveillance guidelines focus on HCC in the setting of chronic viral hepatitis or cirrhosis.[9] However, a growing body of evidence suggests that a third or more of NAFLD-related HCC develops in patients without a known history of cirrhosis.[10–15] Some studies have also found that patients with non-viral etiologies of HCC are diagnosed at more advanced stages, possibly due to lower rates of surveillance.[14–16] More data are needed to understand the epidemiology of HCC associated with non-viral etiologies, particularly NAFLD, in order to inform guidelines moving forward.

A clear-cut diagnosis of NAFLD or its inflammatory counterpart, non-alcoholic steatohepatitis (NASH), is not always possible at the time of HCC diagnosis. Over time, hepatic steatosis may be replaced by fibrosis and cirrhosis, and the metabolic derangements associated with NAFLD, such as obesity, may not be apparent in end-stage liver disease.[17] As such, there is increasing acknowledgment that a significant proportion of cryptogenic HCC – that is, HCC in the absence of chronic viral infection, alcohol use, or other diagnosed liver disease – is likely due to NAFLD.[5,18–20]

To augment the body of knowledge on cryptogenic HCC, we conducted a retrospective cohort study of 3,878 consecutive HCC patients diagnosed between 2004 and 2014 in the US and Taiwan comparing the clinical characteristics and survival of viral-related HCC against those of cryptogenic HCC.

Patients and Methods

Study Design and Patient Population

This retrospective cohort study involved 3,878 consecutive cases of HBV-related, HCV-related or cryptogenic HCC seen at two tertiary hospitals in the United States and one in Taiwan between 2004 and 2014. HCC diagnosis was based on histology, cytology, or noninvasive criteria recommended by the American Association for the Study of Liver Diseases (AASLD).[9] The study protocol was approved by the institutional review boards of the Stanford University Medical Center, the Mayo Clinic in Rochester, and Kaohsiung Medical University Hospital. An exemption from informed consent was granted due to the minimal risk posed to participants in this chart review study.

Adults aged 18 or older were eligible for inclusion if they had HCC and an underlying diagnosis of HBV, HCV, or if their HCC was cryptogenic. Diagnoses of HBV and HCV were based on serological testing as well as nucleic acid tests for viremia. Cryptogenic HCC was defined as HCC in the absence of any history of regular alcohol use and without a confirmed chronic liver disease such as chronic hepatitis B or C, autoimmune or metabolic liver disease such as primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis or Wilson's disease. Patients

with HCC in the presence of multiple underlying liver diseases (e.g. HBV and HCV co-infection) were excluded. Alcohol intake was not routinely quantified, but cases of HCC deemed to be alcohol-related by the examining physicians (as documented in their clinical notes) were excluded. Patient inclusion and exclusion are illustrated in Supplemental Figure 1.

Definition of Cirrhosis

Cirrhosis status was determined based on histology, imaging and chart review. Patients were considered to have cirrhosis if they had F4 fibrosis on histology, if they had clinical evidence of portal hypertension (platelets <120,000/μL, splenomegaly, ascites or gastroesophageal varices on imaging) or if they had hepatic decompensation (hepatic encephalopathy, ascites, variceal bleeding) within 6 months of HCC diagnosis.

Tumor Staging and Survival Outcomes

Tumor stage was assessed by the Milan criteria for transplant and the Barcelona clinic liver cancer (BCLC) staging system. Tumor size and other imaging characteristics were derived from computed tomography (CT) or magnetic resonance imaging (MRI).

Survival data was based on the date of HCC diagnosis and the date of death or last follow-up date.

Statistical analysis

Descriptive statistics of categorical variables were reported as proportions (%), while continuous variables were reported as means with standard deviations or medians with interquartile ranges. Comparisons of descriptive statistics were made using the Student's t-test, the chi-square test, or the Mann-Whitney U test for normally-distributed continuous variables, categorical variables, and non-normally distributed continuous variables, respectively.

Five-year overall survival was the primary outcome. The primary predictor variable was HCC etiology (HBV, HCV or cryptogenic). Secondary predictors included ethnicity, cirrhosis, tumor

stage and treatment strategy. Treatments such as liver transplantation, surgical resection and radiofrequency ablation (RFA) were considered treatments with curative intent, while treatments such as transcatheter arterial chemoembolization (TACE), radioembolization (RE) and sorafenib were considered palliative. Univariate and multivariate survival models were constructed using Cox proportional hazards models. Relevant variables that were significant (defined as association with $p<0.05$) in the univariate analysis were included in the multivariate model. Kaplan-Meier survival curves and 5-year survival rates for independent subgroups were compared using the log-rank test.

All statistical analyses were performed in Stata, version 14 (Stata Corporation, College Station, Texas). Statistical significance was defined as a two-tailed *p* value of <0.05.

Results

Baseline Patient Clinical Characteristics

Of the 3,878 HCC patients, 696 (18.0%) were cryptogenic, 1,304 (33.6%) were HBV-related and 1,878 (48.4%) were HCV-related. The median date of HCC diagnosis was 2008.5 for cryptogenic HCC patients, 2008 for HBV-HCC patients, and 2009 for HCV-HCC patients. Baseline clinical and laboratory characteristics of the patients by HCC etiology are shown in Tables 1 and 2. Compared to patients with HBV-HCC or HCV-HCC, those with cryptogenic HCC were older, had higher BMIs, and were more likely to have metabolic comorbidities such as obesity, diabetes and hypertension.

Clinically apparent cirrhosis was less common among cryptogenic HCC patients; 66.8% of cryptogenic patients had cirrhosis compared to 74.7% of HBV-HCC patients ($p=0.001$) and 85.9% of HCV-HCC patients ($p<0.001$).

Tumor characteristics

Table 3 compares tumor characteristics across the three etiologies. Patients with cryptogenic HCC had larger tumors and more advanced disease at presentation than patients with HBV-HCC or HCV-HCC. The median maximum tumor size of cryptogenic HCC patients was 6.0cm at

diagnosis compared to 3.9cm for HBV-HCC and 3.2cm for HCV-HCC (p<0.001 for both comparisons). Cryptogenic HCC patients were more likely to have extrahepatic metastases (16.2%) compared to HBV-HCC (11.2%, p=0.002) and HCV-HCC (6.7%, p<0.001). Less than one-third (28.2%) of cryptogenic HCC patients met Milan criteria for transplantation compared to nearly half of HBV-HCC patients (45.4%) and 55.8% of HCV-HCC patients (p<0.001 for both comparisons).

Treatment allocation

Despite having more advanced tumors at presentation, cryptogenic HCC patients were significantly more likely to receive treatments with curative intent compared to patients with viral etiologies (31.5% for cryptogenic HCC, 23.0% for HBV-HCC; p<0.001, and 26.0% for HCV-HCC; p=0.011) (Table 4). Resection in particular was more common among cryptogenic HCC patients (26.6%) than in HBV-HCC (16.5%, p<0.001) or HCV-HCC patients (11.2%, p<0.001).

Overall survival

Average length of follow-up was 1.63 years (SD: 1.97 years). The average length of follow-up by etiology was 1.1 years (SD: 1.51 years) for the cryptogenic group, 1.6 years (SD: 2.07 years) for the HBV group and 1.8 years (SD: 2.00 years) for the HCV group. The rate of loss to follow-up at 5 years was not significantly different between the cryptogenic HCC group and either of the viral HCC groups (47.0% cryptogenic, 51.7% HBV, 46.8% HCV; crypto vs. HBV p=0.06, crypto vs. HCV p= 0.92).

Five-year overall survival was worse among cryptogenic HCC patients (16.3%) compared with either HBV-HCC (31.9%, p<0.001) or HCV-HCC patients (27.7%, p<0.001) (Figure 1A). This result persisted after stratification by liver cirrhosis (Figure 1B-C). Cirrhotic cryptogenic HCC patients had worse 5-year survival than cirrhotic viral HCC (19.4% vs. 26.5%, p<0.001). Similarly, non-cirrhotic cryptogenic HCC patients had worse 5-year survival than non-cirrhotic viral HCC (28.2% vs. 47.7%, p<0.001).

Since cryptogenic HCC patients underwent curative treatments at a higher rate than viral HCC patients, we also examined survival by etiology for patients receiving either surgical resection or RFA as their primary HCC therapy. Cryptogenic HCC patients undergoing either resection or RFA still had worse 5-year overall survival (38.1%) than either HBV-HCC (67.3%, $p<0.001$) or HCV-HCC (45.2%, $p=0.02$) (Figure 1D).

Predictors of survival

Favorable predictors of 5-year survival in univariate Cox proportional hazard models included female gender, younger age, Asian or Hispanic ethnicity (compared to Caucasian ethnicity), absence of cirrhosis, absence of CAD, meeting Milan criteria, curative or palliative treatments (compared to no treatment), and viral etiology (Table 5). In the multivariate analysis, viral etiology was no longer a significant predictor of survival. Significant independent predictors of survival were Asian or Hispanic ethnicity, absence of cirrhosis, lower MELD score, meeting Milan criteria, and curative or palliative treatments.

Analysis by US vs. Taiwan sites

The distribution of etiologies and treatment strategies differed between the US and Taiwan sites. The majority of the cryptogenic and HCV-HCC patients were from the US whereas the majority of the HBV-HCC patients were from Taiwan. The US sites were more likely to perform curative treatments such as transplant (13.9% vs 0.1%, $p<0.001$), resection (19.6% vs. 12.7%, $p<0.001$) and RFA (11.3% vs. 6.4%, $p<0.001$) (Supplemental Table 1). However, cryptogenic HCC patients had worse survival than viral HCC patients at both US and Taiwan sites. At the US sites, 5-year overall survival was 16.6% for the cryptogenic HCC patients compared to 39.8% and 27.9% for the HBV-HCC and HCV-HCC patients, respectively ($p<0.001$ for both) (Supplemental Figure 2A). At the Taiwan site, 5- year overall survival was 15.6% for the cryptogenic HCC patients, 27.5% for the HBV-HCC patients ($p=0.03$) and 26.2% for the HCV-HCC patients ($p<0.001$) (Supplemental Figure 2B).

HCC surveillance

Data on HCC surveillance was available for 984 patients from Stanford University Medical Center and the Mayo Clinic. Surveillance was defined as US or triphasic CT imaging of the liver at 6 month intervals prior to the diagnosis of HCC. Surveillance status was determined through manual chart review.

Of these, 330 had cryptogenic HCC, 160 had HBV-HCC, and 494 had HCV-HCC. HCV-HCC patients had a significantly higher rate of surveillance than cryptogenic HCC patients (38.3% vs. 18.8%, p=0.001). There was a trend towards a higher rate of surveillance among the HBV-HCC patients compared with the cryptogenic HCC patients (26.3% vs. 18.8%, p=0.058).

Among those under surveillance, there were no significant differences in tumor size or stage (based on metastases and Milan criteria) across etiologies (Supplemental Table 2). Among those not under surveillance, the cryptogenic group had larger and more advanced tumors than either the HBV or HCV groups (Supplemental Table 3).

Patients under surveillance had a 5-year survival of 22.5% compared to 17.4% for those not under surveillance (p<0.001) (Supplemental Figure 3). HCC surveillance was a positive predictor of survival in univariate analysis (Table 5). However, surveillance was not included in the multivariate model due to the lack of data from all sites.

Discussion

In this large study of 3,878 HCC patients, we found that relative to patients with HBV- or HCV-HCC, patients with cryptogenic HCC were less likely to have cirrhosis, had larger tumors, had more advanced disease, and had worse 5-year overall survival. However, HCC etiology was not an independent predictor of survival after adjusting for covariates such as ethnicity, cirrhosis status, tumor stage, and treatment strategy.

It should be noted that we found worse survival in the cryptogenic HCC group despite that group being more likely to receive treatments with curative intent, particularly surgical resection. It is possible that resection is more commonly offered to this group of patients because cirrhosis is less prevalent compared to patients with viral HCC. However, cryptogenic HCC patients

receiving resection or RFA still had worse survival compared to viral HCC patients receiving the same treatments. The advanced stage of cryptogenic HCC at presentation is likely an important contributor to this discrepancy. Cryptogenic HCC patients may already have occult metastases at presentation, or may require larger sections of liver to be resected or ablated. These patients also had more comorbidities which could reduce overall survival, such as CAD and diabetes, though neither of these were independent predictors of survival in our model.

In a subset analysis of patients for whom we had HCC surveillance data, we found that the cryptogenic group had lower rates of surveillance than either of the viral groups. Those who had prior HCC surveillance had better survival than those who did not. Among the patients under surveillance, there were no significant differences in tumor size or stage across the three etiologies. These findings suggest that a lack of adequate surveillance contributed to the differences between the cryptogenic and viral groups in tumor stage and survival.

There may have been several barriers to adequate HCC surveillance in cryptogenic HCC patients. First, one third of cryptogenic HCC patients in our cohort did not have cirrhosis and hence would not have met current criteria for HCC surveillance. Second, prior studies have reported lower HCC surveillance rates for NAFLD-related cirrhosis compared to other forms of cirrhosis, perhaps due to lack of awareness about the risk of NAFLD progressing to HCC.[14–16] Third, the sensitivity of ultrasound surveillance may be limited in the NAFLD/cryptogenic HCC population. Obesity and NAFLD cirrhosis have both been associated with inadequacy of ultrasound for the detection of hepatic tumors.[21,22] These latter two factors may have contributed to our finding that even among cirrhotic patients, cryptogenic HCC patients had worse survival. Increasing provider awareness of the risk of HCC in NAFLD may improve early detection, and more work is needed to determine whether or how CT and MRI screening should be incorporated into HCC surveillance strategies for patients with NAFLD or obesity.

The strengths of our study include its large size and diverse patient population. To our knowledge, this is the largest international cohort that has been assembled to compare viral and non-viral HCC. Our data is also consistent with previous studies which found that NAFLD-HCC often arises in patients without clinically apparent cirrhosis and that NAFLD-HCC tends to

present with larger tumors and at later stages.[10–16,23–25] A nationwide survey in Japan found cirrhosis in 62% of NAFLD-HCC cases, while a US Department of Veterans Affairs study found cirrhosis in 58.3% of NAFLD-HCC patients; we found cirrhosis in 66.8% of cryptogenic HCC patients in our study, consistent with these prior reports.[13,14]

Ours is also the largest study, thus far, to evaluate survival in the cryptogenic HCC population. Survival data from prior studies have been mixed, though the larger studies generally have had results similar to ours.[14,15,25,26] One study from Taiwan involving 366 cryptogenic HCC patients found worse long-term overall survival in the cryptogenic group compared to the viral/alcoholic HCC group; this difference was no longer significant after controlling for confounding variables.[25] An Italian study involving 145 NAFLD-HCC patients found a similar pattern: worse overall survival in the uncorrected analysis and similar survival when controlling for covariates.[15] The aforementioned Veterans Affairs study by Mittal et al. included 120 NAFLD-HCC patients and did not find any difference in 1-year survival compared to alcohol or HCV-HCC.[14] Their results may differ from ours due to a shorter follow-up period and factors specific to the veteran population.

There are a number of limitations to our study. First, the study is retrospective in design, though our primary outcome is overall survival, an objective and clear outcome. Our cohort is also drawn from tertiary referral centers and may not be representative of the wider population of HCC patients. However, our cohort is geographically diverse. For most patients in our cohort, cirrhosis was diagnosed based on imaging, laboratory values or clinical history rather than liver histology. These criteria are not sensitive for subclinical cirrhosis and may underestimate the prevalence of cirrhosis in our cohort. We are also limited to discussing cryptogenic HCC rather than NAFLD-HCC. We cannot reliably obtain formal diagnoses of NAFLD-HCC from our data despite individual chart review, as hepatic steatosis is not reliably present in patients with advanced liver disease. It should also be noted that we did not evaluate for occult HBV infection, which is defined as HBV DNA in the liver of a patient with negative HBsAg, Occult HBV infection may contribute to “cryptogenic” HCC in high prevalence areas such as Taiwan.[27]

In summary, we found that one third of cryptogenic HCC (most of which is likely related to NAFLD) presented in patients without clinically apparent cirrhosis. Furthermore, these cryptogenic HCC patients were diagnosed at later stages of disease, had larger tumors and had worse overall survival. The epidemiology of non-viral non-alcoholic HCC is different from that of viral HCC and management guidelines should take this into account as NAFLD becomes an increasingly prevalent risk factor for HCC.

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Tables

Table 1: Baseline patient clinical characteristics, by HCC etiology

	Cryptogenic (N=696)	HBV (N=1304)	*P* value	HCV (N=1878)	*P* value	Overall (N=3878)
Age† (yrs)	67.2 +/- 13.4	58.3 +/- 12.2	<0.001	63.0 +/- 9.9	<0.001	62.2 +/- 11.8
Male	440 (63.2%)	1074 (82.4%)	<0.001	1248 (66.5%)	0.125	2762 (71.2%)
Asian	317 (45.6%)	1251 (95.9%)	<0.001	1040 (55.4%)	<0.001	2608 (67.3%)
U.S. site	412 (59.2%)	349 (26.8%)	<0.001	1054 (56.1%)	0.162	1815 (46.8%)
History of regular alcohol use	0 (0%)	380 (29.3%)	<0.001	801 (43.0%)	<0.001	1181 (30.7%)
Body mass index† (kg/m^2)	27.7 +/- 6.2	24.4 +/- 4.0	<0.001	26.0 +/- 5.3	<0.001	25.8 +/- 5.2
Hypertension (HTN)	354 (58.2%)	403 (31.7%)	<0.001	855 (47.1%)	<0.001	1612 (43.6%)
Diabetes (DM)	278 (45.7%)	299 (23.5%)	<0.001	594 (32.8%)	<0.001	1171 (31.8%)

≥2 of obesity[‡], HTN, DM	297 (44.8%)	295 (22.9%)	<0.001	604 (32.5%)	<0.001	1196 (31.4%)
Coronary artery disease	130 (21.5%)	40 (3.1%)	<0.001	108 (6.0%)	<0.001	278 (7.6%)
Symptomatic at diagnosis	395 (58.0%)	491 (39.1%)	<0.001	670 (42.8%)	<0.001	1556 (44.4%)
Cirrhosis	338 (66.8%)	919 (74.7%)	0.001	1497 (85.9%)	<0.001	2754 (79.2%)
Ascites	198 (30.8%)	345 (27.2%)	0.099	442 (24.3%)	0.001	985 (26.4%)
Encephalopathy	56 (8.4%)	79 (6.2%)	0.063	152 (8.3%)	0.92	287 (7.6%)

[†]Reported as mean +/- standard deviation

[‡]Obesity defined as BMI ≥30 for non-Asians and ≥25 for Asians (both East Asian and South Asian)

P values are for the comparison to cryptogenic

Table 2: Baseline patient laboratory characteristics, by HCC etiology

	Cryptogenic (N=696)	HBV (N=1304)	*P* value	HCV (N=1878)	*P* value	Overall (N=3878)
Platelet count[‡] (K/μL)	183.5 (IQR 121-259)	152 (IQR 104-217)	<0.001	114 (IQR 76-163)	<0.001	137 (IQR 89-197)
Total bilirubin[‡] (mg/dL)	0.9 (IQR 0.6-1.5)	1 (IQR 0.7-1.5)	0.003	1.1 (IQR 0.7-1.7)	<0.001	1 (IQR 0.7-1.6)
Albumin[†] (g/dL)	3.5 +/- 0.6	3.5 +/- 0.6	0.323	3.3 +/- 0.6	<0.001	3.4 +/- 0.6
International normalized	1.1	1.1	<0.001	1.1	<0.001	1.1

ratio‡	(IQR 1-1.2)	(IQR 1-1.2)		(IQR 1-1.3)		(IQR 1-1.2)
Aspartate transaminase‡ (U/L)	55 (IQR 36-95)	59 (IQR 38-108)	0.068	80.5 (IQR 52-124)	<0.001	69 (IQR 43-115)
Alanine transaminase‡ (U/L)	42 (IQR 27-61)	48 (IQR 34-75)	<0.001	67 (IQR 40-107)	<0.001	69 (IQR 43-115)
Log_{10} AFP‡ (ng/dL)	3.3 (IQR 1.6-7.2)	4.3 (IQR 2.3-6.9)	<0.001	3.7 (IQR 2.3-6)	0.008	3.8 (IQR 2.2-6.4)
CTP A§	124 (47.7%)	508 (62.9%)	<0.001	719 (56.0%)	0.027	1351 (57.5%)
CTP B	113 (43.5%)	247 (30.6%)		488 (38.1%)		848 (36.1%)
CTP C	23 (8.9%)	53 (6.6%)		76 (5.9%)		152 (6.5%)
MELD‡	9 (IQR 7-12)	9 (IQR 7-11)	0.787	9 (IQR 8-13)	0.001	9 (IQR 7-12)

†Reported as mean +/- standard deviation

‡Reported as median with interquartile range

§Child-Turcotte Pugh class calculated for cirrhotic patients only

AFP: Alpha-fetoprotein

MELD: Model for end stage liver disease

P values are for the comparison to cryptogenic

Table 3: Tumor characteristics, by HCC etiology

	Cryptogenic (N=696)	HBV (N=1304)	*P* value	HCV (N=1878)	*P* value	Overall (N=3878)
Max. tumor	6.0	3.9	<0.001	3.2	<0.001	3.7

size (cm)	(IQR 3.4-9.7)	(IQR 2.4-7.3)		(IQR 2.1-5.2)		(IQR 2.3-6.5)
Multifocal	276 (44.5%)	342 (33.5%)	<0.001	602 (35.0%)	<0.001	1220 (36.3%)
Vascular invasion	127 (19.7%)	203 (17.9%)	0.347	232 (13.0%)	<0.001	562 (15.8%)
Extrahepatic metastasis	107 (16.2%)	140 (11.2%)	0.002	123 (6.7%)	<0.001	370 (9.9%)
Within Milan criteria	187 (28.2%)	530 (45.4%)	<0.001	974 (55.8%)	<0.001	1691 (47.3%)
BCLC C/D	214 (46.8%)	323 (35.5%)	<0.001	363 (26.4%)	<0.001	900 (32.8%)

BCLC: Barcelona Clinic Liver Cancer stage

P values are for the comparison to cryptogenic

Table 4: Treatment allocation, by HCC etiology

	Cryptogenic (N=696)	HBV (N=1304)	*P* value	HCV (N=1878)	*P* value	Overall (N=3878)
Transplant	13 (3.2%)	21 (1.7%)	0.062	132 (8.3%)	<0.001	166 (5.1%)
Resection	124 (26.6%)	204 (16.5%)	<0.001	180 (11.2%)	<0.001	508 (15.3%)
RFA	39 (9.3%)	76 (6.2%)	0.029	154 (9.5%)	0.888	269 (8.2%)
TACE	252 (54.6%)	651 (52.2%)	0.381	1039 (61.1%)	0.011	1942 (56.9%)
RE	6 (5.2%)	10 (3.5%)	0.449	46 (6.0%)	0.727	62 (5.3%)
Sorafenib	11 (2.8%)	26 (2.1%)	0.447	37 (2.3%)	0.621	74 (2.3%)
Curative intent	174 (31.5%)	291 (23.0%)	<0.001	448 (26.0%)	0.011	913 (25.8%)

Primary treatment						
Transplant	13 (2.4%)	21 (1.7%)		132 (7.7%)		166 (4.7%)
Resection/RFA	161 (29.1%)	270 (21.4%)		316 (18.3%)		747 (21.1%)
TACE/RE	243 (43.9%)	622 (49.2%)	0.005	893 (51.7%)	<0.001	1758 (49.6%)
Sorafenib	6 (1.1%)	20 (1.6%)		16 (0.9%)		42 (1.2%)
No treatment	130 (23.5%)	331 (26.2%)		369 (21.4%)		830 (23.4%)

Curative intent: Transplant, resection or radiofrequency ablation

RFA: Radio-frequency ablation

TACE: Transcatheter arterial chemoembolization

RE: Radioembolization

P values are for the comparison to cryptogenic

Table 5: Predictors of five-year mortality

	Univariate		Multivariate	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male	1.14 (1.02-1.28)	0.017	0.96 (0.83-1.11)	0.593
Age	1.01 (1.00-1.01)	0.019	1.00 (1.00-1.01)	0.492
Ethnicity[†]				
- Caucasian	1	Reference	1	Reference
- Asian (Taiwan)	0.89 (0.79-1.00)	0.049	0.82 (0.68-0.99)	0.039

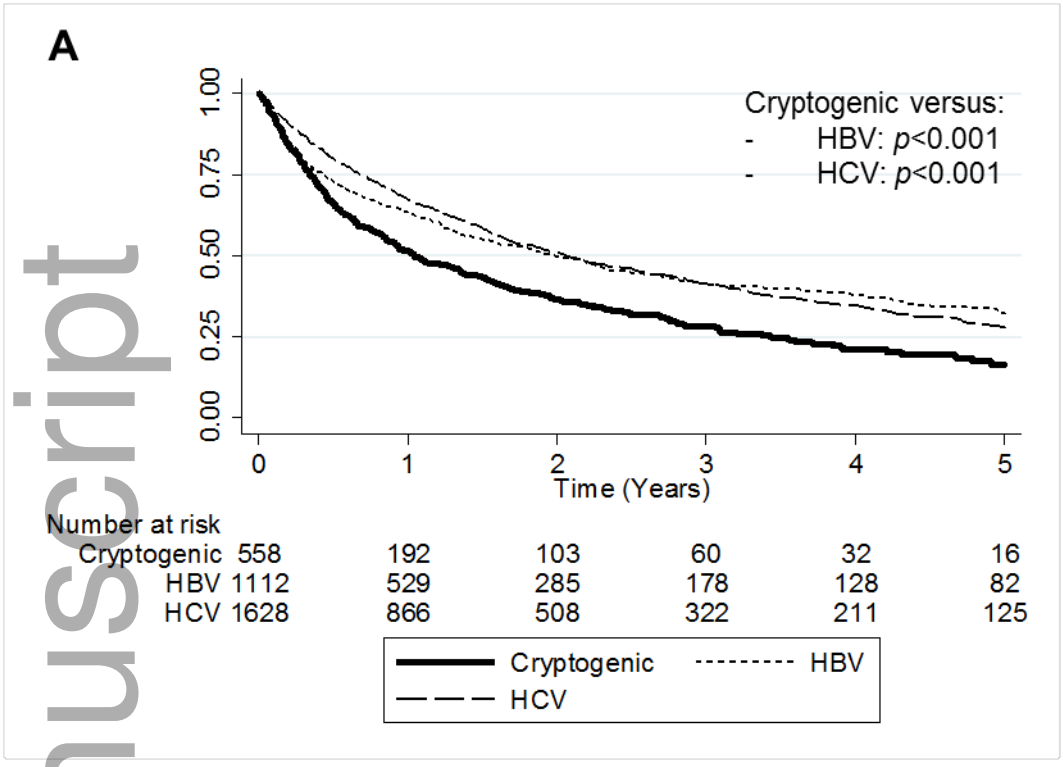
- Asian (US)	0.59 (0.50-0.69)	<0.001	0.51 (0.40-0.64)	<0.001
- African-American	1.06 (0.74-1.52)	0.733	0.89 (0.52-1.51)	0.657
- Hispanic	0.69 (0.56-0.86)	0.001	0.59 (0.45-0.77)	<0.001
Cirrhosis	1.55 (1.34-1.79)	<0.001	1.41 (1.19-1.68)	<0.001
Diabetes	1.02 (0.92-1.14)	0.687		
Coronary artery disease	1.37 (1.15-1.63)	<0.001	1.17 (0.87-1.59)	0.300
MELD	1.05 (1.04-1.06)	<0.001	1.05 (1.04-1.06)	<0.001
Within Milan criteria	0.30 (0.27-0.34)	<0.001	0.33 (0.29-0.38)	<0.001
HCC Surveillance	0.54 (0.42-0.70)	<0.001		
Primary treatment				
- No treatment	1	Reference	1	Reference
- Curative	0.09 (0.08-0.11)	<0.001	0.10 (0.08-0.12)	<0.001
- Palliative	0.33 (0.29-0.36)	<0.001	0.35 (0.30-0.40)	<0.001
Etiology				
- Cryptogenic	1	Reference	1	Reference
- HBV	0.69 (0.60-0.80)	<0.001	0.99 (0.80-1.22)	0.901
- HCV	0.66 (0.58-0.75)	<0.001	0.83 (0.68-1.02)	0.083

[†]Caucasian, N=752; Asian (Taiwan), N=1655; Asian (US), N=510; African-Am., N=54; Hispanic, N=208

Figure Legends

Figure 1: Five-year overall survival for patients with cryptogenic and viral HCC. (A) Overall survival, by HCC etiology. (B) Overall survival for cirrhotic patients only, by HCC etiology. (C) Overall survival for

non-cirrhotic patients only, by HCC etiology. (D) Overall survival for patients undergoing resection or radiofrequency ablation as their primary treatment, by HCC etiology



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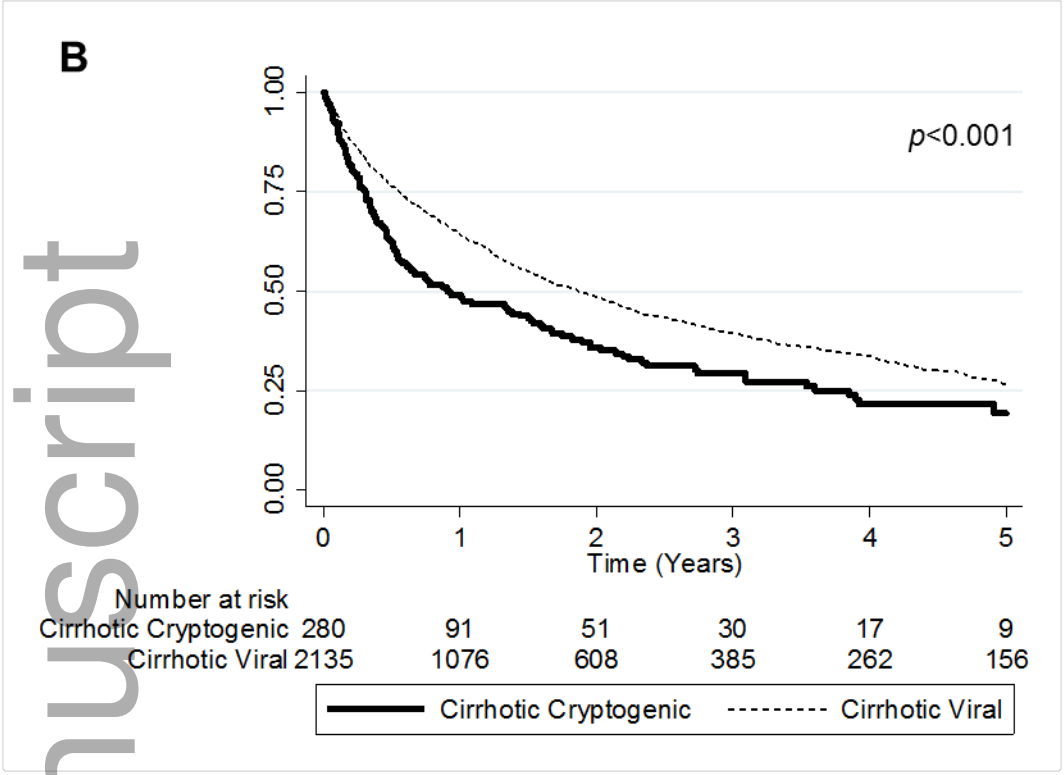

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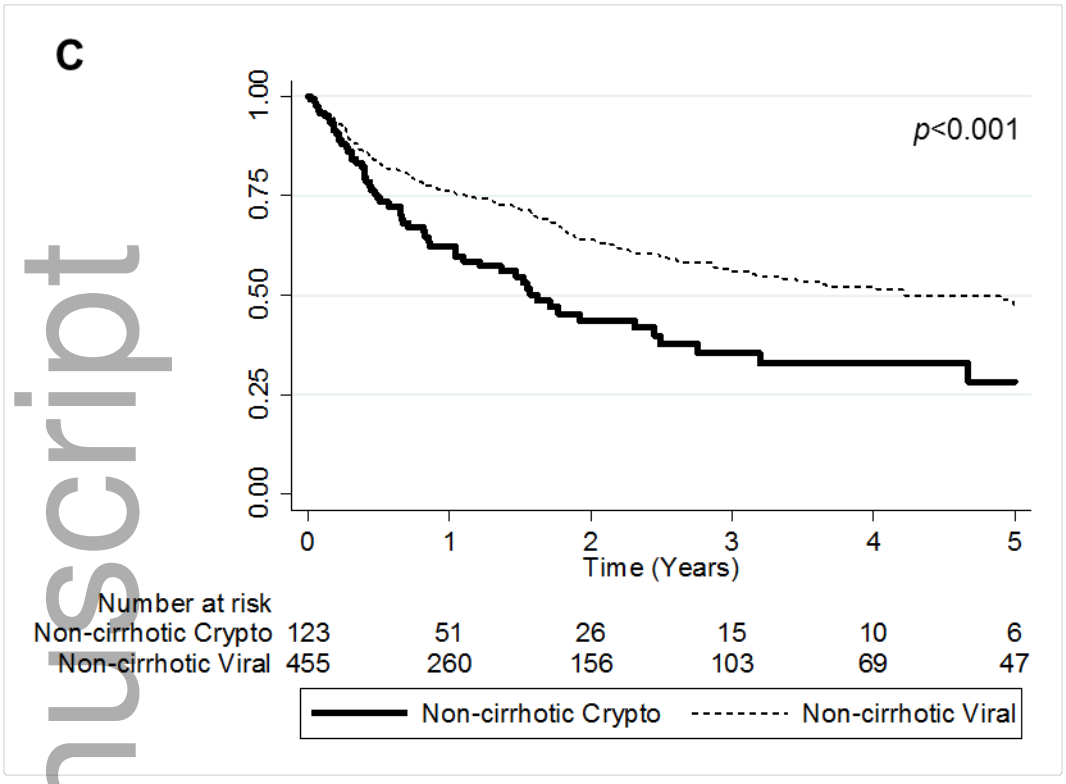

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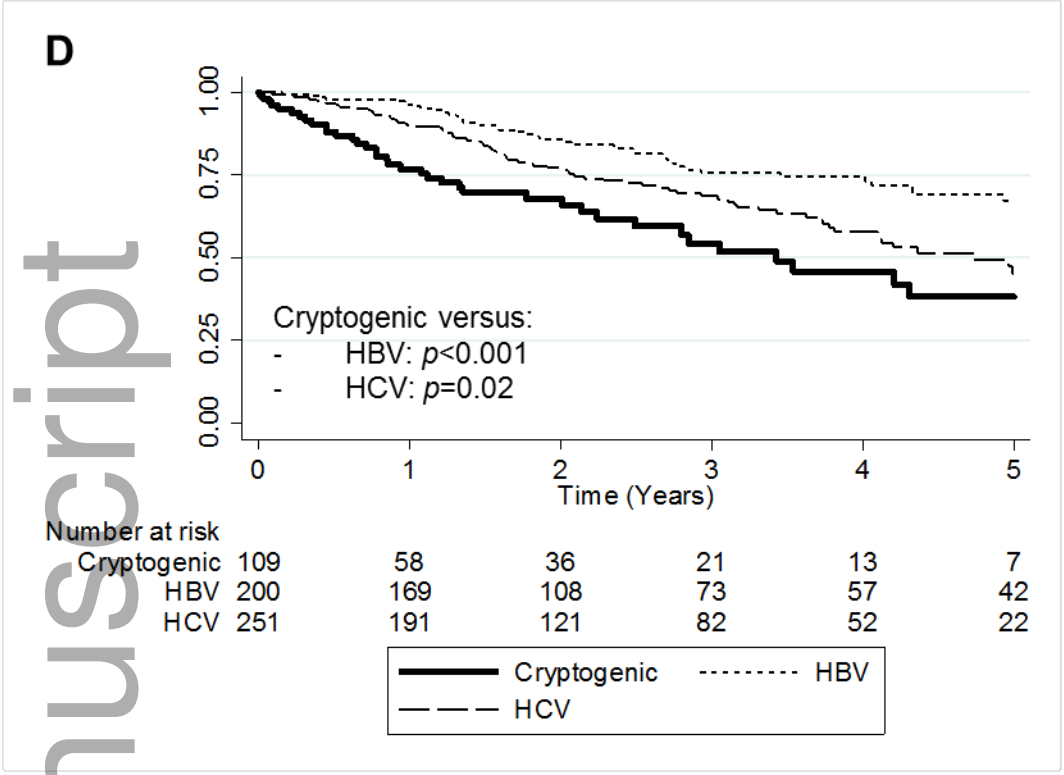

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