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Title: Antiviral Therapy is Associated with Improved Survival but Underutilized in Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma: Real-World East and West Experience

Running Title: Antiviral therapy in HBV-related HCC

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Abbreviations: HCC, hepatocellular carcinoma. HBV, hepatitis B virus. CHB, chronic hepatitis B. LT, liver transplant. TACE, transarterial chemoembolization. CPT, Child-Pugh-Turcotte. MELD, model for end-stage liver disease. BCLC, Barcelona clinic liver cancer.

Summary:

Background: Hepatitis B virus (HBV) is the leading cause of hepatocellular carcinoma (HCC) worldwide. It remains incompletely understood in the real world how antiviral therapy affects survival after HCC diagnosis. Methods: This was an international multicenter cohort study of 2,518 HBV-related HCC cases diagnosed between 2000 and 2015. Cox proportional hazards models were utilized to estimate hazard ratios (HR) with 95% confidence intervals (CI) for antiviral therapy and cirrhosis on patients' risk of deaths. Results: Approximately 48% of patients received antiviral therapy at any time, but only 17% were on therapy at HCC diagnosis (38% at US centers, 11% at Asian centers). Antiviral therapy would have been indicated for >60% of the patients not on antiviral therapy based on American criteria. Patients with cirrhosis had lower five-year survival (34% vs. 46%; $p < 0.001$) while patients receiving antiviral therapy had increased five-year survival compared to untreated patients (42% vs. 25% with cirrhosis and 58% vs. 36% without cirrhosis; $p < 0.001$ for both). Similar findings were seen for other patient subgroups by cancer stages and cancer treatment types. Antiviral therapy was associated with a decrease in risk of death, whether started before or after HCC diagnosis (adjusted HR 0.62 and 0.79, respectively; $p < 0.001$). Conclusion: Antiviral therapy improved overall survival in patients with HBV-related HCC across cancer stages and treatment types but was severely underutilized at both U.S. and Asia centers. Expanded use of antiviral therapy in HBV-related HCC and better linkage-to-care for HBV patients are needed.

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Introduction:

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide with nearly 600,000 deaths in 2008,[1] and hepatitis B virus (HBV) infection is the most common cause of HCC.[2] Up to 20-40% of patients with HBV infection may develop HCC in the absence of clinically-apparent cirrhosis.[3, 4] The advent of highly potent antiviral therapy has offered the possibility of greatly decreasing the incidence of liver-related complications, including cirrhosis and HCC, in patients with chronic hepatitis B (CHB).[5, 6]

While antiviral medications are known to reduce the risk of HCC in patients with CHB,[7] it is less well-understood how they influence the overall survival of patients with established HCC, with most data only focusing on patients undergoing curative therapy for HCC.[8] A 2013 randomized controlled trial comparing nucleot(s)ide analogs to placebo in patients with HBV-related HCC treated with partial hepatectomy found that antiviral therapy decreased the risk of HCC recurrence, HCC-related mortality, and overall mortality.[9] These findings are supported by an earlier meta-analysis of nine cohorts and a national database study showing that HCC patients receiving curative therapy for HCC and treated with antiviral agents had decreased overall mortality and recurrence rate.[10, 11] Likewise, antiviral therapy after radiofrequency ablation is associated with decreased HCC recurrence.[12] The data on antiviral therapy in patients treated with palliative therapy, including transarterial chemoembolization (TACE) and sorafenib are more limited, but in the case of TACE, a randomized controlled trial demonstrated that antiviral therapy increases survival.[13-15]

Currently, the presence of HCC is not considered an indication for antiviral medications in international guidelines for the management of CHB.[16-18] In addition, lifelong antiviral medications may not be reimbursed by third-party payers in certain areas such as Taiwan if patients have HCC but no cirrhosis.[19] Thus, the question of how much viral suppression can reduce mortality among HBV-related HCC patients can have important policy implications. Related to this issue is the "cascade of care" for patients with CHB, which describes the reasons for which rates of treatment for CHB are suboptimal.[20] Many patients with CHB have not even been diagnosed, and among those who are diagnosed many have not established care with the medical system.[21] Even among those with access to appropriate medical care, treatment rates of CHB are suboptimal for numerous reasons including patient loss to follow-up, financial difficulties, and misconceptions about indications for

antiviral therapy.[22] A greater understanding of the use of antiviral therapy in HBV-related HCC may provide further insight into how CHB patients interact with the healthcare system.

The goal of this study was to examine the effect of antiviral therapy on overall survival of patients with HBV-related HCC, taking into account the presence or absence of cirrhosis in a real-world cohort of East and West patients.

Patients and Methods:

Study design and patient population

We performed an international multicenter cohort study of HBV-related HCC at five medical centers. The inclusion criteria were CHB (defined as positive serum hepatitis B surface antigen, detectable HBV DNA, or on antiviral therapy for a history of CHB) and a new diagnosis of HCC (by pathology or imaging based on 2010 American Association for the Study of Liver Diseases criteria).[23] Patients with prior HCC or liver transplant were excluded. Patients were screened via an ICD-9 diagnosis query for HCC and included in the cohort if the above criteria were met based on individual chart review.

The Kaohsiung Memorial University Hospital cohort included consecutive 1,261 patients diagnosed between 2000 and 2015. The Asan Medical Center cohort included 496 randomly-selected patients diagnosed between 2005 and 2015. The Stanford University Medical Center cohort included 453 consecutive patients diagnosed with HCC between 2000 and 2014. The Hanyang University Medical Center cohort included 289 consecutive patients seen in clinic between 2005 and 2015. The Mayo Clinic cohort included 44 patients diagnosed between 2005 and 2011, as previously reported [24]. This study was approved by the Institutional Review Boards at Stanford University (Stanford, CA, USA) and each of the other participating centers.

Selection bias is decreased by the use of consecutive patients. Study size was not pre-determined and was based on the number of patients diagnosed with HCC between certain time periods.

Definition of cirrhosis and antiviral treatment

Laboratory data, imaging findings, and HCC and cancer treatment modalities were obtained from patients' medical records. Patients were designated as having cirrhosis if they were deemed to have cirrhosis based on hepatology notes, or if there was pathological evidence of fibrosis stage 4, clinical evidence of portal hypertension (otherwise-unexplained splenomegaly or platelet count < 120,000/μL, ascites, or gastroesophageal varices on imaging), prior hepatic decompensation (hepatic encephalopathy, ascites, variceal gastrointestinal

bleeding), or laboratory evidence of decreased synthetic function (total bilirubin > 2.0 mg/dL or international normalized ratio > 1.2 without alternative explanation). Antiviral therapy status was determined by chart review and pharmacy records. Criteria for antiviral therapy were based on American Association for the Study of Liver Disease and Asia-Pacific Association for the Study of the Liver guidelines.[16, 17]

Tumor staging and survival outcomes

Tumor characteristics were determined by triphasic computed tomography or magnetic resonance imaging. Patients were followed from the date of diagnosis with HCC and either death or last follow-up date in the medical record. For the Stanford and Mayo cohorts, patients not known to be deceased and whose last visit to the medical center was before January 1, 2015, we also performed a National Death Index registry search from 1979-2014. The National Death Index registry is a centralized database of death record information on file in state vital statistics offices with over 90% completion for most states and 99% for the state of California where the Stanford cohort is located [25]. For the Kaohsiung cohort, telephone interview with families were also conducted to obtain additional follow-up data.

Antiviral therapy indications

Four different standards of antiviral therapy were used: American Association for the Study of Liver Disease guidelines,[16] Asia-Pacific Association for the Study of the Liver,[26] Ministry of Health and Welfare for the Republic of Korea,[27] and National Health Insurance Administration for Taiwan.[28] Local guidelines were defined as American Association for the Study of Liver Disease guidelines for United States centers, Ministry of Health and Welfare reimbursement criteria for Korean centers, and National Health Insurance Administration for the Taiwan center (Supp. Table 1).

Statistical Analysis

Descriptive statistics were reported as proportion (%) for categorical variables, and mean ± standard deviation (SD) or median (and range) for continuous variables. Normally distributed continuous variables were compared by Student's *t* tests. Non-parametric statistics were applied when continuous variables were not normally distributed. Chi-squared tests were used to compare categorical variables. In this study, the primary outcome was overall survival of HCC patients. Person-years of follow-up were calculated for each patient as the time from dates of HCC diagnosis to the date of death or to the last date when patients were last known to be alive. Mortality rates by various disease status were calculated and expressed per 100 person-years. Kaplan-Meier methods were utilized to depict the overall survival of patients with or without antiviral therapy; patients lost to follow-up were censored. Statistical differences in overall survival by various subgroups were compared and examined by log-rank tests. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and

95% confidence intervals (CIs) relating antiviral therapy and other risk factors with overall survival. Lead time analysis was performed as previously described[29, 30]. Statistical significance was defined as a 2-tailed *P* value < 0.05. Missing data were excluded from analysis. All statistical analyses were performed using Stata 11.0 (Stata Corporation, College Station, TX).

Results:

Baseline clinical/tumor characteristics:

The overall cohort consisted of 2,518 patients, of whom 73% had cirrhosis, 81% were male, and 98% were Asian. Baseline clinical and laboratory characteristics of the patients in this cohort by antiviral therapy status are shown in **Table 1**. Among the patients with cirrhosis, 30% had had a history of hepatic decompensation with variceal bleeding, hepatic encephalopathy, or ascites, and 38% had Child-Pugh-Turcotte (CPT) class B or C disease.

In total, 49% of patients had ever received antiviral therapy at any time (**Fig. 1**). However, only 17% were on treatment at time of HCC diagnosis (**Fig. 1**). Proportion of patients receiving antiviral therapy before their diagnosis of HCC did not differ between those with or without cirrhosis (17.9% vs. 15.3%; $p = 0.12$; **Supp. Fig. 1A**). We next focused on the 83% of patients who were not on antiviral therapy at time of HCC diagnosis, in particular on whether treatment would have been indicated for these patients. There was considerable variation in whether or not antiviral therapy was indicated depending on the specific guideline and on cirrhosis status. Over 80% of patients with decompensated cirrhosis met criteria based on national and international guidelines, while <10% of patients without cirrhosis did (**Fig. 2**). The widest variation between guidelines was seen in patients with compensated cirrhosis, where 84% of patients met American standards while only 4% met Taiwan reimbursement criteria and 44% met Korea reimbursement and Asia-Pacific criteria for antiviral therapy ($p < 0.0001$) (**Fig. 2**). Centers in different countries could have patients with different viral characteristics, but even when matching the patients of each country to the reimbursement guidelines in those countries, the overall trend persisted, where antiviral therapy was more frequently indicated in patients with decompensated cirrhosis than compensated cirrhosis than no cirrhosis (**Fig. 3**).

Of the patients who were not on therapy at time of HCC diagnosis, 37% were later started on antiviral therapy (**Fig. 1**). Patients with cirrhosis were more likely to receive antiviral therapy after HCC diagnosis and more likely to receive antiviral therapy at any time than those without cirrhosis (49.9% vs. 43.1%; $p < 0.001$; **Supp. Fig. 1A**). Of note, antiviral therapy is reimbursed in Korea for patients with detectable HBV DNA and HCC,[27] but HBV DNA was detected in 68% of patients who never received antiviral therapy after HCC diagnosis.

Though rates of antiviral therapy were well below 50% at time of HCC diagnosis at all centers, it was higher at the US centers than the Taiwan or Korea centers (40% vs. 12% vs. 10%; $p < 0.001$ for three-way comparison; **Supp. Fig. 1B**). After HCC diagnosis, 68% of the US and 61% of the Korea center patients were on antiviral therapy, compared to only 31% in the Taiwan center (**Supp. Fig. 1B**; $p < 0.001$ for three-way comparison). There was no difference in antiviral therapy use based on date of HCC diagnosis 2005 or before, 2006-2010, or 2011 or later: 52%, 52%, and 49% of patients received antiviral therapy at any time, respectively, in these time periods ($p = 0.22$).

Patients receiving antiviral therapy were younger (56.4 vs. 59.0 years; $p < 0.001$) and more often had cirrhosis (76% vs. 70%; $p < 0.001$) than those not receiving antiviral therapy (**Table 1**). The antiviral medications most commonly used were entecavir (49.5%), lamivudine (37.9%), tenofovir (14.9%), and adefovir (11.0%), with little use of telbivudine (3.1%) and interferon-containing regimens (1.8%). Patients with cirrhosis more frequently received antiviral therapy, and those receiving antiviral therapy were less likely to have decompensated cirrhosis and had lower CPT class and model for end-stage liver disease (MELD) scores than those who did not receive antiviral therapy ($p < 0.1$). In addition, regardless of cirrhosis status, patients receiving antiviral therapy had earlier cancer stage, based on Barcelona clinic liver cancer (BCLC) stage, smaller maximum tumor size, and decreased prevalence of multifocal tumors, vascular invasion, and extrahepatic metastasis ($p < 0.001$).

Regarding HCC by cirrhosis status, patients with cirrhosis had smaller maximum tumor size than those without cirrhosis (5.2 vs. 5.8 cm; $p = 0.004$) but more often had multifocal tumors (55% vs. 42%; $p < 0.001$). Compared to patients without cirrhosis, HCC patients with cirrhosis also had a greater prevalence of vascular invasion and extra-hepatic metastasis, as well as a higher BCLC stage ($p < 0.001$ for all comparisons).

Cancer Treatment:

Supp. Table 2 illustrates cancer treatment based on presence or absence of cirrhosis. Patients with cirrhosis were less likely to receive cancer treatment than patients without cirrhosis (82.4% vs. 88.7%; $p < 0.001$), particularly partial hepatectomy (16.4% vs. 39.8%; $p < 0.001$), though they were more likely to undergo LT (4.4% vs. 1.0%; $p < 0.001$). While patients with cirrhosis more often received liver-directed therapy (65.5% vs. 53.5%; $p < 0.001$), this difference was largely driven by transarterial chemoembolization rather than curative ablations.

When comparing cancer-directed treatment modalities based on antiviral therapy status (**Supp. Table 3**), patients receiving antiviral therapy were more likely to receive any treatment and most individual treatments

including resection, LT, and liver-directed therapy. As with cirrhosis, the difference in liver-directed therapy was driven primarily by palliative transarterial chemoembolization and external radiation therapy.

Mortality rates and overall survival:

Table 2 shows the mortality rates by various disease status and treatment types. In total, there were 1415 deaths after 6384 person-years of follow-up, yielding overall mortality of 22.2 per 100 person-years in the study population. Overall, patients with cirrhosis had increased mortality rate compared to those without cirrhosis ($p < 0.001$). As expected, mortality was higher with higher CPT class, BCLC stage, and use of curative therapies ($p < 0.05$ for all).

Fig. 4 shows overall survival based on antiviral therapy status. Survival was significantly higher in patients receiving antiviral therapy (**Fig. 4A**), and notably both among those with cirrhosis (42% vs. 25%; $p < 0.001$; **Fig. 4B**) and those without cirrhosis (58% vs. 36%; $p < 0.001$; **Fig. 4C**). Subgroup analysis of five-year survival based on antiviral treatment status is shown in **Table 3**. Overall, patients receiving antiviral therapy had greater five-year survival compared to untreated patients ($p < 0.001$). This trend was seen in patients with and without cirrhosis, as well as in all Child-Pugh classes among patients with cirrhosis. Patients receiving antiviral therapy had higher survival than untreated patients with BCLC stages 0/A, B, and C/D ($p < 0.001$). These differences were also significant in patients receiving various cancer treatment types, from hepatic resection and liver transplant to tumor-directed treatment such as TACE/transarterial radioembolization, and even among patients who received only supportive care ($p < 0.05$).

Patients receiving antiviral therapy before HCC diagnosis may have improved access to medical care including HCC screening, which might result in lead-time bias so that the increased survival could merely reflect earlier diagnosis without improvement in outcomes. To address this question, we performed sensitivity analysis based on timing of antiviral therapy, i.e. only after HCC diagnosis vs. before HCC diagnosis (**Supp. Table 4**). Patients receiving therapy before HCC diagnosis were older and had smaller maximum tumor size and more frequently had multifocal disease, vascular invasion, and extrahepatic metastases, as well as more advanced BCLC stage (**Supp. Table 4**). On analysis unadjusted for lead time, antiviral therapy before HCC diagnosis was associated with decreased mortality vs. antiviral therapy only after HCC diagnosis (14.46 vs. 19.85 deaths per 100 person-years, $p = 0.0008$, **Supp. Fig. 2A** and **Supp. Table 5**). This difference persisted after lead-time analysis with estimated sojourn 70 and 140 days (**Supp. Fig. 2B-C**), but not at a sojourn of 210 or 280 days (**Supp. Fig. 2D-E**).

We also compared patients receiving antiviral therapy only after HCC diagnosis with those not receiving antiviral therapy at all. Here, there was no significant difference in maximum tumor size, proportion of multifocal tumors, or vascular invasion (**Supp. Table 6**). However, patients not receiving antiviral therapy had greater proportion of extrahepatic metastasis and higher BCLC stage (42.2 vs. 32.7%; $p < 0.05$ for both comparisons; **Supp. Table 6**). Screening is a related issue which may be related to access to care. Data on screening were available for 1,224 patients (49%). HCC screening rates in patients receiving no antiviral therapy were lower than those in patients receiving antiviral therapy before HCC diagnosis ($p < 0.001$) but were no different in patients receiving antiviral therapy after HCC diagnosis ($p = 0.58$).

Predictors of survival:

Table 4 shows predictors of mortality among HBV-related HCC patients. On unadjusted analysis, prognostic factors associated with increased mortality included younger age, male sex, cirrhosis, decompensated cirrhosis (CPT stage B and C), higher MELD score, more advanced BCLC stage, and the Taiwan center ($p < 0.05$ for all). Conversely, factors associated with decreased morality included treatment with surgery (resection or liver transplant) or with either sorafenib or liver-directed therapy, antiviral therapy at any time, duration of antiviral therapy both before and after HCC diagnosis, and antiviral therapy with newer agents (entecavir or tenofovir) ($p < 0.05$ for all). We included relevant predictors associated with mortality in the multiple regression model to estimate the adjusted HR and 95% CI of each predictor: age, sex, cirrhosis status, MELD, treatment type, BCLC stage, and country. We also included antiviral treatment status, stratified as no therapy, therapy only after HCC diagnosis, and therapy before HCC diagnosis. In this model, antiviral therapy either before or only after HCC diagnosis was independently associated with decreased mortality (adjusted HR 0.62 and 0.79, respectively; $p < 0.001$; **Table 4**). In this model, the Taiwan center was no longer independently associated with increased mortality. On subanalysis of the patients for whom screening information was available, both screening and antiviral therapy were associated with increased survival in a multivariate analysis model (**Supp. Table 7**).

Discussion:

In this study, we characterized a cohort of patients with HBV-related HCC stratified by antiviral therapy utilization and cirrhosis status. We found that the use of antiviral medications at any time in HBV-related HCC patients was associated with a 20-40% reduction in overall mortality of these patients, a sizable effect especially when compared to the modest survival benefits seen with many standard therapy for HCC such as palliative liver-directed therapy and sorafenib.[31, 32] The benefit of antiviral therapy holds across a range of different cancer stages including BCLC stage C/D and treatment types and even in patients receiving supportive care only. In addition, while there was significant differences in the rates of antiviral utilizations and overall mortality among

US vs. Taiwan vs. Korea centers, there was no difference in overall survival based on country of study sites in this multicenter international study after adjustment was made for antiviral therapy use.

There is extensive evidence that antiviral therapy in patients with CHB decreases risk of liver-related complications including liver decompensation and HCC development.[6, 33, 34] Our current study demonstrates that antiviral therapy was associated with significantly reduced risk of death in a wide range of patients, from those without cirrhosis to those with cirrhosis and advanced liver disease, from those with early to advanced cancer stage, and from those receiving curative therapy to those receiving only palliative therapy or even supportive care only. Antiviral therapy could increase survival following HCC diagnosis in either the long- or short-term through different mechanisms. In the long run, antiviral therapy could decrease HCC recurrence and/or HCC progression. Previous studies showed antiviral therapy was associated with decreased HCC recurrence and increased survival among patients with HBV-related HCC undergoing surgery with curative intent.[9, 10] The long-term beneficial effects would be more significant in patients with early-stage HCC and compensated liver disease. In the short term, antiviral therapy may counter the destabilizing effect by HCC on liver function, which may be more important in patients with more advanced HCC and/or more impaired liver function. This study found that the increase in survival with antiviral therapy was seen in a range of severity of liver disease and HCC stage, and, if anything, may have been more pronounced in patients with more advanced disease. In addition, choice of antiviral therapy used may be important: use of newer antiviral agents, i.e. tenofovir or entecavir, was associated with improved survival compared to use of lamivudine or adefovir (**Table 4**).

Disappointingly, in this multinational cohort, there was a strikingly low rate of antiviral therapy. In particular, there was a much lower rate of antiviral use in the Asian sites compared to the US sites though antiviral therapy was still severely underutilized in the US cohort with only 40% receiving antiviral therapy at HCC diagnosis and only 68% total at any time. There are two potential explanations for these low uses: that patients did not meet local criteria for antiviral therapy use (i.e. existing guidelines did not recognize these patients as high-risk[35, 36]) or that they did meet criteria but nonetheless did not receive antiviral therapy. Our data suggest that both of these explanations may be true. Regarding the possibility of inadequacy of guidelines, we note that <10% of patients without cirrhosis met any guideline criteria for antiviral therapy despite developing HCC. Further, there is wide discrepancy between different guidelines in what proportion of patients with compensated cirrhosis would have met criteria for antiviral therapy (**Fig. 2 and 3**). These differences in guidelines on management of compensated cirrhosis with CHB one of the most prominent findings in this study and suggest this may be a target for future guideline development.

Our data also suggest poor linkage to care. Among the patients not on treatment at time of HCC diagnosis, >40% of those with cirrhosis met local and international criteria for antiviral therapy (other than Taiwan reimbursement guidelines). This figure is even higher for decompensated cirrhosis. However, only 17% of patients were on antiviral therapy at time of HCC diagnosis. This result is consistent with the poor linkage to care well known among HBV-infected patients with major gaps ranging from under screening and delayed diagnosis to suboptimal evaluation of patients with known HBV infection and undertreatment of patients who meet professional society guideline criteria for treatment.[20-22] Inadequate linkage to care has other consequences as well: patients receiving antiviral therapy before HCC diagnosis had higher rates of HCC screening and were diagnosed with HCC at an earlier stage, compared to among patients receiving antiviral therapy only after HCC diagnosis or not at all. Further, on lead time bias analysis, an estimated sojourn in HCC diagnosis of at least 210 days (a highly conservative estimate) was needed to adjust for the difference in mortality between patients receiving antiviral therapy before vs. only after HCC diagnosis (**Supp. Fig. 1**).

It should be noted that antiviral treatment rate before HCC diagnosis was suboptimal in all of our study centers. This included US patients from two major university referral centers, which suggests that financial coverage is unlikely to be the only major barrier to antiviral therapy in patients with chronic hepatitis B. In a prior study of more than 1,000 mostly Asian American patients with CHB from the San Francisco Bay area (including Stanford University Medical Center), financial difficulty was the reason for no antiviral therapy in under 10% of patients who met the American Association for the Study of Liver Diseases and/or US Panel guideline criteria for antiviral therapy.[22] Rather, the most commonly cited reasons were the desire for further follow-up by patients and/or physicians and the perception that the patients' serum alanine aminotransferase levels were not elevated even though they met guideline criteria.[22] Since CHB is a largely asymptomatic disease until onset of advanced HCC or end-stage liver disease, appropriate management often requires both patients and care providers to be better informed of the natural history of the disease and the need for regular monitoring and preventive therapy.

HBV-related HCC can occur in the absence of liver cirrhosis. According to prior studies, no overt cirrhosis is seen in 20-40% of patients with HCC in primarily Asian cohorts[37-40] and approximately 10% in non-Asian cohorts.[41, 42] In this study, we found that 27% of patients did not have recognizable cirrhosis. However, for those with cirrhosis, overall survival following HCC diagnosis was lower when compared to those without cirrhosis. This finding holds even when controlling for factors such as BCLC stage, treatment type, and MELD score. The most likely explanation for this finding is that there is a higher incidence of second HCC development in patients with cirrhosis. Indeed, in this cohort, the five-year survival in patients who underwent liver transplant was identical in patients with cirrhosis and those without cirrhosis (83% vs. 86%; $p = 0.91$), and

the reason for this is likely that liver transplant is the only available treatment option which removed the diseased and precancerous livers. Very few transplants were performed in the Asian centers, which somewhat skews these data compared to what would be expected in a US cohort. It is important to note that patients with cirrhosis and antiviral therapy demonstrated improved survival compared to their untreated counterparts, and antiviral medications may be an important component of managing patients with cirrhosis and HCC.

One limitation of this study was that the vast majority of patients were of Asian ethnicity. Whether the findings can be applied to patients of other ethnicities requires further evaluation. Because of lack of longitudinal HBV DNA data, our data likely underestimate the proportion of patients for whom therapy was ever indicated, since patients may have had higher HBV DNA concentration at an earlier date, which may argue against our claim that guidelines are inadequate for identifying high-risk patients. Finally, this study was retrospective in design so we were not able to ascertain the reasons for lack of antiviral therapy. A strength of this study was that it included a large number of HCC patients with HBV infection in Asian populations seen at both American as well as Asian centers. Further, all of the chart review procedures were standardized at each study site using the same case report form with similar definitions for the major outcome and predictor variables such as antiviral therapy, liver cirrhosis, and HCC.

In summary, we report here the largest cohort of diverse HBV-related HCC patients from several medical centers from three countries. We found that antiviral therapy at any time was significantly associated with 20-40% lower mortality and this beneficial effect was independent of age, cirrhosis status, severity of cirrhosis, cancer stage, and cancer treatment. Unfortunately, this study also found an alarmingly low rate of antiviral therapy utilization in centers in the US as well as Asia with the majority of patients not receiving any antiviral therapy before their HCC diagnosis, even though a large proportion of them met both Asian and US treatment guideline criteria for therapy. Our data support more widespread use of antiviral therapy in patients with HBV-related HCC, while highlighting the needs for improved linkage to care and earlier treatment with antiviral therapy in high-risk patients. In addition, the discrepancy between guidelines of management of patients with compensated cirrhosis have significant real-world implications on which patients are eligible for antiviral therapy. Additional prospective studies are needed to understand and overcome the barriers to appropriate management of patients with HBV infection.

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Table 1. Clinical and Tumor Characteristics, Stratified by Antiviral Therapy Use

Characteristic	No antivirals (N = 1283)	Antivirals (N = 1235)	P value
Age at cancer diagnosis	59.0 ± 12.0	56.4 ± 10.8	<**0.001**
Male	80.0%	82.8%	0.073
Asian	98.7%	97.9%	0.085
Any decompensation	26.6%	20.7%	**0.001**
Antivirals before cancer diagnosis	N/A	36.9%	N/A
Antivirals used			
Lamivudine	N/A	37.7%	N/A
Adefovir		11.0%	
Telbivudine		3.0%	

Entecavir		49.0%	
Tenofovir		14.3%	
Interferon (including pegylated)		1.9%	
Other		0.7%	
Mean Child-Pugh score	6.6 ± 1.8	6.4 ± 1.6	**0.012**
Liver cirrhosis	70.0%	76.0%	**0.001**
Child-Pugh class			
A	64.8%	67.6%	**0.008**
B	27.8%	28.0%	
C	7.4%	4.4%	
Model for end-stage liver disease score	11.1 ± 5.2	10.2 ± 4.1	**<0.001**
Maximum tumor size	6.0 ± 4.5	4.8 ± 4.0	**<0.001**
Number of tumors			
Unifocal	44.8%	52.1%	**<0.001**
Multifocal	55.2%	47.9%	
Vascular invasion	28.5%	20.8%	**<0.001**
Extrahepatic metastasis	12.8%	7.5%	**<0.001**
Barcelona clinic liver cancer stage			
0	7.3%	10.4%	**<0.001**
A	24.7%	37.3%	
B	25.8%	24.8%	
C	34.3%	22.6%	
D	8.0%	4.9%	

Table 2. Overall Mortality Rates by Various Disease Stage and Treatment Types

Group		Total Number	Deaths	Person-Years of Follow-Up	Mortality (per 100 person-years)
Overall		2518	1415	6384.24	22.2
Cirrhosis	No cirrhosis	681	312	1943.64	16.1
	Cirrhosis, Child-Pugh A	1096	555	3187.25	17.4

	Cirrhosis, Child-Pugh B	541	396	878.85	45.1
	Cirrhosis, Child-Pugh C	133	103	146.15	70.5
Barcelona Clinic Liver Cancer Stage	0/A	973	306	3687.16	8.3
	B	618	374	1637.43	22.8
	C/D	853	681	866.29	78.6
Antiviral Therapy Use	No antiviral therapy	1283	783	2423.2	32.3
	Antiviral therapy	1235	632	3961.04	16.0
Treatment	Resection	572	155	2141.79	7.2
	Liver transplant	87	22	575.69	3.8
	Ablative Therapy	204	61	805.93	7.6
	TACE/TARE/XRT	1420	863	3852.33	22.4
	Sorafenib	122	87	122.85	70.8
	Supportive care only	401	319	334.26	95.4

559 TACE/TARE/XRT, Transarterial chemoembolization/radioembolization and external radiation therapy.

560

561 **Table 3. Five-year Survival Rates by Disease Stage and Treatment Types**

Group		**Five-year survival (%)**		**P value**
		No antiviral therapy	Antiviral therapy	
Overall		27.9	45.3	**<0.0001**
Cirrhosis	No cirrhosis	36.1	58.4	**<0.0001**
	Cirrhosis, Child-Pugh A	34.8	50.5	**<0.0001**
	Cirrhosis, Child-Pugh B	7.2	25.3	**<0.0001**
	Cirrhosis, Child-Pugh C	7.2	29.8	**0.0062**
Barcelona clinic liver cancer stage	0/A	58.0	69.8	**0.0002**
	B	23.6	34.9	**0.0003**
	C/D	9.1	14.0	**<0.0001**
Treatment	Resection	64.9	74.5	**0.0034**
	Liver transplant	50.0	86.7	**0.017**
	Ablative therapy	67.2	63.3	0.89
	TACE/TARE/XRT	25.6	40.3	**<0.0001**
	Sorafenib	9.3	9.4	0.44
	Supportive care only	7.1	11.3	**0.037**

562 TACE/TARE/XRT, transarterial chemoembolization/radioembolization and external radiation therapy

563

564 **Table 4. Predictors of Mortality of Hepatocellular Carcinoma Patients with Hepatitis B Virus Infection**

Characteristic		**Unadjusted HR (95% CI)**	***P*-value**	**Adjusted HR (95% CI)**	***P*-value**
Age (per year)		0.99 (0.98 – 0.99)	0.033	0.98 (0.97 – 0.99)	**<0.001**
Male sex		1.23 (1.06 – 1.43)	0.006	0.98 (0.83 – 1.16)	0.80
Cirrhosis status	No cirrhosis	(Referent)		(Referent)	
	Cirrhosis	1.42 (1.03 – 1.96)	0.032	1.25 (1.06 – 1.47)	**0.008**
	Cirrhosis, Child-Pugh A	0.98 (0.84 – 1.13)	0.74		
	Cirrhosis, Child-Pugh B	2.54 (2.18 – 2.96)	<0.001		
	Cirrhosis, Child-Pugh C	4.10 (3.25 – 5.17)	<0.001		
Model of end stage liver disease score (per point)		1.10 (1.09 – 1.11)	<0.001	1.05 (1.04 – 1.07)	**<0.001**
Treatment type	Supportive care only	(Referent)		(Referent)	
	TACE/TARE/XRT	0.33 (0.29 – 0.38)	<0.001	0.38 (0.32 – 0.46)	**<0.001**
	Resection/RFA/PEA	0.09 (0.08 – 0.11)	<0.001	0.15 (0.12 – 0.20)	**<0.001**
	Liver transplant	0.04 (0.02 – 0.07)	<0.001	0.06 (0.03 – 0.13)	**<0.001**
Diagnosis date	2000-2005	(Referent)			
	2006-2010	1.07 (0.93 – 1.23)	0.35		
	2011 and after	0.89 (0.76 – 1.03)	0.12		
Barcelona clinic liver cancer stage	0/A	(Referent)		(Referent)	
	B	2.94 (2.49 – 3.46)	<0.001	2.47 (2.04 – 2.99)	**<0.001**
	C/D	8.41 (7.23 – 9.77)	<0.001	5.86 (4.91 – 7.00)	**<0.001**
Antiviral therapy					
	No antivirals	(Referent)		(Referent)	
	Antivirals prior to HCC diagnosis	0.45 (0.38 – 0.54)	<0.001	0.62 (0.50 – 0.76)	**<0.001**
	Antivirals only after HCC diagnosis	0.62 (0.54 – 0.70)	<0.001	0.79 (0.68 – 0.92)	**0.002**
Duration of antiviral therapy before cancer diagnosis (per year)		0.78 (0.72 – 0.83)	<0.001		
Duration of antiviral therapy after cancer		0.66 (0.63 – 0.70)	<0.001		

diagnosis (per year)					
Antiviral type	Lamivudine or adefovir	(Referent)			
	Entecavir or tenofovir	0.77 (0.65 – 0.92)	0.004		
	Other	0.96 (0.68 – 1.37)	0.83		
Country	United States	(Referent)		(Referent)	
	Taiwan	1.36 (1.18 – 1.57)	<0.001	1.15 (0.93 – 1.42)	0.20
	Korea	0.85 (0.72 – 1.02)	0.054	0.99 (0.78 – 1.26)	0.93

HR, hazard ratio; CI, confidence interval; TACE/TARE/XRT: transarterial chemoembolization/transarterial radioembolization/external radiation therapy. RFA, radiofrequency ablation. PEA, percutaneous ethanol ablation.

Figure Legends:

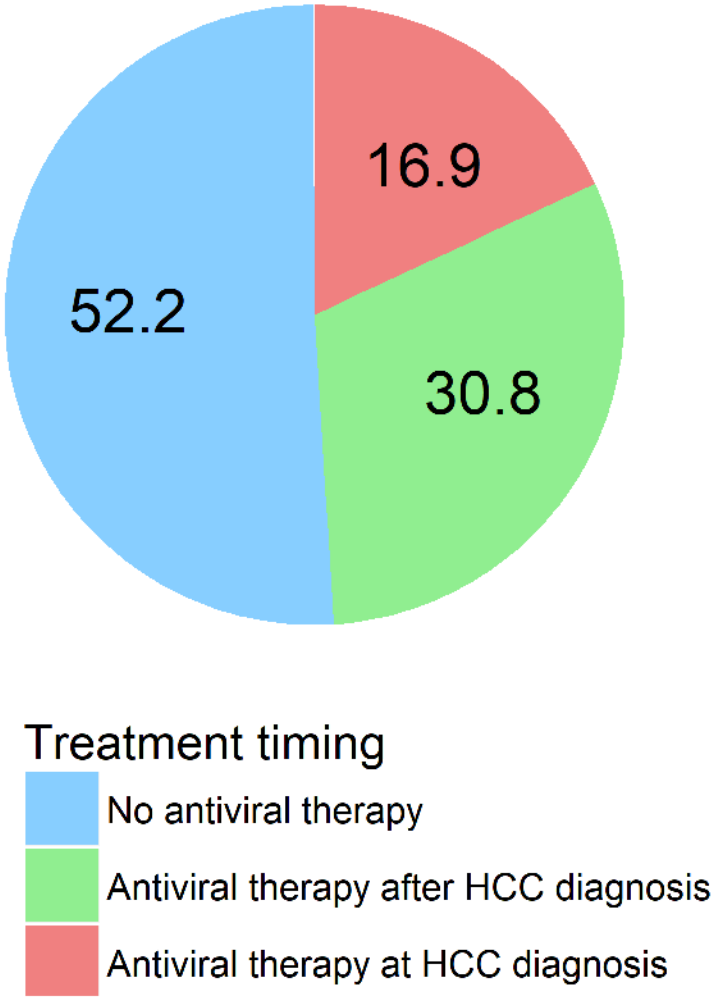
Figure 1: Treatment with antiviral therapy. Percentage of patients receiving treatment with antiviral therapy, either before hepatocellular carcinoma diagnosis (red), after hepatocellular carcinoma diagnosis (green), or never (blue). Numbers represent percentages of patients in each category.

Figure 2: Indication for treatment with antiviral therapy. For patients who were not on antiviral therapy at time of HCC diagnosis, y axis shows percentage of patients for whom antiviral therapy would have been indicated, based on guidelines applied uniformly to all centers. Data are divided based on cirrhosis status: decompensated cirrhosis, compensated cirrhosis, and no cirrhosis. Four sets of guidelines were used: AASLD (American Association for the Study of Liver Diseases; grey),[16] APASL (Asia-Pacific Association for the Study of the Liver; yellow),[26] Ministry of Health and Welfare for the Republic of Korea (purple),[27] and National Health Insurance Administration for Taiwan (green).[28]

Figure 3: Indication for treatment with antiviral therapy. For patients who were not on antiviral therapy at time of HCC diagnosis, y axis shows percentage of patients for whom antiviral therapy would have been indicated, based on local guidelines in the country to which the respective medical centers belong. Data are divided based on cirrhosis status: decompensated cirrhosis, compensated cirrhosis, and no cirrhosis. Local

guidelines were defined as American Association for the Study of Liver Disease guidelines for United States centers,[16] Ministry of Health and Welfare reimbursement criteria for Korean centers,[27] and National Health Insurance Administration for the Taiwan center.[28]

Figure 4: Overall Survival by Antiviral Therapy. Overall survival for patients with hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC), based on antiviral therapy status. (A) Overall cohort. (B) Patients with cirrhosis. (C) Patients without cirrhosis. "No antivirals" refers to patients who were never treated with antiviral therapy directed at HBV, whereas "antivirals" refers to treatment with antiviral agents at any time.



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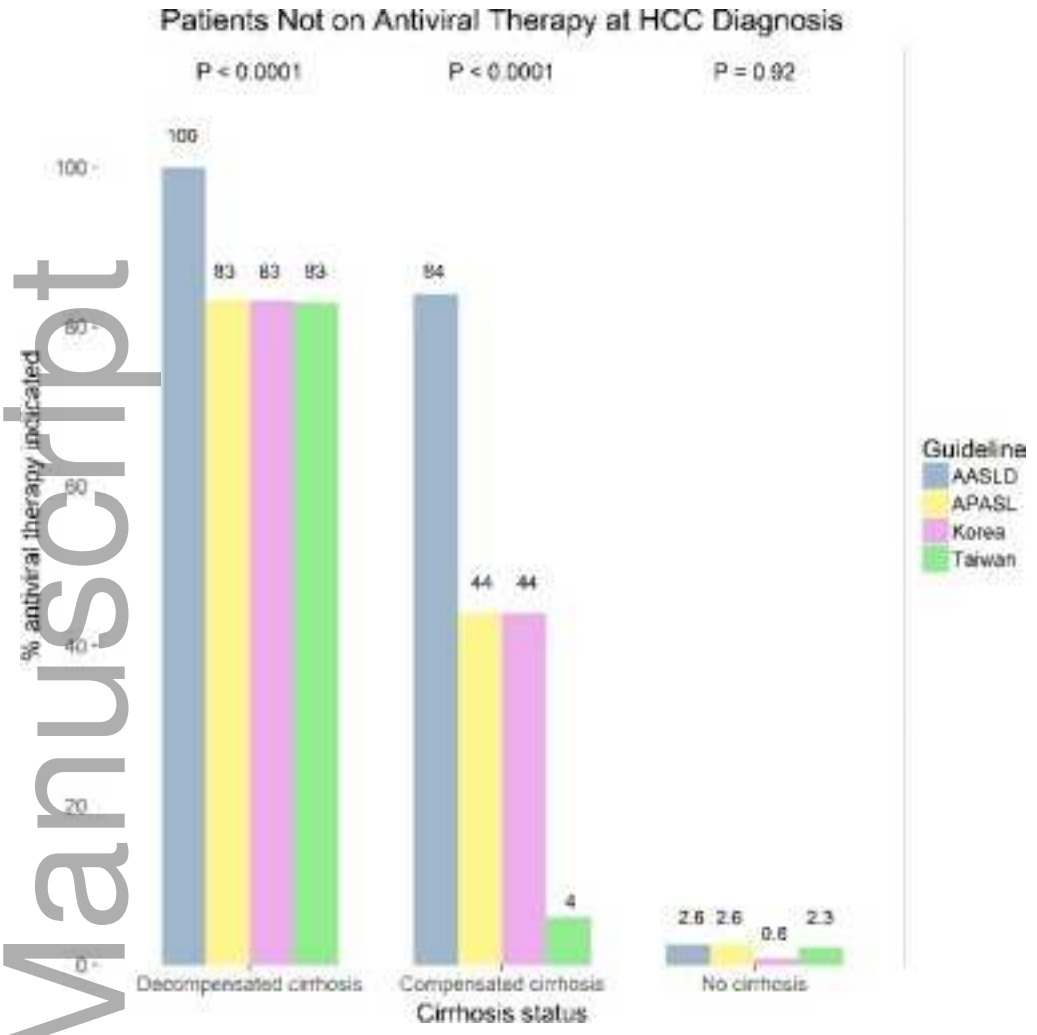

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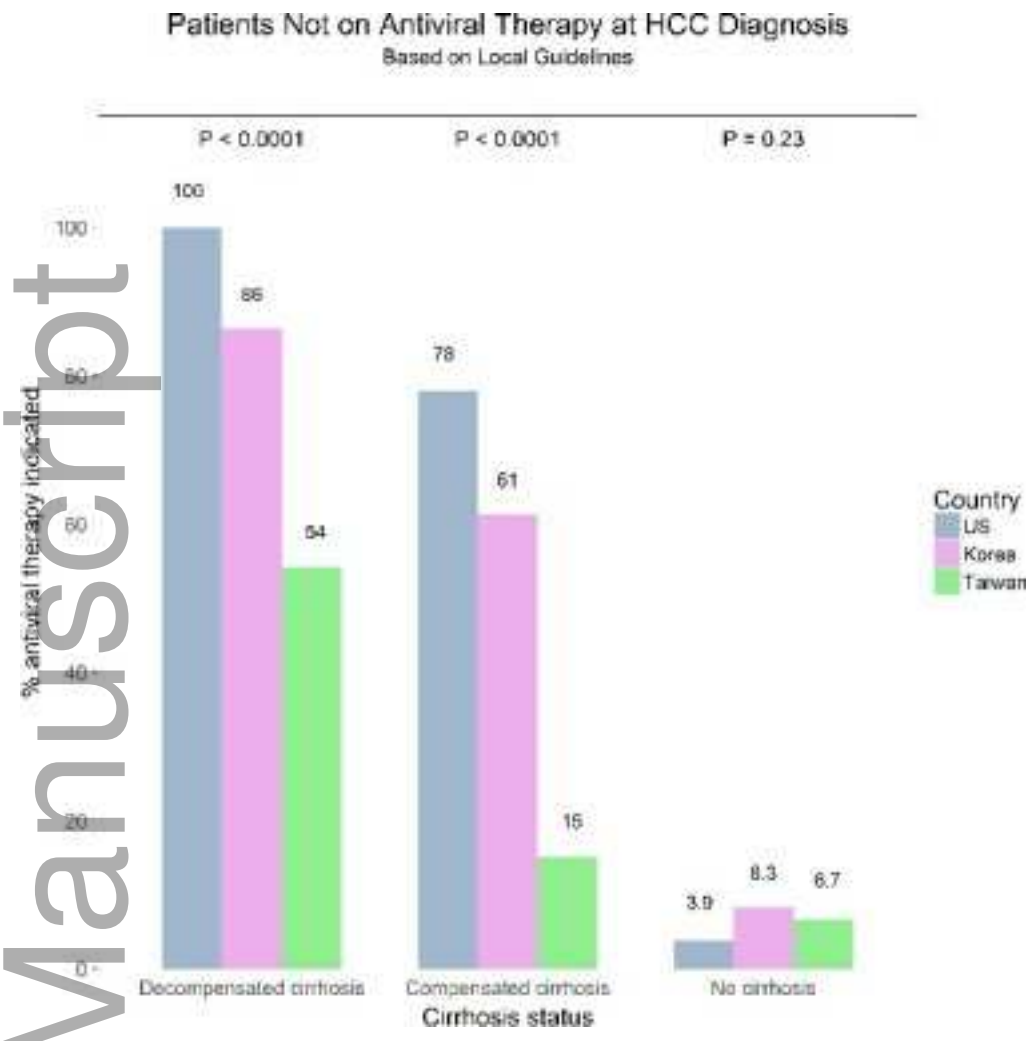

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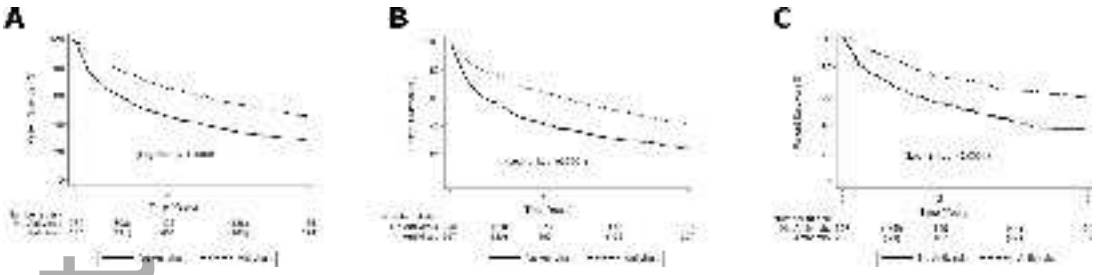

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