Increasing antiviral treatment uptake improves survival in patients with HBV-related HCC

Authors

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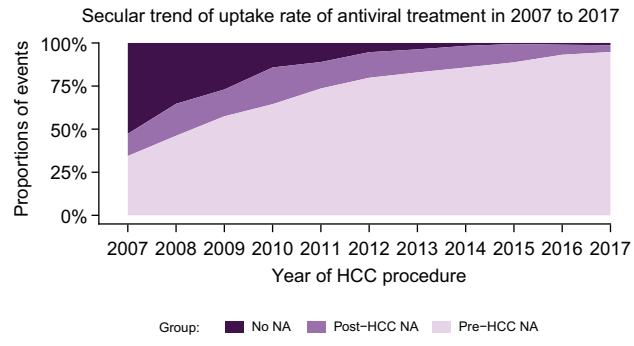
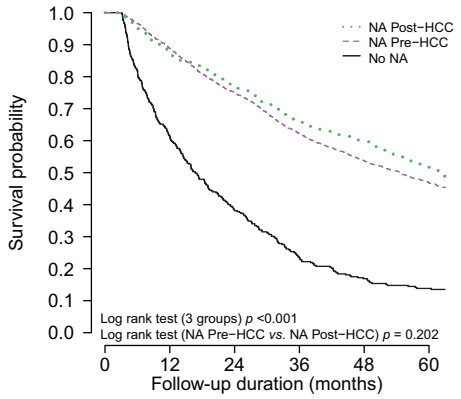
Graphical abstract



N° at risk											
No NA	98	78	85	50	41	22	15	8	3	4	3
Post-HCC NA	24	41	49	75	57	61	54	60	51	23	9
Pre-HCC NA	64	102	181	227	273	328	335	410	427	368	217
Total	186	221	315	352	371	411	404	478	481	395	229



N° at risk						
No NA	407	237	142	82	56	44
Post-HCC NA	2,932	2,438	1,787	1,233	871	607
Pre-HCC NA	504	421	344	266	212	153

Highlights

- Antiviral treatment improves survival in patients with chronic hepatitis B-related HCC.
- The uptake of antiviral treatment in HCC patients was suboptimal in the past (47.3% in 2007), but dramatically improved to 98.3% in 2017.
- The timing of antiviral treatment (before or after HCC occurrence) does not matter that much in terms of patient survival.
- Antivirals should be started soon after HCC has been diagnosed in patients with chronic hepatitis B who are not already on them.

Lay summary

More and more patients who have hepatitis B-related liver cancer received antiviral treatment over the past decade. The timing of starting antiviral treatment, regardless of whether it was before or after liver cancer happens, does not really matter in terms of survival benefits.

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Research article

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Increasing antiviral treatment uptake improves survival in patients with HBV-related HCC

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Background & Aims: Antiviral treatment is known to improve survival in patients with chronic hepatitis B (CHB)-related hepatocellular carcinoma (HCC). Yet, the treatment uptake in CHB patients remains low. We aimed to report the secular trend in antiviral treatment uptake from 2007–2017, and to compare the effect of different nucleos(t)ide analogue (NA) initiation times (before *vs.* after HCC diagnosis) on survival.

Methods: A 3-month landmark analysis was used to compare overall survival in patients not receiving NA treatment (*i.e.* no NA), patients receiving NAs after their first HCC treatment (*i.e.* post-HCC NA), and patients receiving NAs ≤3 months before their first HCC treatment (*i.e.* pre-HCC NA). A propensity score-weighted Cox proportional hazards model was used to balance clinical characteristics between the 3 groups and to estimate hazard ratios (HRs).

Results: The uptake of antiviral treatment in HCC patients increased from 47.3% in 2007 to 98.3% in 2017. The pre-HCC NA group contributed mostly to the uptake rate, which increased from 72.7% to 96.0% in the past decade. In addition, 3,843 CHB patients (407 no NA; 2,932 pre-HCC NA; 504 post-HCC NA) with HCC, receiving at least 1 type of HCC treatment, were included in the analysis. Lack of NA treatment at the time of HCC diagnosis increased the risk of death (weighted HR 3.05; 95% CI 2.70–3.44; p <0.001). The impact of the timing of NA treatment was insignificant (weighted HR 0.90; 95% CI 0.78–1.04; p = 0.161).

Conclusions: The uptake of antiviral treatment in HCC patients increased over the past decade. NA treatment, regardless of whether it was initiated before or after HCC diagnosis, improved survival. It is never too late to initiate NA treatment, even after HCC diagnosis.

Introduction

HBV-related hepatocellular carcinoma (HCC) is common in Asia because this chronic viral infection is endemic.[1] Despite advances in HCC treatment, HBV-related HCC is still associated with a high recurrence rate and hence high mortality.[2] Antiviral therapy with oral nucleos(t)ide analogues (NAs) reduces the risk of HCC recurrence and death in chronic hepatitis B (CHB) patients treated by surgical resection.[3,4] The survival benefit is related to lower tumour recurrence rate and improved liver function after antiviral treatment.[4]

The World Health Organization set the target to reduce 65% mortality from chronic HBV infection by 2030.[5] This goal is to be achieved by reducing new HBV infections by 90% and treating 80% of CHB patients if they are eligible for antiviral treatment.[5] HCC is always the leading cause of death in CHB patients.[6] Whilst increasing treatment options were available for HCC over the past decade,[7,8] NA treatment is 1 of the key modalities for secondary and tertiary prevention for HCC.[9] Unfortunately, the uptake rate of antiviral treatment could be as low as 5% even in developed countries.[10] This consequence increases the likelihood of hepatic decompensation and hence limits the HCC treatment options. With the evolving international treatment guidelines for CHB patients[11–13] and improving the availability and safety profile of NA,[14] it would be important to study treatment uptake and compliance to international treatment guidelines in CHB patients who have developed HCC.

In the current study, we aimed to determine the secular trend of antiviral treatment uptake in a territory-wide HBV-related HCC cohort in Hong Kong from 2007 to 2017. We also aimed to investigate the impact of NA treatment on the overall survival of these HCC patients. The effect of NA treatment commenced before and after HCC treatment was evaluated.

Keywords: Entecavir; Hazard ratio; Lamivudine; Local ablative therapy; Propensity scores; Surgical resection; Transarterial chemoembolisation.

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Patients and methods

Study design and data source

We performed a territory-wide registry cohort study by retrieving data from the Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority, Hong Kong.[15] It covers the electronic health records, use of medications, and laboratory results from all public hospitals and clinics in Hong Kong, and it represents data of approximately 80% of the local population.[16,17] The study protocol was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

Participants

CHB patients who developed HCC and received HCC treatment procedures, defined by positive HBsAg for at least 6 months together with diagnosis codes and/or procedure codes of HCC from 1 January 2007 to 31 December 2017, were included. HCC, together with all other concomitant medical conditions, including cirrhosis, ascites, and hepatic encephalopathy, was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. Patients with missing demographics, co-infected with HCV or HDV based on the ICD-9-CM diagnosis codes and viral and/or serological markers, and co-infected with HIV based on the ICD-9-CM diagnosis codes were excluded. Patients were followed until death and censored at last follow-up date (31 December 2018).

Data collection

Data were retrieved in October 2019. Baseline date was defined as the date of first HCC treatment procedure. Demographics data, including gender and date of birth, were captured. Serum HBV DNA was available as a routine laboratory test since year 2012; thus, the majority of patients did not have serum HBV DNA results in 2007–2011. Exposures to NAs (*i.e.* lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir disoproxil fumarate [TDF], and tenofovir alafenamide) and (PEGylated)-interferon for any duration were also captured. Patients were categorised into no NA group if they did not receive NA throughout the follow-up period, pre-HCC NA group if they had received NA before HCC treatment, and post-HCC NA group if they had received NA after HCC treatment.

HCC treatment procedures

HCC treatments were defined by procedure codes for the following 5 major categories: surgical resection, liver transplantation, local ablative therapy, transarterial chemoembolisation (TACE), and systemic therapies. Non-curative HCC treatments were defined as TACE only, systemic therapies only, or TACE/systemic therapies in combination with any other treatments. In the 3-month landmark analysis (Table 1), different procedures coded within 3 months from the index procedure were defined as combination treatments.

Clinical outcomes

The primary outcome was death. Death and its date were ascertained using data from both CDARS and Hong Kong Death Registry. All deaths that happened during the study period from January 2007 to December 2018 were retrieved and analysed.

Statistical analysis

Data were analysed using SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) and R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Qualitative and quantitative differences between subgroups were analysed by Fisher's exact test or Chi-square test of independence for categorical parameters and 1-way analysis of variance or Kruskal-Wallis test for continuous parameters, as appropriate. All statistical tests were 2-sided. Statistical significance was taken as p <0.05. The crude incidence rates of death (in events/100 person-years) with 95% CIs were determined for no NA, pre-HCC NA, and post-HCC NA patients.

Random forest-based multivariate imputation by chained equations (MICE) was performed to minimise imputation error for both continuous and categorical variables. Twenty multiple imputations were obtained with all missing data assumed as missing at random. As covariates with high missing rate would increase sampling variability than necessary, covariates with over 50% missing rate (*i.e.* HBV DNA) were excluded in the imputation model. The imputed variables (missing percentage) were HBeAg status (22.9%), platelet counts (14.6%), serum albumin (0.3%), alanine aminotransferase (ALT) (0.05%), aspartate aminotransferase (0.3%), alpha-fetoprotein (AFP) (32.4%), prothrombin time (3.8%), gamma-glutamyl transpeptidase (GGT) (0.4%), and serum creatinine (4.6%). These covariates, together with the event indicator and Nelson-Aalen estimator of the cumulative hazard at the time of event or censoring, were included in the imputation model.

Overall survival was estimated by Kaplan-Meier method; log-rank test was applied to compare the survival probabilities of patients with different timing of NA use. On multivariable analyses, Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% CIs for all-cause death; forward stepwise selection was used to select significant covariates. The overall coefficient estimates and standard errors were computed by combining the estimates obtained in each individual multiple imputation data set using Rubin's rules. A 3-month landmark analysis (*i.e.* by excluding patients who died during the 3 months exposure period and those who had follow-up of less than 3 months), with follow-up duration up to 5 years from the landmark date, was adopted to avoid immortal time bias in patients who received treatment after baseline. A 6-month landmark analysis was conducted as sensitivity analysis.

Inverse probability of treatment weighting (IPTW) using propensity scores (PSs) was used in our secondary analysis. We estimated PS, the conditional probability of receiving NA before HCC, by generalised boosted models. The balance of covariates by PS was assessed by 2 summary statistics: the absolute standardised mean difference (ASMD) and the Kolmogorov-Smirnov (KS) statistic. Both mean and maximum of either ASMD or KS were the 4 stopping rules for assessing the covariate balance between no NA, pre-HCC NA, and post-HCC NA (*i.e.* ASMD >0.2 and/or KS >0.1 as an indication of imbalance).[18] PS weights of average treatment effect on the treated were calculated by the stopping rule with the greatest effective sample size and the best subgroup balance. Weighted Cox proportional hazards model was used to estimate the treatment effect; standard error of the HRs was estimated by robust estimator. The use of robust variance estimator can overestimate the sampling variability of the HRs, regardless of which set of weights used.[19] Therefore, we took the bootstrap estimator, which tended to give a narrower and less biased CI as the sensitivity analysis.

Table 1. Baseline clinical characteristics included in 3-month landmark analysis.

Three-month landmark analysis (death), N = 3,843	No NA, n = 407	Pre-HCC NA, n = 2,932	Post-HCC NA, n = 504	*p* value
Male gender, n (%)	328 (80.6)	2,402 (81.9)	419 (83.1)	0.610
Age (year)	65.9 (11.6)	61.7 (10.3)	58.9 (11.2)	<0.001
Platelet* (×10^9/L)	174.0 (102.5)	130.7 (65.6)	158.4 (81.5)	<0.001
Missing, n (%)	1 (0.2)	8 (0.3)	4 (0.8)	
Prothrombin time* (second)	13.2 (2.2)	13.9 (3.0)	14.5 (4.1)	<0.001
Missing, n (%)	4 (1.0)	11 (0.4)	0 (0.0)	
Albumin* (g/L)	30.8 (6.2)	33.8 (6.1)	31.9 (6.5)	<0.001
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Total bilirubin* (μmol/L)	25.0 (15.8)	27.4 (27.3)	27.1 (21.6)	0.089
Missing, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0)	
Creatinine* (μmol/L)	87.5 (54.4)	91.8 (66.6)	84.8 (29.3)	0.011
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
ALT* (IU/L)	95.0 (46.0; 200.5)	120.5 (48.0; 271.0)	191.0 (91.8; 376.0)	<0.001
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
AST* (IU/L)	86.0 (42.5; 189.0)	66.9 (34.8; 207.7)	112.0 (41.0; 304.0)	<0.001
Missing, n (%)	180 (44.2)	914 (31.2)	211 (41.9)	
MELD score	9.6 (2.6)	10.2 (3.1)	10.6 (3.1)	<0.001
Missing, n (%)	0 (0.0)	1 (0.0)	0 (0.0)	
Child-Pugh score	6.4 (1.0)	6.2 (1.2)	6.3 (1.2)	<0.001
Missing, n (%)	0 (0.0)	1 (0.0)	0 (0.0)	
APRI	1.5 (0.7; 3.5)	1.7 (0.7; 4.8)	2.0 (0.7; 5.4)	0.240
Missing, n (%)	180 (44.2)	921 (31.4)	212 (42.1)	
Forns index	8.0 (2.0)	8.3 (2.0)	7.7 (2.1)	0.001
Missing, n (%)	316 (77.6)	1,627 (55.5)	367 (72.8)	
FIB-4 index	4.3 (2.0; 8.6)	4.9 (1.9; 10.1)	4.1 (1.7; 8.9)	0.490
Missing, n (%)	180 (44.2)	921 (31.4)	212 (42.1)	
AFP* (IU/ml)	65.5 (7.8; 1,097.8)	18.0 [4.7; 185.8] IU/ml	35.9 (6.1; 312.0)	<0.001
Missing, n (%)	3 (0.7)	24 (0.8%)	16 (3.2)	
Positive HBeAg†, n (%)	33 (21.3)	504 (21.1%)	63 (21.6)	0.979
Missing, n (%)	252 (61.9)	547 (18.7%)	213 (42.3)	
HBV DNA*, log IU/ml	2.74 (1.00; 5.38)	1.30 (0.84; 2.69)	2.76 (1.00; 5.48)	<0.001
Missing, n (%)	371 (91.2)	1663 (56.7)	307 (60.9)	
HCC treatments, n (%)				
OT only	91 (22.4)	1,071 (36.5)	281 (55.8)	<0.001
LAT only	38 (9.3)	728 (24.8)	60 (11.9)	<0.001
TACE only	251 (61.7)	736 (25.1)	83 (16.5)	<0.001
LT only	0 (0.0)	94 (3.2)	8 (1.6)	<0.001
Combination therapy, n (%)	27 (6.6)	303 (10.3)	72 (14.3)	0.001
OT + others	20 (4.9)	200 (6.8)	65 (12.9)	<0.001
LT + others	0 (0.0)	16 (0.5)	3 (0.6)	0.319
LAT + others	17 (4.2)	210 (7.2)	33 (6.5)	0.078
TACE + others	18 (4.4)	188 (6.4)	46 (9.1)	0.014
Any TACE	269 (66.1)	924 (31.5)	129 (25.6)	<0.001
NA use, n (%)				
Duration of NA use† (year)	0 (0)	2.2 (2.8)	4.7 (3.3)	<0.001
Lamivudine	0 (0.0)	512 (17.5)	59 (11.7)	<0.001
Adefovir dipivoxil	0 (0.0)	273 (9.3)	14 (2.8)	<0.001
Entecavir	0 (0.0)	2,680 (91.4)	488 (96.8)	<0.001
Telbivudine	0 (0.0)	204 (7.0)	23 (4.6)	<0.001
TDF/TAF	0 (0.0)	394 (13.4)	28 (5.6)	<0.001
Any NA	0 (0.0)	2,932 (100)	504 (100)	
Concomitant drugs‡, n (%)				
Oral hypoglycaemic agents	77 (18.9)	609 (20.8)	88 (17.5)	0.315
Metformin	73 (18.5)	609 (21.7)	93 (19.4)	0.427
Insulin	44 (10.8)	300 (10.2)	24 (4.8)	<0.001
Statins	31 (7.6)	417 (14.2)	0 (0.0)	<0.001
NSAID	205 (50.4)	1,572 (53.6)	219 (43.5)	<0.001

Male gender, Positive HBeAg, HCC treatments, and Concomitant drugs were analysed by Chi-square test of independence. Types of NA use were analysed by Fisher's exact test. Duration of NA use, Age, Platelet, Prothrombin time, Albumin, Total Bilirubin, Creatinine, MELD score, Child-Pugh score, and Forns Index were analysed by 1-way analysis of variance. ALT, AST, APRI, FIB-4 index, AFP, and HBV DNA were analysed by Kruskal-Wallis test. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; APRI, aspartate-aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4; LAT, local ablative therapy; LT, liver transplantation; MELD, model for end-stage liver disease; NA, nucleos(t)ide analogue; OT, operation/surgical resection; TACE, transarterial chemoembolisation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

* The *p* value was calculated based on log-transformed values.

† Duration of exposure was measured up to the latest follow-up date. ALT, AST, APRI, FIB-4, and AFP were expressed in median [IQR], whereas other continuous variables were expressed in mean ± SD.

‡ All concomitant medications were represented as binary parameters.

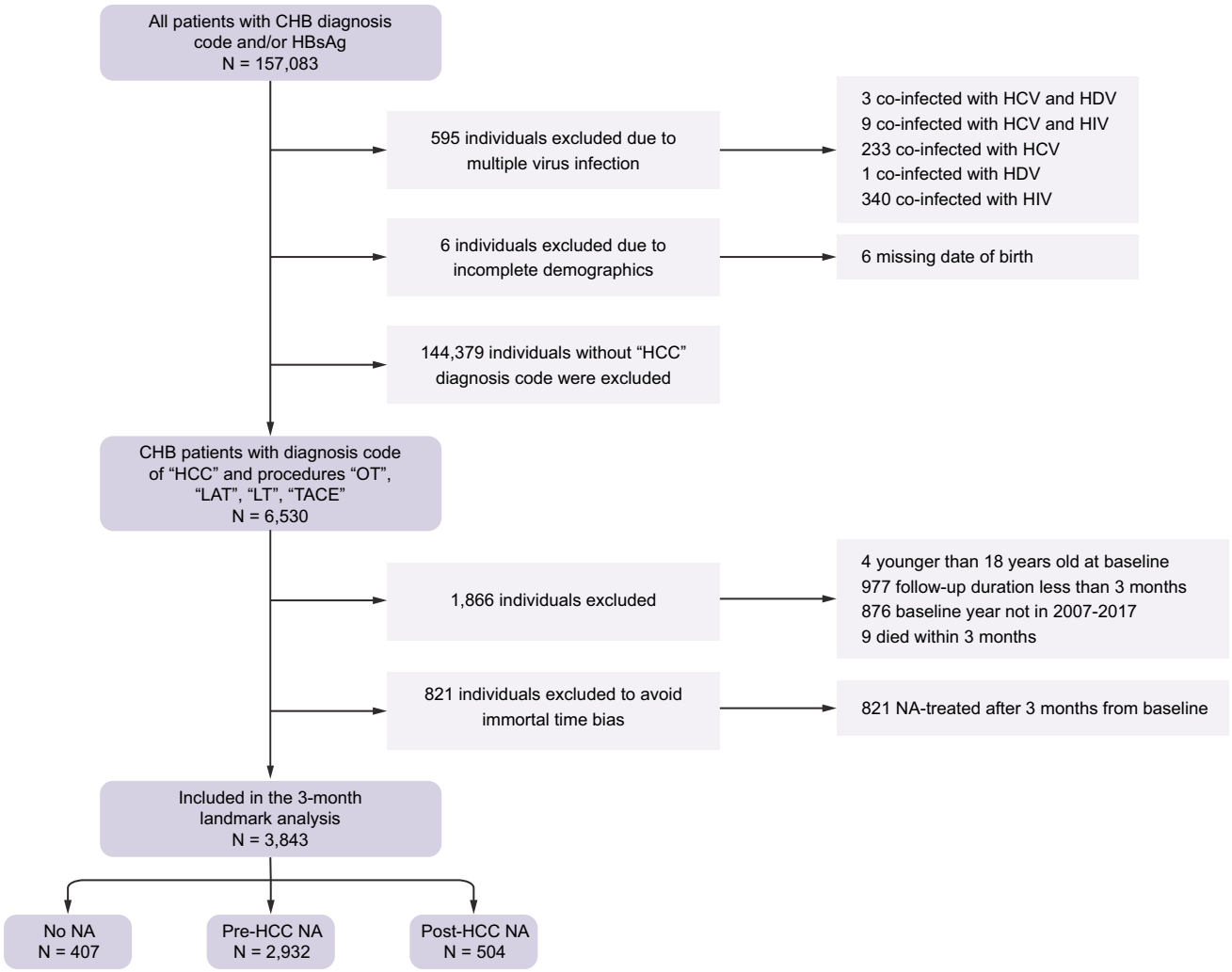


Fig. 1. Selection of patients with CHB-related HCC in the 3-month landmark analysis. CHB, chronic hepatitis B; LAT, local ablative therapy; LT, liver transplantation; NA, nucleos(t)ide analogue; OT, surgical resection; TACE, transarterial chemoembolisation.

Results

Patient characteristics

In this study, 157,083 CHB patients were identified by the ICD-9-CM code of HBV and positive HBsAg. We excluded 595 patients who were co-infected with HCV, HDV, HIV, or various combination of viral hepatitis; and 6 patients whose dates of birth were missing; 6,530 out of 12,103 patients (*i.e.* patients with CHB-related HCC and with complete demographics) were coded with the procedure codes of HCC treatments. We further excluded 1,866 patients from the 3-month landmark analysis, as 977 participants were followed for less than 3 months; 876 patients had their first HCC procedure before 2007 or after 2017, 9 patients died within 3 months, and 4 patients were younger than 18 years at baseline. To avoid immortal time bias, we also eliminated 821 patients who had NA treatment 3 months after baseline. Finally, 3,843 patients were included in the study cohorts (Fig. 1; 407 [no NA], 2,932 [pre-HCC NA], and 504 [post-HCC NA]). In the sensitivity analysis of 6-month landmark analysis (Fig. S1), 3,749 (323 [no NA], 2,785 [pre-HCC NA], and 641 [post-HCC NA]) patients were included. The main reason of no NA treatment was unknown diagnosis of HBV before the presentation with symptomatic HCC (251/407; 61.7%). HCC surveillance was more common with serum AFP assay every 3–4 months and liver ultrasound every 6–12 months (Table S1).

The median (inter-quartile range [IQR]) follow-up durations for no NA, pre-HCC NA, and post-HCC NA cohorts were 1.02 [0.32; 2.42], 2.30 [1.08; 4.27], and 3.01 [1.27; 5.00] years, respectively. Patients in post-HCC NA group were younger and had better liver function (Table 2). The ages of patients were 65.9 ± 11.6, 61.7 ± 10.3, and 58.9 ± 11.2 years in no NA, pre-HCC NA, and post-HCC NA patients, respectively. Forns and fibrosis-4 (FIB-4) indices, 2 indirect serum markers of fibrosis, were the lowest in the post-HCC NA group (Forns: 7.7 ± 2.1; FIB-4: median 4.1 [IQR 1.7; 8.9]). The majority of NA-treated patients had received entecavir (92.2%), followed by lamivudine (16.7%) and TDF (12.3%).

Secular trend of antiviral treatment uptake in HCC patients

Figure 2 illustrates the number of patients with CHB-related HCC who received NA therapy from 2007 to 2017. Overall, the number of patients receiving NA treatment before or after the diagnosis of HCC increased gradually over time, with a sharp increase in 2008 because of change in reimbursement policy. The uptake rate increased from 47.3% (88/186 patients) in 2007 to 64.7%

Table 2. Estimated crude incidence rates and adjusted HRs of death (with 95% CIs) for no NA, pre-HCC NA, and post-HCC NA patients with CHB-related HCC.

		No NA n = 407	Pre-HCC NA n = 2,932	Post-HCC NA n = 504	*p* value
	Follow-up (year)	1.02 (0.32; 2.42)	2.30 (1.08; 4.27)	3.01 (1.27; 5.00)	<0.001
	Median survival* (year)	1.15 (0.38; 2.69)	4.30 (1.76; NA)	4.91 (2.00; NA)	
	No. of events/No. at risk (%)	327/407 (80.3)	1,226/2,932 (41.8)	216/504 (42.9)	<0.001
	Incidence rate (95% CI)	50.4 ([45.1; 56.1)	16.3 (15.4; 17.2)	14.5 (12.6; 16.6)	
All HCC treatments	Cox proportional hazards model				
	Multivariable-adjusted HR (95% CI)	1.88 (1.64; 2.16)	1 (reference)		<0.001
	Multivariable-adjusted HR (95% CI)		1 (reference)	0.88 (0.76; 1.02)	0.095
	IPTW Cox proportional hazards model (with robust sandwich-type variance estimator)				
	PS-weighted and multivariable-adjusted HR (95% CI)	3.05 (2.70; 3.44)	1 (reference)		<0.001
	PS-weighted and multivariable-adjusted HR (95% CI)		1 (reference)	0.90 (0.78; 1.04)	0.161
	IPTW Cox proportional hazards model (with bootstrap variance estimator)				
	PS-weighted and multivariable-adjusted HR (95% CI)	3.05 (2.66; 3.49)	1 (reference)		<0.001
	PS-weighted and multivariable-adjusted HR (95% CI)		1 (reference)	0.90 (0.78; 1.04)	0.156
OT only	Cox proportional hazards model (subgroup analysis)				
	Multivariable-adjusted HR (95% CI)	1.93 (1.41; 2.64)	1 (reference)		<0.001
	Multivariable-adjusted HR (95% CI)		1 (reference)	0.98 (0.77; 1.25)	0.856
LAT only	Multivariable-adjusted HR (95% CI)	1.90 (1.23; 2.93)	1 (reference)		0.004
	Multivariable-adjusted HR (95% CI)		1 (reference)	0.91 (0.60; 1.37)	0.644
TACE only	Multivariable-adjusted HR (95% CI)	1.68 (1.42; 2.00)	1 (reference)		<0.001
	Multivariable-adjusted HR (95% CI)		1 (reference)	0.92 (0.70; 1.21)	0.54
Curative treatment	Multivariable-adjusted HR (95% CI)	1.80 (1.41; 2.28)	1 (reference)		<0.001
	Multivariable-adjusted HR (95% CI)		1 (reference)	0.90 (0.74; 1.09)	0.269
Non-curative treatment	Multivariable-adjusted HR (95% CI)	1.95 (1.65; 2.29)	1 (reference)		<0.001
	Multivariable-adjusted HR (95% CI)		1 (reference)	0.85 (0.67; 1.08)	0.178

Follow-up (year) was analysed by 1-way analysis of variance. No. of events/No. at risk (%) was analysed by chi square test. CHB, chronic hepatitis B; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LAT, local ablative therapy; LT, liver transplantation; NA, nucleos(t)ide analogue; OT, surgical resection; PS, propensity score; TACE, transarterial chemoembolisation.

* NA indicates more than 25% of the participants have not failed in the follow-up period.

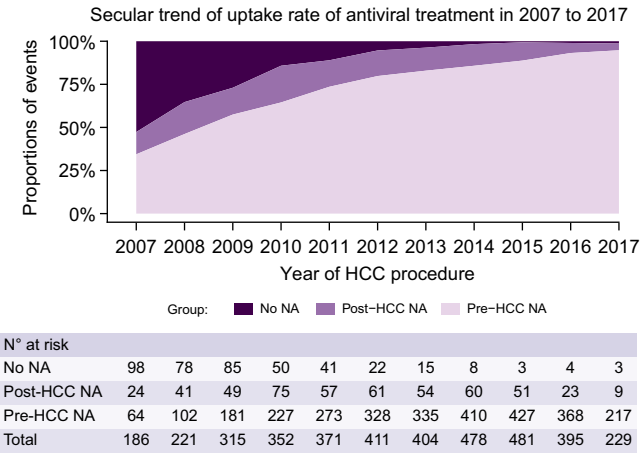


Fig. 2. Secular trend of uptake rate of antiviral treatment in 2007–2017. NA, nucleos(t)ide analogue.

(143/221 patients) in 2008. In 2014, the uptake rate plateaued off and remained unchanged over the next 3 years; over 98% (470/478) patients received NA treatment. In NA-treated patients, the proportion of post-HCC NA decreased from 12.9% in 2007 to 3.9% in 2017 and peaked at 21.3% in 2010. The majority of patients with NA treatment were in the pre-HCC NA group.

Distribution of HCC treatments

Patients with post-HCC NA treatment or pre-HCC NA treatment were more likely to receive HCC treatments of curative intent; 2,008 (68.5%) and 375 (74.4%) patients had surgical resection, liver transplantation, and/or local ablative therapy, respectively. Non-curative HCC treatments were more commonly offered to patients without NA treatment. In addition, 269 (66.1%) patients had TACE or TACE combined with other HCC treatments; 402 (10.5%) patients had combination of HCC treatments (*i.e.* surgical resection ± liver transplantation ± local ablative therapy ± TACE; 27 patients in the no NA group, 303 in the pre-HCC NA group, and 72 in the post-HCC NA group; Fig. 3).

Death

During the study period, the death rate (95% CI) was 50.4 (45.1; 56.1), 16.3 (15.4; 17.2), and 14.5 (12.6; 16.6) per 100 person-years in no NA, pre-HCC NA, and post-HCC NA patients, respectively. The risk factors of death included age (adjusted hazard ratio [aHR] 1.01; 95% CI 1.00–1.01; p <0.001), AFP (aHR 1.35; 95% CI 1.30–1.41; p <0.001), GGT (aHR 1.38; 95% CI 1.17–1.63; p <0.001), hepatic encephalopathy (aHR 1.74; 95% CI 1.25–2.43; p <0.001), and no NA treatment (aHR 1.88; 95% CI 1.64–2.16; p <0.001). The protective factors were high serum albumin (aHR 0.97; 95% CI 0.96–0.98; p <0.001), ALT (aHR 0.78; 95% CI 0.69–0.89; p <0.001), and curative HCC treatment (aHR 0.42; 95% CI 0.37–0.46; p <0.001). The timing of NA treatment (post-HCC *vs.* pre-HCC NA) did not reach statistical significance (aHR 0.88; 95% CI 0.76–1.02; p = 0.095) (Table S2).

Impact of NA treatment in different HCC treatments

The negative impact of no NA treatment was shown across different HCC treatment subgroups. The impact of no treatment was most obvious in the non-curative treatment subgroup (aHR 1.95; 95% CI 1.65–2.29; p <0.001; Table S3) and least but still

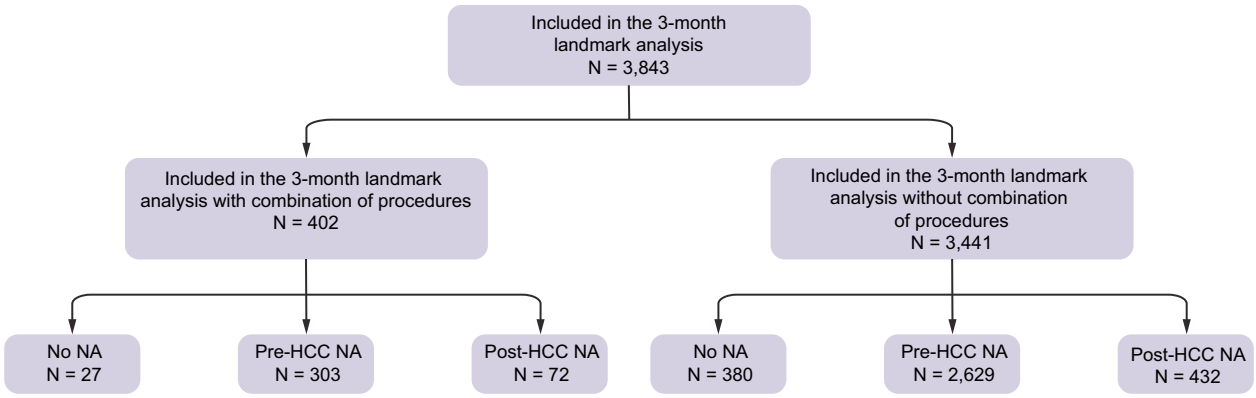


Fig. 3. Combination treatments of patients with CHB-related HCC in the 3-month landmark analysis. CHB, chronic hepatitis B; NA, nucleos(t)ide analogue.

significant in the TACE subgroup (aHR 1.68; 95% CI 1.42–2.00; p <0.001; Table S5). All different HCC treatment subgroups showed consistent results that post-HCC NA treatment had minimal impact on death (aHR ranged from 0.85 to 0.98; p values ranged from 0.178 to 0.856; Table S3–S7). On-treatment complete viral suppression improved overall survival in both pre- and post-HCC NA cohorts (Fig. 4). The protective effect of NA treatment remained after adjusting for pathological characteristics of tumour, namely Barcelona Clinic Liver Cancer grade, tumour size and number, and macrovascular invasion (Table S16).

Sensitivity analysis based on clinical factors

A few key clinical factors influencing survival of patients with HCC or likelihood of benefitting from NA treatment have been included in the sensitivity analysis. Tumour size (aHR 2.16; 95% CI 1.53–3.07; p <0.001), multifocal tumour (aHR 1.92; 95% CI 1.36–2.72; p <0.001), macrovascular invasion (aHR 2.50; 95% CI 1.32–4.73; p = 0.005), and no NA (aHR 3.31; 95% CI 2.18–5.05; p <0.001) were the risk factors of death. Yet, after adjusting for all these tumour characteristics, NA treatment remained a protective factor. The negative impact of no NA treatment is consistently shown across different time periods of HCC diagnosis (*i.e.* 2007–2010, 2011–2014, and 2015–2017). Amongst those who were cirrhotic, the 5-year overall survival rates for Child class A and Child class B plus C were 63% and 36%, respectively, with significant difference between the 2 groups (Fig. S2).

Secondary analysis after PS weighting

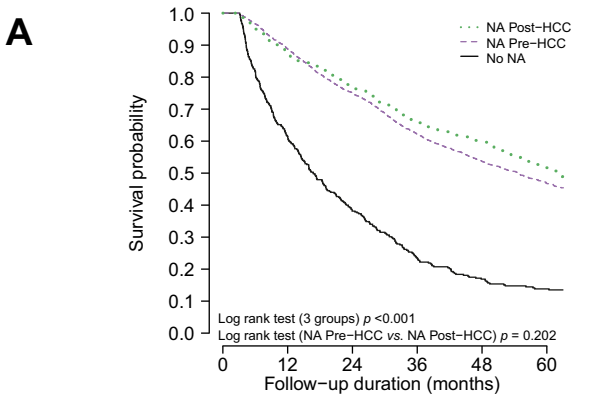
IPTW attained balance on the covariates such that the 3 cohorts had comparable baseline clinical characteristics (Table 3). After IPTW, the effect of NA was stronger when comparing the pre-HCC NA group with the no NA group (PS aHR 3.05; 95% CI 2.70–3.44 by robust estimator, p <0.001; and PS aHR 3.05; 95% CI 2.66–3.49 by bootstrap estimator; p <0.001). In addition, timing of NA (*i.e.* post-HCC NA *vs.* pre-HCC NA) did not significantly contribute to death (PS aHR 0.90; 95% CI 0.78–1.04 by robust estimator; p = 0.161; and PS aHR 0.90; 95% CI 0.78–1.04 by bootstrap estimator; p = 0.156).

Discussion

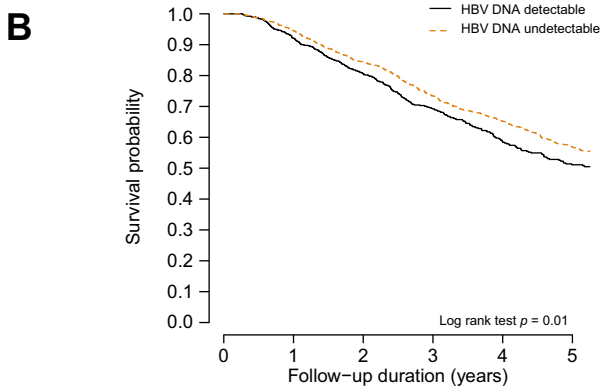
This retrospective territory-wide cohort study illustrates that the secular trend of NA treatment uptake has increased over time. The benefits of NA treatment in patients with HBV-related HCC were observed regardless of whether it was initiated before or after HCC diagnosis. A significant risk reduction in death in NA-treated patients was found consistently in different HCC treatment groups. Whilst the benefit was most obvious in patients who received curative HCC treatments, it was also demonstrated in those treated with TACE.

The relaxation of reimbursement policy for NA treatment, coupled with the introduction of newer NAs over the past decades, accelerated the NA uptake.[20] Patients with low socioeconomic status could not afford long-term NA treatment before it became reimbursed. Only patients with advanced liver disease (*e.g.* cirrhosis and decompensated) were provided NA treatment in the initial days when it was available in Hong Kong; most other patients, even after HCC developed, had to receive NA treatment as a self-financed item. Some patients with significant disease activity (raised ALT and high viral load) had to delay NA treatment, as patients had to have persistently elevated ALT for at least 6 months. Furthermore, serum HBV DNA assay was not routinely provided to patients before 2012, so that not all patients had their viral activity properly assessed to initiate NA treatment appropriately. With the introduction of entecavir in 2008 and TDF in 2014 as reimbursed, HA Drug Formulary first-line antiviral agents had dramatically improved the situation. One possible reason why a minimal, negligible number of patients are still in the no NA group was that their serious health condition hindered the treatment. The median survival of patients in the no NA group was shorter than that of the other 2 groups. Possibly, these patients were more likely to succumb at 1 year after any HCC treatment, and therefore did not receive NA treatment (*i.e.* antiviral drugs are unlikely to make a difference in patients with terminal malignancy).

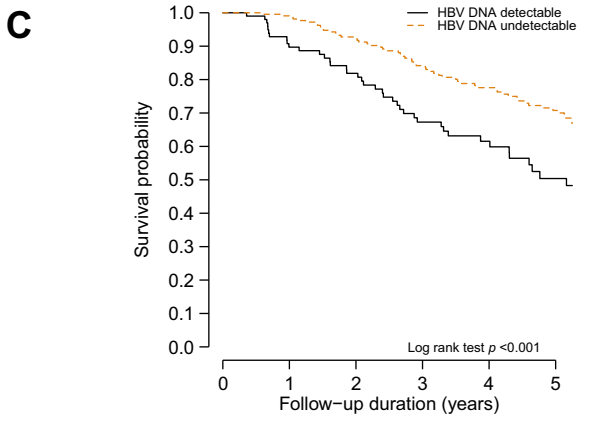
Variation in reimbursement policies in Asian countries resulted in 2 negative impacts, including the conflicting findings on the efficacy of the newer generations of NAs (*i.e.* entecavir and TDF) with those of older generations (*i.e.* lamivudine and adefovir) in improving overall survival and overestimating antiviral treatment survival benefits.[21] Entecavir and tenofovir are the preferable first-line NAs given their high genetic barrier to drug resistance mutations and potent antiviral effects.[22] Logically, it is believed that a better, more potent antiviral treatment would further improve survival in patients with CHB-related HCC.[23] However, 1 large meta-analysis in China (21 studies with 8,072 patients) found that entecavir is not significantly superior to other NAs, including lamivudine or adefovir, in survival benefit



N° at risk						
No NA	407	237	142	82	56	44
Post-HCC NA	2,932	2,438	1,787	1,233	871	607
Pre-HCC NA	504	421	344	266	212	153



N° at risk						
HBV DNA detectable	881	755	553	375	252	172
HBV DNA undetectable	1,208	1,064	832	607	441	303
Survival probability (detectable)		0.89	0.78	0.67	0.56	0.50
Survival probability (undetectable)		0.92	0.82	0.71	0.63	0.55
***p* value**		0.09	0.01	0.03	0.01	0.01



N° at risk						
HBV DNA detectable	101	86	71	51	37	24
HBV DNA undetectable	224	212	182	147	122	94
Survival probability (detectable)		0.89	0.78	0.67	0.60	0.48
Survival probability (undetectable)		0.97	0.90	0.81	0.76	0.67
***p* value**		<0.001	<0.001	<0.001	<0.001	<0.001

Fig. 4. Survival analysis for 3-month landmark analysis. (A) All patients, and (B) and (C) patients with or without complete viral suppression after NA initiation in (B) pre-HCC NA and (C) post-HCC NA cohorts. NA, nucleos(t)ide analogue.

for CHB-related HCC patients after curative treatment.[24] Most patients in China are often prescribed low-cost antiviral drugs, such as generic lamivudine or adefovir. Patients might not have fulfilled the Asian Pacific Association for the Study of the Liver guidelines, or the vast majority of the eligible users had been missed out, and consequently came up with the inconsistent results.[25] Luckily, the majority of NA-treated patients in Hong Kong had the new class of NAs since 2008. We shall anticipate a much better overall survival in patients with antiviral treatment in the future. A recent Taiwanese nationwide study once again confirmed the positive correlation between nucleoside analogue use and overall survival in patients with CHB-related HCC.

To our knowledge, there have been few studies that report the secular trend of antiviral treatment uptake as well as direct comparisons on the effect of different NA initiation timing in overall survival. Most publications stressed only the post-operative antiviral treatment effect on survival in patients with CHB-related HCC.[26] In the present study, we revealed that patients who had received NA treatment before any HCC procedures had better survival than those without NA. Our findings confirmed that NA treatment could significantly improve survival by approximately 68% (minimum aHR across all subgroups [TACE only] 1.68; 95% CI 1.42–2.00) regardless of the HCC treatment types. Based on a study of 2,362 patients who underwent resection for CHB-related HCC (326 patients receiving antiviral treatment; 2,036 not receiving antiviral treatment), Li *et al.* found that the group with antiviral treatment had better survival than the control group (5-year overall survival rate 69.1% *vs.* 56.3%; p <0.001).[27]

Interestingly, post-HCC NA, which may be regarded as a 'delay' in suppressing the virus, had benefited HCC patients in a similar degree to those who had been taking NA before HCC occurrence. This observation gives a positive motivation to doctors and patients that it is never too late to start NA treatment as tertiary prophylaxis of HCC. HBV resulted in an estimated 887,000 deaths in 2016, with more than 70% related to HCC.[28] Increasing NA treatment uptake would substantially reduce death and help achieve the target of reducing mortality by 65% by 2030.[5] This large population-based study echoed the plan on hepatitis elimination.

Our study has the strength of a huge sample size from this territory-wide database, which led to high statistical power and robust estimators because of large sample size, together with robust, well-validated diagnosis and procedures coding. Data from real-life cohorts represent a broader spectrum of patients than those in randomised controlled trials, which increases the applicability of our findings to routine clinical practice. Nonetheless, our study has several limitations, such as its retrospective nature, missing data, and confounding effects in the relationship between risk of death and NA therapy. First, missing data or incomplete data sets would lead to statistical power reduction, biased estimations, and invalid conclusions. MICE was introduced to rectify our analysis. Low imputation error and small prediction differences between imputation models were proven. We hoped that multiple imputations could narrow the uncertainty about missing values, and hence the unnecessary variability. An additional chart review was also done to confirm the validity of HBV and HCC treatments, with an accuracy of 90%. Second, the measured and unmeasured confounding factors may distort the observed association between NA therapy and the risk of death. IPTW was adopted to adjust the potential confounders, such as laboratory parameters and medications in the

Table 3. Comparison of baseline characteristics before and after PS weighting (first imputation).

	Unadjusted				Weighted			
Parameter	**No NA**	**NA pre-HCC**	**NA post-HCC**	**ASMD**	**No NA**	**NA pre-HCC**	**NA post-HCC**	**ASMD**
Age (year)	65.9 (11.6)	61.7 (10.3)	58.9 (11.2)	0.41	63.2 (10.8)	61.7 (10.3)	61.5 (10.4)	0.13
Male gender, n (%)	328 (80.6)	2,402 (81.9)	419 (83.1)	0.03	1,521 (83.9)	2,402 (81.9)	1,846 (83.5)	0.05
Positive HBeAg, n (%)	67 (16.5)	569 (19.4)	93 (18.5)	0.04	333 (18.4)	569 (19.4)	355 (16.1)	0.02
Platelet	173.8 (102.4)	130.7 (65.6)	158.1 (81.2)	0.66	140.1 (70.9)	130.7 (65.6)	137.3 (65.3)	0.18
Albumin	30.8 (6.2)	33.8 (6.1)	31.9 (6.5)	0.49	33.4 (5.9)	33.8 (6.1)	33.5 (6.1)	0.08
Total bilirubin	25.0 (15.8)	27.4 (27.3)	27.1 (21.6)	0.09	25.4 (15.3)	27.4 (27.3)	25.7 (18.6)	0.05
ALT	95.0 (46.0; 201.0)	120.5 (48.0; 271.0)	191.0 (91.8; 376.0)	0.39	101.0 (53.0; 193.0)	120.5 (48.0; 271.0)	135.0 (59.0; 270.4)	0.14
AST	65.0 (35.0; 162.0)	61.0 (33.6; 189.1)	103.0 (38.0; 295.2)	0.25	60.0 (35.0; 153.0)	61.0 (33.6; 189.1)	77.0 (36.0; 216.9)	0.08
AFP	61.8 (7.9; 1,092.0)	18.0 (4.7; 187.8)	35.0 (6.1; 312.0)	0.43	15.0 (5.5; 177.5)	18.0 (4.7; 187.8)	21.8 (5.5; 153.8)	0.11
Curative treatment, n (%)	138 (33.9)	2,008 (68.5)	375 (74.4)	0.74	1,116.2 (61.6)	2,008.0 (68.5)	1,523.5 (69.0)	0.18
Creatinine	87.5 (54.4)	91.8 (66.6)	84.8 (29.3)	0.12	92.3 (73.0)	91.8 (66.6)	85.2 (27.7)	0.1
INR	1.2 (0.2)	1.2 (0.3)	1.3 (0.4)	0.22	1.2 (0.2)	1.2 (0.3)	1.2 (0.3)	0.14
GGT	78.0 (39.0; 152.0)	65.0 (36.0; 128.0)	59.0 (34.0; 110.1)	0.19	69.4 (36.0; 129.0)	65.0 (36.0; 128.0)	64.0 (38.0; 120.0)	0.14
Ascites, n (%)	14 (3.4)	208 (7.1)	11 (2.2)	0.19	80 (4.4)	208 (7.1)	64 (2.9)	0.17
HE, n (%)	0 (0.0)	59 (2.0)	1 (0.2)	0.14	0 (0.0)	59 (2.0)	16 (0.7)	0.14
Insulin, n (%)	44 (10.8)	300 (10.2)	24 (4.8)	0.18	216 (11.9)	300 (10.2)	122 (5.5)	0.09
Metformin, n (%)	73 (17.9)	609 (20.8)	93 (18.5)	0.1	295 (16.3)	609 (20.8)	442 (20.0)	0.05
NSAID, n (%)	205 (50.4)	1,572 (53.6)	219 (43.5)	0.07	865 (47.7)	1,572 (53.6)	969 (43.9)	0.08
OHA, n (%)	77 (18.9)	609 (20.8)	88 (17.5)	0.06	330 (18.2)	609 (20.8)	427 (19.3)	0.08
Statins, n (%)	31 (7.6)	417 (14.2)	4 (0.8)	0.21	121 (6.7)	417 (14.2)	19 (0.9)	0.1

Data are shown as mean (SD), median (IQR), or n (%).
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASMD, absolute standardised mean difference; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HE, hepatic encephalopathy; INR, international normalised ratio; NA, nucleos(t)ide analogue; OHA, oral hypoglycaemic agent; PS, propensity score.

multivariable model. The sensitivity analysis could explain the eventual differences of risk of death amongst patients in the no NA, pre-HCC NA, and post-HCC NA groups. Third, even though we had retrieved all medical records of interested individuals, some patients might be lost to follow-up. Some patients might have the treatments provided by private hospitals, and some patients might have been started on NA before entering the public system, such that CDARS could not capture their clinical data. The true beneficial impact of NA on reducing death might have been underestimated. Fourth, we analysed only all-cause mortalities rather than the liver-related deaths because of the lack of information on the cause of death. Fifth, HBV DNA was not included in any part of this analysis because of the sizeable missing proportion. The strong association between HBV DNA viral load and mortality risk is often reported. Excluding HBV DNA is for the sake of imputation quality and accuracy for further regression models and IPTW. Lastly, the landmark period and definition of combination therapy within a 3-month interval were arbitrary. Our sensitivity analysis proves that findings are robust.

In conclusion, this territory-wide, retrospective cohort study illustrated that the uptake of antiviral treatment in CHB-related HCC patients increased over the past decade. NA treatment, regardless of whether it was initiated before or after HCC diagnosis, improved survival. It is never too late to initiate NA treatment, even after HCC diagnosis, as it would still improve patient survival.

Abbreviations

AFP, alpha-fetoprotein; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; ASMD, absolute standardised mean difference; CDARS, Clinical Data Analysis and Reporting System; CHB, chronic hepatitis B; GGT, gamma-glutamyl transpeptidase; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IPTW, inverse probability of treatment weighting; IQR, inter-quartile range; KS, Kolmogorov-Smirnov; MICE, multivariate imputation by chained equations; NA, nucleos(t)ide analogue; PS, propensity score; TACE, transarterial chemoembolisation; TDF, tenofovir disoproxil fumarate.

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Conflicts of interest

VWS Wong has served as an advisory committee member for 3vbio, AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, and Terns, and a speaker for Bristol Myers Squibb, Echosens, Gilead Sciences, and Merck. He has also received an unrestricted grant from Gilead Sciences. TCFY has served as an advisory committee member and a speaker for Gilead Sciences. HLYC has served as an advisory committee member for AbbVie, APTORUM, Aligos, Arbutus, Hepion, Intellia, Janssen, Gilead, MedImmune, Merck, Roche, Vir Biotechnology, GRAIL, Vaccitech, and VenatoRx, and as a speaker for Mylan, Gilead, and Roche. GLHW has served as an advisory committee member for Gilead Sciences and Janssen, and as a speaker for Abbott, AbbVie, Bristol Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche. She received a research grant from Gilead. The other authors declare that they have no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

VWKH, BWYY, YKT, TCFY, and GLHW had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for the study concept and design. VWKH, BWYY, YKT, TCFY, and GLHW were responsible for data acquisition and analysis. All authors were responsible for data interpretation and drafting and critical revision of the paper for important intellectual content.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2020.100152.

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