Research article

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Baveno VII criteria for recompensation predict transplant-free survival in patients with hepatitis B-related decompensated cirrhosis

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Background & Aims: The latest Baveno VII consensus has provided guidance for identifying patients who have truly recompensated from those with hepatic decompensation. This study aimed to evaluate patients' transplant-free survival in three different stages of cirrhosis.

Methods: All patients with chronic HBV infection and liver cirrhosis treated with oral nucleos(t)ide analogues from March 2006 to December 2022 were identified from a territory-wide database in Hong Kong. Patients with follow-up duration of <1 year were excluded. Participants were classified into three mutually exclusive groups: (1) no decompensated events (*i.e.* compensated group); (2) decompensated events occurred (*i.e.* decompensated group); or (3) decompensated events occurred followed by recompensation according to Baveno VII criteria (*i.e.* recompensated group). A time-dependent Cox proportional hazard model was adopted for evaluation. The follow-up period was 5 years.

Results: A total of 4,701 patients with cirrhosis and HBV who were treated with entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) were identified. During a median follow-up of 5 years (interquartile range 3.7, 5 years), 3,327 (70.8%), 1,347 (29.2%), and 265 (5.6%) patients had compensated, decompensated, and recompensated cirrhosis, respectively, at least once before the end of the study. In the time-dependent multivariable model, the recompensated group had similar transplant-free survival compared with the compensated group (adjusted hazard ratio 1.16; 95% CI 0.72–1.86; $p = 0.536$). The 5-year transplant-free survival rate was 89.3% for the compensated group, whereas it was 76.0% for the recompensated group, reflecting a minimal difference between the two groups.

Conclusions: The clinical significance of recompensation of cirrhosis in improving patient outcomes for individuals with CHB infection was highlighted in this study. Early identification and treatment with nucleos(t)ide analogues might promote hepatic recompensation and thus reduce mortality in patients with CHB.

Impact and implications: The latest Baveno VII consensus introduces the new concept of hepatic recompensation, which refers to the reversal of the structural and functional changes of cirrhosis after removal, cure, or suppression of the aetiology of cirrhosis. It is essential to investigate the transplant-free survival rates of patients who are able to achieve hepatic recompensation, as this has significant implications for the medical resources required to manage liver failure and transplantation. This study features the clinical significance of hepatic recompensation by comparing patient outcomes of those who achieve it to those who do not. The early identification and use of antiviral treatment with nucleos(t)ide analogues is a pivotal strategy to promote hepatic recompensation, which has the potential to significantly reduce mortality rates in patients with chronic HBV infection and ultimately aid in the elimination of hepatitis.

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Introduction

The latest Baveno VII consensus discussed the new concept of hepatic recompensation, which suggests regression of the structural and functional changes of cirrhosis after removal, cure, or suppression of the aetiology of cirrhosis.[1] This is particularly relevant in patients with chronic hepatitis B virus (HBV)

infection, as we now have potent antiviral treatment with nucleos(t)ide analogues (NAs), leading to complete viral suppression in the vast majority, followed by improved necroinflammation and liver fibrosis, and hence reduced risk of hepatic decompensation and hepatocellular carcinoma (HCC).[2,3] A significant proportion of patients who first presented with decompensated cirrhosis would have their liver function improved with NA treatment.[4]

Although the latest Baveno VII recompensation criteria are helpful to identify such patients, the long-term prognosis of patients who recompensated has yet to be defined. For example, it is well known that clinically significant portal hypertension (CSPH) may persist despite recompensation.[5,6] Therefore, the Baveno VII consensus recommends against stopping non-selective beta-blockers (NSBBs), unless there is evidence that CSPH has resolved.[1] It would be crucial to elucidate the transplant-free survival of patients who are capable of achieving hepatic recompensation, which has considerable implications for medical resources needed to manage hepatic decompensation and liver transplantation. Data on the timeframe necessary to consider a patient truly recompensated are also warranted. In this study, we aimed to evaluate patients' survival in three different stages of cirrhosis.

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. CDARS facilitates the retrieval of clinical data captured from different operational systems for analysis and reporting, and provides good quality information to support clinical and management decisions by integrating the clinical data in the data warehouse.[7] It covers the electronic health records, use of medications, and laboratory results from all public hospitals and clinics in Hong Kong and represents data of approximately 80% of the local population.[8] The study protocol was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Study population

All patients with HBV-related cirrhosis treated with first-line potent NAs (*i.e.* entecavir, tenofovir disoproxil fumarate [TDF], and tenofovir alafenamide fumarate [TAF]) between March 2006 and December 2022 were identified. Patients were excluded if they had incomplete demographic data; were <18 years old; were dispensed with lamivudine, adefovir, telbivudine, interferon, or pegylated interferon; had undergone liver transplantation before enrolment; had been followed up for <1 year; and had no available results of HBV DNA.

Compensated cirrhosis was defined by the presence of any diagnosis codes of cirrhosis, portal hypertension, and varices without any diagnosis of decompensating events. Decompensated cirrhosis was defined by the presence of any of the decompensating events. During the study period, subjects were classified into three mutually exclusive groups: group 1 – had a diagnosis of cirrhosis and remained in a compensated cirrhosis state during the study period (*i.e.* compensated group); group 2 – experienced at least one decompensating event during the study period, but did not achieve recompensation (*i.e.* decompensated group); or group 3 – achieved at least one occurrence of recompensation according to Baveno VII criteria during the study period (*i.e.* recompensated group).

Patients were followed until the occurrence of decompensated cirrhosis (in the compensated group), resolution of decompensating events (in the recompensated group), liver transplantation, death, last follow-up date (31 December 2022), or up to 5 years of follow-up, whichever came first (in any group).

Definitions of events

Decompensating events

Decompensating events were defined by ascites, spontaneous bacterial peritonitis, variceal haemorrhage (VH), hepatic encephalopathy (HE), and hepatorenal syndrome according to the *International Classification of Diseases*, 9th edn – clinical modification (ICD-9-CM) codes retrieved from the CDARS. Specifically, the first decompensating events included ascites, VH, and HE, and were defined as the first occurrence of decompensation in each patient. Further decompensating events were defined as non-duplicate decompensating events, including spontaneous bacterial peritonitis, jaundice, and hepatorenal syndrome, that occurred after the first decompensating event.

Removal/suppression/cure of the primary aetiology of cirrhosis

Removal/suppression/cure of the primary aetiology of cirrhosis was indicated by complete viral suppression or HBsAg seroclearance. Complete viral suppression was defined as undetectable serum HBV DNA (<20 IU/ml), while on NA treatment maintained until the last clinic visit. HBsAg seroclearance was defined as loss of HBsAg detectability once or more during the follow-up period.

Stable improvement of liver function tests

Stable improvement of liver function tests, as validated by Wang *et al.*,[9] was defined by a model for end-stage liver disease (MELD) score <10 and/or liver function test within Child–Pugh Class A (albumin >35 g/L, international normalised ratio <1.5, and total bilirubin <34 μmol/L).

Recompensated cirrhosis

Recompensated cirrhosis was defined by partial regression of the structural and functional changes of cirrhosis after removal of the aetiology of cirrhosis as stated in Baveno VII. The recompensation criteria must satisfy these three requirements: (1) attainment of HBsAg seroclearance or complete viral suppression during follow up; (2) absence of decompensating events from the last decompensated state in the next 12 months; and (3) MELD <10 and/or Child–Pugh Class A.

Treatment and follow-up

For the evaluation of transplant-free survival, the baseline date was defined as the earliest date of cirrhosis or decompensating event diagnosis. For the identification of prognostic factors for recompensation, baseline date was defined as the earliest date of decompensating event diagnosis. Demographic data, including sex and date of birth, were captured. Liver and renal biochemistries, virological and haematological parameters, relevant diagnoses and procedures, concomitant drugs, and other laboratory parameters were collected.

Recompensation date was defined as the latest date of the following dates: (1) the earliest date of achievement of HBsAg seroclearance or complete viral suppression during follow up;

(2) the earliest date in the next 12 months when no decompensating events have occurred since the last decompensation; and (3) the earliest date of achieving MELD <10 and/or Child–Pugh Class A.

At baseline, patients were grouped into either compensated or decompensated groups owing to the left-truncated data property; then recompensation emerged during follow up.

Multiple transitions between decompensation and recompensation were possible, for example, if a patient's liver condition has worsened (*i.e.* did not fulfil one of the Baveno VII criteria) after recompensation, he/she would be considered decompensated again. The 'divide-and-conquer' paradigm was applied to define the dates of recurrent decompensation.

Outcome assessment

The primary outcome was transplant-free survival, defined as survival free from all-cause death or liver transplantation. Liver transplantation was identified by the ICD-9-CM codes (V42.7 and 50.59).

Statistical analysis

Data were analysed using Julia (1.7.3; JuliaHub, Cambridge, MA, USA), and R (4.2.0; The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed in mean ± standard deviation or median (interquartile range [IQR]), as appropriate, whereas categorical variables were presented as number (percentage). Qualitative and quantitative differences between subgroups were analysed using Chi-square or Fisher's exact tests for categorical parameters and the one-way ANOVA or Kruskal–Wallis test for continuous parameters, as appropriate.

Inappropriate missing data handling would lead to a faulty conclusion by reducing the statistical power of a study and/or creating biased estimates owing to selection bias. The imputed baseline variables (missing percentage) were fasting glucose (35.1%), hepatitis B e antigen status (32.2%), prothrombin time (25.2%), alpha-foetoprotein (AFP) (12.2%), international normalised ratio (9.8%), platelet counts (3.0%), creatinine (2.6%), total bilirubin (2.4%), alanine aminotransferase (ALT) (2.3%), and albumin (2.3%). ALT, total bilirubin, AFP, and platelet counts at baseline were log-transformed when inserted into the model. These covariates, together with the event indicator were included in the imputation model.[10] All imputed values were constrained within plausible ranges.

Transplant-free survival

The Cox proportional hazard model with a time-dependent covariate (time-dependent model) was adopted to investigate the association between the current stage of cirrhosis and transplant-free survival. Product-limit estimates of survival functions that correspond to stages of cirrhosis were created using the Simon–Makuch method.[11] This method performs similar to the Kaplan–Meier method but is able to accommodate time-dependent covariates. Between-group comparisons were analysed using the Mantel–Byar test. We included male sex, age, platelet counts, creatinine, the occurrence of HCC, and the presence of diabetes as fixed covariates. Stages of cirrhosis (*i.e.* compensation, decompensation, and recompensation) were modelled as time-dependent covariates according to previously stated rules on multiple transitions.

Adjusted hazard ratios (aHRs) with 95% CI were estimated using the Cox proportional hazard model. Schoenfeld's global test was used to test the proportional hazard assumption in all regression models, which did not detect any significant violations. The overall coefficient estimates and standard errors were computed by combining the estimates obtained in each multiple imputation dataset using Rubin's rules. All statistical tests were two-sided. The threshold for statistical significance was set at p <0.05. Sensitivity analysis was performed by excluding non-liver related death. Subgroup analysis was also conducted in patients with or without complete viral suppression.

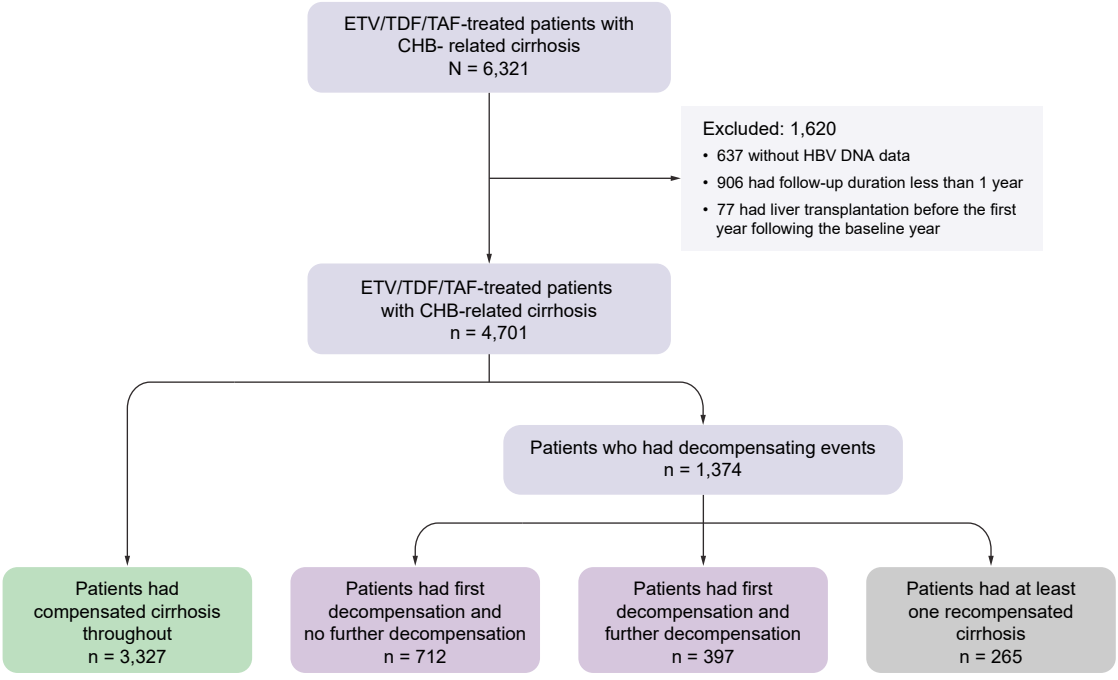


Fig. 1. Patient flowchart.

Table 1. Clinical characteristics of all entecavir (ETV)/tenofovir disoproxil fumarate (TDF)/tenofovir alafenamide (TAF)-treated patients with chronic hepatitis B-related cirrhosis at baseline.

Clinical characteristics	All patients N = 4,701	Compensated cirrhosis[†] n = 3,327	Decompensated cirrhosis[‡] n = 1,109	Recompensated cirrhosis[§] n = 265	*p* value[*]	*p* value[**]	*p* value[***]	*p* value[****]
Follow-up duration (yr)	5 [3.7,5]	5 [4.2,5]	4.7 [2.6,5]	5 [4.4,5]	<0.001	<0.001	0.857	<0.001
Deaths	840 (18)	331 (10)	491 (44)	18 (7)	<0.001	<0.001	0.106	<0.001
Liver transplantation	47 (1)	10 (0)	36 (3)	1 (0)	<0.001	<0.001	0.570	0.005
Duration of first decompensation (yr)	2.5 [1.1,4.0]	/	2.0 [0.4,4.0]	3.0 [2.0,4.0]	/	/	/	<0.001
Duration of first recompensation (yr)	1.1 [0.5,1.9]	/	/	1.1 [0.5,1.9]	/	/	/	/
Demographics[#,¶]								
Age (years)	59.9 ± 11.3	59.3 ± 11.2	60.8 ± 11.4	63.7 ± 11	<0.001	<0.001	<0.001	<0.001
Male sex	3,444 (73)	2,417 (73)	853 (77)	174 (66)	<0.001	0.005	0.012	<0.001
Comorbidities[#,¶]								
Diabetes	568 (12)	111 (3)	375 (34)	82 (31)	<0.001	<0.001	<0.001	0.394
Dyslipidaemia	1,019 (22)	219 (7)	640 (58)	160 (60)	<0.001	<0.001	<0.001	0.423
Hepatocellular carcinoma	390 (8)	132 (4)	229 (21)	29 (11)	<0.001	<0.001	<0.001	<0.001
Hypertension	1,245 (26)	246 (7)	807 (73)	192 (72)	<0.001	<0.001	<0.001	0.936
Decompensating events								
Ascites	1,024 (22)	/	836 (75)	188 (71)	/	/	/	0.162
Gastric variceal bleeding	91 (2)	/	75 (7)	16 (6)	/	/	/	0.671
Hepatic encephalopathy	464 (10)	/	372 (34)	92 (35)	/	/	/	0.738
Hepatorenal syndrome	81 (2)	/	68 (6)	13 (5)	/	/	/	0.467
Oesophageal variceal bleeding	391 (8)	/	320 (29)	71 (27)	/	/	/	0.559
Spontaneous bacterial peritonitis	249 (5)	/	212 (19)	37 (14)	/	/	/	0.049
Laboratory results[††]								
Alpha foetoprotein (μg/L)	4.3 [2.5,10.7]	4.1 [2.5,9.8]	5.3 [2.9,15.2]	4.4 [2.5,10.4]	<0.001	<0.001	0.658	0.011
Missing	497 (11)	282 (8)	174 (16)	41 (15)				
Albumin (g/L)	34.9 ± 7.7	37.4 ± 6.8	29.1 ± 6.4	28.7 ± 6.1	<0.001	<0.001	<0.001	0.385
Missing	127 (3)	101 (3)	23 (2)	3 (1)				
Alanine aminotransferase (IU/L)	38 [26,62.3]	37 [25,62]	41 [28,66.1]	35.5 [24,58]	0.003	0.003	0.206	0.007
Missing	127 (3)	101 (3)	23 (2)	3 (1)				
Creatinine (μmol/L)	87.4 ± 71.8	85.4 ± 64.5	92.4 ± 85.8	91.4 ± 90.4	0.014	0.005	0.160	0.872
Missing	143 (3)	116 (3)	24 (2)	3 (1)				
Total bilirubin (μmol/L)	24.7 ± 33.6	20.3 ± 26.1	35.1 ± 46.4	36.6 ± 40.1	<0.001	<0.001	<0.001	0.634
Missing	130 (3)	104 (3)	23 (2)	3 (1)				
Gamma-glutamyl transferase (IU/L)	128.4 ± 201.4	102.7 ± 152	192.1 ± 273.6	188.1 ± 300.7	<0.001	<0.001	<0.001	0.886
Missing	2,441 (52)	1,722 (52)	583 (53)	136 (51)				
Haemoglobin (g/dl)	12.4 ± 2.8	12.9 ± 2.8	11.5 ± 2.7	11 ± 2.6	<0.001	<0.001	<0.001	0.055
Missing	1,763 (38)	1,302 (39)	370 (33)	91 (34)				
Fasting blood sugar (mmol/L)	6.2 ± 2.3	6.1 ± 2.1	6.5 ± 2.8	6.7 ± 2.9	<0.001	<0.001	<0.001	0.333
Missing	1,646 (35)	1,070 (32)	476 (43)	100 (38)				
International normalised ratio	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.2	1.4 ± 0.3	<0.001	<0.001	<0.001	0.020
Missing	418 (9)	368 (11)	45 (4)	5 (2)				
Prothrombin time (s)	13.4 ± 3	12.7 ± 2.9	14.7 ± 2.8	15.3 ± 2.8	<0.001	<0.001	<0.001	0.002
Missing	751 (16)	635 (19)	90 (8)	26 (10)				
Platelet (× 10^9/L)	131.4 ± 70	140.8 ± 67.9	109.8 ± 72.7	105.7 ± 56.5	<0.001	<0.001	<0.001	0.395
Missing	167 (4)	139 (4)	25 (2)	3 (1)				
Positive HBeAg[§]	709 (22)	543 (22)	148 (24)	18 (12)	0.004	0.425	0.002	<0.001
Missing	1,492 (32)	892 (27)	490 (44)	110 (42)				
Positive HBsAg[§]	3,916 (97)	2,789 (98)	928 (97)	199 (84)	<0.001	0.127	<0.001	<0.001
Missing	655 (14)	475 (14)	151 (14)	29 (11)				
HBV DNA viral load (IU/ml)	308.5 [10,456,225]	100 [10,287,250]	31,250 [20,1,320,000]	668.7 [10,298,597.2]	<0.001	<0.001	0.520	0.004
Positive HBV DNA[§]	1,926 (85)	1,374 (83)	428 (92)	124 (81)	<0.001	<0.001	0.395	<0.001
Missing	2,436 (52)	1,681 (51)	644 (58)	111 (42)				
Triglycerides (mmol/L)	1.1 ± 0.9	1.1 ± 0.9	1.2 ± 0.7	1.2 ± 0.9	0.755	0.457	0.852	0.816
Missing	1,850 (39)	1,213 (36)	526 (47)	111 (42)				
Total cholesterol (mmol/L)	4.2 ± 1.3	4.3 ± 1.2	4.2 ± 1.5	3.9 ± 1.2	<0.001	0.099	<0.001	0.015
Missing	1,840 (39)	1,204 (36)	524 (47)	112 (42)				
LDL-cholesterol (mmol/L)	2.5 ± 0.9	2.6 ± 0.8	2.5 ± 1.1	2.2 ± 0.7	<0.001	0.055	<0.001	0.003
Missing	1,964 (42)	1,300 (39)	549 (50)	115 (43)				
HDL-cholesterol (mmol/L)	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	1.3 ± 0.6	<0.001	0.005	0.001	0.212
Missing	1,988 (42)	1,320 (40)	551 (50)	117 (44)				
Use of drugs[#,¶]								
ACEI	1,007 (21)	662 (20)	274 (25)	71 (27)	<0.001	<0.001	0.012	0.512
Anticoagulant	168 (4)	108 (3)	43 (4)	17 (6)	0.026	0.336	0.015	0.096

(*continued on next page*)

Table 1 (*continued*)

Clinical characteristics	All patients N = 4,701	Compensated cirrhosis[†] n = 3,327	Decompensated cirrhosis[‡] n = 1,109	Recompensated cirrhosis[§] n = 265	*p* value[*]	*p* value[**]	*p* value[***]	*p* value[****]
Antiplatelet	523 (11)	364 (11)	122 (11)	37 (14)	0.321	>0.999	0.014	0.209
ARB	202 (4)	140 (4)	42 (4)	20 (8)	0.015	0.595	0.014	0.011
Beta blocker	1,887 (40)	1,192 (36)	552 (50)	143 (54)	<0.001	<0.001	<0.001	0.240
Calcium channel blocker	96 (2)	40 (1)	41 (4)	15 (6)	<0.001	<0.001	<0.001	0.167
Insulin	428 (9)	252 (8)	140 (13)	36 (14)	<0.001	<0.001	<0.001	0.683
Thiazide diuretics	361 (8)	241 (7)	94 (8)	26 (10)	0.162	0.176	0.137	0.544
Lipid-lowering agent	574 (12)	413 (12)	121 (11)	40 (15)	0.131	0.190	0.224	0.066
OHA	1,075 (23)	696 (21)	309 (28)	70 (26)	<0.001	<0.001	<0.049	0.638
Use of antiviral therapy (ever exposed)[#,¶]								
ETV	4,678 (100)	3,307 (99)	1,106 (100)	265 (100)	0.188	0.233	0.396	0.634
TDF	198 (4)	139 (4)	49 (4)	10 (4)	0.897	0.800	0.874	0.751
TAF	108 (2)	72 (2)	31 (3)	5 (2)	0.433	0.243	0.832	0.537
Severity of cirrhosis								
Child–Pugh score	6 [5,7]	5 [5,6]	7 [6,7]	7 [6,8]	<0.001	<0.001	<0.001	0.112
MELD score	5.5 ± 4.3	4.7 ± 3.9	7.3 ± 4.5	7.6 ± 4.6	<0.001	<0.001	<0.001	0.369

ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; HbA1c, haemoglobin A1c; MELD, model for end-stage liver disease; OHA, oral antihyperglycemic agent.
[†] Patients had compensated cirrhosis throughout.
[‡] Patients had persistent decompensated cirrhosis over study period.
[§] Patients had at least one recompensated cirrhosis over study period.
[#] Binary parameters were expressed as n (%), percentages were based on non-missing data.
[¶] All co-morbidities and use of drugs were represented as binary parameters.
[††] Alpha fetoprotein, Alanine aminotransferase, and HBV DNA viral load were expressed in median [interquartile range].
[*] Chi-square or Fisher's exact tests with Bonferroni correction compared all three groups of patients.
[**] Chi-square or Fisher's exact tests with Bonferroni correction compared patients with compensated cirrhosis and patients with persistent decompensation.
[***] Chi-square or Fisher's exact tests with Bonferroni correction compared patients with compensated cirrhosis and patients with at least one recompensation.
[****] Chi-square or Fisher's exact tests with Bonferroni correction compared patients with persistent decompensation and patients with persistent decompensation.

Results

Baseline characteristics

We identified 6,321 individuals who had cirrhosis and were treated with entecavir, TDF and/or TAF; 1,620 were excluded according to the inclusion and exclusion criteria (Fig. 1). Eventually, 4,701 patients with HBV-related cirrhosis receiving first-line potent NAs were included for analysis. Of these patients, 3,327 (71%) had compensated cirrhosis, 1,109 (24%) had persistent decompensated cirrhosis, and 265 (6%) patients had experienced at least one episode of recompensated cirrhosis during the study period. At baseline, the mean age was 59.9 ± 11.3 years; 3,444 (73%) patients were male; 4,678 (>99%), 198 (4%), and 108 (2%) patients were first treated with entecavir, TDF, and TAF, respectively. Ascites (1,024, 22%), HE (464, 10%), and oesophageal variceal bleeding (391, 8%) were the most common decompensated events (Table 1). HCC was more prevalent in patients with decompensated cirrhosis (2329, 21%) compared with patients with compensated cirrhosis (132, 4%) or recompensated cirrhosis (29, 11%). Patients with compensated cirrhosis had lower mean MELD scores (4.7 ± 3.9) and median Child–Pugh scores (5 [5, 6]) compared with their counterparts, whereas patients had persistent decompensation (7.3 ± 4.5 and 7 [6, 7], respectively) and patients had at least one recompensation (7.6 ± 4.6 and 7 [6, 8]) had comparable scores.

Transplant-free survival

At a median (IQR) follow-up of 5 (3.7,5) years, 840 (18%) patients died, of which 331 (10%) were from the compensated group, 491 (42%) from the decompensated group, and 18 (8%) from the recompensated group. Additionally, 47 (1%) patients had undergone liver transplantation during follow-up, with 10 (0.3%) from the compensated group, 36 (3%) from the decompensated group, and one (0.5%) from the recompensated group. Among 331 compensated patients who died, 171 (52%) deaths were liver-related. The main causes of liver-related deaths were HCC (134, 78%) and cirrhosis (14, 8%) (Table 2). Among 491 decompensated patients who died, 311 (63%) deaths were liver-related. The main causes of liver-related deaths were HCC (195, 63%) and cirrhosis (60, 19%). Among 18 recompensated patients who died, eight (44%) deaths were liver-related. The main causes of liver-related deaths were HCC (5, 63%) and cirrhosis (2, 25%) (Table 3). The 2-, 3-, and 5-year transplant-free survival were 94% (94–95%), 89% (88–90%), and 80% (78–81%), respectively. The transplant-free survival of compensated group (3-, 5-year transplant-free survival: 94.1% [93.2%, 94.8%], 89.3% [88.2%, 90.4%]) was better than that of the recompensated group (3-, 5-year transplant-free survival: 87.5% [46.5%, 97.7%], 76.0% [51.5%, 89.3%]) and decompensated group (3-, 5-year transplant-free survival: 72.5% [69.7%, 75.0%], 51.3% [48.3%, 54.3%]) at all time points during the study period (Fig. 2). On the time-dependent multivariable analysis, with the group membership being a time-dependent factor, patients in the recompensated group had a slightly higher risk of transplant-free survival compared with the compensated group, although the difference was not statistically significant (aHR [95% CI] 1.16 [0.72, 1.86], $p = 0.536$). Age, high level of creatinine, presence of HCC at baseline, and cirrhosis decompensation were the risk factors of transplant-free mortality (Table 4).

Sensitivity analysis by excluding non-liver related deaths from the time-dependent multivariable Cox regression model was conducted to ensure the robustness of our findings. Male sex (aHR 1.44 [1.15, 1.80], $p = 0.002$), older age (aHR 1.02 [1.01, 1.03], p <0.001), lower platelet count (aHR 0.62 [0.43, 0.91], $p = 0.014$), and presence of HCC at baseline (aHR 4.31 [3.55, 5.24], p <0.001) remained significant risk factors for transplant-free survival (Table 5). In addition, decompensated cirrhosis was associated with an approximate sixfold higher risk of transplant-free survival (aHR 6.10 [5.02, 7.40], p <0.001) compared with compensated cirrhosis, whereas the association between recompensated

Table 2. Death and liver transplantation outcomes in patients with compensated, decompensated, and recompensated chronic hepatitis B-related cirrhosis at the end of follow-up. Data are presented as n (%).

	Compensated n = 3,327	Decompensated n = 1,159	Recompensated n = 215
All-cause deaths	331 (10.0)	491 (42.4)	18 (8.4)
Liver transplantation	10 (0.3)	36 (3.1)	1 (0.5)

Table 3. Death numbers and causes of liver-related deaths in patients within the compensated, decompensated, and recompensated cirrhosis groups.

	Compensated n = 331	Decompensated n = 491	Recompensated n = 18
Liver-related deaths	171 (51.7)	311 (63.3)	8 (44.4)
Causes of liver-related deaths			
Cirrhosis	14 (8.2)	60 (19.3)	2 (25)
Hepatocellular carcinoma	134 (78.4)	195 (62.7)	5 (62.5)
Hepatic failure	20 (11.7)	46 (14.8)	1 (12.5)
Hepatitis	3 (1.8)	10 (3.2)	0 (0)

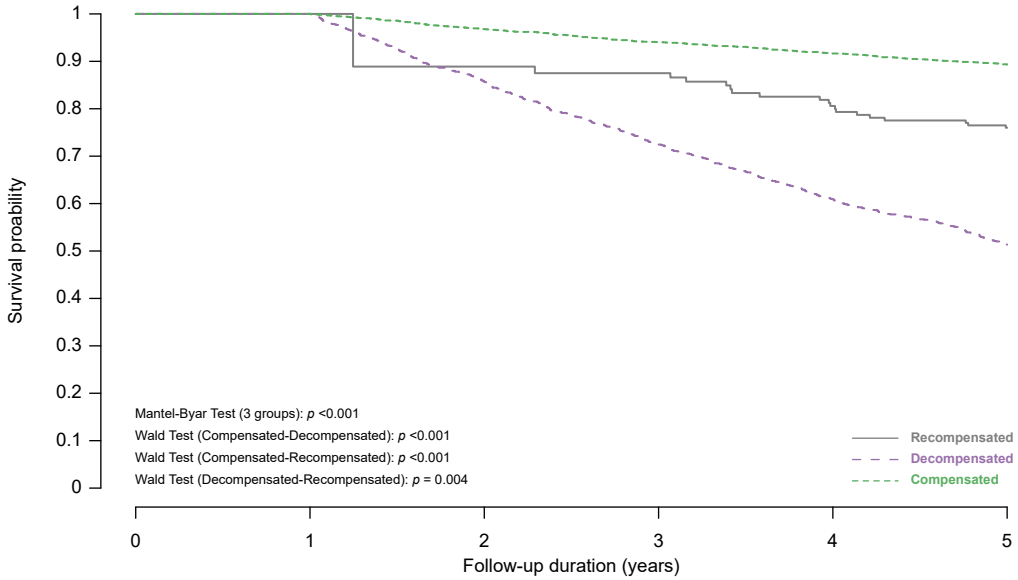
Data are presented as n (%).

cirrhosis and transplant-free survival was not statistically significant (aHR 1.26 [0.64, 2.48], $p = 0.514$). These findings suggest that cirrhosis decompensation is a significant risk factor of poor transplant-free survival even after excluding non-liver related deaths.

Subgroup analysis for viral suppression was performed, in view of the fact that complete viral suppression is a prerequisite to be defined as recompensation (Table 6). Results on incomplete viral suppression subgroup in time-dependent analysis showed that patients in the recompensated group had lower risk of transplant-free mortality, yet without reaching statistical significance (aHR 0.77 [0.37, 1.58], $p = 0.473$). However, it should be noted that the true effect may be masked by the limited sample size of incomplete viral suppression subgroup (n = 1,834).

Recompensation rate, death, and liver transplantation in patients with more severe liver disease

Table 7 shows that 29 (7.4%) patients with HCC at baseline had recompensation, compared with 236 (5.5%) patients without HCC. The incidence rate of was higher in patients with HCC (20.9 recompensation per 1,000 person-years [95% CI] [14.1, 29.9]) compared with those without HCC (12.9 recompensation per 1,000 person-years [95% CI] [11.3, 14.7]). A higher proportion of patients with HCC died during the study period (198, 50.8%) compared with those without HCC (642, 14.9%). The incidence rate of liver-related death was also higher in patients with HCC (135.1 deaths per 1000 person-years [95% CI] [116.9, 155.3]) compared with those without HCC (34.4 deaths per 1000 person-years [95% CI] [31.8, 37.1]). The incidence rate of liver



Number of Deaths						
Recompensated	0	0	1	2	11	19
Decompensated	0	0	152	299	426	527
Compensated	0	0	115	205	277	341

Fig. 2. Survival analysis of different stages of cirrhosis. Pairwise comparisons were performed using the univariate time-dependent Cox regression's Wald test results with Bonferroni correction to compare pairwise differences in transplant-free survival among patients with different cirrhosis stages as a time-dependent covariate in the model. The level of significance was set at p <0.05 divided by the number of pairwise comparisons performed. Mantel-Byar test was used to compare overall differences in transplant-free survival among patients with different cirrhosis stages. The analysis was conducted as a stratified log-rank test, which adjusts the effect of an intermediate state in the transition from one stage to another. The level of significance was set at p <0.05 for the overall comparison.

Table 4. Regression analysis.

Covariates	Multivariable aHR [95% CI]	*p* value
Male sex	1.172 [0.998,1.376]	0.054
Age	1.033 [1.027,1.040]	<0.001
Platelet count	0.636 [0.471,0.859]	0.003
Creatinine	1.001 [1.000,1.002]	0.002
Positive HBeAg	1.074 [0.876,1.317]	0.492
HCC	2.913 [2.468,3.438]	<0.001
Diabetes	1.083 [0.919,1.278]	0.342
Compensated cirrhosis[†]	Referent	
Decompensated cirrhosis	4.650 [4.001,5.404]	<0.001
Recompensated cirrhosis	1.161 [0.724,1.864]	0.536

Main analysis, transplant-free survival as primary outcome. Multivariable analysis on factors associated with liver transplantation and/or all-cause death by time-dependent Cox proportion hazard model.
[†] Different stages of cirrhosis were analysed as the time-dependent covariate.

Table 5. Regression analysis.

Covariates	Multivariable aHR [95% CI]	*p* value
Male sex	1.435 [1.145,1.798]	0.002
Age	1.021 [1.013,1.030]	<0.001
Platelet count	0.623 [0.427,0.908]	0.014
Creatinine	0.999 [0.997,1.001]	0.229
Positive HBeAg	1.035 [0.799,1.341]	0.794
HCC	4.311 [3.546,5.241]	<0.001
Diabetes	1.004 [0.814,1.238]	0.970
Compensated cirrhosis[†]	Referent	
Decompensated cirrhosis	6.096 [5.021,7.401]	<0.001
Recompensated cirrhosis	1.255 [0.635,2.478]	0.514

Sensitivity analysis on factors associated with liver transplantation and/or liver-related death. Multivariable analysis on factors associated with liver transplantation and/or all-cause death by time-dependent Cox proportion hazard model.
[†] Different stages of cirrhosis were analysed as the time-dependent covariate.

transplantation was higher in patients with HCC (6.1 cases per 1000 person-years [95% CI] [2.8, 11.7]) compared with those without HCC (2.0 per 1000 person-years [95% CI] [1.4, 2.8]).

Recompensation rate in patients with or without new-onset VH or HE

A total of 934 (19.9%) patients had new-onset VH or HE during follow-up. Similar numbers of patients achieved recompensation in the presence or absence of new-onset VH or HE, with a recompensation rate ratio of 5.06 to 1 for patients with VH or HE compared with those without any of those. The incidence rate estimate per 1,000 person-years in patients with HCC and patients without HCC were 41.4 [35.0, 48.7] and 7.4 [6.1, 8.8], respectively (Tables 7 and 8).

Subgroup analysis of patients with persistent decompensation

Among the 1,109 (23.6%) patients who had persistent decompensation, 712 (64.2%) did not experience any further decompensating event. The two most common first decompensating events were ascites (240, 60.5% in patients with further decompensation; 435, 61.1% in patients without further decompensation) and VH (82, 20.7% in patients with further decompensation; 205, 28.8% in patients without further decompensation), regardless of further decompensation status. However, patients who experienced further decompensation were more likely to develop spontaneous bacterial peritonitis (165, 41.6%) and hepatic encephalopathy (161, 40.6%) as subsequent decompensating events.

Discussion

This was the first territory-wide real-world cohort study to establish the clinical significance of hepatic recompensation, a new concept in the era of potent antiviral treatment with NAs which often lead to complete viral suppression and hence improvement in liver function. Our study found no statistically significant difference in transplant-free survival between the recompensated and compensated groups. However, these findings suggest that achieving hepatic recompensation may confer a similar survival advantage as maintaining compensated liver function. Our results have important implications for the management of patients with cirrhosis and highlight the need for continued monitoring and treatment to prevent disease progression. Further research with larger sample sizes is needed to confirm these findings and explore other potential factors that may impact transplant-free survival.

A recent prospective study demonstrated a very high rate of complete viral suppression in 92% and hence hepatic recompensation in 60% of 283 subjects with HBV-related cirrhosis after 120 weeks of entecavir treatment.[9] The Baveno VII definition of recompensation was validated by these investigators with

Table 6. Regression analysis.

	Incomplete viral suppression[†]		Complete viral suppression[‡]	
Covariates	Multivariable aHR [95% CI]	*p* value	Multivariable aHR [95% CI]	*p* value
Male sex	1.182 [0.941,1.486]	0.152	1.158 [0.731,1.833]	0.534
Age	1.040 [1.030,1.049]	<0.001	1.046 [1.024,1.067]	<0.001
Platelet count	0.615 [0.403,0.937]	0.024	0.922 [0.360,2.361]	0.865
Creatinine	1.002 [1.001,1.002]	<0.001	1.001 [0.999,1.003]	0.421
HCC	2.874 [2.261,3.653]	<0.001	1.795 [0.970,3.321]	0.066
Diabetes	1.175 [0.923,1.495]	0.191	0.711 [0.401,1.260]	0.246
Compensated cirrhosis[§]	Referent			
Decompensated cirrhosis	3.496 [2.828,4.323]	<0.001	10.689 [6.065,18.839]	<0.001
Recompensated cirrhosis	0.766 [0.370,1.584]	0.473	1.198 [0.397,3.615]	0.750

Subgroup analysis in patients with available baseline HBV DNA, transplant-free survival is of interest. Patients who had available baseline HBV DNA data were included in the subgroup analysis. Multivariable analysis on factors associated with liver transplantation and/or all-cause death by time-dependent Cox proportion hazard model.
HCC, hepatocellular carcinoma.
[†] Patients who had baseline detectable HBV DNA viral load or detectable HBsAg were included in the incomplete viral suppression group; 1,926 patients were in the incomplete viral suppression subgroup.
[‡] Patients who had baseline undetectable HBV DNA viral load were included in the complete viral suppression group; 339 patients were in the complete viral suppression subgroup.
[§] Different stages of cirrhosis were analysed as the time-dependent covariate.

Table 7. Summary of recompensation, death and liver transplantation rates in various subgroups with or without more severe liver disease at baseline.

Severe liver disease	HCC	
Subgroup	**With HCC n = 390**	**Without HCC n = 4,311**
Recompensation		
Number of recompensation cases	29 (7.4)	236 (5.5)
Time to recompensation from first diagnosis of cirrhosis, median [IQR]	3.23 [2.44, 4.03] years	3.01 [2.02,3.95] years
Incidence rate per 1,000 person-years [95% CI]	20.9 [14.1, 29.9]	12.9 [11.3, 14.7]
Death		
Number of deaths	198 (50.8)	642 (14.9)
Liver-related deaths	160 (41.0)	330 (7.7)
Incidence rate per 1,000 person-years [95% CI]	135.1 [116.9, 155.3]	34.4 [31.8, 37.1]
Liver transplantation		
Number of liver transplantations	9 (2.3)	38 (0.9)
Incidence rate per 1,000 person-years [95% CI]	6.1 [2.8, 11.7]	2.0 [1.4, 2.8]

Data are presented as n (%) unless otherwise indicated.
HCC, hepatocellular carcinoma.

Table 8. Summary of recompensation, death, and liver transplantation rates in various subgroups with or without new-onset VB or HE at baseline.

Severe liver disease	VB or HE	
Subgroup	**With VB or HE n = 934**	**Without VB or HE n = 3,767**
Recompensation		
Number of recompensation cases	147 (15.7)	118 (3.1)
Time to recompensation from first diagnosis of cirrhosis, Median [IQR]	2.76 [1.93, 3.93] years	3.23 [2.30, 4.16] years
Incidence rate per 1,000 person-years [95% CI]	41.4 [35.0, 48.7]	7.4 [6.1, 8.8]
Death		
Number of deaths	330 (35.3)	510 (13.5)
Liver-related deaths	226 (24.2)	264 (7.0)
Incidence rate per 1,000 person-years [95% CI]	86.4 [77.4, 96.3]	31.2 [28.6, 34.1]
Liver transplantation		
Number of liver transplantations	26 (2.8)	21 (0.6)
Incidence rate per 1,000 person-years [95% CI]	6.8 [4.4,10.0]	1.3 [0.8, 2.0]

Data are presented as n (%).
HE, hepatic encephalopathy; VB, variceal haemorrhage.

laboratory-based criteria, namely MELD score <10, and/or serum albumin, total bilirubin, and INR within Child–Pugh A (*i.e.* serum albumin above 35 g/L, total bilirubin below 34 μmol/L, and INR below 1.5).[9] These laboratory-based criteria are helpful and user friendly, as they have provided objective and readily-available criteria whenever the patients have their laboratory parameters reassessed.

Untreated patients with decompensated HBV-related cirrhosis are known to have a grave prognosis, with a 5-year survival rate as low as 14–35%.[4,12] Potent NAs have revolutionised the outcome of patients with decompensated HBV-related cirrhosis. A multicentre study of more than 1,000 patients with HBV-related cirrhosis (291 untreated from historical cohort, 797 treated with TDF) unequivocally demonstrated an impressively reduced risk of HCC (aHR 0.46), decompensating events (aHR 0.28), and death or liver transplantation (aHR 0.06) in the treated group.[13] Risk of decompensation may further decrease over time after functional cure of HBV.[14] Hence the novel HBV treatment for functional cure currently under development may bring more hepatic recompensation over time.[15]

This new concept of recompensation emphasises the importance of removal, suppression or cure of the aetiology of cirrhosis; this would be most applicable in chronic viral hepatitis as potent antiviral treatments are available.[16,17] We confirmed the fact that CSPH may persist despite recompensation, fortunately with risk reduced by nearly 75%, and hence most of our patients continued NSBBs throughout the follow-up period. With such a conservative approach, only one-fifth of our patients had new-onset VH or HE. It also took longer time to recompensation if the first decompensation event was VH (1.75 years), compared with those with the first decompensation event as HE (1.37 years). A recently sequential application of von Willebrand factor antigen to platelet ratio (VITRO) for individuals who were unclassifiable with regard to CSPH by Baveno VII criteria may contribute by reducing the proportion of 'unclassifiable' patients and hence refined prognostication.[18]

In this study, the primary statistical challenge was to accurately evaluate the relationship between transplant-free survival and recompensation in patients with cirrhosis. The data on transitions between stages of cirrhosis were limited, which made it challenging to accurately estimate the effect of recompensation on transplant-free survival. To address this limitation, we utilised a time-dependent model, which allowed us to assess the effect of recompensation on different stages of cirrhosis over time. However, the results of this model may have been influenced by the relatively small number of patients who experienced decompensation during the follow-up period.

The strength of our study includes the large sample size, which is by far the largest real-life cohort study of HBV cirrhosis, with close to 5,000 patients in total. CDARS provides robust demographic data, diagnosis coding system and death information, complete serial laboratory parameters and drug

information which facilitated the analysis of the impact of co-morbidities, use of medications, and clinical events. Data from real-life cohorts represent a wider spectrum of patients than those from randomised controlled trials, in which patients with multiple co-morbidities are often excluded. Findings from real-life cohorts are thus more readily applicable to routine clinical practice.

Nonetheless, our study also had a few limitations. First, our study may be influenced by biases stemming from missing data and irregular laboratory measurements, which are common in registry studies. While CDARS serves as a comprehensive and dependable data source, there remains the possibility of reporting bias, which could have impacted the quality of our findings. Nonetheless, the large size of our cohort can help to mitigate these biases to some extent. Additionally, certain laboratory assays such as serum HBV DNA may exhibit variability across institutions, operators, and time periods. Fortunately, all public virology laboratories in Hong Kong adopted very similar assays, for example, the Roche COBAS® AmpliPrep/COBAS® TaqMan® HBV Test v2.0 is used for measuring serum HBV DNA. Also, the detection limit and technology of HBV DNA has changed significantly, particularly in a few landmark years: 2003, when the detection limit was lowered to 2,000 IU/ml, and 2010–11, when the detection limit was further lowered to 10–20 IU/ml. Second, we might have missed some co-morbidities of milder severity as a result of missed coding, such as hypertension, diabetes mellitus, cardiovascular disease, early-stage chronic kidney disease, etc. In clinical practice, different criteria may be used to make diagnoses, which can affect how the information is coded in the computer system. To address this, we looked at more specific codes and the use of other drugs for co-morbidities that do not depend solely on diagnosis codes. Fourth, ascertainment bias may affect the reliability of the study owing to inaccurate entry of all hepatic events; however, the use of single ICD-9-CM codes in CDARS for the diagnosis of key events such as HCC was previously validated to be 99% accurate when referenced to clinical, laboratory, imaging, and endoscopy results from electronic medical records.[2] Fifth, the exact time of HBV diagnosis could be earlier than we identified as some laboratory results for viral markers came from private laboratories before patients entered the public healthcare system; diagnosis coding was also not mandatory before 2008. Sixth, other unmeasured or uncaptured factors might have confounded the results. Finally, while the CDARS registry is an invaluable resource because of its large cohort size, it is important to highlight that using such a registry as a study database comes with its own limitations. Specifically, it is susceptible to reporting bias, as it is typically utilised by everyday physicians who may inadvertently introduce biases in their reporting.

In summary, this territory-wide real-world cohort study to establish the clinical significance of hepatic recompensation, which is linked to improved patient outcome compared with those who failed to achieve hepatic recompensation. Our findings support the early identification and use of antiviral treatment with NAs to facilitate hepatic recompensation. This would contribute to hepatitis elimination by significantly reducing mortality in patients with chronic HBV infection.

Abbreviations

AFP, alpha-foetoprotein; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; CDARS, Clinical Data Analysis and Reporting System; CSPH, clinically significant portal hypertension; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; ICD-9-CM, International Classification of Diseases 9th edition clinical modification; IQR, interquartile range; MELD, model for end-stage liver disease; NAs, nucleos(t)ide analogues; NSBBs, non-selective beta-blockers; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VH, variceal haemorrhage.

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Conflicts of interest

GLHW has served as an advisory committee member for Gilead Sciences and Janssen. She has also served as a speaker for Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead, and Janssen. VWSW has served as an advisory committee member for 3V-BIO, AbbVie, Allergan, Echosens, Gilead Sciences, 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 a research grant from Gilead Sciences. HLYC is an advisor for Aligos, Aptorum, Arbutus, Janssen, Gilead, GSK, Roche, Vaccitech, Vir Biotechnology, and Viron Therapeutics; and a speaker for Gilead, Roche, and Viatris. TCFY has served as an advisory committee member and a speaker for Gilead Sciences.

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

Authors' contributions

Full access to all of the data in the study and responsibility for the integrity of the data and accuracy of the data analysis: VWKH, GLHW, YKT, MSML, TFY, TCFY. Responsible for the study concept and design: all authors. Acquisition and analysis of data: VWKH, GLHW, YKT, MSML, TFY, TCFY. Responsible for the interpretation of data, drafting, and critical revision of the manuscript for important intellectual content: all authors.

Data availability statement

The data that support the findings of this study are available from the Clinical Data Analysis and Reporting System managed by the Hospital Authority, Hong Kong. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from GLHW with the permission of the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100814.

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Author names in bold designate shared co-first authorship

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