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# Severe hepatitis B flares with hepatic decompensation after withdrawal of nucleos(t)ide analogues: A population-based cohort study

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## Summary

**Background:** Finite nucleos(t)ide analogue (NUC) therapy has been proposed as an alternative treatment strategy for chronic hepatitis B (CHB).

**Aim:** To quantify the incidence of severe hepatitis flares following NUC cessation in everyday clinical practice.

**Methods:** This population-based cohort study enrolled 10,192 patients (male 71.7%, median age 50.9 years, cirrhosis 10.7%) who had received first-line NUCs for at least 1 year before discontinuing treatment. The primary outcome was severe flare with hepatic decompensation. We used competing risk analyses to assess event incidences and associated risk factors.

**Results:** During a median follow-up of 2.2 years, 132 patients developed severe flares with hepatic decompensation, yielding a 4-year cumulative incidence of 1.8% (95% confidence interval [CI], 1.5%–2.2%). Significant risk factors were cirrhosis (adjusted sub-distributional hazard ratio [aSHR], 2.74; 95% CI, 1.82–4.12), manifestations of

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portal hypertension (aSHR, 2.46; 95% CI, 1.45–4.18), age (aSHR, 1.21 per 10 years; 95% CI, 1.03–1.42) and male sex (aSHR, 1.58; 95% CI, 1.04–2.38). In patients without cirrhosis or portal hypertension ($n = 8863$), the 4-year cumulative incidence of severe withdrawal flares stood at 1.3% (95% CI, 1.0%–1.7%). For those patients with available data confirming adherence to the standard stopping rules ($n = 1274$), the incidence was 1.1% (95% CI, 0.6%–2.0%).

**Conclusions:** Severe flares with hepatic decompensation were observed in 1%–2% of patients with CHB after stopping NUC therapy in daily practice. Risk factors included older age, cirrhosis, portal hypertension and male sex. Our findings argue against NUC cessation as part of routine clinical care.

## 1 | INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a serious global public health problem.[1] In the management of patients with chronic hepatitis B (CHB), treatment with nucleos(t)ide analogue (NUC) has been shown to improve clinical outcomes,[2] but continuous treatment is usually required to sustain viral inhibition.[3] Seroclearance of hepatitis B surface antigen (HBsAg) predicts durable remission off NUC and may serve as the treatment endpoint.[4] Nonetheless, it rarely occurs with current regimens[5] and long-term to indefinite treatment is usually recommended.[6]

In view of various concerns such as prolonged drug exposure, medication adherence and expense for a treatment course that could be lifelong, a finite strategy was put forth to allow NUC withdrawal prior to HBsAg seroclearance.[7] Additionally, a higher chance of HBsAg seroclearance was reported in patients who stopped NUC than in those who continued the treatment.[8,9] However, viral replication almost always reactivates and often leads to hepatitis flares.[10,11] While an episode of HBV flare-up might be self-limited or even conducive to HBsAg seroclearance,[9,12] it could progress to liver failure and result in fatality.[9,13] Risks of these serious outcomes following treatment withdrawal need to be quantified to inform the decision of stopping or continuing NUC therapy.

Existent literature on the serious consequences of withdrawal flares remained limited, as recently shown in a systematic review.[11] Available data did not permit estimation of the event incidences and/or identification of risk factors for serious clinical outcomes, to which sample size and event number were crucial.[14] In order to address the knowledge gap, we analysed a national healthcare database to quantify the incidences of severe flares with hepatic decompensation and subsequent mortality in patients with CHB who stopped NUC therapy. Besides, associated risk factors were explored.

## 2 | METHODS AND MATERIALS

### 2.1 | Study design and setting

This is a population-based cohort study based on data retrieved from the National Health Insurance Laboratory Databases (NHILD) in Taiwan,[15] where the National Health Insurance (NHI) is a single-payer system implemented since 1995 and a compulsory program covering over 99.9% of the Taiwanese population.[16] NHILD is provided by the NHI Administration and made accessible to academic investigators.[15] The coding was initially based on the International Classification of Diseases, Revision 9, Clinical Modification (ICD-9-CM) and transitioned to the ICD-10-CM in 2016 (Table S1). Laboratory results were added to the database since December 2014.[15] The current study was conducted in compliance with the Declaration of Helsinki with approval of the institutional review board at the Taipei Veterans General Hospital (protocol number: 2017-08-005CC#1).

### 2.2 | Study population

We screened all patients diagnosed with CHB and treated with NUC therapy in the NHI program. Inclusion criteria were age ≥18 years, a diagnosis of CHB, treatment of either entecavir or tenofovir disoproxil fumarate (TDF) for at least 1 year, and discontinuation of the regimen. Exclusion criteria were prior treatment with NUC or interferon, hepatitis C virus or human immunodeficiency virus co-infection, alcohol-associated liver disease and serious illness such as malignancy, organ transplantation or severe autoimmune disorders, as listed in the registry of catastrophic illness patient database (Table S2).[16] Because laboratory data were not available until December 2014, the current study started on 1 January 2015 and ended on 31 December 2018, the latest date of data availability.

### 2.3 | The healthcare policy on antiviral treatment for CHB in Taiwan

The viral hepatitis therapy program in Taiwan has reimbursed the insured for anti-HBV therapy since 1 October 2003 (Table S3). In brief, treatment was indicated for jaundice (serum bilirubin ≥2 mg/dL), coagulopathy (prolongation of prothrombin time ≥3s), liver cirrhosis, curatively treated HCC, use of immunosuppressants, high viral load (HBV DNA above $10^6$ IU/mL) at the third trimester of pregnancy, and

active CHB defined by HBV DNA ≥2000 IU/mL with a substantial elevation of serum alanine aminotransferase (ALT) above two times the upper limit of normal (ULN).

In principle, reimbursement was finite, with a maximum of 3 years for HBeAg-negative patients without special indications. For HBeAg-positive patients, treatment was reimbursed for until HBeAg seroconversion occurred, followed by a consolidation period of up to 1 year (Table S3). Notably, the criterion of cirrhosis required histological proof or evidence of portal hypertension (e.g. oesophagogastric varices or splenomegaly) in addition to typical liver images. A prerequisite of HBV DNA ≥2000 IU/mL was also required during the study period. Therefore, a clinical diagnosis of cirrhosis without overt features of portal hypertension or data of pretreatment HBV DNA ≥2000 IU/mL did not indicate long-term NUC therapy.

The reimbursement criteria for retreatment were similar to those for treatment initiation. Thus, patients generally did not resume treatment for isolated virological relapse without ALT flares.

### 2.4 | Exposure definition and outcome measurement

The baseline for outcome observation was set at the day of treatment withdrawal. Data recorded at or prior to the baseline were extracted to characterise the study population. Cirrhosis was defined by the specific diagnostic code. The presence of portal hypertension was defined by records of ascites, oesophagogastric varices or hepatic encephalopathy (Table S1). Patients without cirrhosis or portal hypertension and with available data to confirm the fulfilment of the standard stopping rules were considered "eligible". The rules required HBeAg seroconversion with treatment consolidation if pretreatment HBeAg was positive, and persistent remission of viremia with HBV DNA undetected in serum if pretreatment HBeAg was negative.[7,17] All "eligible" patients were documented to be HBeAg-negative with undetectable HBV DNA at treatment cessation. The duration of treatment consolidation was counted after HBeAg seroconversion and HBV DNA undetectability in HBeAg-positive and -negative patients, respectively.

The primary outcome was a severe hepatitis flare with hepatic decompensation, defined as serum ALT rising above five times ULN (i.e. >200 U/L, as ULN was conventionally set at 40 U/L) accompanied with (within 3 months) hyperbilirubinemia >2 mg/dL and prothrombin time >15 s. The secondary outcome was mortality or liver transplantation that subsequently occurred within 6 months of the flare episode. HBsAg seroclearance that occurred after NUC cessation was also analysed as a secondary outcome.

Outcome observation ended upon death, liver transplantation or 31 December 2018. Observations of withdrawal flares were censored 6 months after the resumption of antiviral treatment to prevent incorrectly attributing other causes of hepatitis to treatment cessation. The observation for HBsAg seroclearance was not censored on retreatment.

### 2.5 | Statistical analyses

Continuous variables were summarised by medians along with their interquartile ranges (IQRs) and categorical ones were expressed with numbers and percentages. Cumulative incidences of the study outcomes were estimated with adjustment for death or liver transplantation as the competing risk event.[18] Factors associated with the study outcomes were explored by the competing risk regression method developed by Fine and Gray.[19] The analysis was prespecified to include variables without missing data in more than 90% of the study population to avoid biased esitmates.[20,21] No data was imputed. Because the multivariable analysis was explorative, potentially relevant factors were all retained in the fully adjusted model. All estimates were reported together with a 95% confidence interval (CI). All statistical tests were two-sided. A $p$ value below 0.05 defined statistical significance. The analysis was performed with SAS Enterprise Guide (version 7.2, SAS Institute) and R (version 3.6.3, R Foundation).

## 3 | RESULTS

### 3.1 | Baseline characteristics of the study population

From 1 October 2003 through 1 January 2020, 218,388 CHB patients were screened and 10,192 patients were eligible and enrolled (Figure S1). Their baseline characteristics were summarised in Table 1. In brief, the study population was characterised by a male predominance and a median age of 50.9 years. There were 1092 (10.7%) patients with a clinical diagnosis of cirrhosis and 465 (4.6%) patients with a record of prior liver failure. Most patients were treated for 3 years. HBeAg prior to treatment was mostly (67.8%) negative in patients with the data. At treatment cessation, undetectable HBV DNA was confirmed in the majority (70.9%) of patients with available data and the median of serum ALT was 24 (IQR, 17, 36) U/L. In patients diagnosed with cirrhosis, compensated status was documented in all with laboratory data at treatment cessation (Table S4).

### 3.2 | Clinical events following treatment withdrawal

The study population was followed up for a median duration of 2.2 (IQR, 1.1, 3.0) years. A total of 3360 patients resumed treatment and the cumulative rate of retreatment was 48.7% (95% CI, 46.6%–50.9%) at 4 years. Besides, 2254 patients developed acute flares with serum ALT >200 U/L regardless of serum bilirubin or prothrombin time. The 4-year cumulative incidence of acute flare was 30.7% (95% CI, 29.4%–32.0%). HBsAg seroclearance occurred in 113 patients after treatment cessation and the cumulative incidence at year 4 was 1.9% (95% CI, 1.5%–2.4%).

Severe flares with hepatic decompensation occurred in 132 patients. The cumulative incidences were 1.0% (95% CI, 0.8%–1.2%) and 1.8% (95% CI, 1.5%–2.2%) in years 1 and 4, respectively (Figure 1A). The annual incidence rate was significantly higher in the first year (Table S5). After severe withdrawal flares, 38 patients subsequently died and 13 underwent liver transplantation. The cumulative incidences of subsequent mortality or liver transplantation were respectively 0.39% (95% CI, 0.28%–0.54%) and 0.69% (95% CI, 0.50%–0.92%) at years 1 and 4 (Figure 1B). The annual incidence rate of mortality/liver transplantation was also significantly highest in the first year (Table S5).

**TABLE 1** Characteristics of the study population at treatment withdrawal.

| Characteristics | All ($N = 10,192$) |
|---|---|
| Sex | |
| Female, *n* (%) | 2884 (28.3) |
| Male, *n* (%) | 7308 (71.7) |
| Age, years | 50.9 (41.5, 59.3) |
| Pretreatment HBeAg status ($n = 6203$) | |
| HBeAg-positive, *n* (%) | 1998 (32.2) |
| HBeAg-negative, *n* (%) | 4205 (67.8) |
| Cirrhosis[a], *n* (%) | 1092 (10.7) |
| Record of portal hypertension[b], *n* (%) | 465 (4.6) |
| Diabetes mellitus, *n* (%) | 2752 (27.0) |
| Hypertension, *n* (%) | 3528 (34.6) |
| Dyslipidaemia, *n* (%) | 4575 (44.9) |
| Antiviral regimen | |
| Entecavir, *n* (%) | 6921 (67.9) |
| Tenofovir, *n* (%) | 3271 (32.1) |
| Treatment duration, year | 3.0 (3.0, 3.0) |
| Serum alanine aminotransferase ($n = 8517$), U/L | 24 (17, 36) |
| Serum aspartate aminotransferase ($n = 8219$), U/L | 24 (20, 30) |
| Serum HBV DNA undetectable ($n = 4243$), *n* (%) | 3008 (70.9) |
| Serum total bilirubin ($n = 4815$), mg/dL | 0.73 (0.54, 1.0) |
| Platelet count ($n = 2919$), $10^9$/L | 194 (152, 238) |

[a]Cirrhosis was defined by a specific diagnostic code.

[b]Defined by a record of hepatic events such as ascites, oesophageal or gastric varices, or hepatic encephalopathy.

## 3.3 | Associated risk factors for the study outcomes

In the fully adjusted regression model (Table S6), significant risk factors for severe flares were older age (adjusted sub-distribution hazard ratio [SHR], 1.21 per 10 years; 95% CI, 1.03–1.42), male sex (adjusted SHR, 1.58; 95% CI, 1.04–2.38), liver cirrhosis (adjusted SHR, 2.74; 95% CI, 1.82–4.12) and portal hypertension (adjusted SHR, 2.46; 95% CI, 1.45–4.18). We further found the risk started to increase from 50 years onwards (Figure S2).

In the model for subsequent mortality or liver transplantation (Table S7), significant risk factors were older age (adjusted SHR, 1.42 per 10 years; 95% CI, 1.11–1.82), liver cirrhosis (adjusted SHR, 5.84; 95% CI, 3.21–10.62) and hypertension (adjusted SHR, 2.0; 95% CI, 1.03–3.88).

## 3.4 | Study outcomes stratified by risk factors at treatment withdrawal

Occurrences of the study outcomes according to the associated risk factors were detailed in Table 2. How these risk factors stratified the incidences of severe withdrawal flares and subsequent mortality/liver transplantation was illustrated in Figures 2 and 3, respectively. In 8863 patients without cirrhosis or portal hypertension, the cumulative incidences of severe flares and subsequent mortality/liver transplantation at year 4 were 1.3% (95% CI, 1.0%–1.7%) and 0.40%

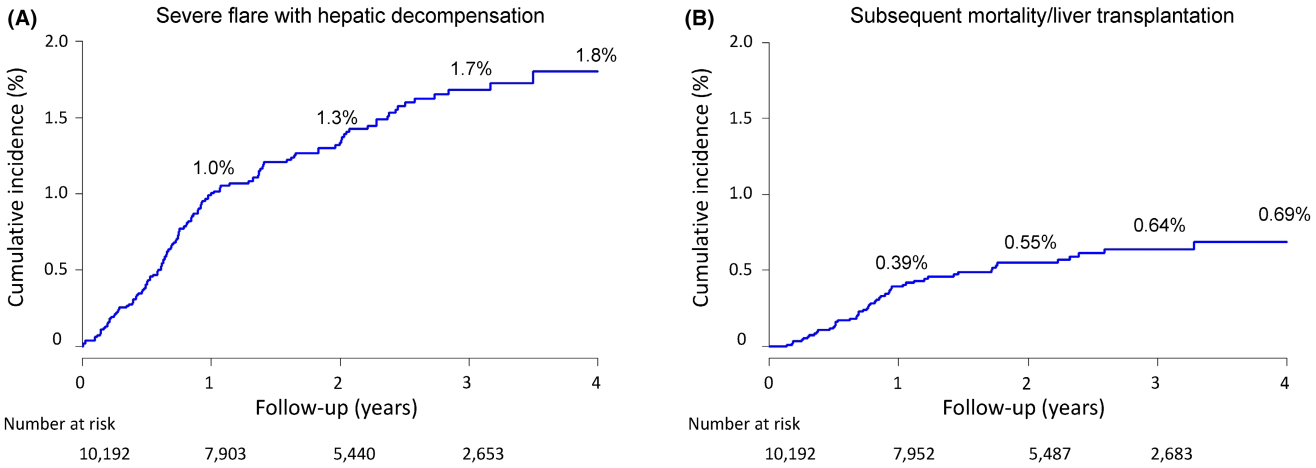


**FIGURE 1** The cumulative incidences of the study outcomes: severe flare with hepatic decompensation (A, left panel) and subsequent morality or liver transplantation (B, right panel). Estimation of the incidence was adjusted for death that preceded severe withdrawal flares as a competing risk event.

(95% CI, 0.25%–0.62%), respectively. Their risk was further stratified by age ≥ or < 50 years (Table 3).

Among the 8863 patients without cirrhosis or portal hypertension, 1274 patients had available data to document the attainment of negative HBeAg and undetectable HBV DNA followed by a period of treatment consolidation (median duration of 1.23 years, IQR, 0.66–2.0 years). In this "eligible" sub-cohort, 10 patients developed severe withdrawal flares with hepatic decompensation and 3 patients subsequently died or received a liver transplant, with the 4-year cumulative incidences at 1.1% (95% CI, 0.6%–2.0%) and 0.31% (95% CI, 0.09%–0.87%), respectively. HBsAg seroclearance was documented in 22 of the "eligible" patients with a 4-year cumulative incidence of 4.1% (95% CI, 1.7%–8.3%). The incidences of serious adverse events did not significantly differ between the "eligible" sub-cohort and the rest of the study population. The incidence of HBsAg seroclearance however, was significantly higher in "eligible patients" than in those whose eligibility was unfulfilled or unclear (Table 4).

### 3.5 | Off-therapy monitoring and retreatment timing

Among the 132 patients who developed severe flares with hepatic decompensation, 126 had records of outpatient visits after treatment withdrawal and 125 of them (95%) had laboratory data of serum ALT, bilirubin or prothrombin time (Table S8). Prior to the event, they were followed up with a median frequency of 2.4 (IQR, 1.5–3.6) visits every 3 months. The median level of serum ALT was 40 (IQR, 25–78) U/L at the last visit, which preceded the severe flare by a median of 67 (IQR, 35–131) days. Reimbursement for retreatment was documented in 124 (94%) patients. Treatment was resumed on the same day of the index laboratory results or earlier in 100 (76%) patients (Figure S3).

## 4 | DISCUSSION

In this nationwide study based on Taiwanese patients who discontinued first-line NUCs in routine clinical care, the incidences of severe flares with hepatic decompensation and subsequent mortality/liver transplantation were respectively 1.8% (95% CI, 1.5%–2.2%) and 0.69% (95% CI, 0.50%–0.92%) cumulatively at 4 years after NUC withdrawal. The risk was significantly higher in the first year but it lingered throughout the study period. Moreover, clinical diagnosis of cirrhosis, manifestations of portal hypertension, age and male sex were significant risk factors associated with severe withdrawal flares. After patients without cirrhosis or portal hypertension were excluded, the 4-year cumulative incidence of severe withdrawal flares remained at 1.3% (95% CI, 1.0%–1.7%). Severe flares with hepatic decompensation still occurred at a 4-year cumulative incidence of 1.1% (95% CI, 0.6%–2.0%) in the sub-cohort with documented "eligibility" for stopping treatment. Taken together, our findings quantify the risk of NUC withdrawal in a real-world setting. They also highlight the inadequacy of a fixed reimbursement policy and the current rules for treatment cessation in ensuring patient safety.

NUC withdrawal is known to trigger HBV reactivation with ALT flares in patients with CHB. Because a flare could be clinically silent,[22] the incidence of acute flares (ALT >5 times ULN) reported in the current study (cumulatively 30.7% at 4 years) could be an underestimate. In a study that employed a stringent protocol for off-therapy monitoring, Liu and colleagues reported that acute flares

**TABLE 2** Occurrences of the Study Outcomes as Stratified by Risk Factors at Treatment Withdrawal.

| | Severe flare with hepatic decompensation | | Mortality or liver transplantation subsequent to severe flare with hepatic decompensation | |
|---|---|---|---|---|
| | Case number | 4-year cumulative incidence, 95% CI | Case number | 4-year cumulative incidence, 95% CI |
| Overall, $N = 10{,}192$ | 132 (1.3%) | 1.8% (1.5%–2.2%) | 51 (0.50%) | 0.69% (0.50%–0.92%) |
| Liver cirrhosis | | | | |
| Yes, $n = 1092$ | 44 (4.2%) | 4.9% (3.6%–6.6%) | 27 (2.5%) | 3.1% (2.1%–4.5%) |
| No, $n = 9100$ | 88 (1.0%) | 1.4% (1.1%–1.8%) | 24 (0.26%) | 0.39% (0.24%–0.61%) |
| Age at withdrawal | | | | |
| ≥50 years, $n = 5335$ | 93 (1.7%) | 2.4% (1.9%–3.0%) | 42 (0.79%) | 1.1% (0.78%–1.54%) |
| <50 years, $n = 4857$ | 39 (0.80%) | 1.2% (0.8%–1.7%) | 9 (0.19%) | 0.24% (0.12%–0.46% |
| Biological sex | | | | |
| Male, $n = 7308$ | 104 (1.4%) | 2.0% (1.6%–2.4%) | 41 (0.56%) | 0.76% (0.53%–1.05%) |
| Female, $n = 2884$ | 28 (1.0%) | 1.4% (0.9%–2.0%) | 10 (0.35%) | 0.51% (0.26%–0.93%) |
| Presence of portal hypertension | | | | |
| Yes, $n = 408$ | 20 (4.9%) | 6.9% (4.3%–10.5%) | 7 (1.7%) | 2.2% (0.97%–4.3%) |
| No, $n = 9784$ | 112 (1.1%) | 1.6% (1.3%–2.0%) | 44 (0.45%) | 0.63% (0.45%–0.86%) |

*Note*: Estimation of the incidence was adjusted for death that preceded severe withdrawal flares as a competing risk event.

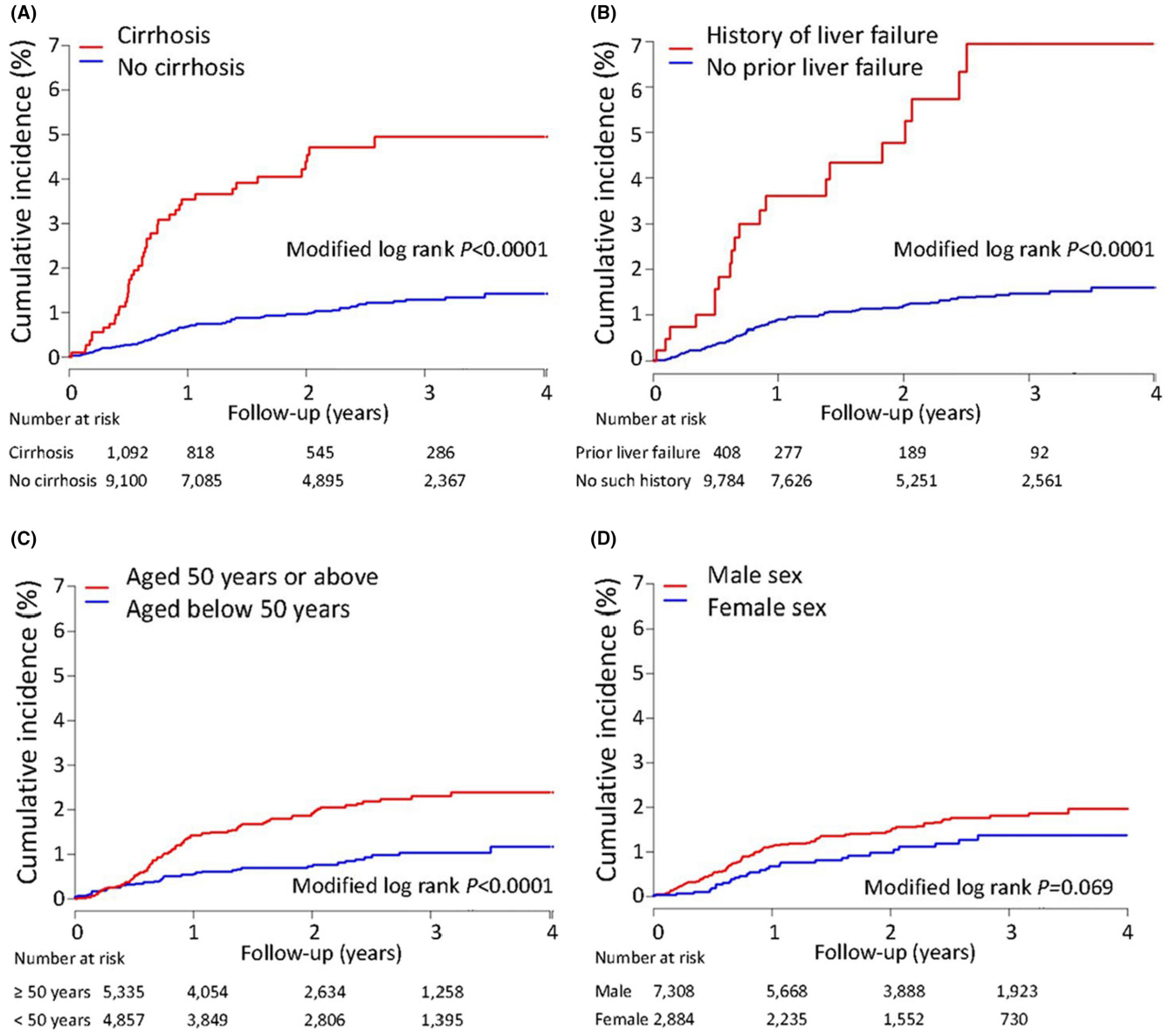


**FIGURE 2** The incidences of severe withdrawal flares with hepatic decompensation between patient subgroups stratified by cirrhosis (A), past history of liver failure (B), age ≥ or < 50 years (C), and biological sex (D). Estimation of the incidence was adjusted for death that preceded severe withdrawal flares as a competing risk event. Statistical comparison was carried out using the modified log-rank test developed by Grey.

(also ALT >5 times ULN) occurred in 516 (41.8%) of 1234 study participants within 2 years following the cessation of entecavir or TDF treatment.[23] Most concerning withdrawal flare is the risk of hepatic decompensation. Nevertheless, existing reports of withdrawal flares leading to hepatic decompensation have been limited to isolated cases, with little quantitative analysis.[9,13,23,24] Without empirical data to quantify the risk, absence of evidence might be misinterpreted as evidence of absence.[25] The existing literature on serious adverse events following NUC withdrawal is sparse. This scarcity of data could inadvertently lead to a false sense of security.[26,27]

Our findings strongly discourage NUC withdrawal in patients with cirrhosis or portal hypertension, regardless of their viral load or whether their hepatic function is compensated. Although an increased risk in these vulnerable patients might be expected, it is crucial to note some experts actively advocate for the cessation of NUCs in patients with cirrhosis.[28] This approach is even recommended as a feasible option in the current APASL guideline and guidance.[7,17] In fact, reports highlighting the risk of withdrawal flares in patients with a clinical diagnosis of cirrhosis or portal hypertension are lacking. Thus, our findings address a critical gap in current knowledge, despite the rarity of such practice in most parts of the world.

This population-based study offers empirical evidence that challenges the restrictive policy on NUC reimbursement in Taiwan. Without concrete data to directly assess the outcomes of such a practice, there is no basis for discussion and it might be argued that the policy is the new paradigm.[28,29] To enhance the generalizability

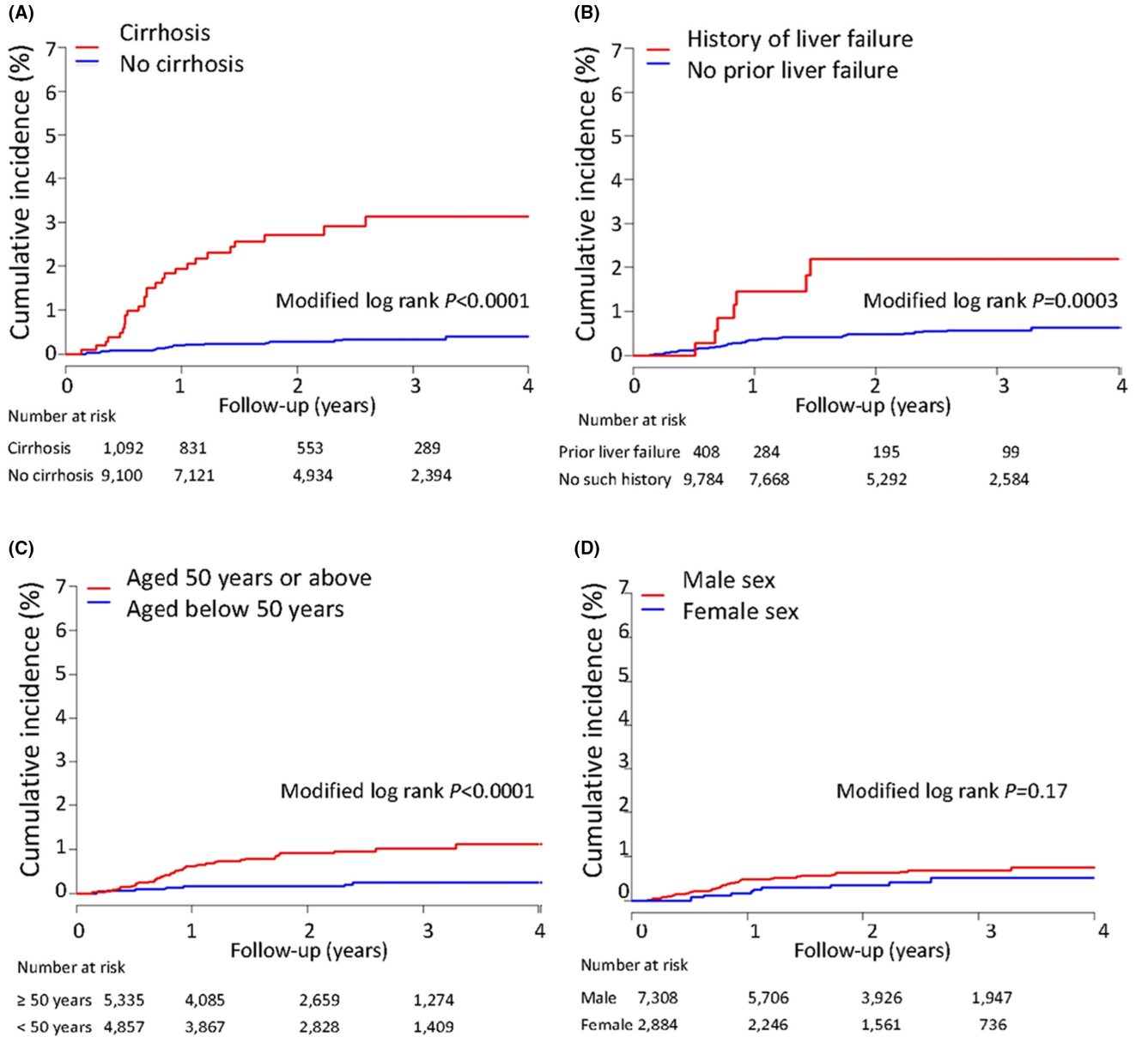


**FIGURE 3** The incidences of mortality or liver transplantation subsequent to severe withdrawal flares as stratified by cirrhosis (A), past history of liver failure (B), age ≥ or < 50 years (C), and biological sex (D). Estimation of the incidence was adjusted for death that preceded severe withdrawal flares as a competing risk event. Statistical comparison was carried out using the modified log-rank test developed by Grey.

**TABLE 3** Study outcomes in patients without cirrhosis or portal hypertension.

| | Severe flare with hepatic decompensation | | Mortality or liver transplantation subsequent to severe flare with hepatic decompensation | |
|---|---|---|---|---|
| | Case number | 4-year cumulative incidence, 95% CI | Case number | 4-year cumulative incidence, 95% CI |
| Subpopulation, $n = 8863$ | 82 (0.93%) | 1.3% (1.0%–1.7%) | 24 (0.27%) | 0.40% (0.25%–0.62%) |
| Age at withdrawal | | | | |
| ≥50 years, $n = 4388$ | 53 (0.66%) | 1.8% (1.3%–2.3%) | 17 (0.16%) | 0.61% (0.33%–1.05%) |
| <50 years, $n = 4475$ | 29 (1.2%) | 0.96% (0.60%–1.48%) | 7 (0.38%) | 0.22% (0.09%–0.45%) |

*Note*: Estimation of the incidence was adjusted for death that preceded severe withdrawal flares as a competing risk event.

**TABLE 4** Study outcomes in patients with documented 'eligibility' for treatment cessation compared to the rest of the study population.

| | "Eligible" sub-cohort | Other patients without cirrhosis or portal hypertension | *p** | Rest of the population including cirrhosis or portal hypertension | *p** |
|---|---|---|---|---|---|
| Patient number, *n* | 1274 | 7589 | | 8918 | |
| Severe withdrawal flares, *n* | 10 | 72 | | 122 | |
| 4-year cumulative incidence (95% CI) | 1.10% (0.56%–1.97%) | 1.35% (1.03%–1.75%) | 0.84 | 1.86% (1.52%–2.25%) | 0.33 |
| Subsequent death or liver transplant, n | 3 | 21 | | 48 | |
| 4-year cumulative incidence (95% CI) | 0.31% (0.09%–0.87%) | 0.40% (0.24%–0.64%) | 0.86 | 0.72% (0.53%–0.97%) | 0.32 |
| HBsAg clearance, n | 22 | 69 | | 91 | |
| 4-year cumulative incidence (95% CI) | 4.13% (1.68%–8.33%) | 1.58% (1.17%–2.09%) | <0.0001 | 1.71% (1.33%–2.18%) | 0.0003 |

Abbreviation: CI, confidence interval.

*Statistical comparison with the "eligible" sub-cohort.

of our study, we not only excluded patients with cirrhosis or portal hypertension but also identified a sub-cohort of "eligible" patients to stop NUCs. Our analyses indicate that the current "stopping rules" do not guarantee the safety of NUC withdrawal. The incidence of severe flares with hepatic decompensation was similarly high, regardless of whether patients had "confirmed eligibility." In fact, data from this population-based study align with estimates from recent hospital-based studies or meta-analyses,[30,31] which assess the risk of severe withdrawal flares even when adhering to guideline recommendations. Documenting sustained virological remission (defined by negative HBeAg and undetectable HBV DNA followed by a period of treatment consolidation), however, remains essential for patients wishing to stop NUCs. Our findings indicate that this is associated with a higher chance of achieving HBsAg seroclearance.

While our findings may assist with risk stratification, they should not be misinterpreted to suggest that treatment withdrawal is safe for patients without any risk factors. A young (under 50 years of age) patient without cirrhosis or portal hypertension could still succumb to liver failure resulting from severe withdrawal flares. The risk is arguably low (0.22% with a 95% CI of 0.09%–0.45% at 4 years) but not negligible (Table 3). Similarly, the time pattern of severe withdrawal flares requires careful interpretation. The incidence was significantly higher in the first year, but it did not level off by the end of observation. How to predict an uneventful cessation of NUC therapy is still unclear, and further research is warranted.[32]

Posttreatment management is central for determining the occurrence and consequences of withdrawal flares, yet a validated protocol is still unavailable.[7,32] According to the current APASL guidelines, it is recommended that patients should be monitored monthly in the initial 3 months and then every 3–6 months thereafter.[7,17] In the current study, the frequency of posttreatment monitoring before the severe flare event was 2.4 (IQR, 1.5, 3.6) visits every 3 months. Serum ALT at the last visit preceding the flare was generally unremarkable. Besides, most patients immediately restarted treatment upon the episode of severe flares if not earlier. These data implicated that medical neglect did not account for the majority of serious consequences following NUC withdrawal and reaffirmed that acute HBV flare-up could be unpredictable with potential irreversibility.[22] The timing of retreatment is crucial to determine the risk of HBV flares. However, the criteria to reinitiate NUCs are contentious without a consensus.[7] Based on findings from both the current study and previous ones,[33–35] treatment resumption is recommended in cases of severe virological relapse with a high viral load, without the need to wait for clinical flares to occur.

In this real-world study, the off-therapy monitoring and decision to restart treatment were based on routine practice as per local guidelines or reimbursement policy, without a standardised protocol. We did not seek to explore posttreatment management as a risk predictor because it would be confounded by changes in clinical conditions. For instance, the intensity of follow-up could be driven by a rise in viremia, which would confound the association with outcomes of a flare.[36] Overlooking such confounding could have generated spurious associations between management and outcomes.[37] A prospective study comparing different protocols, ideally assigned through randomization, is required to clarify the effects of posttreatment management.

We acknowledged the following limitations. First, this population-based study was designed to reflect routine clinical care in the real world, where missing data was inevitable, especially for laboratory measurements.[38] HBV DNA was not frequently measured at the end of NUC therapy, in part because the fixed duration of reimbursement would remain unchanged regardless of the measurement results. Despite this limitation, the study outcome could still be determined, as most ALT flares in Asians with CHB are caused by HBV reactivation.[39] Additionally, the study population was carefully defined to exclude other common liver diseases. Second, the

current study only captured acute ALT flares and did not address long-term events such as incident HCC. Further research is warranted to clarify the consequences in the long run. Third, causality of the uncovered association was unclear. For instance, we could not ascertain the cause of the association between hypertension and mortality/liver transplantation following HBV flares. In our opinion, it might reflect the importance of hypertension in assessing mortality risk overall.[40] Fourth, it is beyond the scope of the current study to assess biomarkers such as viral antigens for selecting candidates to stop NUCs. Lastly, the healthcare policy on NUC therapy for CHB is uniquely restrictive in Taiwan and ethnicity may affect off-NUC outcomes. Caution is advisable before generalising our findings to other countries or ethnic groups.

In summary, severe HBV flares with hepatic decompensation occurred at a cumulative incidence of 1% at year one and 1.8% at year four following NUC withdrawal. Cirrhosis, portal hypertension, age and male sex were significant associated risk factors. Severe withdrawal flares and subsequent deaths still occurred in patients without cirrhosis or portal hypertension as well as in patients with "documented eligibility" for stopping treatment. Our findings indicate that the practice of finite NUC therapy should only be considered for highly motivated and clearly informed patients through shared decision-making, including a detailed presentation of the uncertainty surrounding withdrawal flares. A reimbursement policy that imposes a fixed treatment duration cannot be endorsed.

## AUTHOR CONTRIBUTIONS

**Yao-Chun Hsu:** Conceptualization (lead); data curation (supporting); formal analysis (equal); funding acquisition (equal); investigation (lead); methodology (lead); project administration (supporting); resources (supporting); supervision (equal); visualization (equal); writing – original draft (lead); writing – review and editing (lead). **Yi-Hsian Lin:** Data curation (equal); formal analysis (lead); methodology (equal); software (lead); visualization (equal); writing – review and editing (supporting). **Teng-Yu Lee:** Conceptualization (supporting); investigation (supporting); methodology (supporting); writing – review and editing (supporting). **Mindie H. Nguyen:** Conceptualization (supporting); investigation (supporting); methodology (supporting); supervision (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Cheng-Hao Tseng:** Conceptualization (supporting); investigation (supporting); methodology (supporting); resources (supporting); writing – review and editing (supporting). **Hsiu J. Ho:** Data curation (supporting); formal analysis (supporting); methodology (supporting); software (supporting); visualization (supporting); writing – review and editing (supporting). **Feng-Yu Kao:** Data curation (equal); formal analysis (supporting); methodology (supporting); project administration (supporting); resources (supporting); software (equal); writing – review and editing (supporting). **Jaw-Town Lin:** Conceptualization (supporting); funding acquisition (supporting); project administration (supporting); resources (supporting); supervision (supporting); writing – review and editing (supporting). **Chen-Yi Wu:** Data curation (supporting); funding acquisition (supporting); methodology (supporting); project administration (supporting); resources (supporting); software (supporting); writing – review and editing (supporting). **Chun-Ying Wu:** Conceptualization (equal); data curation (supporting); funding acquisition (equal); investigation (supporting); methodology (supporting); project administration (lead); resources (equal); software (supporting); supervision (lead); writing – original draft (supporting); writing – review and editing (equal). All authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

Yao-Chun Hsu has received lecture fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences and Novartis, served as an advisory committee member for Gilead Sciences, and received research grants from Gilead Sciences. Yi-Hsian Lin reported no conflicts of interest. Teng-Yu Lee has received grants from Merck Sharp & Dohme and Gilead Sciences and served as an advisory board member for Gilead and Bristol-Myers Squibb. Mindie H. Nguyen has received research support from Pfizer, Gilead Sciences, Enanta, Vir Biotech, Glycotests, B. K. Kee Foundation and the National Cancer Institute and has served as an advisory board member or consultant for Gilead, Intercept, Novartis, Eisai, Bayer, Exact Science, Laboratory of Advanced Medicine, Spring Bank and Janssen. Cheng-Hao Tseng has received lecture fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Bayer and Roche. Hsiu J. Ho reported no conflicts of interest. Feng-Yu Kao reported no conflicts of interest. Jaw-Town Lin reported no conflicts of interest. Chen-Yi Wu reported no conflicts of interest. Chun-Ying Wu reported no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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