Supplementary Appendix

Zhong Z, *et al. Ann Rheum Dis* 2022; 81:584–591. doi: 10.1136/annrheumdis-2021-221650

Supplementary Table S1. Eligibility Criteria

Inclusion Criteria
1. Aged ≥ 18 years;
2. Diagnosis of uveitis in unilateral or bilateral eyes;
3. Seropositive for the hepatitis B core antibody and negative for hepatitis B surface antigen;
3. Individuals qualified in health condition according to medical history, laboratory data, physical examination, chest x-rays, and 12-lead electrocardiogram results taken during screening;
4. Those who provide written informed consent;
5. Individuals are willing and able to follow visiting plans, treatment plans, laboratory examinations, and other study procedures.
Exclusion Criteria
1. Hepatitis C, hepatitis D, alcoholic liver disease, primary biliary cirrhosis, or autoimmune liver disease;
2. Confirmed or suspected infectious uveitis, including but not limited to tuberculosis, cytomegalovirus, Lyme disease, toxoplasmosis, infectious uveitis caused by Human T-lymphotropic virus 1, herpes zoster virus or herpes simplex virus;
3. History of moderate to severe congestive heart failure (New York Heart Association classification III or IV), recent cerebrovascular accidents;
4. Severe kidney disease, chronic renal failure, or dialysis treatment;
5. Severe liver disease or liver fibrosis;
6. Severe pulmonary disease, grade 3 or 4 (COPD or oxygen-dependent emphysema);
7. Masquerade syndrome, such as eye lymphoma, leukemia, choroid melanoma, etc.;
8. Individuals with a history of malignant tumors in other tissues and organs, who have received or are undergoing treatment for malignant tumors, or whose remission period of malignant tumors is less than 5 years;
9. HIV positive individuals during screening;
10. Individuals with chronic recurrent infection and active tuberculosis may have a history of invasive infection at the time of screening (e.g., listeriosis, histoplasmosis);
11. Receiving anti-TB treatment;
12. Being receiving anti-viral therapy for hepatitis virus;
13. Serum alanine aminotransferase (ALT) concentrations above normal;
14. HBV DNA level $\geq 1 \times 10^7$ IU/mL;
15. Addicted to drugs, alcohol or psychotropic substances;
16. Severe mental disorders (e.g., schizophrenia, treatment-resistant bipolar disorder, current severe depression);
17. Women of reproductive age who are pregnant or lactating and who are unwilling or unable to use the acceptable contraceptive methods prescribed in the program during the study period;
18. For any reason, the researchers do not consider this study suitable for individuals.

Supplementary Table S2. Laboratory Tests, Medical Device, Reagents and Reference Ranges Used in the Study

Item	Unit	Reference Range		Medical Device
		Lower Limit	Upper Limit	
ALT	U/L	Male: 9 Female: 7	Male: 50 Female: 40	Roche Cobasc 311 autoanalyzer (Roche Diagnostics Inc., Basel, Swiss)
AST	U/L	Male: 15 Female: 13	Male: 40 Female: 35	
Total bilirubin	μmol/L	Male: 0 Female: 0	Male: 26 Female: 21	
Creatinine	μmol/L	12-59 years old: Male: 57 Female: 41 60-120 years old: Male: 57 Female: 41	12-59 years old: Male: 97 Female: 73 60-120 years old: Male: 111 Female: 81	
HBsAg	IU/mL	-	0.05	Commercial enzyme immunoassay kits (ARCHITECT i4000, Abbott, Wiesbaden, Germany)
Anti-HBs	mIU/mL	-	10.00	
HBeAg	S/CO	-	1.00	
Anti-HBe	S/CO	1.00	-	
Anti-HBc	S/CO	-	1.00	
HBV DNA	IU/mL	-	1×10^2	Roche Cobas Z480 real-time detection system (Roche systems)

Supplementary Table S3. Definitions of Outcomes

Outcome	Definition
HBV reactivation	In HBsAg-positive, anti-HBc-positive patients: (i) A ≥2 log (100-fold) increase in HBV DNA compared to the baseline level, or (ii) HBV DNA ≥3 log (1,000) IU/mL in a patient with previously undetectable level (since HBV DNA levels fluctuate), or (iii) HBV DNA ≥4 log (10,000) IU/mL if the baseline level is not available. In HBsAg-negative, anti-HBc-positive patients*: (i) HBV DNA is detectable, or (ii) Reverse HBsAg seroconversion occurs (reappearance of HBsAg).
Hepatitis flare	Three-fold or more increase in ALT that exceeds the ULN (50 U/L) and an absolute increase of ALT that exceeded 100 U/L.
Severe hepatitis	A hepatitis flare with an increase of ALT to more than 10 fold of ULN or bilirubin to more than 1.5 fold of ULN.

Abbreviations: HBsAg, Hepatitis B surface antigen; Anti-HBc, antibody against Hepatitis B core antigen; ALT, alanine aminotransferase; ULN, upper limit of normal.

* Our study only involved those participants with an HBsAg-negative, anti-HBc-positive status.

Reference: Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology (Baltimore, Md) 2018;67:1560-99.

Supplementary Table S4. Hazard Ratios of Cumulative Prednisone Dose for Primary Composite Outcome in Cubic Spline Analyses

Cumulative Prednisone Dose (mg)	Hazard Ratio	Lower Limit of 95% CI	Upper Limit of 95% CI
0	0.93	0.37	2.33
56	1.00	0.41	2.46
502	1.85	0.87	3.92
1004	3.06	1.54	6.10
1506	3.72	1.96	7.08
2008	3.43	1.99	5.93
2510	2.53	1.71	3.74
3012	1.57	1.31	1.89
3514	0.87	0.82	0.92
4016	0.45	0.33	0.61
4518	0.23	0.13	0.39
5020	0.12	0.06	0.26
6024	0.05	0.02	0.13
7028	0.03	0.01	0.09
8032	0.02	0.01	0.09

Data are shown for Figure in the main text. Hazard ratios for the primary composite outcome were estimated with a multivariable Cox regression analysis adjusted for cyclosporine daily dose, age, sex, body mass index, Hepatitis B surface antibody status, serum alanine aminotransferase level, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, best corrected visual acuity in the worse-seeing eye, aspartate aminotransferase level, total bilirubin level and creatinine level.

Zhong Z, *et al. Ann Rheum Dis* 2022; 81:584–591. doi: 10.1136/annrheumdis-2021-221650

Supplementary Table S5. Hazard Ratios of Time-Weighted Average Prednisone Dose for Primary Composite Outcome in Cubic Spline Analyses

Time-Weighted Average Prednisone Dose (mg/day)	Hazard Ratio	Lower Limit of 95% CI	Upper Limit of 95% CI
0	0.01	0.00	2.93
2	0.03	0.00	2.22
4	0.08	0.00	1.74
6	0.20	0.03	1.39
8	0.47	0.19	1.16
10	1.03	0.99	1.08
12	1.77	0.91	3.43
14	2.72	0.87	8.55
16	3.27	0.84	12.72
18	3.45	0.81	14.64
20	3.89	0.89	17.11
21	4.37	1.00	19.06
22	5.05	1.17	21.84
24	6.76	1.57	29.02
26	8.85	2.04	38.35
28	11.60	2.62	51.38
30	15.19	3.31	69.75

Data are shown for Figure in the main text. Hazard ratios for the primary composite outcome were estimated with a multivariable Cox regression analysis adjusted for cyclosporine daily dose, age, sex, body mass index, Hepatitis B surface antibody status, serum alanine aminotransferase level, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, best corrected visual acuity in the worse-seeing eye, aspartate aminotransferase level, total bilirubin level and creatinine level.

Zhong Z, *et al. Ann Rheum Dis* 2022; 81:584–591. doi: 10.1136/annrheumdis-2021-221650

Supplementary Table S6. Subgroup Analyses Evaluating Time-Weighted Average Prednisone Dose with Risk for the Primary Composite Outcome of HBV Reactivation, Hepatitis Flare and Severe Hepatitis

Subgroups	No. with Event/Total No.				Crude Incidence, 100py				Inverse Probability Weighted Incidence*, 100py				P value for interaction§
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Overall	1/328	15/346	22/494	13/135	0.35	5.06	6.16	12.67	0.75	4.89	5.64	16.67	-
Anti-HBs													0.42
Anti-HBs (-)	0/121	7/129	6/147	5/64	0	6.79	6.03	10.22	0.00	6.25	4.34	24.81	
Anti-HBs (+)	1/207	8/217	16/347	8/71	0.57	4.18	6.21	14.91	1.10	4.21	6.27	13.06	
Use of Cyclosporine													0.47
Cyclosporine users	1/27	7/222	14/378	6/106	4.32	3.36	5.11	6.94	1.62	2.75	4.99	8.94	
Cyclosporine nonusers	0/301	8/124	8/116	7/29	0	9.12	9.60	43.30	0.00	9.29	6.39	27.42	
ALT Level													0.82
ALT ≤ 20 U/L	0/226	6/235	7/313	5/74	0	3.07	2.95	8.93	0.00	3.12	2.89	7.63	
ALT > 20 U/L	1/102	9/111	15/181	8/61	1.25	8.92	12.50	17.17	3.23	7.93	11.57	32.46	

Abbreviations: Anti-HBs, antibody against Hepatitis B surface antigen; ALT, alanine aminotransferase.

*Each observation was weighted by the inverse of the probability of a patient being in each quartile. The probability was generated using the multinomial logistic regression with cyclosporine daily dose, age, sex, body mass index, Hepatitis B surface antibody status, serum alanine aminotransferase level, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, best corrected visual acuity in the worse-seeing eye, aspartate aminotransferase level, total bilirubin level and creatinine level as independent variables.

§P values of interaction between each subgroup variable and time-weighted average prednisone dose quartiles estimated in a multivariable Cox regression model. Variables in the model included age, sex, body mass index, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, best corrected visual acuity in the worse-seeing eye, the baseline serum alanine aminotransferase level (or categorized as ≤ 20 U/L vs. > 20 U/L), aspartate aminotransferase level, total bilirubin level, creatinine level, Hepatitis B surface antibody status, cyclosporine daily dose (or categorized as cyclosporine users vs. nonusers), time-weighted average prednisone dose quartiles and the interaction term between each subgroup variable and time-weighted average prednisone dose quartiles.

Supplementary Table S7. Risk for Primary Composite Outcome on the Basis of Baseline Anti-HBs

Baseline Variables	Adjusted Hazard Ratio (95% CI)†
Anti-HBs Serological Status	
Anti-HBs negative	1 [Reference]
Anti-HBs positive	0.99 (0.54-1.80)
Anti-HBs Level	
Anti-HBs < 20 mIU/mL	1 [Reference]
Anti-HBs ≥ 20 mIU/mL	0.82 (0.47-1.45)
Anti-HBs Level	
Anti-HBs < 100 mIU/mL	1 [Reference]
Anti-HBs ≥ 100 mIU/mL	0.83 (0.44-1.55)

Abbreviations: Anti-HBs, antibody against Hepatitis B surface antigen.

†Data were estimated in the multivariate Cox regression model with adjustment for covariables including age, sex, body mass index, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancies, uveitis laterality, best corrected visual acuity in the worse-seeing eye, the baseline serum alanine aminotransferase level, aspartate aminotransferase level, total bilirubin level, creatinine level, cyclosporine daily dose and time-weighted average prednisone dose quartiles.

Zhong Z, *et al. Ann Rheum Dis* 2022; 81:584–591. doi: 10.1136/annrheumdis-2021-221650

Supplementary Table S8. Literature Referring to the Directed Acyclic Graph in Supplementary Figure S4

No.	Reference
1	Mikulska M, Nicolini L, Signori A, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. Clin Microbiol Infect. 2014;20(10):O694-O701.
2	Loomba R, Liang TJ. Hepatitis B Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. Gastroenterology. 2017;152(6):1297-309.
3	Seto WK, Chan TS, Hwang YY, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(33):3736-43.
4	Wong GL, Wong VW, Hui VW, et al. Hepatitis Flare During Immunotherapy in Patients With Current or Past Hepatitis B Virus Infection. Am J Gastroenterol. 2021;116(6):1274-1283.
5	Chen MH, Wu CS, Chen MH, et al. High Risk of Viral Reactivation in Hepatitis B Patients with Systemic Lupus Erythematosus. Int J Mol Sci. 2021;22(17):9116.
6	Tohme RA, Bulkow L, Homan CE, et al. Rates and risk factors for hepatitis B reactivation in a cohort of persons in the inactive phase of chronic hepatitis B-Alaska, 2001-2010. J Clin Virol.2013;58(2):396-400.
7	Rehm M, Rothenbacher D, Iacoviello L, et al. Chronic kidney disease and risk of atrial fibrillation and heart failure in general population-based cohorts: the BiomarCaRE project [published online ahead of print, 2021 Nov 26]. ESC Heart Fail. 2021;10.1002/ehf2.13699.
8	Wang A, Tian X, Wu S, et al. Metabolic Factors Mediate the Association Between Serum Uric Acid to Serum Creatinine Ratio and Cardiovascular Disease [published online ahead of print, 2021 Nov 15]. J Am Heart Assoc. 2021;e023054.
9	Gentile F, Sciarrone P, Zamora E, et al. Body mass index and outcomes in ischaemic versus non-ischaemic heart failure across the spectrum of ejection fraction. Eur J Prev Cardiol. 2021;28(9):948-955.
10	Lind V, Hammar N, Lundman P, et al. Impaired fasting glucose: a risk factor for atrial fibrillation and heart failure. Cardiovasc Diabetol. 2021;20(1):227.
11	Nguyen A, Adams H, Gin J, et al. Total serum bilirubin is an independent risk factor for coronary artery disease in men compared to women. Acta Cardiol. 2016;71(6):685-689.
12	Trevisan A, Giuliani A, Scapellato ML, et al. Sex Disparity in Response to Hepatitis B Vaccine Related to the Age of Vaccination. Int J Environ Res Public Health. 2020;17(1):327
13	Di Lello FA, Blejer J, Alter A, et al. Hepatitis B surface antibodies seroprevalence among people born before and after implementation of universal HBV vaccination. Vaccine. 2020;38(12):2678-2682.
14	Wei M, Dong L, Wang F, et al. The Prevalence of Hypertension in the Population without Awareness of the Disease: Data from a Rural Town of Shandong Province, China. Int J Hypertens. 2021;2021:9672994.
15	Zou M, Guo D, Chen A, et al. Prevalence of visual impairment among older Chinese population: A systematic review and meta-analysis. J Glob Health. 2021;11:08004.

Supplementary Table S9. Sensitivity Analyses with Suitable Minimally Sufficient Adjustment Sets Identified by the Directed Acyclic Graph

Analysis‡	Covariates	Hazard Ratio (95% CI)*			
		Q2 vs. Q1	Q3 vs. Q1	Q4 vs. Q1	Per quartile increase⊖
Cumulative Prednisone Dose					
Primary analysis	*The full set*‖	6.03 (2.60-14.01)	0.51 (0.17-1.52)	0.06 (0.01-0.49)	0.46 (0.33-0.65)
Minimally adjustment set 1	*ALT level, AST level, Age, Anti-HBs status, BCVA in the worse-seeing eye, BMI, Dose of cyclosporine used, Sex, Uveitis laterality*	6.02 (2.63-13.77)	0.50 (0.17-1.48)	0.06 (0.01-0.51)	0.46 (0.33-0.65)
Minimally adjustment set 2	*ALT level, AST level, Age, Anti-HBs status, BCVA in the worse-seeing eye, BMI, Creatinine level, Dose of cyclosporine used, Sex*	6.19 (2.68-14.31)	0.51 (0.17-1.50)	0.06 (0.01-0.53)	0.46 (0.33-0.64)
Minimally adjustment set 3	*ALT level, AST level, Age, Anti-HBs status, BCVA in the worse-seeing eye, BMI, Diabetes, Dose of cyclosporine used, Hypertension, Sex*	6.18 (2.70-14.12)	0.51 (0.17-1.52)	0.07 (0.01-0.54)	0.46 (0.33-0.65)
Minimally adjustment set 4	*ALT level, AST level, Age, Anti-HBs status, BMI, Dose of cyclosporine used, Drinking, Sex, Smoking*	5.91 (2.58-13.55)	0.47 (0.16-1.39)	0.06 (0.01-0.49)	0.45 (0.32-0.64)
Minimally adjustment set 5	*ALT level, AST level, Age, Anti-HBs status, BMI, Dose of cyclosporine used, Malignancy, Sex*	6.00 (2.63-13.71)	0.48 (0.16-1.41)	0.06 (0.01-0.51)	0.46 (0.32-0.64)
Minimally adjustment set 6	*ALT level, AST level, Age, Anti-HBs status, BMI, Creatinine level, Dose of cyclosporine used, Educational level, Residence, Sex*	6.19 (2.67-14.34)	0.49 (0.17-1.45)	0.06 (0.01-0.52)	0.45 (0.32-0.64)
Minimally adjustment set 7	*ALT level, AST level, Age, Anti-HBs status, BMI, Diabetes, Dose of cyclosporine used, Educational level, Hypertension, Residence, Sex*	6.12 (2.67-14.04)	0.49 (0.17-1.45)	0.06 (0.01-0.52)	0.46 (0.32-0.64)
Time-Weighted Average Prednisone Dose					
Primary analysis	*The full set*‖	23.90 (3.09-184.65)	24.82 (3.23-190.54)	49.48 (6.24-392.48)	2.15 (1.56-2.98)
Minimally adjustment set 1	*ALT level, AST level, Age, Anti-HBs status, BCVA in the worse-seeing eye, BMI, Dose of cyclosporine used, Sex, Uveitis laterality*	23.10 (3.01-177.30)	24.64 (3.24-187.55)	46.81 (5.92-370.15)	2.11 (1.54-2.91)
Minimally adjustment set 2	*ALT level, AST level, Age, Anti-HBs status, BCVA in the worse-seeing eye, BMI, Creatinine level, Dose of cyclosporine used, Sex*	23.54 (3.06-180.90)	25.71 (3.38-195.48)	48.48 (6.12-384.06)	2.13 (1.55-2.93)
Minimally adjustment set 3	*ALT level, AST level, Age, Anti-HBs status, BCVA in the worse-seeing eye, BMI, Diabetes, Dose of cyclosporine used, Hypertension, Sex*	24.28 (3.16-186.61)	26.75 (3.52-203.49)	48.93 (6.20-386.28)	2.14 (1.56-2.93)

Analysis‡	Covariates	Hazard Ratio (95% CI)*			
		Q2 vs. Q1	Q3 vs. Q1	Q4 vs. Q1	Per quartile increase∋
Minimally adjustment set 4	*ALT level, AST level, Age, Anti-HBs status, BMI, Dose of cyclosporine used, Drinking, Sex, Smoking*	21.07 (2.75-161.60)	24.90 (3.26-190.26)	50.13 (6.32-397.49)	2.20 (1.59-3.05)
Minimally adjustment set 5	*ALT level, AST level, Age, Anti-HBs status, BMI, Dose of cyclosporine used, Malignancy, Sex*	21.45 (2.80-164.18)	26.43 (3.48-200.81)	48.44 (6.12-383.44)	2.16 (1.57-2.97)
Minimally adjustment set 6	*ALT level, AST level, Age, Anti-HBs status, BMI, Creatinine level, Dose of cyclosporine used, Educational level, Residence, Sex*	21.92 (2.86-168.15)	27.52 (3.62-209.50)	50.98 (6.42-404.87)	2.20 (1.60-3.03)
Minimally adjustment set 7	*ALT level, AST level, Age, Anti-HBs status, BMI, Diabetes, Dose of cyclosporine used, Educational level, Hypertension, Residence, Sex*	22.26 (2.90-170.65)	28.50 (3.74-217.14)	50.97 (6.44-403.71)	2.20 (1.60-3.02)

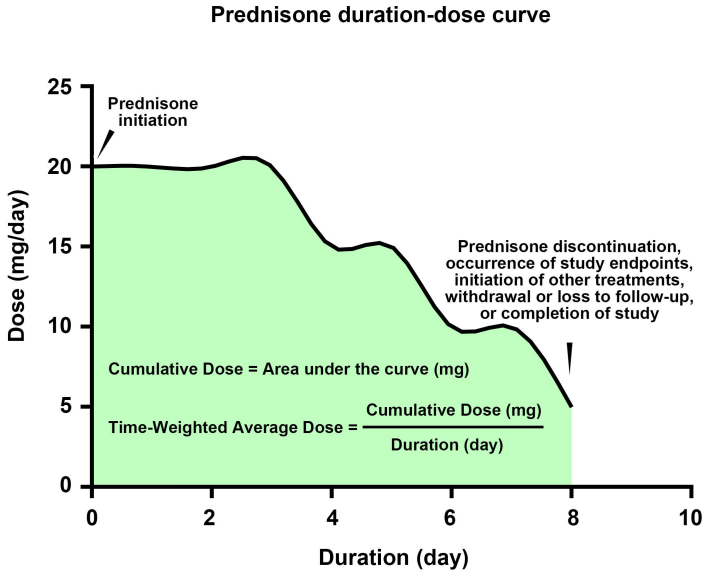
‡Analyses were performed with the multivariable Cox model adjusted for covariates indicated.

*Values are reported according to the quartile (Q) of cumulative prednisone dose and time-weighted average prednisone dose. The cumulative prednisone dose was categorized as: Q1, ≤300 mg; Q2, >300 but ≤3000 mg; Q3, >3000 but ≤6750 mg; Q4, >6750 mg. The time-weighted average prednisone dose was categorized as: Q1, ≤10 mg/day; Q2, >10 but ≤15 mg/day; Q3, >15 but ≤20 mg/day; Q4, >20 mg/day.

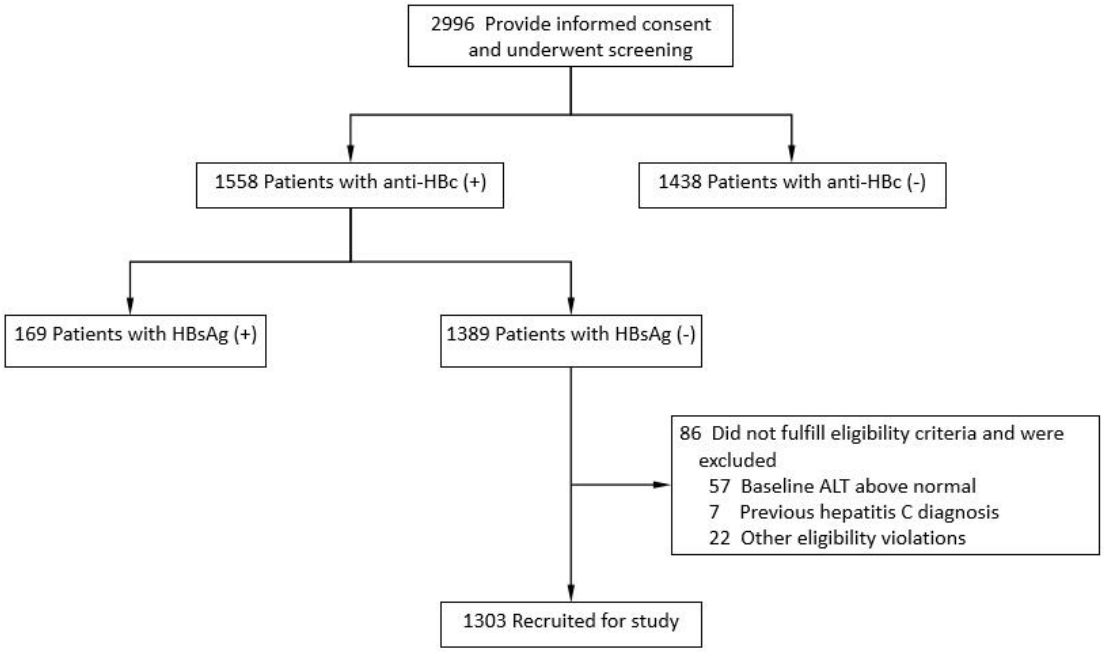
∋Hazard ratios per quartile increase were computed by modeling the factor as a continuous variable.

||Hazard ratios were adjusted for daily dose of cyclosporine used, age, sex, body mass index (BMI), Hepatitis B surface antibody (Anti-HBs) status, serum alanine aminotransferase (ALT) level, residence, educational level, smoking, drinking, hypertension, diabetes, coronary heart disease, malignancy, uveitis laterality, best corrected visual acuity (BCVA) in the worse-seeing eye, aspartate aminotransferase (AST) level, total bilirubin level, and creatinine level.

Supplementary Figure S1. Determination of Cumulative Dose and Time-Weighted Average Dose of Prednisone Use

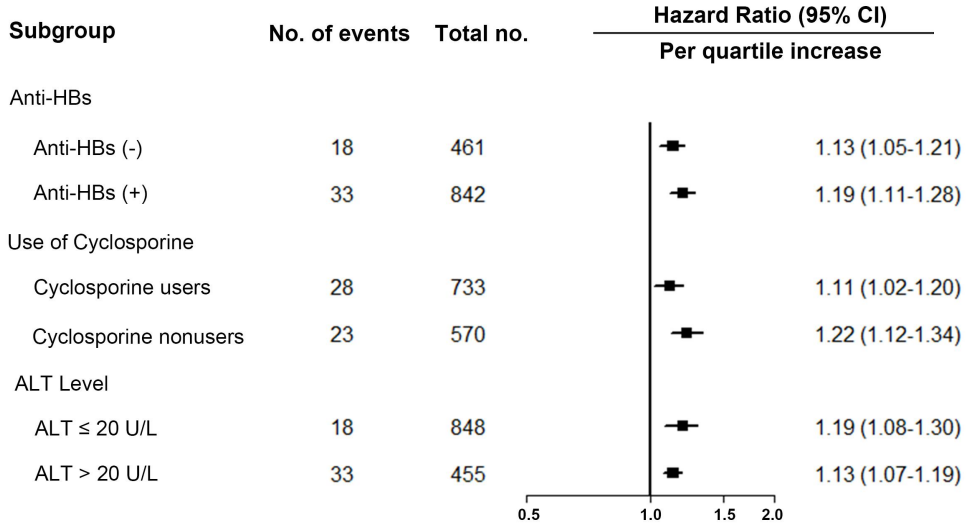


Supplementary Figure S2. Participant Selection Flow Diagram



Supplementary Figure S3. Subgroup Analyses of per Quartile Increase in Time-Weighted Average Prednisone Dose with Risk for the Primary Composite Outcome of HBV Reactivation, Hepatitis Flare and Severe Hepatitis

Hazard ratios for the primary composite outcome were estimated with a multivariable Cox regression analysis adjusted for the full set of covariates.



Supplementary Figure S4. Directed Acyclic Graph Derived from Literature and Expert Knowledge

Nodes represent variables and arrows represent associations between these variables. Numbers represent available information from the literature (see Supplementary Table 8 for full references).