Received: 23 August 2023 | Revised: 18 September 2023 | Accepted: 2 October 2023

DOI: 10.1002/kjm2.12771

ORIGINAL ARTICLE

Kaohsiung Journal of Medical Sciences KJMS WILEY

Pretreatment gamma-glutamyl transferase predicts mortality in patients with chronic hepatitis B treated with nucleotide/nucleoside analogs

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Funding information
Kaohsiung Medical University, Grant/Award Numbers: KMUH109-9R05, MOST 111-2314-B-037-069-MY2; Kaohsiung Medical University Hospital, Grant/Award Numbers: KMUH110-0M03, KMUH110-0M06, KMHK-DK(C)111004,

Abstract

Elevated serum gamma-glutamyl transferase (GGT) levels are associated with chronic hepatitis B (CHB)-related hepatocellular carcinoma. However, their role in predicting mortality in patients with CHB treated with nucleotide/nucleoside analogs (NAs) remains elusive. Altogether, 2843 patients with CHB treated with NAs were recruited from a multinational cohort. Serum GGT levels before and 6 months (Month-6) after initiating NAs were measured to explore their association with all-cause, liver-related, and non-liver-related mortality. The annual incidence of all-cause mortality was 0.9/100 person-years over a follow-up period of 17,436.3 person-years. Compared with patients who survived, those who died had a significantly higher pretreatment (89.3 vs. 67.4 U/L, $p = 0.002$) and Month-6-GGT levels (62.1 vs. 38.4 U/L, $p < 0.001$). The factors associated with all-cause mortality included cirrhosis (hazard ratio [HR]/95% confidence interval [CI]: 2.66/1.92–3.70, $p < 0.001$),

Abbreviations: ALT, alanine aminotransferase; AUROC, area under the receiver operating characteristic; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CI, confidence interval; GGT, gamma-glutamyl transferase; HR, hazard ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NAs, nucleotide/nucleoside analogues; ULN, upper limit of normal.

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KMUH-DK(整)109005~1, KMUH-DK(B) 111002-1, KMHK-DK(C)111006; Ministry of Health and Welfare, Taiwan, Grant/Award Number: MOHW111-TDU-B-221-014007

pretreatment GGT levels (HR/CI: 1.004/1.003–1.006, $p < 0.001$), alanine aminotransferase level (HR/CI: 0.996/0.994–0.998, $p = 0.001$), and age (HR/CI: 1.06/1.04–1.07, $p < 0.001$). Regarding liver-related mortality, the independent factors included cirrhosis (HR/CI: 4.36/2.79–6.89, $p < 0.001$), pretreatment GGT levels (HR/CI: 1.006/1.004–1.008, $p < 0.001$), alanine aminotransferase level (HR/CI: 0.993/0.990–0.997, $p = 0.001$), age (HR/CI: 1.03/1.01–1.05, $p < 0.001$), and fatty liver disease (HR/CI: 0.30/0.15–0.59, $p = 0.001$). Pretreatment GGT levels were also independently predictive of non-liver-related mortality (HR/CI: 1.003/1.000–1.005, $p = 0.03$). The results remained consistent after excluding the patients with a history of alcohol use. A dose-dependent manner of <25, 25–75, and >75 percentile of pretreatment GGT levels was observed with respect to the all-cause mortality (trend $p < 0.001$). Pretreatment serum GGT levels predicted all-cause, liver-related, and non-liver-related mortality in patients with CHB treated with NAs.

KEYWORDS
GGT, HBV, mortality, NA, treatment

1 | INTRODUCTION

Hepatitis B virus (HBV) infection affects approximately 300 million people worldwide. Owing to the growing burden of HBV-related death, it remains a major threat to global public health.[1] The risk factors for chronic hepatitis B (CHB)-related mortality may include but not limit to cirrhosis, hepatocellular carcinoma (HCC), alcohol use, and diabetes.[2,3] Meanwhile, HBV infection has been linked to not only liver-related mortality, but also all-cause mortality in population-based studies from east to west.[2–4] Fortunately, the application of antiviral agents, including nucleotide/nucleoside analogs (NAs), improves long-term outcomes and prolongs patient survival.[5–7] Nevertheless, mortality remains to occur in patients with CHB treated with NAs. Therefore, identifying potential surrogate markers for predicting mortality throughout the course of antiviral therapy is essential.

Gamma-glutamyl transferase (GGT) is located in the cell membranes of various cells and, more commonly, in liver cells.[8] It plays a role in the metabolism of extracellular glutathione. The elevation of serum GGT levels represents adaptation and over-compensation to oxidative stress. In addition to being a seromarker for liver injury, elevated GGT levels have been associated with several systemic diseases, cancer risk, and mortality.[9,10] From the perspective of liver-related events, an elevated serum GGT level has been associated with HCC occurrence in the natural course.[11] Serum GGT levels have also been reported to predict HCC development in patients with CHB[12] and chronic hepatitis C (CHC) treated with curative antivirals.[13] However, the role of GGT levels in predicting mortality in NA-treated patients with CHB remains unclear. Thus, this study aimed to address this issue by enrolling well-characterized patients with CHB from a multi-national, multi-center cohort in East Asia and Europe. Serum GGT levels before and after NA initiation were analyzed to determine their association with mortality in addition to other risk factors.

2 | MATERIALS AND METHODS

2.1 | Patients

Consecutive treatment-naïve patients with CHB who received NAs in 15 medical centers in Taiwan, Japan, Korea, Hong Kong, and Spain from December 2000 to July 2020 were enrolled in this study. The exclusion criteria were as follows: coinfection with human immunodeficiency virus or hepatitis C virus, NA usage for <12 months, mortality within 6 months after initiating NA, and use of NAs for acute hepatitis and liver decompensation. Patients with current active alcoholism were also excluded (>30 g/day), whereas a history of social drinking was recorded as a covariant. The treatment indications were based on local insurance reimbursement regulations or regional guidelines.[12,14–17] Patient follow-up was conducted after NA therapy and ended until the occurrence of mortality, cessation of NA therapy (treatment interruption for ≥12 months), or losing the patient to follow-up, whichever occurred first. This study was conducted in accordance with the principles of the Declaration of Helsinki of 1975, as revised in 2008. This study was approved by the ethics committees of the participating hospitals. Patient identities were de-linked, and de-identified data were sent to the data-coordinating center of Kaohsiung Medical University Hospital for analysis.

2.2 | Laboratory analyses

Liver cirrhosis was diagnosed using transient elastography (FibroScan®; Echosens, Paris, France; >14 kPa)[18]; through histology; or based on the presence of radiological, laboratory, endoscopic, or clinical evidence of portal hypertension (esophageal/gastric varices or ascites) and cirrhosis.[12] The fibrosis-4 index was calculated using the following formula: age (years) × aspartate aminotransferase level

(U/L)/platelet count [10^9/L] × alanine transaminase (ALT) level [U/L])$^{1/2}$. Serum GGT levels before (pretreatment GGT) and 6 months after initiating NAs (Month-6 GGT) were measured to explore the role of dynamic GGT levels in predicting mortality. Fatty liver disease was diagnosed by abdominal sonography by trained physicians, as described previously.[12,19] HCC surveillance was performed every 3–6 months based on the severity of the liver disease at the physician's discretion.

2.3 | Statistical analyses

Frequencies were analyzed between groups using the χ^2 test with Yates correction or Fisher's exact test. Group means, presented as the mean values and standard deviations, were compared using analysis of variance and Student's *t*-test or the Mann–Whitney *U* test. The times of the upper limit of normal (ULN) of GGT were applied alternatively as the covariant to address the consistent association of GGT with mortality.

The area under the receiver operating characteristic curve (AUROC) was used to analyze the best cut-off value of the serum GGT level for predicting mortality. Kaplan–Meier analysis and log-rank tests were performed to compare the cumulative incidence of mortality with respect to various determinants. Cox regression analysis was performed to analyze the factors independently associated with mortality considering the covariates with *p*-values<0.2 in the univariate analysis, whereas missing data on fatty liver disease were coded as "data unavailable" to avoid decrease in sample size in the multivariable regression analysis. Statistical analyses were performed using the IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY). All statistical analyses were based on two-sided hypothesis tests, with statistical significance set at $p < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

In total, 2843 patients with CHB were enrolled in this study (Figure 1). The mean age was 50.1 years; 64.8% of the patients were male. Patients with fatty liver disease accounted for 14.5% ($n = 345$), and liver cirrhosis was present in 26.9% ($n = 765$) of the study population. The pretreatment HBV DNA level was 5.8 $\log_{10}$ IU/mL, and

TABLE 1 Characteristics of the 2843 chronic hepatitis B patients with NAs treatment.

	All patients ($n = 2843$)
Age (years, mean (SD))	50.1 (12.9)
Male, *n* (%)	1843 (64.8)
Diabetes, *n*/N (%)	333/2779 (12.0)
Smoking, *n*/N (%)	936/2482 (37.7)
Alcohol use, *n*/N (%)	997/2314 (43.1)
BMI (kg/m^2, mean (SD))	23.2 (5.0)
AST (U/L, mean (SD))	98.8 (138.3)
ALT (U/L, mean (SD))	141.9 (215.9)
Platelet count (×10^3 U/L, mean (SD))	168.0 (70.2)
FIB-4 (mean (SD))	3.4 (5.8)
Baseline GGT (U/L, mean (SD))	68.7 (75.1)
Month-6 GGT (U/L, mean (SD))	39.8 (57.2)
Baseline AFP (ng/mL, mean (SD))	24.3 (193.9)
Month-6 AFP (ng/mL, mean (SD))	9.0 (93.6)
Cretinine (mg/dL, mean (SD))	0.9 (0.8)
HBeAg seropositivity, *n*/N (%)	1221/2758 (44.3)
HBV DNA ($\log_{10}$ IU/mL, mean (SD))	5.8 (2.2)
Fatty liver, *n*/N (%)	345/2377 (14.5)
Liver cirrhosis, *n* (%)	765 (26.9)
Region, *n*	
Taiwan/Japan/Korea/Hong Kong/Spain	497/1062/872/366/46
TDF/ETV/other NAs[a], *n*/*n*/*n*	483/1697/683

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ETV, entecavir; FIB-4, fibrosis-4 index; GGT, γ-glutamyl transferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; Month-6, 6 months after receiving NAs therapy; NAs, nucleoside/nucleotide analogues; SD, standard deviation; TDF, tenofovir disoproxil fumarate.

[a]Other NAs: lamivudine ($n = 263$), telbivudine ($n = 387$), and NAs combination ($n = 33$).

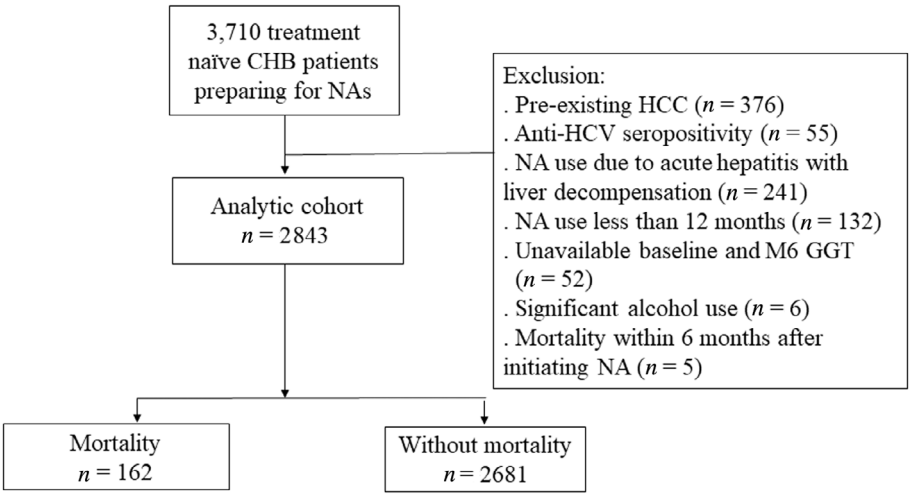

FIGURE 1 Patient flow chart. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Month-6-GGT, gamma-glutamyl transferase level 6 months after initiating antivirals; NA, nucleoside/nucleotide analogs.

44.3% of the patients were seropositive for HBeAg. The most commonly used NA was entecavir (59.7%) followed by tenofovir disoproxil fumarate (17.0%). The GGT level was 68.7 U/L at pretreatment and decreased to 39.8 U/L 6 months after initiating NAs (Table 1). Compared with patients without liver cirrhosis, those with liver cirrhosis had a significantly smaller proportion of fatty liver cases (3.5% vs. 15.3%, $p < 0.001$).

3.2 | Cumulative incidence and causes of mortality

Of the patients, 162 (5.7%) experienced mortality during a mean follow-up period of 6.2 years (range: 0.5–26.1 years). The 1-, 3-, 5-, 8-, and 10-year cumulative incidences of mortality were 0.3% (95% confidence interval [CI]: 0.1%–0.5%), 1.9% (CI: 1.3%–2.5%), 3.6% (CI: 2.7%–4.5%), 7.4% (CI: 5.4%–9.4%), and 9.8%(CI: 7.1%–12.5%), respectively. During a total of 17,436.3 person-years of follow-up, the annual incidence of mortality was 0.9% (CI: 0.8%–1.1%) in the total study population, and was 0.6%, 0.9%, 1.1%, 0.9%, and 1.6% in patients residing in Taiwan, Japan, Korea, Hong Kong, and Spain, respectively.

Among the recorded mortality cases, 97 (59.9%) were due to liver-related mortality, whereas 42 (25.9%) were due to non-liver-related mortality, and 23 cases were undisclosed. In patients with liver-related mortality, 55 patients (56.7%) died due to HCC, and 42 patients (43.2%) died due to cirrhosis-related complications. In patients with non-liver-related mortality, fourteen died due to malignancies other than HCC, eight died due to cardiovascular disease, four died due to sepsis, and thirteen cases were undisclosed.

3.3 | Risk factors for all-cause mortality

Compared with patients who survived, those who died were older (59.3 vs. 49.6 years, $p < 0.001$), had a higher prevalence of diabetes (20.6% vs. 11.5%, $p = 0.001$) and liver cirrhosis (56.2% vs. 25.1%, $p < 0.001$), lower prevalence of fatty liver disease (4.9% vs. 12.6%, $p = 0.001$), higher pretreatment (89.3 vs. 67.4 U/L, $p = 0.002$) and Month-6-GGT levels (62.1 vs. 38.4 U/L, $p < 0.001$), and lower platelet count (149.2×10^3 vs. 169.2×10^3 U/L, $p = 0.01$) and ALT levels (80.4 vs. 145.6 U/L, $p < 0.001$). The Cox-regression analysis revealed that the factors associated with all-cause mortality were liver cirrhosis (hazard ratio [HR]/CI: 2.66/1.92–3.70, $p < 0.001$), age (HR/CI: 1.06/1.04–1.07, $p < 0.001$), ALT level (HR/CI: 0.996/0.994–0.998, $p = 0.001$), and pretreatment GGT levels (HR/CI: 1.004/1.003–1.006,

TABLE 2 Factors associated with all-cause mortality.

				Cox-regression analysis		
All-cause mortality	**Yes, $n = 162$**	**No, $n = 2681$**	***p* value**	**HR**	**95% CI**	***p* value**
Age (years, mean (SD))	59.3 (11.8)	49.6 (12.8)	<0.001	1.06	1.04–1.07	<0.001
Male, *n* (%)	111 (68.5)	1732 (64.6)	0.31			
Diabetes, *n*/N (%)	33/160 (20.6)	300/2619 (11.5)	0.001			
Smoking, *n*/N (%)	54/131 (41.2)	882/2351 (37.5)	0.39			
Alcohol use, *n*/N (%)	58/138 (42.0)	939/2176 (43.2)	0.80			
BMI (kg/m^2, mean [SD])	23.6 (4.8)	23.2 (5.0)	0.37			
Platelet count ($\times 10^3$ U/L, mean (SD))	149.2 (89.1)	169.2 (68.7)	0.01			
ALT (U/L, mean (SD))	80.4 (111.1)	145.6 (222.1)	<0.001	0.996	0.994–0.998	0.001
Cretinine (mg/dL, mean (SD))	0.9 (0.5)	0.9 (0.8)	0.61			
HBV DNA ($\log_{10}$ IU/mL, mean (SD))	5.5 (2.2)	5.8 (2.2)	0.10			
Baseline GGT (U/L, mean (SD))	89.3 (85.1)	67.4 (74.3)	0.002	1.004	1.003–1.006	<0.001
Month-6 GGT (U/L, mean (SD))	62.1 (57.4)	38.4 (56.9)	<0.001			
Baseline AFP (ng/mL, mean (SD))	94.6 (696.4)	20.0 (102.2)	0.21			
Month-6 AFP (ng/mL, mean (SD))	32.9 (243.3)	7.7 (76.5)	0.29			
HBeAg seropositivity, *n*/*N* (%)	59/152 (38.8)	1161/2606 (44.6)	0.17			
Fatty liver						
Yes, *n* (%)	8 (4.9)	337 (12.6)	<0.001			
No, *n* (%)	111 (68.5)	1921 (71.7)				
Data unavailable, *n* (%)	43 (26.5)	423 (15.8)				
Liver cirrhosis, *n* (%)	91 (56.2)	674 (25.1)	<0.001	2.66	1.92–3.70	<0.001
Follow-up period (months, mean (SD))	64.0 (40.5)	74.9 (44.4)	-			

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI: confidence intervals; GGT, γ-glutamyl transferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; Month-6, 6 months after receiving NAs therapy; NAs, nucleotide analogues; SD, standard deviation.

$p < 0.001$) (Table 2). The best cut-off value of pretreatment GGT level for predicting HCC was 68.5 U/L (AUROC, 0.59; $p < 0.001$) (Figure S1). While we defined a pretreatment GGT level ≥70 U/L as a high GGT level and vice versa, the cumulative incidences of all-cause mortality were 0.7%, 1.9%, 4.7%, 10.3%, and 15.4% in patients with high pretreatment GGT levels, which were higher compared to 0.2%, 1.3%, 2.2%, 5.0%, and 8.4% in patients with low pretreatment GGT levels at the 1-, 3-, 5-, 8-, and 10-year follow-ups, respectively ($p < 0.001$) (Figure S2). A high pretreatment GGT level independently predicted all-cause mortality (HR/CI: 2.24/1.58–3.18, $p < 0.001$) (Table S1).

3.4 | Risk factors for liver-related mortality

The annual incidence of liver related mortality was 0.6% (CI: 0.5%–0.7%). Compared to patients without liver-related mortality, those with liver-related mortality were older (56.8 vs. 49.8 years, $p < 0.001$), had a higher prevalence of diabetes (21.1% vs. 11.7%, $p = 0.01$) and liver cirrhosis (70.1% vs. 25.3%, $p < 0.001$), lower prevalence of fatty liver disease (3.1% vs. 12.5%, $p = 0.001$), higher pretreatment (95.5 vs. 67.7 U/L, $p = 0.001$) and Month-6-GGT levels (71.4 vs. 38.6 U/L, $p < 0.001$), and lower platelet count (132.6 $\times$ 10^3 vs. 169.3 $\times$ 10^3 U/L, $p < 0.001$) and ALT levels (78.1 vs. 144.7 U/L, $p < 0.001$). The Cox-regression analysis revealed that the factors associated with liver-related mortality were liver cirrhosis (HR/CI: 4.36/2.76–6.89, $p < 0.001$), age (HR/CI: 1.03/1.01–1.05, $p < 0.001$), pretreatment GGT levels (HR/CI: 1.006/1.004–1.008, $p < 0.001$), ALT level (HR/CI: 0.993/0.990–0.997, $p = 0.001$), and fatty liver disease (HR/CI: 0.30/0.15–0.59, $p = 0.001$) (Table 3).

3.5 | Risk factors for non-liver-related mortality

The annual incidence of non-liver-related mortality was 0.2% (CI: 0.2%–0.3%). Compared with patients without non-liver-related mortality, those with non-liver-related mortality were older (63.7 vs. 49.8 years, $p < 0.001$), had a higher prevalence of diabetes (28.6% vs. 11.8%, $p = 0.003$), lower prevalence of fatty liver disease (9.5% vs. 12.2%, $p = 0.008$), and substantially higher pretreatment GGT levels (85.7 vs. 68.4 U/L, $p = 0.14$). The Cox regression analysis revealed that the factors associated with non-liver-related mortality were age (HR/CI: 1.10/1.07–1.13, $p = 0.001$) and pretreatment GGT levels (HR/CI: 1.003/1.000–1.005, $p = 0.03$) (Table 4).

TABLE 3 Factors associated with liver-related mortality.

				Cox-regression analysis		
Liver-related mortality	**Yes, $n = 97$**	**No, $n = 2723$**	***p* value**	**HR**	**95% CI**	***p* value**
Age (years, mean (SD))	56.8 (10.8)	49.8 (12.9)	<0.001	1.03	1.01–1.05	<0.001
Male, *n* (%)	69 (71.1)	1759 (64.6)	0.19			
Diabetes, *n*/*N* (%)	20/95 (21.1)	312/2661 (11.7)	0.01			
Smoking, *n*/*N* (%)	34/88 (38.6)	897/2385 (37.6)	0.85			
Alcohol use, *n*/*N* (%)	40/83 (48.2)	949/2211 (42.9)	0.34			
BMI (kg/m^2, mean (SD))	23.8 (5.1)	23.2 (5.0)	0.34			
Platelet count ($\times 10^3$ U/L, mean (SD))	132.6 (83.4)	169.3 (69.3)	<0.001			
ALT (U/L, mean (SD))	78.1 (112.4)	144.7 (218.9)	<0.001	0.993	0.990–0.997	0.001
Cretinine (mg/dL, mean (SD))	0.9 (0.5)	0.9 (0.8)	0.72			
HBV DNA ($\log_{10}$ IU/mL, mean (SD))	5.7 (1.9)	5.8 (2.2)	0.64			
Baseline GGT (U/L, mean (SD))	95.5 (80.8)	67.7 (74.7)	0.001	1.006	1.004–1.008	<0.001
Month-6 GGT (U/L, mean (SD))	71.4 (64.2)	38.6 (56.7)	<0.001			
Baseline AFP (ng/mL, mean (SD))	143.2 (876.5)	19.9 (101.6)	0.20			
Month-6 AFP (ng/mL, mean (SD))	48.2 (302.0)	7.6 (76.1)	0.27			
HBeAg seropositivity, *n*/*N* (%)	37/93 (39.8)	1175/2643 (44.5)	0.37			
Fatty liver						
No, *n* (%)	83 (85.6)	1945 (71.5)		1		
Yes, *n* (%)	3 (3.1)	341 (12.5)	0.001	0.30	0.15–0.59	0.001
Data unavailable, *n* (%)	11 (11.3)	437 (16.0)		0.55	0.17–1.80	0.32
Liver cirrhosis, *n* (%)	68 (70.1)	690 (25.3)	<0.001	4.36	2.76–6.89	<0.001
Follow-up period (months, mean (SD))	59.5 (33.9)	74.6 (44.4)	-			

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GGT, γ-glutamyl transferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC: hepatocellular carcinoma; HR, hazard ratio; Month-6, 6 months after receiving NAs therapy; NAs, nucleotide analogues; SD, standard deviation.

TABLE 4 Factors associated with the non-liver-related mortality after HBV NAs use.

				Cox-regression analysis		
Non-liver-related mortality	**Yes, $n = 42$**	**No, $n = 2778$**	***p* value**	**HR**	**95% CI**	***p* value**
Age (years, mean (SD))	63.7 (13.2)	49.8 (12.8)	<0.001	1.10	1.07–1.13	0.001
Male, *n* (%)	27 (64.3)	1801 (64.8)	1.00			
Diabetes, *n*/*N* (%)	12/42 (28.6)	320/2714 (11.8)	0.003			
Smoking, *n*/*N* (%)	15/34 (44.1)	916/2439 (37.6)	0.48			
Alcohol use, *n*/*N* (%)	10/35 (28.6)	979/2259 (43.3)	0.21			
BMI (kg/m^2, mean (SD))	23.8 (4.0)	23.2 (5.0)	0.52			
Platelet count ($\times 10^3$ U/L, mean (SD))	175.2 (98.9)	167.9 (69.6)	0.64			
ALT (U/L, mean (SD))	87.5 (113.2)	143.2 (217.6)	0.10			
Cretinine (mg/dL, mean (SD))	0.9 (0.5)	0.9 (0.8)	0.82			
HBV DNA ($\log_{10}$ IU/mL, mean (SD))	5.0 (2.7)	5.8 (2.2)	0.07			
Baseline GGT (U/L, mean (SD))	85.7 (100.6)	68.4 (74.7)	0.14	1.003	1.000–1.005	0.03
Month-6 GGT (U/L, mean (SD))	50.0 (43.3)	39.6 (57.5)	0.13			
Baseline AFP (ng/mL, mean (SD))	12.9 (19.4)	24.5 (196.0)	0.75			
Month-6 AFP (ng/mL, mean (SD))	4.6 (3.0)	9.1 (94.5)	0.83			
HBeAg seropositivity, *n*/*N* (%)	13/37 (35.1)	1199/2699 (44.4)	0.32			
Fatty liver						
Yes, *n* (%)	4 (9.5)	340 (12.2)	0.008			
No, *n* (%)	24 (57.1)	2004 (72.1)				
Data unavailable, *n* (%)	14 (33.3)	434 (15.6)				
Liver cirrhosis, *n* (%)	16 (38.1)	742 (26.7)	0.11			
Follow-up period (months, mean (SD))	56.9 (41.0)	74.3 (44.2)	-			

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein; BMI, body mass index; CI, confidence interval; GGT, γ-glutamyl transferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; Month-6, 6 months after receiving NAs therapy; NAs, nucleotide analogues; SD, standard deviation.

3.6 | Sensitivity analysis of risk factors for all-cause mortality

To avoid the influence of alcohol use on GGT levels, we further excluded patients who had a history of significant alcohol use, and the result remained consistent in that pretreatment GGT levels independently predicted all-cause mortality (HR/CI: 1.005/1.003–1.008, $p = 0.02$) (Table 5). We further addressed the role of GGT levels in mortality among patients treated with potent NAs, entecavir, and tenofovir disoproxil fumarate. Pretreatment GGT levels remained independently predictive of all-cause mortality (HR/CI: 1.005/1.003–1.007, $p < 0.001$) (Table S2).

The mean value of the ULN of GGT level was 57.7 U/L from the participating sites; the ULN ranged from 49 to 70 U/L in the majority of participating sites. Using GGT ULN as the covariant, pretreatment GGT remained independently predictive of all-cause mortality (HR/CI: 1.32/1.21–1.44, $p < 0.001$) (Table S3). GGT has been associated with HCC and may confound the mortality. We further included newly developed HCC as covariant. The result was consistent that pretreatment GGT levels independently predicted all-cause mortality regardless HCC occurrence (HR/CI: 1.004/1.002–1.006, $p < 0.001$) (Table S4). Moreover, GGT remains to have a predictive role in both cirrhotic (HR/CI: 1.003/1.001–1.005, $p = 0.01$) (Table 5) or non-cirrhotic patients (HR/CI: 1.01/1.01–1.02, $p < 0.001$) (Table S6). The cumulative incidences of all-cause mortality were 1.1%, 3.0%, 4.8%, 11.8%, and 18.3% in patients with >75% of the pretreatment GGT ULN, compared to 0.1%, 0.7%, 2.2%, 5.7%, and 9.8% in patients with 25–75 percentile of the pretreatment GGT ULN, and 0.2%, 1.2%, 1.8%, 3.9%, and 4.9% in patients with <25 percentile of the pretreatment GGT ULN at the 1-, 3-, 5-, 8-, and 10-year follow-ups, respectively (p_{trend} <0.001) (Figure S3).

3.7 | Characteristics of the chronic hepatitis B patients with NAs treatment compared by baseline GGT ≥ 70 and GGT < 70 U/L

Compared with patients who had baseline GGT < 70 U/L, those who had baseline GGT ≥ 70 U/L had a higher prevalence of diabetes (18.4% vs. 9.1%, $p < 0.001$) and liver cirrhosis (35.5% vs. 23.1%, $p < 0.001$), lower platelet count (157.6×10^3 vs. 172.7×10^3 U/L, $p = 0.01$) and higher ALT levels (230.2 vs. 102.4 U/L, $p < 0.001$).

TABLE 5 Factors associated with all-cause mortality after excluding patients with the history of alcohol use.

				Cox-regression analysis		
All-cause mortality	**Yes, *n* = 80**	**No, *n* = 1237**	***p* value**	**HR**	**95% CI**	***p* value**
Age (years, mean (SD))	59.4 (11.9)	50.1 (13.4)	<0.001	1.05	1.03–1.08	<0.001
Male, *n* (%)	42 (52.5)	689 (55.7)	0.58			
Diabetes, *n*/*N* (%)	17/79 (21.5)	135/1215 (11.1)	0.01			
Smoking, *n*/*N* (%)	14/67 (20.9)	255/1118 (22.8)	0.88			
BMI (kg/m^2, mean (SD))	23.9 (4.1)	23.4 (4.3)	0.40			
Platelet count ($\times 10^3$ U/L, mean (SD))	152.9 (90.2)	170.6 (66.0)	0.09			
ALT (IU/L, mean (SD))	81.7 (104.8)	153.0 (231.2)	<0.001			
Cretinine (mg/dL, mean (SD))	0.9 (0.6)	0.9 (1.0)	0.91			
HBV DNA ($\log_{10}$ IU/mL, mean (SD))	5.4 (2.2)	5.9 (2.0)	0.07			
Baseline GGT (U/L, mean (SD))	84.5 (89.4)	58.2 (61.2)	0.01	1.005	1.003–1.008	0.02
Month-6 GGT (U/L, mean (SD))	56.1 (54.5)	32.9 (41.6)	<0.001			
Baseline AFP (ng/mL, mean (SD))	52.2 (302.2)	15.9 (63.4)	0.33			
Month-6 AFP (ng/mL, mean (SD))	5.8 (5.4)	9.7 (112.6)	0.81			
HBeAg seropositivity, *n*/*N* (%)	24/74 (32.4)	526/1201 (43.8)	0.23			
Fatty liver						
Yes, *n* (%)	3 (3.8)	197 (15.9)	<0.001			
No, *n* (%)	54 (67.5)	852 (68.9)				
Data unavailable, *n* (%)	23 (28.8)	188 (15.2)				
Liver cirrhosis, *n* (%)	44 (55.0)	283 (22.9)	<0.001	3.02	1.89–4.83	<0.001
Follow-up period (months, mean (SD))	66.4 (40.8)	78.2 (46.2)	-			

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GGT, γ-glutamyl transferase; HBeAg, Hepatitis B e-antigen; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; Month-6: after receiving 6 months of NAs therapy; NAs, nucleotide analogues; SD, standard deviation.

4 | DISCUSSION

Here, we observed an annual incidence of 0.93% for mortality among patients with CHB receiving NA therapy. Compared to patients with low pretreatment GGT levels, those with high serum GGT levels had a 2.2-fold higher risk of mortality. The cumulative incidence of mortality was 15.4% in patients with high GGT levels compared to that of only 8.4% in those with low GGT levels after a 10-years follow-up. Additionally, a dose-dependent increase in pretreatment GGT levels with respect to mortality was observed. The mortality rate was high at 18.3% in the higher quartile in contrast to only 4.9% in the lower quartile after a 10-year follow up. Furthermore, the clinical utility of the easy-to-test surrogate marker could be generalized to all-cause, liver-related, and non-liver-related mortality in patients with CHB who received NA therapy.

The seroprevalence of HBV has drastically decreased since the launch of HBV vaccination.[17,20] However, HBV remains rampant and leads to liver-related complications, including cirrhosis and HCC-related deaths. Moreover, HBV may increase the risk of not only liver-related mortality, but also all-cause mortality.[2–4] A large Chinese cohort study has demonstrated an increased risk of extrahepatic deaths, including infections, digestive diseases, and cardiocerebral vascular diseases. Another registry cohort study in the United States has demonstrated that patients with CHB have a 1.85-fold higher risk of all-cause mortality and die 14 years younger than the general population.[2] Zhou et al. have reported a similar 1.9-fold higher risk of all-cause mortality in patients with CHB, and an increasing trend has been observed in the mortality rate from past HBV infection (defined as anti-core antibody seropositivity but HBsAg seronegativity) to current HBV infection compared to uninfected controls.[3] The incidence of all-cause mortality in patients with CHB was 1.9%–2.1% per person-year in the aforementioned two studies.[2,3] However, only 6%–24% of the patients with CHB received antiviral agents. Unlike other studies that disclosed diabetes and alcohol as the underlying risk factors for mortality in the natural course,[2,21,22] the current study explicitly disclosed a low mortality rate in NA-treated patients with CHB, and old age and underlying cirrhosis were the two major clinical risk factors for mortality.

GGT levels have traditionally been used as a marker of liver injury. GGT levels counteract oxidative stress by enabling the extracellular metabolism of glutathione.[8] Elevated GGT levels also indicate cellular damage and pro-oxidant activity,[23] and they have been associated with not only liver disease,[24] but also other systemic diseases, such as cardiovascular disease, metabolic disorders, and malignant

neoplasms.[10,25] Meanwhile, elevated GGT levels are associated with liver-related mortality, cardiovascular mortality, and all-cause mortality in the general population.[26] While we focused on patients with CHB, serum GGT levels have been associated with liver disease severity,[27] antiviral treatment efficacy,[12] and HCC invasiveness and prognosis.[12,27–29] For patients with viral-suppressed CHB, serum GGT levels are correlated well with HCC occurrence in NA-treated patients.[12] However, reports regarding their role in predicting mortality in patients with CHB who received antiviral therapy are scarce. In this study, we demonstrated that pretreatment GGT levels predicted CHB-related mortality during a mean follow-up period of over 5 years. A high GGT level may be an indicator of not only liver injury, but also profound oxidative stress, which may be directly or indirectly linked to mortality even when HBV activity is well suppressed.

Meanwhile, GGT levels were associated with the presence of fatty liver disease,[30,31] which has also been linked to all-cause and cardiovascular mortality.[32] The co-existence of fatty liver disease in CHB is a two-edged sword, and its impact on CHB-related outcomes remains controversial.[33,34] The conflicting results may be attributed to different study populations and designs, variable viral status, and the uncertain definition of fatty liver disease. Here, the patients with liver-related mortality had a lower prevalence of fatty liver disease, which may in part be attributed to burn-out fibrosis. Despite the complex interplay between fatty liver disease and viral hepatitis, the current study clearly demonstrated the independent role of serum GGT levels in predicting CHB-related mortality, regardless of fatty liver disease. This result accords with that of a recent Korean study suggesting the strong association of elevated GGT levels with an increased risk of all-cause mortality, irrespective of the presence of fatty liver disease in the general population.[35]

The current study was limited by its inability to exclude drug-induced GGT elevation. Nevertheless, the study outcome was mortality, and none of the patients died of drug-induced liver injury. We also failed to consider all the potential causes of elevated GGT levels associated with mortality. For example, the precise amount of alcohol consumption was not available in this multi-region retrospective cohort study. Nevertheless, GGT levels remained predictive of mortality after strictly excluding patients with a history of alcohol use, indicating the potential role of GGT levels in predicting HBV-related mortality. We have excluded preexisting HCC in the current study, but we regret that the information regarding the timing of newly developed HCC was not available in this multi-national cohort. Nevertheless, we further included newly developed HCC as covariant in terms of the mortality. The result was consistent that pretreatment GGT levels independently predicted all-cause mortality regardless HCC occurrence. In conclusion, pretreatment serum GGT levels predicted all-cause, liver-related, and non-liver-related mortality among patients with CHB. These findings warrant further validation in different study groups and may guide further studies that incorporate surrogate markers into mortality prediction models in patients with CHB.

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CONFLICT OF INTEREST STATEMENT

Chung-Feng Huang has received speaker honoraria from AbbVie, BMS, Bayer, Gilead Sciences, Merck, and Roche. Ming-Lung Yu has received research support from AbbVie, Abbott, BMS, Gilead Sciences, Merck and Roche diagnostics; and served as consultant for AbbVie, Abbott, Ascletis, BMS, Gilead Sciences, J&J, Merck, Novartis, Pharmaessential and Roche diagnostics; and received speaker honoraria from AbbVie, Abbott, BMS, Gilead Sciences, Merck, Pharmaessential and Roche diagnostics. Mindie H. Nguyen has received research support from Pfizer, Enanta, Gilead, Exact Sciences, Vir Biotech, Helio Health, National Cancer Institute, Glycotest, B.K. Kee Foundation and CurveBio; and served as Consultant and/or Advisory Board for Intercept, Exact Science, Gilead, GSK, Eli Lilly, Laboratory of Advanced Medicine. All authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jang T-Y, Liang P-C, Jun DW, Jung JH, Toyoda H, Wang C-W, et al. Pretreatment gamma-glutamyl transferase predicts mortality in patients with chronic hepatitis B treated with nucleotide/nucleoside analogs. Kaohsiung J Med Sci. 2024;40(2):188–97. https://doi.org/10.1002/kjm2.12771