Increased incidence of gastroesophageal reflux disease in patients with chronic hepatitis B virus infection

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Abstract

Background Although chronic liver disease is associated with gastroesophageal reflux disease (GERD), the impact of chronic hepatitis B virus (HBV) infection on this association remains unclear. We thus aimed to evaluate the relationship between chronic HBV infection and GERD.

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Methods In this prospective population-based study, 1,001 adult subjects who underwent an upper gastrointestinal endoscopic examination in a health check-up and completed a gastroesophageal reflux questionnaire were consecutively enrolled. Endoscopic findings were classified according to the Los Angeles classification. Hepatitis B surface antigen was used as a marker of HBV infection. Univariate and multivariate approaches were used to evaluate the effects of chronic HBV infection on GERD.

Results Chronic HBV infection was associated with heartburn sensation [odds ratio (OR) 1.27, 95% confidence interval 1.01–1.61, $P = 0.037$], and erosive esophagitis (adjusted OR 1.75, 1.03–2.97, $P = 0.037$). Although male gender is a risk factor of erosive esophagitis, further analyses stratified by gender and aspartate aminotransferase to platelet ratio index (APRI) showed that chronic HBV infection was associated with erosive esophagitis in female subjects (adjusted OR 2.70, 1.14–6.39, $P = 0.024$) and those with APRI of more than 0.3 (adjusted OR 3.94, 1.73–8.96, $P = 0.001$). Moreover, higher serum aspartate aminotransferase (AST) and triglyceride (TG) levels were risk factors of erosive esophagitis in patients with chronic HBV infection.

Conclusions Our findings indicate a close association between chronic HBV infection and GERD, especially in female subjects and those with higher APRI levels. Moreover, HBV carriers with higher AST or TG levels have higher incidence of erosive esophagitis. The interactions between chronic HBV infection and GERD need further studies.

Keywords Hepatitis B virus · Gastroesophageal reflux disease · Erosive esophagitis · Los Angeles classification · Endoscope · Questionnaire

Abbreviations

HBV	Hepatitis B virus
HCV	Hepatitis C virus
ALT	Alanine transaminase
AST	Aspartate transaminase
ALP	Alkaline phosphatase
AFP	Alfa fetoprotein
TG	Triglyceride
TC	Total cholesterol
HDL	High-density lipoprotein-cholesterol
LDL	Low-density lipoprotein-cholesterol
HbA1c	Hemoglobin A1c
PLT	Platelet count
BMI	Body mass index
GERD	Gastroesophageal reflux disease
EE	Erosive esophagitis
APRI	Aspartate aminotransferase to platelet ratio index
ULN	Upper limit of normal
RDQ	Reflux Disease Diagnostic Questionnaire
NSAID	Non-steroid anti-inflammatory drug
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

Introduction

Hepatitis B virus (HBV) infection can cause acute and chronic liver disease, including chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [1]. Worldwide over 2 billion people have been infected with HBV, and nearly 400 million people are chronic carriers of the virus. Although effective vaccines against HBV infection have been available for more than two decades, chronic HBV infection remains a global public health threat.

Gastroesophageal reflux disease (GERD) affects the quality of patients' life, increases the risk for esophageal adenocarcinoma, impacts public health, increases the economic burden gradually, and is becoming increasingly prevalent in recent years [2]. Identification of risk factors or interaction with other diseases that could serve as the basis for the treatment or prevention of GERD is therefore highly warranted [3]. Several extra-esophageal manifestations have been linked with GERD, such as chronic bronchitis, interstitial pneumonia, bronchial asthma, laryngitis, and coronary artery disease [4]. Although several studies mentioned a link between chronic liver disease and GERD [5, 6], the major limitations included small sample size, specific focus on patients with cirrhosis or quality of life rather than liver disease per se.

Because both chronic HBV infection and GERD are prevalent globally, and have huge impacts on human

health, it is thus important to elucidate the relationship and possible interactions between these two disorders. Taiwan is a country endemic for chronic HBV infection and this advantage prompted us to investigate the relationship between chronic HBV infection and GERD, including GERD symptoms and erosive esophagitis.

Methods

Study design

Cross-sectional design

A prospectively and population-based survey followed by endoscopy and ultrasonography.

Study population

A total of 2,843 general healthy and potentially eligible subjects who underwent health examinations at the Health Management Center of Buddhist Tzu Chi General Hospital, Taipei branch, Taiwan between July and December 2007 were screened. Among them, subjects with obvious epigastric discomforts or GERD or anti-viral therapy were excluded, and followed or treated at the outpatient clinics. 1,021 (35.9%) subjects were willing to respond to the survey, and agreed to receive the upper gastrointestinal endoscopic examination. After excluding 20 subjects with ineligible or insufficient data, 1,001 were finally enrolled (Fig. 1). Chronic HBV infection was defined as the positivity of hepatitis B surface antigen (HBsAg) and a past history of HBV carriage. All of the subjects were negative for anti-HCV or HIV antibody, and none had a known history or serological evidence suggestive of autoimmune liver disease, inheritable disorders such as hemochromatosis or Wilson's disease, renal insufficiency, or a history of drug abuse.

Demographic, serological and biochemical data

The data of age, gender, body weight, body height, body mass index (BMI), waist circumference, serum fasting blood glucose, hemoglobin A1c (HbA1c), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels, and platelet counts were collected.

BMI was calculated as weight in kilograms divided by height in square meters. Blood samples were collected in the morning after 12 h fasting and measured by standard

Fig. 1 The flow diagram of this study

laboratory techniques. Platelet counts were performed by an automated Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan). Serum fasting blood glucose, TG, TC, LDL, HDL, ALP, AST, and ALT levels were measured by an auto analyzer (ROCHE ANALYTICS; Roche Professional Diagnostics, Penzberg, Germany).

Metabolic syndrome was defined according to the latest International Diabetes Federation consensus worldwide definition [7, 8] as the presence of central obesity (a waist circumference ≥ 90 cm for Taiwanese men and ≥ 80 cm for Taiwanese women) plus any two of the following four risk factors: TG concentration ≥ 150 mg/dL, or specific treatment for this lipid abnormality; HDL-cholesterol concentration < 40 mg/dL in men and < 50 mg/dL in women, or specific treatment for this lipid abnormality; blood pressure $\geq 130/85$ mmHg, or treatment of previously diagnosed hypertension; or fasting plasma glucose ≥ 100 mg/dL, or previously diagnosed type 2 diabetes.

Aspartate aminotransferase to platelet ratio index (APRI) was used to assess liver fibrosis severity by the following formula and upper limit of normal (ULN) of serum AST level was set at 40 IU/L as previously described [9]:

$$\text{APRI} = ([\text{AST}/\text{ULN}]/\text{platelet count} [\times 10^9/\text{L}]) \times 100$$

HBsAg and anti-HCV were assayed with commercial kits (Abbott Laboratories, North Chicago, IL, USA).

Questionnaire and additional medical information

The Reflux Disease Diagnostic Questionnaire (RDQ) is a reliable and valid instrument for the diagnosis of GERD that could be easily administered by primary care physicians in community settings. It examines symptoms of heartburn, acid regurgitation and dyspepsia, and contains 12 questions on the frequency, severity, and duration of burning and pain behind breastbone, acid taste in mouth, movement of materials upward from the stomach, and

burning and pain in the upper stomach [10]. Most response options are scaled with categories ranging from one to five points for frequency, severity, and duration of symptoms.

Before receiving upper gastrointestinal endoscopic examination, all patients and controls underwent personal interviews conducted by trained professional interviewers who completed questionnaires and recorded additional medical information, including smoking, alcohol consumption, history of diabetes mellitus, hypertension, and use of the following medications: aspirin or non-steroid anti-inflammatory drugs, histamine 2 receptor antagonist, proton pump inhibitor, over the counter GERD therapy, and anti-viral therapy.

Smoking status was categorized into ever smokers (including past and current smokers at the time of filling in the questionnaires) and never smokers. Alcohol consumption was evaluated by summing the total amount of ethanol (beer, wine and spirits) consumed per week in grams, and categorized into no excessive alcohol intake (< 140 g/week) and excessive alcohol consumer (≥ 140 g/week).

Endoscopic examination

Upper gastrointestinal endoscopy was offered to all participants who responded to the survey. Standardized sedated endoscopic examination of the esophagus, stomach, and duodenum was performed. Eight experienced endoscopists who were blinded to the results of the questionnaire performed all procedures, and one of them (P. C. Wang) reviewed all the endoscopic pictures. The severity of erosive esophagitis was graded from A to D according to the Los Angeles (LA) classification [11]. However, only 20 subjects were graded as B and 1 as C, so we collapsed the grading and the presence of erosive esophagitis defined as yes/or no was used. Any discordance in diagnosis was discussed by at least three experienced endoscopists, and the final diagnosis was made by consensus. We used the

aforementioned methods to avoid interobserver and intra-observer variability.

Ultrasound examination

A GE LOGIO 5 Pro Ultrasound system (GE Medical Systems, Seoul, Korea) with a 4-MHz electronic probe was used to examine the livers. The parenchyma of liver was assessed on the basis of ultrasonographic findings of coarsened or heterogeneous echo pattern, increased parenchymal echogenicity, and nodularity of liver surface as previously described [12], and was classified into the following three categories: normal (N), none of the above findings; parenchymal liver disease (PLD), one of the findings; liver cirrhosis (LC), two or more of the findings.

Ethical considerations

The study was performed in accordance with the principles of the Declaration of Helsinki, and was approved by the Ethical Committee of the Buddhist Tzu Chi General Hospital in Taipei, Taiwan. Written informed consent was obtained from each participant.

Statistical analysis

The data were presented as percentages for categorical variables and mean with standard deviations for continuous variables unless mentioned otherwise. Chi-square tests, *t* tests, and Wilcoxon's tests were used to analyze categorical, parametric continuous and non-parametric variables, respectively. Unadjusted and adjusted odds ratio (OR) and 95% confidence interval (CI) as well as *P* values were estimated for each variable by logistic regression.

To elucidate the associations between chronic HBV infection and GERD, multivariate analyses using a general logistic regression model with serostatus of HBsAg as a dependent variable were conducted. Risk factors of GERD or HBV infection or a *P* value of <0.05 in univariate analysis were candidates to be added into the model. Several factors were known to increase the risk of GERD, such as age, sex, BMI, and metabolic factors, so we finally included erosive esophagitis, age at enrollment, gender, BMI, fasting blood glucose, TC, AST, ALP levels and platelet counts into this model.

To further examine aforementioned relationships in terms of different genders and APRI levels, the 75 percentile of APRI was used as a cutoff point and stepwise linear regression analysis (backward) was performed to examine the association between chronic HBV infection and GERD. The presence of erosive esophagitis was used as dependent variable, and age, sex, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood

pressure (DBP), HBsAg, fasting blood glucose, HbA1c, TG, TC, LDL, HDL level, AST, ALT, history of DM, hypertension, smoking, alcohol consumption, and APRI as independent variables. A *P* value of ≥ 0.2 is the significant level for removal from the model, and a *P* value of <0.1 is the significant level for addition to the model. All analyses were performed with Stata statistical software (version 8.0, Stata Corp., College Station, TX, USA). All tests were two-sided and a *P* value of <0.05 was considered statistically significant.

Results

The characteristics and biochemical profiles of study populations

A total of 1,001 persons (93 HBV carriers and 908 non-HBV subjects) were enrolled. Demographic, biochemical, status of HBsAg, endoscopic and ultrasonographic characteristics of the study population were compared between HBV carriers and non-HBV subjects (Table 1). The mean value of BMI in enrollers fell in the normal range for the Southeast Asian population as a whole. The distribution of BMI was comparable between HBV carriers and non-HBV subjects: <24 kg/m², 54/550 (58.1 vs. 60.6%); 24–27 kg/m², 25/239 (26.9 vs. 26.3%); 27–30 kg/m², 12/86 (12.9 vs. 9.5%); >30 kg/m², 2/33 (2.2 vs. 3.6%). Although the mean value of fasting blood glucose levels tended to be higher in HBV carriers than in non-HBV subjects, the distribution of fasting blood glucose levels was comparable between HBV carriers and non-HBV subjects (*P* = 0.089): <100 mg/dL, 58/615 (62.4 vs. 67.7%); 100–126 mg/dL, 23/230 (24.7 vs. 25.3%); >126 mg/dL, 12/63 (12.9 vs. 6.9%). In contrast, the mean level of APRI was comparable between HBV carriers and non-HBV subjects, but the distribution of APRI levels was different (HBV vs. non-HBV, *P* = 0.005): <25 percentile of APRI, 13/237 (14.0 vs. 26.1%); 25 percentile to 50 percentile, 21/229 (22.6 vs. 25.2%); 50–75 percentile, 23/228 (24.7 vs. 25.1%); >75 percentile, 36/214 (38.7 vs. 23.6%).

Hepatitis B e antigen (HBeAg), a marker representing active replication of HBV, is not routinely screened during the healthy examination in Taiwan. However, we collected available medical records of our HBV carriers and found those who had available HBeAg data were all negative for HBeAg [54/93 (58.1%)].

Associations between chronic HBV infection and GERD

Table 2 shows the multivariate analyses between chronic HBV infection and erosive esophagitis. A *P* value of <0.05

Table 1 Demographic, biochemical features, and components of metabolic syndrome of enrolled subjects

Characteristics	Mean $\pm$ SD or <i>n</i> (%)		OR (95% CI)	<i>P</i> value
	Non-HBV (<i>n</i> = 908)	HBV (<i>n</i> = 93)		
Age (years)	52.0 $\pm$ 11.7	52.2 $\pm$ 9.1	1.00 (0.98–1.02)	0.866
Male [<i>n</i> (%)]	419 (46.1)	54 (58.1)	1.62 (1.05–2.49)	0.028
BMI (kg/m ²)	23.4 $\pm$ 3.4	23.6 $\pm$ 3.1	1.02 (0.96–1.08)	0.549
Waist circumference (cm) ^a	80.4 $\pm$ 9.5	81.5 $\pm$ 9.3	1.01 (0.99–1.03)	0.325
SBP (mmHg)	121.8 $\pm$ 17.0	122.1 $\pm$ 15.7	1.00 (0.99–1.01)	0.882
DBP (mmHg)	75.4 $\pm$ 12.0	77.3 $\pm$ 12.2	1.01 (1.00–1.03)	0.131
Fasting blood glucose (mg/dL)	99.3 $\pm$ 23.8	107.7 $\pm$ 38.3	1.01 (1.00–1.01)	0.002
HbA1c (%) ^a	5.5 $\pm$ 0.7	5.7 $\pm$ 1.2	1.22 (1.00–1.49)	0.037
Diabetes mellitus, yes = 1 [<i>n</i> (%)]	39 (4.3)	6 (6.5)	1.54 (0.63–3.73)	0.339
Hypertension, yes = 1 [<i>n</i> (%)]	157 (17.3)	11 (11.8)	0.64 (0.33–1.23)	0.179
Alcohol, yes = 1 [<i>n</i> (%)]	157 (17.3)	19 (20.4)	1.23 (0.72–2.09)	0.449
Smoking, yes = 1 [<i>n</i> (%)]	73 (8.0)	12 (12.9)	1.69 (0.88–3.25)	0.109
NSAID user, yes = 1 [<i>n</i> (%)]	26 (2.9)	2 (2.2)	0.75 (0.17–3.19)	0.691
Aspirin user, yes = 1 [<i>n</i> (%)]	16 (1.8)	1 (1.1)	0.61 (0.08–4.62)	0.625
AST (IU/L)	24.3 $\pm$ 10.7	26.8 $\pm$ 11.1	1.02 (1.00–1.03)	0.034
ALT (IU/L)	26.9 $\pm$ 21.0	30.2 $\pm$ 20.3	1.01 (1.00–1.01)	0.155
Alkaline phosphatase (AP, IU/L)	68.4 $\pm$ 19.4	72.7 $\pm$ 22.7	1.01 (1.00–1.02)	0.046
Platelet (K/ μ L)	246.1 $\pm$ 59.1	227.7 $\pm$ 68.4	0.99 (0.99–1.00)	0.005
Triglyceride (mg/dL)	132.6 $\pm$ 95.3	121.3 $\pm$ 62.4	1.00 (1.00–1.00)	0.262
Total cholesterol (mg/dL)	196.3 $\pm$ 37.4	188.8 $\pm$ 33.3	0.99 (0.99–1.00)	0.063
LDL (mg/dL)	124.9 $\pm$ 32.6	121.7 $\pm$ 29.9	1.00 (0.99–1.00)	0.357
HDL (mg/dL)	53.3 $\pm$ 14.8	51.3 $\pm$ 14.4	0.99 (0.98–1.01)	0.225
Metabolic syndrome	173 (19.1)	16 (17.2)	0.88 (0.50–1.55)	0.664
Liver sonography (N/PLD/LC)	888/20/0	88/3/2	2.96 (1.30–6.72)	<0.001
APRI	0.28 $\pm$ 0.41	0.32 $\pm$ 0.18	1.17 (0.83–1.67)	0.371
Erosive esophagitis (EE) ^b				
LA classification A/B/C	125/17/1	20/3/0		
Presence of EE, yes = 1 [<i>n</i> (%)]	143 (15.7)	23 (24.7)	1.76 (1.06–2.91)	0.027

Data are shown by mean $\pm$ standard deviation or proportion of the character

N normal liver, *PLD* parenchymal liver disease, *LC* liver cirrhosis, *NSAID* non-steroid anti-inflammatory drug, *APRI* aspartate aminotransferase to platelet ratio index, *EE* erosive esophagitis

^a Three non-HBV enrollers did not have waist circumference data, and two without HbA1c

^b The severity of erosive esophagitis was graded from A to D according to the LA classification. However, only 20 subjects were graded as B and one as C, so we collapsed the grading and the presence of erosive esophagitis defined as yes/or no was used

in univariate analysis (Table 1) was the significance level for addition to the model (see “Statistical analysis”). Erosive esophagitis, higher fasting blood glucose, lower TC, higher ALP levels and lower platelet counts were associated with chronic HBV infection ($P < 0.05$).

Considering the possible confounding effects on the analyses of chronic HBV infection and GERD, we also conducted subgroup analyses with correlates of GERD. The association between erosive esophagitis and chronic HBV infection was unchanged in subjects with waist circumference ≤ 90 cm, LDL ≤ 130 mg/dL, fasting blood glucose level ≥ 100 mg/dL, or lower HDL levels

(supplementary Tables 1, 2), and was similar in subjects without using aspirin or non-steroid anti-inflammatory drugs, or alcohol consumption (supplementary Table 3).

Further evaluation of the associations between chronic HBV infection and GERD symptoms, such as heartburn, acid regurgitation, and dyspepsia (scaled with RDQ points, see questionnaire for details) showed that the sum of RDQ points or the points of each RDQ category were similar between subjects with and without chronic HBV infection, except that HBV carriers had more severe heartburn than non-HBV subjects (OR 1.27, 95% CI 1.01–1.61, $P = 0.037$) (Table 3).

Table 2 Multivariate analyses identifying factors associated with chronic HBV infection ($n = 1,001$)

	OR (95% CI)	<i>P</i> value
Erosive esophagitis	1.75 (1.03–2.97)	0.037
Age (years)	0.99 (0.97–1.01)	0.348
Sex (male = 1)	1.11 (0.69–1.78)	0.677
BMI (kg/m ²)	0.99 (0.93–1.06)	0.849
Fasting blood glucose (mg/dL)	1.01 (1.00–1.01)	0.012
Total cholesterol (mg/dL)	0.99 (0.99–1.00)	0.036
AST (IU/L)	1.01 (0.99–1.03)	0.269
ALP (IU/L)	1.01 (1.00–1.02)	0.027
Platelet (K/ μ L)	0.99 (0.99–1.00)	0.012

Multivariate logistic regression model was used. Use HBsAg (+) as reference and dependent variable, and age, sex, BMI, fasting blood glucose, total cholesterol, AST, ALP, platelet and erosive esophagitis as independent variables

$P < 0.05$ is considered as statistical significance

Factors affecting the associations between chronic HBV infection and GERD

Gender is known to affect the development of GERD and the disease progression in HBV carriers. To adjust the effects of gender and chronic HBV infection on GERD, further analyses stratified by gender revealed a sexual difference on the association of chronic HBV infection with erosive esophagitis. Male subjects with erosive esophagitis had more alcohol consumption, and higher LDL levels, but no increased frequency of chronic HBV infection. In sharp contrast, female subjects with erosive esophagitis were independently associated with chronic HBV infection (adjusted OR 2.70, 1.14–6.39, $P = 0.024$) (Table 4).

Liver cirrhosis is also linked to GERD and is an adverse outcome of chronic HBV infection. In univariate analysis, we consistently found that ultrasonographic liver fibrosis (PLD and cirrhosis) was a significant risk factor of erosive esophagitis [N vs. PLD/LC, 158 (16.2%) vs. 8 (32%), $P = 0.036$]. To examine the effect of liver fibrosis stage on the incidence of GERD in HBV infection, the 75 percentile of APRI (a non-invasive predictor of liver fibrosis and cirrhosis [13–15]) was used as a cutoff point. Multivariate analysis showed that HBV carriers with higher APRI levels had an increased risk of erosive esophagitis than those with lower APRI levels (adjusted OR 3.94, 1.73–8.96, $P = 0.001$) (Table 5).

Finally, stepwise linear regression analysis (backward) was performed to identify factors associated with erosive esophagitis in HBV carriers, and the results showed that higher AST and TG levels were risk factors of erosive esophagitis in HBV carriers (Table 6).

Discussion

In this study, we demonstrated that chronic HBV infection was strongly associated with an increased incidence of GERD, including GERD symptoms and erosive esophagitis. To the best of our knowledge, this is the first prospective population-based study to explore an association between chronic HBV infection and GERD. The increased incidence of GERD in HBV carriers was independent of other known risk factors [16–18]. Moreover, we found a differential association between genders and APRI levels, and chronic HBV infection was an independent risk factor of erosive esophagitis, especially in female subjects and

Table 3 The differences of the Reflux Disease Questionnaire (RDQ) between HBV carriers and non-HBV subjects

Characteristics	Mean $\pm$ SD or <i>n</i> (%)		OR (95% CI)	<i>P</i> value
	Non-HBV (<i>n</i> = 908)	HBV (<i>n</i> = 93)		
Burning feeling behind breastbone, frequency	0.13 $\pm$ 0.51	0.22 $\pm$ 0.67	1.27 (0.93–1.74)	0.118
Burning feeling behind breastbone, severity	0.17 $\pm$ 0.67	0.33 $\pm$ 0.97	1.27 (1.01–1.61)	0.037
Pain behind breastbone, frequency	0.17 $\pm$ 0.60	0.15 $\pm$ 0.51	0.94 (0.64–1.39)	0.767
Pain behind breastbone, severity	0.21 $\pm$ 0.68	0.25 $\pm$ 0.86	1.08 (0.81–1.43)	0.599
Acid taste in mouth, frequency	0.50 $\pm$ 0.98	0.52 $\pm$ 0.96	1.02 (0.82–1.26)	0.887
Acid taste in mouth, severity	0.59 $\pm$ 1.05	0.67 $\pm$ 1.19	1.07 (0.89–1.29)	0.485
Unpleasant movement of material upwards from the stomach, frequency	0.17 $\pm$ 0.61	0.18 $\pm$ 0.62	1.03 (0.73–1.44)	0.882
Unpleasant movement of material upwards from the stomach, severity	0.19 $\pm$ 0.63	0.23 $\pm$ 0.68	1.07 (0.78–1.47)	0.655
Pain in the central of the stomach, frequency	0.42 $\pm$ 0.99	0.54 $\pm$ 1.14	1.11 (0.92–1.34)	0.292
Pain in the central of the stomach, severity	0.54 $\pm$ 1.13	0.72 $\pm$ 1.31	1.13 (0.95–1.33)	0.156
Burning feeling in the central of the stomach, frequency	0.17 $\pm$ 0.65	0.18 $\pm$ 0.66	1.03 (0.76–1.41)	0.841
Burning feeling in the central of the stomach, severity	0.21 $\pm$ 0.74	0.29 $\pm$ 0.92	1.13 (0.88–1.44)	0.335

Data are shown by mean $\pm$ standard deviation or proportion of the character

$P < 0.05$ is considered as statistical significance

Table 4 Multivariate analyses identifying factors associated with erosive esophagitis stratified by gender

	Male (<i>n</i> = 471)		Female (<i>n</i> = 526)	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Alcohol drinking (yes = 1)	1.74 (1.10–2.75)	0.017		
HbA1c (%)	1.21 (0.98–1.49)	0.070	1.79 (1.11–2.89)	0.018
Triglyceride (mg/dL)			1.00 (0.99–1.00)	0.096
HBsAg (+ve = 1)	1.30 (0.67–2.51)	0.435	2.70 (1.14–6.39)	0.024
HDL (mg/dL)	1.01 (1.00–1.03)	0.090		
LDL (mg/dL)	1.01 (1.00–1.02)	0.026		
ALP (IU/L)			0.98 (0.97–1.00)	0.089
SBP (mmHg)	1.01 (1.00–1.03)	0.052	0.99 (0.97–1.01)	0.241
Waist circumference (cm) ^a			1.06 (1.02–1.09)	0.003

Stepwise estimation with backward-selection logistic regression model was used. Use the presence of erosive esophagitis (yes or no) as reference and dependent variable, and age, waist circumference, SBP, DBP, HBsAg, triglyceride, total cholesterol, HbA1c, LDL, HDL level, AST, ALT, ALP levels, history of DM, hypertension, smoking, alcohol consumption and APRI as independent variables

$P \geq 0.2$ is the significant level for removal from the model and $P < 0.1$ is the significant level for addition to the model

^a Three non-HBV enrollers did not have waist circumference data, and two without HbA1c

Table 5 Multivariate analyses identifying factors associated with erosive esophagitis stratified by APRI level

	APRI $\leq 0.3^a$ (<i>n</i> = 737)		APRI > 0.3 (<i>n</i> = 260)	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Alcohol drinking (yes = 1)			2.82 (1.34–5.91)	0.006
Sex (male = 1)	2.71 (1.76–4.19)	<0.001		
BMI (kg/m ²)	0.85 (0.77–0.95)	0.003	1.13 (1.04–1.23)	0.005
HBsAg (+ve = 1)	0.89 (0.42–1.87)	0.760	3.94 (1.73–8.96)	0.001
LDL (mg/dL)	1.01 (1.00–1.02)	0.004		
Waist circumference (cm) ^b	1.05 (1.01–1.09)	0.007		
AST (IU/L)	1.04 (1.00–1.09)	0.062		
HbA1c (%)	1.19 (0.95–1.47)	0.126		

Stepwise estimation with backward-selection logistic regression model was used. Use the presence of erosive esophagitis (yes or no) as reference and dependent variable, and age, sex, waist circumference, SBP, DBP, HBsAg, triglyceride, total cholesterol, HbA1c, LDL, HDL, AST, ALT levels, history of DM, hypertension, smoking, and alcohol consumption as independent variables

$P \geq 0.2$ is the significant level for removal from the model and $P < 0.1$ is the significant level for addition to the model

^a A cut off level of 0.3 was used for APRI, because the 75 percentile of APPI is 0.3060254

^b Three non-HBV enrollers did not have waist circumference data, and two without HbA1c

those with higher APRI levels. Finally, HBV carriers with higher AST or TG levels had an increased incidence of erosive esophagitis.

Several studies indicated a higher frequency of GERD in patients with cirrhosis than those without liver disease [6], and an impaired quality of life in chronic liver disease patients with GERD symptoms [5]. However, their conclusions were undermined by small sample size, enrollment of only patients with cirrhosis, or specific focus on the aspect of life quality. In addition, several risk factors were not analyzed or controlled in previous studies. These factors included age, sex, BMI, metabolic factors, non-steroid anti-inflammatory drug use, and tobacco smoking [2, 19]. In this study, a large health check-up population was

enrolled and all possible risk factors were analyzed at the same time. We not only evaluated the association of chronic HBV infection with endoscopic findings (erosive esophagitis), but also with GERD symptoms. All these measures made our findings more informative and convincing.

Our results demonstrated a gender-related association between chronic HBV infection and GERD. In this study, male gender was a risk factor of erosive esophagitis of all enrollers (OR 2.43, 95% CI 1.63–3.64, $P < 0.001$) (supplementary Table 4), but HBV infection was associated with erosive esophagitis only in females (OR 2.70, 95% CI 1.14–6.39, $P = 0.024$), not in males (OR 1.30, 95% CI 0.67–2.51, $P = 0.435$). The contrary association between

Table 6 Multivariate analyses identifying factors associated with erosive esophagitis in 93 subjects with chronic HBV infection

Characteristics	OR (95% CI)	P value
Sex (male = 1)	3.25 (0.87–12.1)	0.080
Total cholesterol (mg/dL)	1.04 (0.99–1.09)	0.085
Triglyceride (mg/dL)	1.01 (1.00–1.02)	0.021
LDL (mg/dL)	0.96 (0.92–1.01)	0.134
AST (IU/L)	1.11 (1.01–1.23)	0.039
ALT (IU/L)	0.94 (0.88–1.01)	0.097

Stepwise estimation with backward-selection logistic regression model was used. Use the presence of erosive esophagitis (yes or no) as reference and dependent variable, and age, sex, BMI, waist circumference, SBP, DBP, fasting blood glucose, triglyceride, total cholesterol, HbA1c, LDL, HDL, AST, ALT, ALP levels, and APRI as independent variables

$P \geq 0.2$ is the significant level for removal from the model and $P < 0.1$ is the significant level for addition to the model

HBV and non-HBV subjects suggests a close interaction between HBV and sex on the incidence of erosive esophagitis. It is generally believed that estrogen may play a favorable role in the clinical outcomes of chronic HBV infection. A more progressive clinical course and a predominance of cirrhosis as well as HCC in male and postmenopausal female HBV carriers have been observed [20]. In addition, several studies indicated a possible interaction between estrogen/its receptors and HBV, or HBx protein and androgen receptor-responsive gene expression [21]. Taking these lines of evidence together, it is reasonable to speculate that the effect of chronic HBV infection on GERD could be enhanced in female subjects, but attenuated in male subjects. In this study, a stronger association between erosive esophagitis and chronic HBV infection was shown in females than males. These findings not only confirmed an association between chronic HBV and GERD, but also suggested an enhanced association between HBV and GERD in females. Female sex hormones may increase the risk of GERD symptoms through a relaxing effect on the lower esophageal sphincter [22], whether HBV could strengthen this relaxing effect or aggravate GERD through the actions of sex hormone-related mechanisms need further examinations.

The associations of GERD and HBV infection between different stages of hepatic fibrosis are worthy of attention. Although LC has been shown to be associated with the occurrence of GERD, the underlying mechanisms which link both diseases together remained largely unknown. Metabolic syndrome, diabetes mellitus and obesity are known risk factors of LC development [23]. Of particular note is that diabetes mellitus, metabolic syndrome and obesity could also increase the risk of GERD [2]. Thus, metabolic factors may contribute, at least in part, to the linkage between GERD and chronic liver disease. This

speculation was not only supported by our findings that the association between HBV infection and GERD was more prominent in subjects with higher fasting blood glucose or lower HDL levels (supplementary Table 2), but further supported by a recent study in which an association was demonstrated between lower adiponectin level, a key factor of metabolic syndrome [24], and GERD [25]. The emerging evidence seems to shed some light on the mechanisms related to both disorders. In addition, our data also showed a probable additive effect of TG on the occurrence of GERD in HBV carriers. Whether chronic HBV infection could affect the emergence of GERD through metabolic factors as well as related pathways deserve further in vitro and in vivo studies.

Several limitations existed in this study. First, this study was a cross-sectional design, and hence only associations between chronic HBV infection and GERD could be determined. Further studies with longitudinal design and paired controls, such as chronic HCV infection, autoimmune hepatitis, as well as non-alcoholic liver disease, are required to elucidate possible causal relationships. Second, most of the participants were generally healthy, indicating our results may only be applied to asymptomatic HBV carriers. Further studies are necessary to clarify the relationship between GERD and HBV-related chronic hepatitis, cirrhosis or HCC. Third, because few patients with overt liver fibrosis, by which the power to detect a difference may be decreased. We thus used APRI as a surrogate marker to evaluate the severity of liver fibrosis, aiming to increase the power to detect a possible difference between different stages of liver fibrosis. Fourth, because it is not possible to apply both pH-metry and manometric studies to the general population, we only focused on the GERD symptoms and erosive esophagitis. Further evaluation with both methods in HBV cohorts will be informative. Finally, it is difficult to explore all GERD-related factors in a single study. Many factors, such as dietary components, asthma, psychosocial factors, or *Helicobacter pylori* infection have been linked to GERD. Although not fully confirmatory, these associations are clinically important and deserve future studies.

In summary, our data demonstrate a significant association between chronic HBV infection and GERD. The association is differently affected by gender and APRI level. HBV carriers with higher AST or TG levels have an increased incidence of erosive esophagitis. Whether these associations imply an interaction between chronic HBV infection and GERD await further studies.

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Conflict of interest statement P.-J. Chen: consultant for Novartis and Roche. D.-S. Chen: consultant for Novartis and GlaxoSmithKline. J.-H. Kao: consultant for Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Omrix, Roche, and Schering-Plough; on speaker's bureau for Roche, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Schering-Plough. All other authors declare that the answer to the questions on your competing interest form are all no and therefore have nothing to declare.

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