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Non-alcoholic fatty liver disease (NAFLD) and hepatitis B virus (HBV) interplay: Their role in liver disease development

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Abstract

Background and Aims: Hepatitis B virus (HBV) infection is associated with lower risk of non-alcoholic fatty liver disease (NAFLD) in the absence of concurrent metabolic disorder. The aim of this retrospective case-control study is to evaluate the impact of HBV infection on NAFLD patients, the clinical/laboratory characteristics of NAFLD-HBV patients and the NAFLD-HBV coexistence relation with liver disease development.

Methods: The medical charts of 575 NAFLD patients referred to outpatient clinic due to abnormal liver biochemistry and/or the presence of fatty liver were thoroughly reviewed. Finally, 518 patients were included in the study; 402 NAFLD and 116 NAFLD-HBV patients.

Results: NAFLD-HBV patients had significantly lower γ-GT, and platelets, and higher ALP and INR compared to NAFLD patients. Lower percentage of NAFLD-HBV patients were overweight/obese compared to NAFLD patients. NAFLD-HBV patients admitted to hospital more often than NAFLD patients; no difference demonstrated in mortality. In multivariate analysis, HBV coexistence, diabetes mellitus, platelet count and total bilirubin were demonstrated as independent prognostic factors for liver disease development.

Conclusions: NAFLD-HBV comorbidity was associated with reduced body weight, increased hospital admissions risk and liver disease development. NAFLD-HBV coexistence constituted an independent risk factor for liver disease development. Thus, active treatment for both disorders should be recommended.

Key words: *Non-alcoholic fatty liver disease (NAFLD); Hepatitis B virus (HBV); Liver disease; Metabolic disorder; Risk factor*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases, characterized by several degrees of liver damage, ranging from excessive fat accumulation known as hepatic steatosis, to liver injury and liver inflammation, known as nonalcoholic steatohepatitis (NASH), ending up in advanced fibrosis, and liver cirrhosis [1-4]. NAFLD presents a growing global prevalence of roughly 25% in the general population and is closely associated with high rates of hepatocellular carcinoma (HCC), liver transplantation, and mortality [2-4].

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Hepatitis B virus (HBV) infection constitutes a major public health problem worldwide with an estimated prevalence approximately 3.5% [5]. Despite the widespread use of antiviral drugs and vaccination campaigns, there are approximately 350-400 million HBV patients worldwide, who carry high risk of liver cirrhosis and HCC [2,3,6].

Accompanied by the growing prevalence of NAFLD, over recent years, coexistence of NAFLD and HBV is commonly encountered [7]. The accumulating rate of NAFLD among HBV-infected patients is worrying; it is estimated that 29.6% of HBV patients have NAFLD [8,9]. This comorbidity has attracted widespread attention and interest, focusing on the interaction and the association between these two diseases [10,11]. However, great interest is focused on that although NAFLD and chronic hepatitis B (CHB) can collectively deteriorate liver damage and increase the risk of liver cirrhosis and HCC [3,12-15], NAFLD per se seems to present a positive relationship with decreased HBV seromarkers in HBV patients [16-18]. In parallel, HBV patients also exhibited diminished lipidemia incidence [19-21] and NAFLD onset [7,20,22-24].

Thus, the complex interplay between HBV and NAFLD remains vague and their impact on liver disease course is under investigation. The aim of this study was to assess the impact of HBV infection on NAFLD patients and to evaluate their clinical and laboratory characteristics. Secondary aim of the study was to examine the association of HBV-NAFLD coexistence with liver disease development.

MATERIALS AND METHODS

Study population and selection of patients for analysis

Patients referred to the outpatients' clinic of Division of Gastroenterology in University Hospital of Patras, Greece, due to the presence of NAFLD were enrolled to the current retrospective case-control study. In total, the medical charts of 575 NAFLD patients were initially retrieved. In figure 1, the flow chart for inclusion and exclusion criteria for subjects' enrollment in the current study is presented. Therapeutic and diagnostic criteria were applied constantly during the follow-up period. Patients underwent clinical evaluation in the outpatients' clinic at regular intervals according to the current guidelines [25]. Patients with positive serologic markers for hepatitis C (HCV) (n=26), autoimmune hepatitis autoantibodies (n=10),

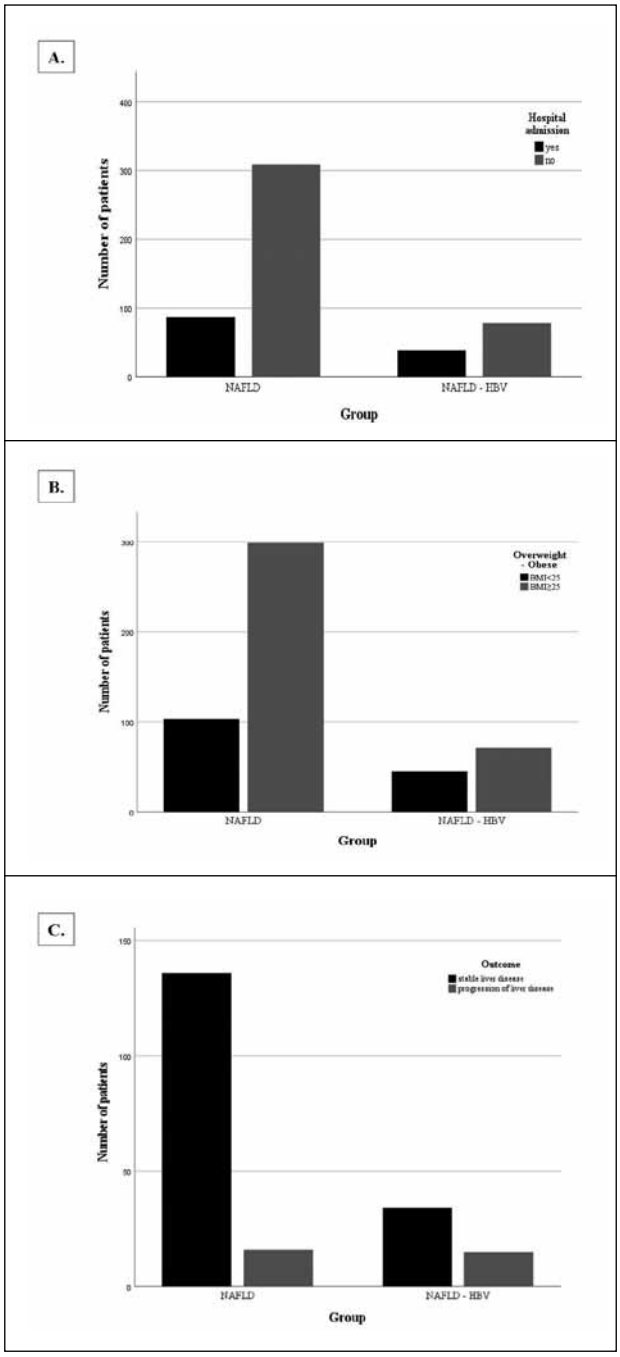

Figure 1. Flow chart of the study design.

primary biliary cirrhosis (PBC) (n=3), hemochromatosis (n=2), human immunodeficiency virus (HIV) (n=1) infection, inflammatory bowel diseases (IBD) (n=3) were excluded from the study [26]. Moreover, excessive alcohol intake (≥210 g/week for men and ≥140 g/week for women) and pregnancy were applied as exclusion criteria [26,27]. Patients who had missing

anthropometry data or metabolic parameters, were not included in this study. Lastly, the presence of liver cirrhosis at baseline was an exclusion criterion, as well. HBV infection alongside NAFLD was reported in 125 patients. Finally, the examined groups of our study comprised 402 individuals with NAFLD and 116 patients with NAFLD and HBV (Figure 1).

Acquisition of clinical data

Participants' demographic data (age, gender, sex), alcohol consumption, smoking, alcohol intake, physical activity, medical history, prior medication use, weight, height, body mass index (BMI), blood pressure, presence of diabetes mellitus, dyslipidemia and hypertension collected from our electronic database. Clinical characteristics were determined according to established criteria [28-31].

Acquisition of laboratory data

Laboratory data were also recorded, including urea, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase (ALP), glutamyl transpeptidase (γ-GT), hemoglobin, platelets (PLTs), total cholesterol, triglycerides, international normalized ratio (INR), alpha-fetoprotein (aFP), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and fasting blood glucose.

Measurements and definitions

Radiologic information was obtained from ultrasound stiffness imaging methods. NAFLD diagnosis was based on the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) - European Association for the Study of Diabetes (EASD) - European Association for the Study of Obesity (EASO) Clinical Practice Guidelines for the Management of NAFLD [25,32]. Obesity was defined according to the Clinical Practice Guidelines for the management of adult obesity by the EASO, as underweight when BMI <18.5, normal range when BMI 18.5–24.9, overweight when BMI 25.0–29.9, obesity when BMI ≥30 [33]. Liver cirrhosis diagnosis was based on clinical, histological, laboratory, and ultrasound findings [34,35].

Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs), while categorical variables were presented as absolute numbers and corresponding percentages. Categorical data were compared using Pearson's chi-squared test or two-sided Fisher's exact test, when applicable. Regarding the continuous variables, Mann-Whitney U test was used to compare differences between two independent groups. Binary logistic regression was performed to assess the risk factors associated with liver disease progression. Liver disease development was defined as a composite endpoint, namely as progression to cirrhosis or HCC development. First, each variable of interest was included in a univariate model and, subsequently, all variables with a p-value<0.05 were included in the multivariate model. A stepwise approach based on backwards elimination was applied. Statistical analysis was performed using the statistical package IBM SPSS version 26.0. The threshold of statistical significance was set at 5% ($p \leq 0.05$).

Ethics

The study protocol was reviewed and approved by the Ethics committee of the University Hospital of Patras, Patras, Greece. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki for medical research involving human subjects.

RESULTS

Patients' characteristics and comparisons between NAFLD-HBV and NAFLD groups

Patients' clinical, demographic, and biochemical characteristics at baseline are presented in Table 1. Overall, 402 patients with NAFLD and 116 patients with NAFLD and HBV were included. Overweight and obese individuals (BMI>25) were significantly higher on NAFLD group (74.4%) compared to NAFLD-HBV group (61.2%) (p=0.007) (Figure 2A). NAFLD-HBV patients presented significantly lower levels of serum γ-GT (p<0.001) and platelets (p=0.041), whereas ALP levels (p=0.023) and INR (p=0.028) were statistically higher in NAFLD-HBV compared to NAFLD group.

NAFLD *versus* NAFLD-HBV patients' outcomes

Hospital admissions, development of liver cirrhosis, development of HCC and mortality were examined as the final outcomes in our study groups. The results showed that the hospital admissions were significantly higher in the NAFLD-HBV group (35.8%) compared to the NAFLD group (22%) (p=0.004) (Table 2 and Figure

Table 1. *Patients' demographics, main clinical and biochemical characteristics at baseline.*

	NAFLD-HBV		NAFLD		
Variable	N	Percentage (%)	N	Percentage (%)	p-value
Sex (M/F)	67/49	57.8/42.2	208/194	51.7/48.3	0.291
Smoking (yes)	34	29.3%	115	28.6%	0.906
BMI>25 (kg/m²)	71	61.2%	299	74.4%	0.007
Hypertension (yes)	47	40.5%	153	38.1%	0.665
Diabetes Mellitus (yes)	33	28.4%	103	25.6%	0.551
Dyslipidemia (yes)	80	68.9%	293	72.9%	0.413
Variable	Median	IQR	Median	IQR	p-value
Age (years)	53	44.5-63.5	53	42-61	0.746
AST (U/L)	40	24.5-55	36	25-58	0.783
ALT (U/L)	45.5	29-79	54.5	31-81.5	0.208
γ-GT (U/L)	33.5	19-75	55	29-109	<0.001
ALP (U/L)	114.5	87-180	98	70-160	0.023
Total Bilirubin (mg/dL)	0.7	0.52-0.9	0.7	0.5-1.0	0.876
Direct Bilirubin (mg/dL)	0.2	0.105-0.3	0.2	0.11-0.22	0.442
Urea (mg/dL)	33	25-40.5	33	28-39	0.710
Creatinine (mg/dL)	0.9	0.8-1.0	0.9	0.8-1.0	0.862
Fasting glucose (mg/dL)	95	87.5-114	101	92-114	0.060
Cholesterol (mg/dL)	216	191.5-244.5	215	187-245	0.957
LDL-cholesterol (mg/dL)	140	102-156	132.5	109.5-161.3	0.737
HDL-cholesterol (mg/dL)	51	41-60	48	40-58.5	0.572
Triglycerides (mg/dL)	126	93.5-173.5	136	100-187	0.225
Hb (g/dL)	14	13-15	14	13.1-15.3	0.330
Plt (cells/μL)	212	172-265	226	190-270.5	0.041
INR	1.0	1.0-1.14	1.0	0.955-1.065	0.028
aFP (ng/ml)	3.3	2.07-5.27	2.9	2.1-4.3	0.101
Liver Stiffness (kPa)	7.4	6/65-12.05	8.1	5.85-10.15	0.685
Weight (kg)	81	70-93.5	83	72-92	0.522
BMI	28.6	25-31.6	29.1	26.6-31.93	0.176

NAFLD: non-alcoholic fatty liver disease, HBV: hepatitis B virus, N: number of patients, M/F: male/female, IQR: interquartile range, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: Gamma-Glutamyl Transferase, ALP: Alkaline phosphatase, LDL: low-density lipoprotein, HDL: LDL high-density lipoprotein, Hb: hemoglobin, Plt: platelets, INR: International normalized ratio, aFP: alpha-fetoprotein, BMI: body mass index

2B). The cumulative mortality rate was 1.7% (2 out of 116 patients) in the NAFLD-HBV group compared to 1.8% (7 out of 400 patients) in the NAFLD group (p=0.999).

Liver disease development

NAFLD-HBV group presented more progressive liver disease compared to NAFLD group (p<0.001). Especially, 20.4% of NAFLD-HBV patients developed liver cirrhosis compared to 7.6% of the NAFLD patients (p=0.011) (table 2). As far as HCC development, 7.4% of the NAFLD-HBV group developed HCC, compared to 1.1% of the NAFLD group (p=0.025) (Table 2). Figure 2C

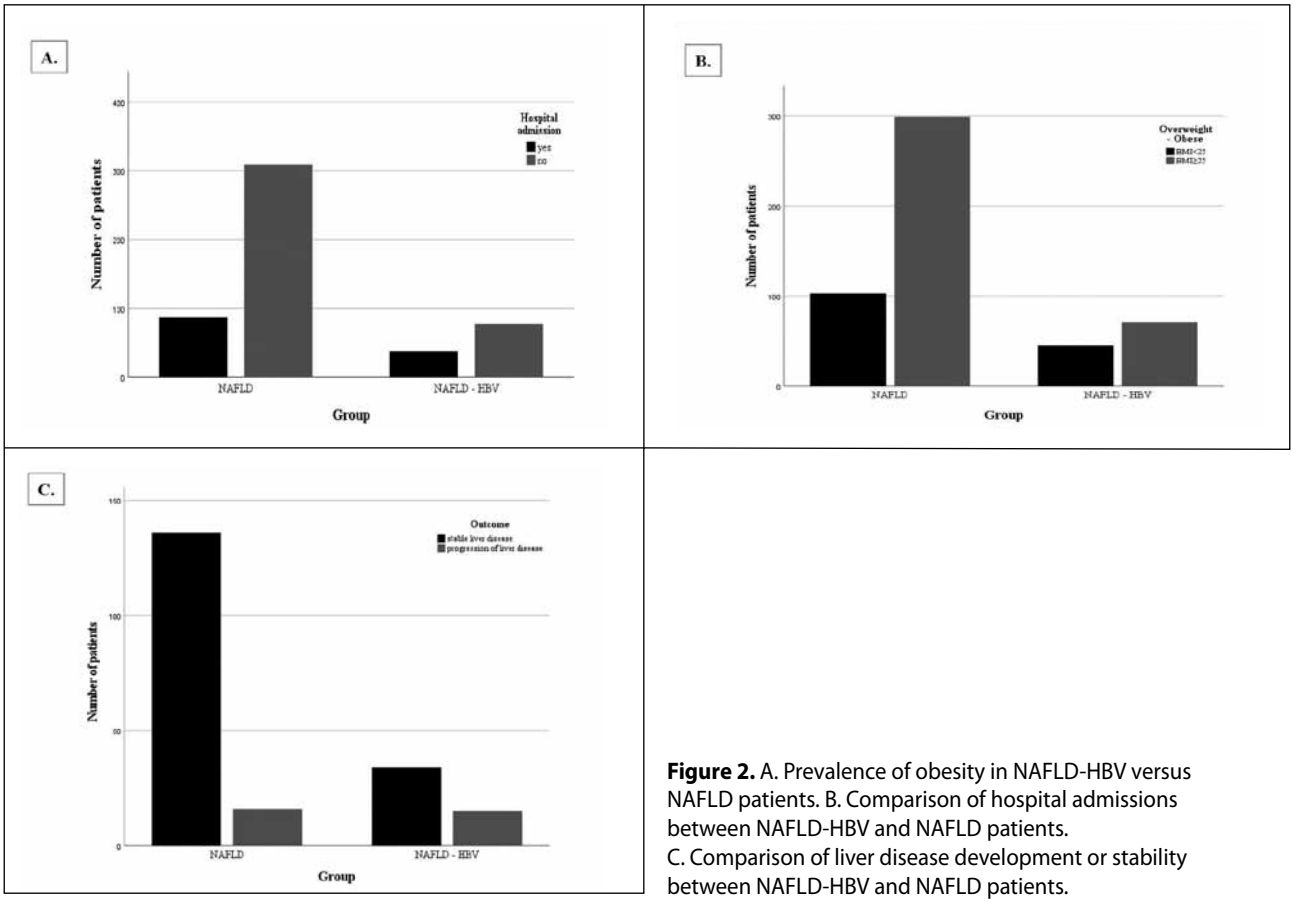

Figure 2. A. Prevalence of obesity in NAFLD-HBV versus NAFLD patients. B. Comparison of hospital admissions between NAFLD-HBV and NAFLD patients. C. Comparison of liver disease development or stability between NAFLD-HBV and NAFLD patients.

presents liver disease development or stability among the examined groups.

Binary regression analyses were applied, exploring the factors associated with liver disease development (progression to cirrhosis or HCC development) (Table 3). HBV coexistence (p=0.001), hemoglobin levels (p=0.014), platelet count (p<0.001), total bilirubin (p=0.003) and the presence of diabetes mellitus (p=0.005) were identified as significant predictors in univariate models. In the multivariate analysis, the HBV coexistence (aOR=3.509, 95% CI: 1.201-10.254, p=0.022), the presence of diabetes mellitus (aOR=3.375, 95% CI: 1.176-9.683, p=0.024), the platelet count (aOR=0.976, 95% CI: 0.965-0.987, p<0.001) and the total bilirubin levels (aOR=1.785, 95% CI: 1.145-2.781, p=0.01) were demonstrated as independent prognostic factors for liver disease development.

Table 2. *Patients' outcomes in NAFLD-HBV versus NAFLD patients*

Patients' outcomes	NAFLD-HBV		NAFLD		p-value
	N	Percentage (%)	N	Percentage (%)	
Hospital admission	38/106	35.8%	87/396	22 %	0.004
HCC development	4/54	7.4%	2/184	1.1%	0.025
Liver cirrhosis development	11/54	20.4%	14/184	7.6%	0.011
Liver disease progression (cirrhosis or HCC development)	15/54	27.8%	16/184	8.7%	<0.001
Death	2/116	1.7%	7/400	1.8%	0.999

NAFLD: non-alcoholic fatty liver disease, HBV: hepatitis B virus, N: number of patients, HCC: hepatocellular carcinoma

Table 3. *Univariate and multivariate analysis of factors associated with risk for disease development (progression to cirrhosis or HCC development).*

Variable	Univariate Analysis	OR (95% CI)	Multivariate Analysis	aOR (95% CI)
Age (years)	0.192	1.021 (0.989-1.055)		
Gender*	0.481	1.321 (0.609-2.865)		
BMI (kg/m²)	0.131	1.057 (0.984-1.135)		
HBV coexistence	0.001	3.75 (1.688-8.332)	0.022	3.509 (1.201-10.254)
Diabetes Mellitus	0.005	3.125 (1.418-6.886)	0.024	3.375 (1.176-9.683)
Hypertension	0.234	1.597 (0.739-3.449)		
Dyslipidemia	0.387	0.685 (0.291-1.614)		
Liver Stiffness	0.055	1.185 (0.974-2.055)		
Hemoglobin (g/dL)	0.014	0.759 (0.61-0.946)	0.166	0.801 (0.585-1.097)
Platelet count (10⁹/L)	<0.001	0.971 (0.96-0.982)	<0.001	0.976 (0.965-0.987)
ALT (IU/L)	0.126	1.002 (0.999-1.005)		
AST (IU/L)	0.061	1.003 (1-1.006)		
γ-GT (IU/L)	0.589	1.001 (0.998-1.004)		
ALP (IU/L)	0.855	0.999 (0.996-1.003)		
Total Bilirubin (mg/dL)	0.003	1.89 (1.238-2.886)	0.01	1.785 (1.145-2.781)
Creatinine (mg/dL)	0.774	1.178 (0.385-3.609)		

OR: odds ratio, aOR: adjusted odds ratio, CI: confidence interval, BMI: body mass index, HBV: hepatitis B virus, ALT: alanine aminotransferase, AST: aspartate aminotransferase, γ-GT: Gamma-glutamyl transferase, ALP: alkaline phosphatase

*Reference category for gender is male.

DISCUSSION

The coexistence of NAFLD and HBV is a topic which has gained increasing interest as both diseases establish abnormalities on the liver histopathology and enzymes that potentiate end-stage liver disease alongside with HCC [2,8,9]. Emerging evidence has surprisingly demonstrated a potential "competitive relationship" between CHB and NAFLD; reduced HBV markers in NAFLD patients and lower risk of NAFLD presence in HBV patients. The current study focuses on the impact of HBV infection on NAFLD patients evaluating their clinical and laboratory parameters and the risk of patients' outcomes and liver disease development.

Obesity, diabetes mellitus and metabolic syndrome (MetS) are independent risk factors for liver cirrhosis and HCC in patients with CHB, proposing a synergistic role of metabolic factors and CHB on HCC pathogenesis [36-38]. Given that NAFLD is the main liver-related manifestation of obesity and metabolic disorders, HBV infection overlapping with NAFLD is likely to further induce the liver cirrhosis and HCC risk.

Our results showed that overweight - obese individuals' rate was significantly higher on NAFLD subjects compared to NAFLD-HBV, a finding that probably explains the reduced rates of comorbidity with NAFLD reported in the literature. However, the biochemical analyses did not reveal a propitious profile in any group; although NAFLD-HBV patients presented abnormal values of ALP, the NAFLD group presented impaired levels of γ-GT. Recent data claimed that HBV infection was associated with lower risk of NAFLD in patients without metabolic disorders. The regional epidemiology and risk factors of NAFLD in CHB patients has been studied extensively in China [11]. A hospital-based study with 14,452 patients indicated that the prevalence of NAFLD ranged from 29.9% to 35.8% in CHB, which was lower in past-infection prevalence rate compared to the general population, as also suggested by prior findings [2,11]. A cross-sectional study of 33,439 Taiwanese subjects displayed an inverse correlation between HBV infection and NAFLD prevalence [22]. Another study using as reference the proton magnetic resonance spectroscopy (MRS), demonstrated a lower prevalence of fatty liver in HBV patients than in patients without HBV [7,20]. Taking all these data into consideration, the current evidence supports that HBV infection could act as a protective shield for NAFLD [17,20,21,39]. However, due to the relatively small sample sizes of the studies, authors concluded that the delineation of the NAFLD role in NAFLD-HBV patients is still far to be reached and further research is needed. Additionally, another point of consideration is that the aforementioned studies did not compare the HBV infected population to the non-infected, restricting their liability and the interpretation of results [2]. Lastly, several data from bedside studies are opposed to the results from basic research regarding the association between HBV infection and NAFLD [17,20,21,39].

One more finding of the current study was that the NAFLD-HBV group was at higher risk of hospital admissions and developing severe complications, including liver cirrhosis and HCC compared to NAFLD group, suggesting that HBV coexistence increases the risk of end-stage liver disease in NAFLD patients. The effect of HBV-NAFLD on liver disease progression remained significant after adjustment for potential confounding factors. These results are consistent with previous studies reporting that NAFLD was an independent risk factor for HCC development in HBV patients whose HBV DNA was suppressed [10]. Other studies reported that concurrent NAFLD augmented the risk of HCC among patients with CHB [3,13]. The effect of NAFLD on HCC development may have additive influence on HBV patients. Despite, HBV affects the NAFLD incidence, the coexistence of NAFLD-HBV may independently augment the HCC risk, which is probably performed by the same mechanism that NAFLD alone promotes HCC.

Some limitations of the current study should be acknowledged. Firstly, this study has retrospective design, and the second limitation concerns its monocentric nature.

In conclusion, our study demonstrated that NAFLD-HBV comorbidity was associated with reduced body weight, increased risk of hospital admissions and end-stage liver disease development. Moreover, although both diseases are well-known to augment the risk of chronic liver diseases and HCC, our study demonstrated that the coexistence of these disorders also constituted an independent critical risk factor for liver disease development. Thus, as NAFLD and CHB deteriorated clinical outcomes, active treatment for both disorders should be recommended.

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