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ORIGINAL ARTICLE

Air pollution causes abnormal alanine aminotransferase levels in patients with chronic hepatitis B

Tyng-Yuan Jang[a,b,c], Yu-ting Zeng[d], Po-Cheng Liang[b], Chih-Da Wu[d,e], Yu-Ju Wei[b], Pei-Chien Tsai[b], Po-Yao Hsu[b],Yi-Shan Tsai[b], Ming-Yen Hsieh[b], Yi-Hung Lin[b], Meng-Hsuan Hsieh[b], Chih-Wen Wang[b], Jeng-Fu Yang[b], Ming-Lun Yeh[b], Chung-Feng Huang[b], Wan-Long Chuang[b], Jee-Fu Huang[b], Batbold Batsaikhan[f], Chia-Yen Dai[b,g,h,*], Pau-Chung Chen[d,i,j,k,*], Ming-Lung Yu[b,h]

[a]Ph.D. Program in Environmental and Occupational Medicine, College of Medicine, Kaohsiung Medical University and National Health Research Institutes, Kaohsiung, Taiwan, ROC; [b]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital; College of Medicine and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC; [c]Department of Internal Medicine, Pingtung Hospital, Ministry of Health and Welfare, Pingtung, Taiwan, ROC; [d]Department of Geomatics, National Cheng Kung University, Tainan, Taiwan, ROC; [e]Innovation and Development Center of Sustainable Agriculture, National Chung Hsing University, Tainan, Taiwan, ROC; [f]Department of Internal Medicine, Institute of Medical Sciences & Department of Health Research, Graduate School, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [g]College of Professional Studies, National Pingtung University of Science and Technology, Pingtung, Taiwan; [h]School of Medicine, College of Medicine and Center of Excellence for Metabolic-Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan, ROC; [i]Department of Public Health, National Taiwan University, Taipei, Taiwan, ROC; [j]Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan, ROC; [k]National Institute of Environmental Health Sciences, National Health Research Institutes, Miaoli, Taiwan, ROC

Abstract

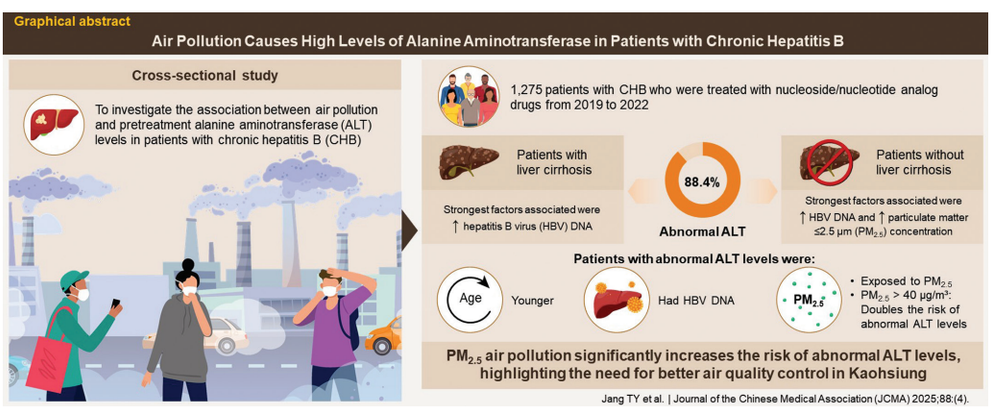
Background: To investigate the association between air pollution and abnormal alanine aminotransferase levels in patients with chronic hepatitis B treated with nucleotide/nucleoside analogs (NAs).

Methods: This cross-sectional study enrolled 1275 patients with chronic hepatitis B treated with nucleotide/NAs from 2019 to 2022 in Kaohsiung and analyzed the incidence and risk factors for abnormal alanine aminotransferase levels. Daily air pollutant concentrations were estimated for the year before enrollment.

Results: Abnormal alanine aminotransferase levels were observed in 1127 patients (88.4%) before treatment with nucleotide/NAs. Logistic regression analysis revealed that the strongest factor associated with abnormal alanine aminotransferase levels was the level of hepatitis B virus DNA (odds ratio/CI: 1.40/1.25-1.57; $p < 0.001$), followed by concentration of particulate matter ≤2.5 μm in diameter (1.05/1.02-1.08; $p < 0.001$) and liver cirrhosis (0.27/0.17-0.42; $p < 0.001$). Among patients without cirrhosis, logistic regression analysis revealed that the strongest factors associated with abnormal alanine aminotransferase levels were the level of hepatitis B virus DNA (odds ratio/CI: 1.52/1.28-1.82; $p < 0.001$) and concentration of particulate matter ≤2.5 μm in diameter (1.06/1.101-1.11; $p = 0.01$). Among patients with cirrhosis, logistic regression analysis revealed that the strongest factor associated with abnormal alanine aminotransferase levels was hepatitis B virus DNA level (odds ratio/CI: 1.28/1.12-1.48; $p = 0.001$).

Conclusion: Higher concentrations of particulate matter ≤2.5 μm in diameter caused elevated baseline alanine aminotransferase levels in patients with chronic hepatitis B receiving nucleotide/NA therapy. The impact of particulate matter ≤2.5 μm in diameter on abnormal alanine aminotransferase levels was particularly pronounced in patients without cirrhosis.

Keywords: Air pollution; alanine aminotransferase; Hepatitis B virus; Nucleotide/nucleoside analogs; Particulate matter



1. INTRODUCTION

Hepatitis B virus (HBV) infection is endemic in Taiwan and its prevalence has decreased since the introduction of the HBV vaccine.[1] Chronic hepatitis B (CHB) causes liver inflammation.[1,2] The risk factors for CHB-related liver inflammation include HBV DNA levels, liver fibrosis, fatty liver diseases, and metabolic derangement.[3] Antiviral treatments such as nucleotide/nucleoside analogs (NAs) can improve hepatic inflammation and fibrosis.[4,5]

Air pollution causes hepatic inflammation that can progress to chronic liver disease.[6] Air pollution impedes the normalization of liver function in patients with CHB treated with NAs.[7] Air pollution is not only associated with advanced liver fibrosis in patients with chronic liver disease[8] but also with liver cancer.[9,10] A previous study demonstrated that air pollution and seropositivity for hepatitis B surface antigen (HBsAg) were associated with the occurrence of hepatocellular carcinoma (HCC) and had synergistic effects after adjusting for confounding factors.[11] However, no study has reported an association between baseline alanine aminotransferase (ALT) levels and air pollution in patients with CHB treated with NAs.

Therefore, we aimed to investigate the association between air pollution and pretreatment ALT levels in CHB patients treated with NAs using a well-characterized cohort.

2. METHODS

2.1. Patients

This retrospective study consecutively enrolled patients with CHB who were treated with NAs at a medical center in Kaohsiung from 2019 to 2022. Patients were followed up from the beginning of NA treatment. Indications for NA therapy were based on the National Health Insurance Reimbursement Regulations of the Ministry of Health and Welfare in Taiwan.[1,12]

The inclusion criteria were as follows: (1) Liver decompensation, denoted by total bilirubin ≥2 mg/dL or prolonged prothrombin time ≥3 seconds and NAs administration for 3 years. (2) Liver cirrhosis with HBV DNA level ≥2000 IU/mL; NAs were administered lifelong. (3) Hepatitis B e-antigen (HBeAg)-positive with an HBV DNA level ≥20 000 IU/mL and ALT level ≥2 times the upper limit of normal (ULN) on two occasions 3 months apart or ALT ≥5 times the ULN. NAs therapy can be stopped after at least 1 year of consolidation therapy after HBeAg seroconversion with HBV DNA undetectable by polymerase chain reaction (PCR) and persistently normal ALT levels. (4) HBeAg-negative with HBV DNA level ≥2000 IU/mL with an ALT level ≥2 times the ULN on two occasions 3 months apart. Treatment cessation can be considered after treatment for at least 2 years, with undetectable HBV DNA documented on three separate occasions, 6 months apart. In the cohort, 423 patients (37.1%) had liver decompensation, 317 patients (24.9%) had liver cirrhosis with HBV DNA levels >2000 IU/mL, and 39.3% were HBeAg seropositive, meeting National Health Insurance (NHI) criteria.

Patients were excluded if they had any of the following conditions: co-infection with human immunodeficiency virus or hepatitis C virus (HCV), alcoholism (consuming ≥20 g of alcohol daily), ongoing interferon-based therapy, use of NAs for chemotherapy prophylaxis, and pre-existing HCC before the use of NAs.

This study was conducted in accordance with the principles of the 1975 Declaration of Helsinki, revised in 2013. This study was approved by the Ethics Committee of Kaohsiung Medical University Hospital. All patients provided informed consent before enrollment (IRB number: KMUHIRB-E(II)-20230117).

2.2. Laboratory analyses

Biochemical analyses were performed using a multichannel autoanalyzer (Hitachi Inc., Tokyo, Japan). The HBsAg levels were detected using a standard quantitative chemiluminescent microparticle immunoassay (ARCHITECT HBsAg; Abbott Diagnostics, Chicago, IL). Serum HBV DNA levels were examined using a standardized, automated, quantitative polymerase chain reaction assay (COBAS TaqMan HBV test; Roche Diagnostics, Branchburg, NJ; detection limit: 12 IU/mL).[13] Abnormal ALT levels were defined as >40 IU/L. Liver cirrhosis was diagnosed based on transient elastography (FibroScan; Echosens, Paris, France; threshold: >12 kPa),[14] histologic investigation; or the presence of radiological, laboratory, endoscopic, or clinical evidence of portal hypertension and/or cirrhosis. Fatty liver was diagnosed by trained physicians using abdominal ultrasonography, as previously described.[15–17] The Fibrosis-4 index score was calculated using the following formula: age (years) × aspartate aminotransferase (U/L)/(platelets [10^9/L] × $ALT^{1/2}$ [U/L]).

2.3. Air pollution exposure

Individual exposure to air pollutants, including particulate matter ≤2.5 μm in diameter ($PM_{2.5}$), particulate matter ≤10 μm in diameter (PM_{10}), NO_2, and O_3, was evaluated using various hybrid spatial prediction models with daily air pollutant measurements from several Taiwan Air Quality Monitoring (TAQM) stations. Briefly, the daily average $PM_{2.5}$ and PM_{10} concentrations were measured at approximately 70 TAQM stations from 2006 to 2022. The daily average NO_2 and O_3 concentrations were measured at 73 TAQM stations between 2000 and 2022. Measurements of air pollutants before 2014 were used to develop prediction models for estimating individual air pollutant exposure, and data after 2014 were used to verify the reliability of the model. Other details of air pollutant assessments have been described previously.[7,8,11] In the geocoding process for linking participants' addresses to air pollutants, we first converted the participants' addresses into longitudinal and latitudinal coordinates. Next, using QGIS (version 3.28), we performed a spatial join analysis to project each participant's location within the corresponding township. Based on the individuals' date of recruitment (baseline), we calculated their average exposure to air pollutants within these townships and used this as a measure of their cumulative exposure to air pollution.

In this study, we used township-level average air pollutant concentrations to represent an individual's cumulative exposure. This decision was based on the consideration that people generally spend a significant amount of time engaging in activities within the townships where they reside, rather than being confined solely to their residential addresses. Therefore, the overall average concentration of air pollutants at the township level is considered a more accurate reflection of an individual's actual

*Address correspondence. Dr. Chia-Yen Dai, Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tzyou Road, Kaohsiung 807, Taiwan, ROC. E-mail address: daichiayen@gmail.com (C.-Y. Dai); Dr. Pau-Chung Chen, Institute of Environmental and Occupational Health Sciences, National Taiwan University, 17, Xu-Zhou Road, Taipei 100, Taiwan, ROC. E-mail address: pchen@ntu.edu.tw (P.-C. Chen).

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exposure than estimates based strictly on household-level data. The 10-fold cross-validation R^2 values for the prediction models were approximately 0.87 for $PM_{2.5}$, 0.85 for O_3, 0.70 for NO_2, and 0.89 for PM_{10}.

2.4. Statistical analyses

Frequencies were compared between the groups using the chi-square (χ^2) test with Yates' correction or Fisher exact test. Data are presented as mean ± SD. Data were compared using analysis of variance, Student's *t* test, or the nonparametric Mann–Whitney *U* test. A stepwise logistic regression analysis was applied to analyze the factors independently associated with abnormal ALT levels by analyzing the covariates with *p* values <0.1 in the univariate analysis or the factors considered to have potential and clinical relevance. Statistical analyses were performed using IBM Statistical Product and Service Solutions version 25 (IBM Corp., Armonk, NY). All statistical analyses were based on two-sided hypothesis tests, with *p* values <0.05 considered statistically significant.

3. RESULTS

3.1. Patient characteristics

We initially recruited 3000 patients with CHB who received NA treatment (Fig. 1). After excluding patients with pre-existing HCC (n = 370), those using NAs for chemotherapy prophylaxis (n = 811), those with anti-HCV seropositivity (n = 118), those receiving interferon-based therapy (n = 33), those with unavailable addresses (n = 271), those with alcoholism (consuming ≥20 g/d of alcohol) (n = 67), and those with unavailable ALT levels (n = 55), 1275 patients were enrolled in the final analysis.

The mean age of the participants was 48.2 years, and 72.8% were male. The mean HBV DNA level was 5.9 $\log_{10}$ IU/mL. Patients with liver cirrhosis accounted for 28.8% (n = 367) of the study population (Table 1). The average annual air pollutant exposure levels were 40.0 μg/m^3 for $PM_{2.5}$, 71.1 μg/m^3 for PM_{10}, 21.5 parts per billion (ppb) for NO_2, and 28.3 ppb for O_3. The Pearson correlation coefficients between pollutants are provided in Supplementary Table 1, http://links.lww.com/JCMA/A311. Supplementary Table 2, http://links.lww.com/JCMA/A311, presents a basic statistical summary including the mean, SD, median, and interquartile range (minimum [Q1] and maximum [Q3]).

Table 1

Characteristics of the 1275 chronic hepatitis B patients preparing for NAs treatment

	All patients (n = 1275)
Age (y, mean [SD])	48.2 (14.0)
Male, n (%)	928 (72.8)
Diabetes, n/N (%)	174/1156 (15.1)
BMI (kg/m^2, mean [SD])	24.6 (4.1)
AST (IU/L, median [IQR])	105.0 (229.0)
ALT (IU/L, median [IQR])	144.0 (402.2)
Platelet count (×10^3 u/L, mean [SD])	165.7 (74.4)
FIB-4 (median [IQR])	3.0 (4.9)
HBV DNA ($\log_{10}$ IU/mL, mean [SD])	5.9 (1.9)
HBeAg seropositivity (%)	500/1271 (39.3)
Liver cirrhosis, n (%)	367 (28.8)
Fatty liver, n/N (%)	338/1057 (32.0)
Baseline $PM_{2.5}$ (μg/m^3, mean [SD])	40.0 (7.0)
Baseline PM_{10} (μg/m^3, mean [SD])	71.1 (10.5)
Baseline ozone (ppb, mean [SD])	28.3 (2.8)
Baseline NO_2 (ppb, mean [SD])	21.5 (5.2)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; FIB-4 = fibrosis-4 index; HBeAg = Hepatitis B e-antigen; HBV = hepatitis B virus; IQR = interquartile range; NAs = nucleoside/nucleotide analogs; NO_2 = nitrous oxide; $PM_{2.5}$ = particulate matter 2.5; PM_{10} = particulate matter 10.

3.2. Factors associated with abnormal ALT levels

Abnormal ALT levels before treatment were reported in 1127 (88.4%) patients. Patients with abnormal ALT levels were younger (47.4 vs 54.0 years; $p < 0.001$) and had higher HBV DNA levels (6.1 vs 4.6 $\log_{10}$ IU/mL; $p < 0.001$), concentrations of $PM_{2.5}$ (40.3 vs 37.5 μg/m^3; $p < 0.001$), PM_{10} (71.6 vs 67.1 μg/m^3; $p < 0.001$), and NO_2 (21.7 vs 20.3 ppb; $p = 0.01$), incidence of fatty liver (33.6% vs 17.0 %; $p < 0.001$), and HBeAg seropositivity (42.2% vs 17.7%; $p < 0.001$), and lower incidence of liver cirrhosis (25.5% vs 54.1%; $p < 0.001$) than those with normal ALT levels (Table 2).

Logistic regression analysis revealed that HBV DNA level was the strongest factor associated with abnormal ALT levels

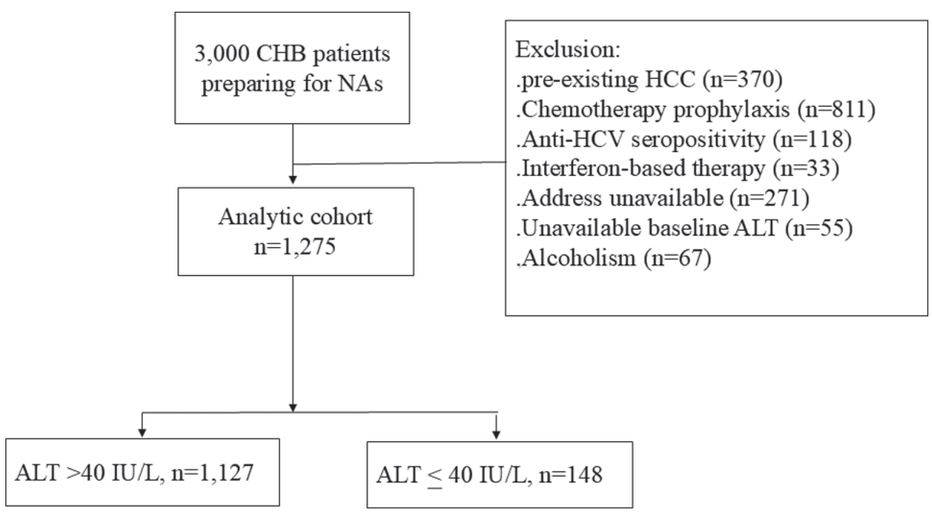

Fig. 1 Flowchart of patient enrollment. ALT = alanine aminotransferase; CHB = chronic hepatitis B; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NAs = nucleoside/nucleotide analogs.

Table 2

Factors associated with the abnormal ALT[a]

				Logistic regression analysis		
Abnormal ALT	**Yes, n = 1127**	**No, n = 148**	**Univariate *p* value**	**OR**	**95% CI**	***p***
Age (y, mean [SD])	47.4 (14.0)	54.0 (13.2)	<0.001	0.99	0.97-1.01	0.44
Male, n (%)	829 (73.6)	99 (66.9)	0.09	1.39	0.83-2.30	0.21
Diabetes, n/N (%)	147/1013 (14.5)	27/143 (18.9)	0.17			
BMI (kg/m^2, mean [SD])	24.6 (4.1)	24.7 (4.0)	0.83			
Platelet count (×10^3 u/L, mean [SD])	165.0 (69.7)	107.7 (103.8)	0.53			
Creatinine (mg/dL, mean [SD])	1.0 (1.1)	1.2 (1.7)	0.20			
HBV DNA (log10 IU/mL, mean [SD])	6.1 (1.8)	4.6 (1.9)	<0.001	1.40	1.25-1.57	<0.001
HBeAg seropositivity, n/N (%)	474/1124 (42.2)	26/147 (17.7)	<0.001	1.50	0.77-2.94	0.23
Fatty liver, n/N (%)	320/951 (33.6)	18/106 (17.0)	<0.001	1.35	0.73-2.47	0.34
Liver cirrhosis, n (%)	287 (25.5)	80 (54.1)	<0.001	0.27	0.17-0.42	<0.001
Baseline $PM_{2.5}$ (μg/m^3, mean [SD])	40.3 (6.8)	37.5 (7.8)	<0.001	1.05	1.02-1.08	<0.001
Baseline PM_{10} (μg/m^3, mean [SD])	71.6 (10.3)	67.1 (12.0)	<0.001	1.01	0.97-1.06	0.56
Baseline ozone (ppb, mean [SD])	28.3 (2.8)	28.6 (2.8)	0.33			
Baseline NO_2 (ppb, mean [SD])	21.7 (5.1)	20.3 (5.6)	0.01	1.00	0.95-1.06	0.96

ALT = alanine aminotransferase; BMI = body mass index; HBeAg = Hepatitis B e-antigen; HCC = hepatocellular carcinoma; HBV = hepatitis B virus; NO_2 = Nitrous oxide; OR = odds ratio; $PM_{2.5}$ = particulate matter 2.5; PM_{10} = particulate matter 10.
[a]ALT > 40 IU/L.

Table 3

Factors associated with the abnormal ALT[a] in non-cirrhotic patients

				Logistic regression analysis		
Abnormal ALT	**Yes, n = 840**	**No, n = 68**	**Univariate *p***	**OR**	**95% CI**	***p***
Age (y, mean [SD])	45.0 (13.9)	55.0 (13.7)	<0.001	0.97	0.94-1.00	0.05
Male, n (%)	614 (73.1)	38 (55.9)	0.003	1.27	0.59-2.74	0.54
Diabetes, n/N (%)	96/754 (12.7)	7/66 (10.6)	0.85			
BMI (kg/m^2, mean [SD])	24.3 (4.1)	23.9 (4.2)	0.42			
Platelet count (×10^3 u/L, mean [SD])	181.7 (66.5)	220.7 (113.0)	0.01	1.00	0.99-1.00	0.05
Creatinine (mg/dL, mean [SD])	1.0 (1.0)	1.4 (2.1)	0.18			
HBV DNA (log10 IU/mL, mean [SD])	6.3 (1.8)	4.4 (2.2)	<0.001	1.52	1.28-1.82	<0.001
HBeAg seropositivity, n/N (%)	409/839 (48.7)	13/68 (19.1)	<0.001	0.82	0.29-2.33	0.71
Fatty liver, n/N (%)	297/726 (40.9)	12/46 (26.1)	0.06	2.02	0.89-4.58	0.09
Baseline $PM_{2.5}$ (μg/m^3, mean [SD])	40.6 (6.8)	36.2 (8.4)	<0.001	1.06	1.01-1.11	0.01
Baseline PM_{10} (μg/m^3, mean [SD])	72.0 (10.3)	65.5 (12.7)	<0.001	0.98	0.92-1.04	0.45
Baseline ozone (ppb, mean [SD])	28.2 (2.7)	28.3 (2.8)	0.76			
Baseline NO_2 (ppb, mean [SD])	21.9 (5.1)	20.7 (5.2)	0.11			

ALT = alanine aminotransferase; BMI = body mass index; HBeAg = Hepatitis B e-antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; NO_2 = nitrous oxide; OR = odds ratio; $PM_{2.5}$ = particulate matter 2.5; PM_{10} = particulate matter 10.
[a]ALT > 40 IU/L.

(odds ratio [OR]/CI: 1.40/1.25-1.57; $p < 0.001$), followed by $PM_{2.5}$ concentration (OR/CI: 1.05/1.02-1.08; $p < 0.001$) and liver cirrhosis (OR/CI: 0.27/0.17-0.42; $p < 0.001$). The optimum cutoff value of the $PM_{2.5}$ concentration associated with abnormal ALT levels was 41.6 μg/m^3 (area under the receiver operating characteristic curve: 0.61; $p < 0.001$). Considering $PM_{2.5}$ concentration >40 μg/m^3 as the threshold, the logistic regression analysis revealed that the strongest factor associated with abnormal ALT levels was $PM_{2.5}$ concentration >40 μg/m^3 (OR/CI: 2.03/1.28-3.20; $p = 0.002$), followed by HBV DNA level (OR/CI: 1.40/1.25-1.58; $p < 0.001$) and liver cirrhosis (OR/CI: 0.27/0.17-0.42; $p < 0.001$).

3.3. Factors associated with abnormal ALT levels among patients without cirrhosis

We further analyzed the factors associated with abnormal ALT levels, stratified by liver cirrhosis. Among patients without cirrhosis, those with abnormal ALT levels were younger (45.5 vs 55.0 years; $p < 0.001$) and had higher HBV DNA levels (6.3 vs 4.4 $\log_{10}$ IU/mL; $p < 0.001$), concentrations of $PM_{2.5}$ (40.6 vs 36.2 μg/m^3; $p < 0.001$) and PM_{10} (72.0 vs 65.5 μg/m^3; $p < 0.001$), and incidence of HBeAg seropositivity (48.7% vs 19.1%; $p < 0.001$), and lower platelet count (181.7 × 10^3/μL vs 220.7 × 10^3/μL; $p = 0.01$) than those with normal ALT levels (Table 3).

Logistic regression analysis revealed that the strongest factors associated with abnormal ALT levels were HBV DNA level (OR/CI: 1.52/1.28-1.82; $p < 0.001$) and $PM_{2.5}$ concentration (OR/CI: 1.06/1.101-1.11; $p = 0.01$). The use of quartiles to assess exposure to air pollutants confirmed these results, and we identified a significant trend for $PM_{2.5}$ (Table 4).

3.4. Factors associated with abnormal ALT levels among patients with cirrhosis

Among patients with cirrhosis, those with abnormal ALT levels had higher HBV DNA levels (5.6 vs 4.8 $\log_{10}$ IU/mL; $p <$

Table 4

Adjusted ORs, 95% CI, and *p* trend values for the association between $PM_{2.5}$ and abnormal ALT[a] in non-cirrhotic patients, according to quartiles of the distribution

Pollutant	Quartile	OR (95% CI)
$PM_{2.5}$	1 (<34.65)	1.00
	2 (34.65-41.23)	4.64 (1.50-14.31)
	3 (41.23-45.74)	7.19 (2.05-25.24)
	4 (>45.74)	2.93 (1.23-7.00)
	p trend	0.001

Models adjusted for the age, sex, platelet, HBV DNA, HBeAg seropositivity, fatty liver, $PM_{2.5}$, and PM_{10} in to multivariate analysis.

ALT = alanine aminotransferase; HBeAg = Hepatitis B e-antigen; HBV = hepatitis B virus; OR = odds ratio; $PM_{2.5}$ = particulate matter 2.5.

[a]ALT >40 IU/L.

0.001) than those with normal ALT levels. Logistic regression analysis revealed that HBV DNA level was the strongest factor associated with abnormal ALT levels (OR/CI: 1.28/1.12-1.48, $p = 0.001$) (Table 5).

4. DISCUSSION

This study found that abnormal ALT levels were associated with HBV DNA levels and $PM_{2.5}$ concentrations after adjusting for confounding factors in patients with CHB receiving NA treatment. $PM_{2.5}$ concentrations >40 μg/m³ were linked to a 2-fold increased risk of abnormal ALT levels. Patients in the highest quartile of annual $PM_{2.5}$ concentration exposure had a 3-fold increased risk of abnormal ALT levels compared with those in the lowest quartile. The impact of $PM_{2.5}$, on abnormal ALT levels was particularly pronounced in patients without cirrhosis.

HBV infection causes hepatic inflammation, which leads to abnormal ALT levels. Factors associated with abnormal ALT levels in patients with CHB include HBV DNA levels, fatty liver disease, metabolic effects, and alcohol use.[3] The use of NAs improves ALT levels,[18] retards fibrosis progression, decreases the incidence of cirrhosis and HCC, and[12] improves long-term survival.[17] Normalized ALT levels are an important indicator of disease control during NA treatment. Previous studies have shown that NAs improve ALT levels in HBeAg-negative patients without cirrhosis with a low viral load after 1 year of therapy, after adjusting for confounding factors.[7,19] Older age and prior NA therapy were positively associated with HBsAg loss, while current NA therapy was negatively associated with HBsAg loss in patients with CHB having a low viral load.[20]

Air pollution can trigger inflammation and oxidative damage, which can lead to chronic liver disease.[6] Air pollution contributes to fatty liver disease[21] and triggers impaired liver function. Air pollution impedes the normalization of ALT levels in patients with CHB treated with NAs.[7] Furthermore, air pollution is associated with advanced liver fibrosis in patients with chronic liver disease.[8] A dose-dependent correlation between air pollution and severity of hepatic fibrosis has been noted. Moreover, air pollution is also associated with liver cancer.[9,10] A previous study demonstrated that air pollution and HBsAg seropositivity were associated with HCC occurrence and had synergistic effects after adjusting for confounding factors.[11] Air pollution may accelerate the development of HCC in patients with CHB and cirrhosis receiving NA treatment.[22] No previous study has reported an association between pretreatment ALT levels and air pollution in patients with CHB treated with NAs.

$PM_{2.5}$ has been associated with elevated ALT levels[23] and increased incidence of liver fibrosis[8] and liver cancer.[11,24] However, its role in patients with CHB before treatment has not yet been elucidated. In this study, we found that high concentrations of $PM_{2.5}$ and high HBV DNA levels caused hepatic inflammation after adjusting for confounding factors. Indications for NA therapy in CHB are based on the clinical phase of CHB.[25] However, there may be a gray zone in which the features do not correspond to any specific phase. Some hepatologists suggest NA therapy only if the HBV DNA level is >2000 IU/mL.[26] $PM_{2.5}$ has been associated with hepatic complications, may lower the efficacy of NA treatment in patients residing in areas with high air pollution.

This study had some limitations. First, air pollutant exposure was calculated as the mean value for 1 year before the patient was enrolled. We did not compare the effects of the different time intervals or longer observation periods. Second, we did not have comprehensive data on the socioeconomic background, smoking status, alcohol consumption, inactive carrier

Table 5

Factors associated with the abnormal ALT[a] in cirrhotic patients

				Logistic regression analysis		
Abnormal ALT	**Yes, n = 287**	**No, n = 80**	**Univariate *p***	**OR**	**95% CI**	***p***
Age (y, mean [SD])	54.5 (11.4)	53.2 (12.9)	0.37			
Male, n (%)	215 (74.9)	61 (76.2)	0.88			
Diabetes, n/N (%)	51/259 (15.7)	20/77 (26.0)	0.27			
BMI (kg/m², mean [SD])	25.4 (4.1)	25.3 (3.7)	0.91			
Platelet count (×10³ u/L, mean [SD])	117.0 (54.8)	129.4 (73.8)	0.18			
Creatinine (mg/dL, mean [SD])	1.1 (1.0)	1.1 (1.2)	0.94			
HBV DNA (log10 IU/mL, mean [SD])	5.6 (1.8)	4.8 (1.5)	<0.001	1.28	1.12-1.48	0.001
HBeAg seropositivity, n/N (%)	65/285 (22.8)	13/79 (16.5)	0.28			
Fatty liver, n/N (%)	23/225 (10.2)	6/60 (10.0)	1.00			
Baseline $PM_{2.5}$ (μg/m³, mean [SD])	39.5 (6.6)	38.5 (7.3)	0.26			
Baseline PM_{10} (μg/m³, mean [SD])	70.4 (10.2)	68.3 (11.4)	0.13			
Baseline ozone (ppb, mean [SD])	28.6 (2.9)	28.7 (2.8)	0.69			
Baseline NO_2 (ppb, mean [SD])	21.1 (5.3)	20.0 (5.9)	0.13			

ALT = alanine aminotransferase; BMI = body mass index; HBeAg = Hepatitis B e-antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; NO_2 = nitrous oxide; OR = odds ratio; $PM_{2.5}$ = particulate matter 2.5; PM_{10} = particulate matter 10.

[a]ALT > 40 IU/L.

status, or active hepatitis. A few of the patients in this study were inactive carriers. Among patients with normal ALT, more than 50% had liver cirrhosis. The small number of patients made further analyses difficult. Third, metabolic-associated steatotic liver disease was not considered. A strength of this study is that air pollution remained an independent risk factor for abnormal ALT levels after adjusting for confounding factors. To our knowledge, this is the first report on the association between air pollution and abnormal ALT levels in patients with CHB treated with NAs.

In conclusion, high $PM_{2.5}$ concentrations were associated with abnormal ALT levels in patients with CHB treated with NAs. The impact of $PM_{2.5}$ on abnormal ALT levels was particularly pronounced in patients without cirrhosis. Further studies are warranted to determine long-term outcomes in these patients.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A311.

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