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ORIGINAL ARTICLE

Air pollution as a potential risk factor for hepatocellular carcinoma in Taiwanese patients after adjusting for chronic viral hepatitis

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Abstract

Background: Air pollution is a risk factor for hepatocellular carcinoma (HCC). However, the effect of air pollution on HCC risk in patients with hepatitis remains unclear.

Methods: This cross-sectional study recruited 348 patients with chronic hepatitis who were tested for serum hepatitis B surface antigen (HBsAg) and for antibodies against hepatitis B core antigen (HBcIgG) and hepatitis C virus (anti-HCV) in 2022. The diagnosis of HCC was based on the International Classification of Diseases, 10th revision (ICD-10). Daily estimates of air pollutants were aggregated into mean estimates for the previous year based on the date of recruitment or HCC diagnosis.

Results: Out of 348 patients, 12 had HCC (3.4%). Patients with HCC were older (71.7 vs 50.9 years; $p = 0.004$), had higher proportion of HBsAg seropositivity (41.7% vs 5.1%; $p < 0.001$), and substantially higher levels of particulate matter 2.5 ($PM_{2.5}$) (21.5 vs 18.2 μg/m^3; $p = 0.05$). Logistic regression analysis revealed that the factors associated with HCC were age (odds ratio [OR]: 1.10; CI, 1.03-1.17; $p = 0.01$), $PM_{2.5}$ level (OR: 1.51; CI, 1.02-2.23; $p = 0.04$), and HBsAg seropositivity (OR: 6.60; CI, 1.51-28.85; $p = 0.01$) (Table 3). There was a combined effect of $PM_{2.5}$ and HBsAg seropositivity on the risk of HCC development (OR: 22.17; CI, 3.33-147.45; $p = 0.001$).

Conclusion: In this study, we demonstrated that $PM_{2.5}$ and HBsAg seropositivity were associated with HCC occurrence and had synergistic effects after adjusting for confounding factors.

Keywords: Air pollution; Chronic hepatitis; Cross-sectional study; HBsAg; Hepatocellular

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is among the top 10 causes of death in Taiwan. The risk factors for HCC include chronic hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) infections, alcohol, and metabolic associated fatty liver disease (MAFLD).[1,2] The HBV prevalence rates were high in the era before universal hepatitis B vaccination.[3,4] Meanwhile, antiviral therapy, including nucleoside/nucleotide analogs (NAs), might decrease liver disease progression and reduce the incidence of liver-related complications and HCC.[5]

Globally, approximately 70 million individuals are infected with HCV.[6] Patients with chronic HCV infection may develop HCC and liver-related complications.[7,8] The HCV eradication program has been eagerly implemented in Taiwan in recent years.[9] The program aims to eliminate HCV infections by 2025.

The recently discovered MAFLD has been reported to cause HCC.[10] However, there are conflicting data on the association between MAFLD and HCC in Asian patients.[11,12] Air pollution might cause MAFLD and progress to liver cirrhosis and HCC.[13–15] Animal studies have suggested that air pollution could trigger oxidative damage and inflammation, which might be involved in the development of chronic liver disease and progression to fibrosis.[16]

$PM_{2.5}$, hepatitis B surface antigen (HBsAg), and anti-HCV seropositivity were demonstrated to be independent factors of HCC development before the era of potent antiviral agents in a Taiwanese study.[17] However, the relationship between air pollution and HCC in the era of potent antiviral agents remains unclear. Therefore, we aimed to address this issue by analyzing patients who completed a hepatitis survey.

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2. METHODS

2.1. Patients

Patients who tested for serum HBsAg, hepatitis B core antigen (HBcIgG), and anti-HCV in 2022 at a government hospital in Taiwan were enrolled in this cross-sectional study (Fig. 1). Patients were excluded if they had preexisting HCC, alcoholism, or lacked residential address. This study was conducted in accordance with the Declaration of Helsinki (1975), as revised in 2013. This study was approved by the ethics committee of Kaohsiung Medical University Hospital.

2.2. Laboratory analyses

A standard quantitative chemiluminescent microparticle immunoassay was used to determine HBsAg levels (ARCHITECT HBsAg; Abbott Diagnostics). Levels of HCV antibody (anti-HCV) were measured using a third-generation enzyme immunoassay (Abbott Laboratories, North Chicago, IL). Antibodies against HBcIgG were detected using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Abbott Laboratories, North Chicago, IL). Alcoholism was defined as >20 g/d of alcohol consumption. HCC diagnosis was based on the International Classification of Diseases, 10th revision (ICD-10), and the ICD codes were C22.0, C22.3, C22.7, and C22.9.

2.3. Air pollution exposure

Individual exposure to air pollutants, such as $PM_{2.5}$, NO_2, O_3, and benzene, was evaluated using various hybrid spatial prediction models with daily air pollutant measurements from several air quality monitoring (TAQM) stations in Taiwan. Briefly, daily average $PM_{2.5}$ concentrations were measured from approximately 70 Taiwan air quality monitoring (TAQM) stations from 2006 to 2022. The daily average NO_2 and O_3 concentrations were collected from 73 TAQM stations from 2000 to 2022, and the average benzene concentrations were measured from 2003 to 2022. The measurements of air pollutants before 2014 were used to develop prediction models to estimate individual air pollutant exposure, and the data after 2014 were used as external data to verify the model reliability.

Several geospatial and land-use datasets, including land-use inventory (eg, residential areas, farmlands, green spaces, point of interest [POI] landmark data, and digital road network map), Moderate Resolution Imaging Spectroradiometer (MODIS) data, Normalized Difference Vegetation Index (NDVI) database, and Digital Terrain Model (DTM) datasets, were used as predictor variables of air pollutants in the prediction models. In addition, meteorological data (eg, daily average temperature and relative humidity) measured by the TAQM stations were also used in some prediction models. All geospatial and land-use variables were extracted from different circular buffer ranges surrounding the TAQM stations to represent neighborhood land-use conditions.

Regarding the prediction models of air pollutants, a hybrid kriging/land-use regression (LUR) model was built to assess the spatiotemporal variation in daily $PM_{2.5}$ concentrations in Taiwan. A hybrid kriging/LUR model with a machine-learning algorithm (eXtreme Gradient Boosting [XGBoost]) was developed to predict the daily NO_2 concentrations in Taiwan. The daily O_3 and benzene concentrations were estimated using the LUR model and the LUR with an ensemble machine-learning algorithm (GBoost, Categorical Boosting [CatBoost], and XGBoost, respectively). The 10-fold cross-validation (CV) methodology with CV-R^2, adjusted CV-R^2, and CV root mean square error (CV-RMSE) values was applied to assess the goodness of fit and robustness of the model. Finally, the daily estimates of air pollutants were aggregated into the mean estimate for the previous year based on the date of recruitment or HCC diagnosis. The detailed information on the collected air pollutant data, geospatial/land-use datasets, and prediction model procedures has been presented in previous studies.[18–20]

2.4. Statistical analyses

The frequencies were analyzed between groups using the chi-square (χ^2) test with Yates correction or Fisher exact test. Group means were calculated as means ± SDs. They 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 HCC occurrence by analyzing the covariates with $p < 0.1$ in the univariate analysis or factors considered to have potential and clinical relevance. Statistical analyses were performed using SPSS 25 statistical package (SPSS, Chicago, IL). All statistical analyses were based on two-sided hypothesis tests, with $p < 0.05$ considered statistically significant.

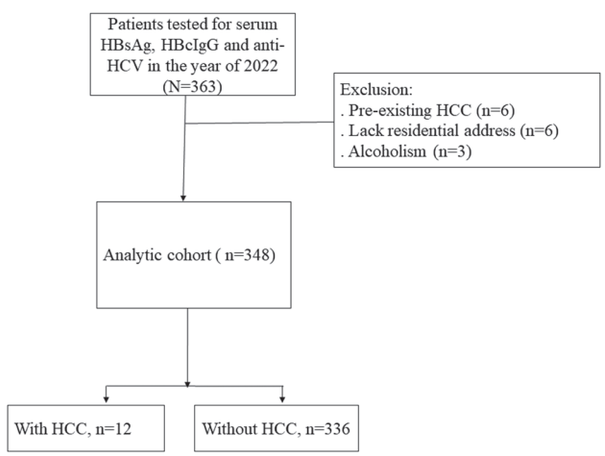

Fig. 1 The flowchart of the patient enrollment. HBcIgG = hepatitis B core antibody; HBsAg= hepatitis B surface antigen; HCC= hepatocellular carcinoma; HCV= hepatitis C virus.

3. RESULTS

3.1. Patient characteristics

In total, 348 patients were recruited for this study. The mean age was 51.6 years (range, 1-94 years), and 54.9% were male. Among the patients, 6.3% were HBsAg-positive, 49.4% were HBc IgG-positive, and 13.5% were HCV-positive (Table 1).

Table 1

Characteristics of the 348 patients

	All patients (n = 348)
Age, y (mean [SD])	51.6 (21.1)
Male, n (%)	191 (54.9)
HBsAg seropositive, n (%)	22 (6.3)
HBcIgG seropositive, n (%)	172 (49.4)
Anti-HCV seropositive, n (%)	47 (13.5)
$PM_{2.5}$, μg/m^3 (mean [SD])	18.2 (2.9)
Ozone, ppb (mean [SD])	36.0 (5.8)
NO_2, ppb (mean [SD])	10.1 (2.8)
Benzene, ppbC (mean [SD])	2.4 (0.5)
Alcoholism, n (%)	0 (0)
HCC, n (%)	12 (3.4)

HBcIgG = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV= hepatitis C virus; NO_2 = nitrous oxide; $PM_{2.5}$ = particulate matter 2.5.

No alcoholism was observed. HCC accounted for 3.4% of the patients.

3.2. Factors associated with HCC occurrence

The patients with HCC were older (71.7 vs 50.9 years; p = 0.004), had higher proportion of HBsAg seropositive (41.7% vs 5.1%; $p < 0.001$), and substantially higher levels of $PM_{2.5}$ (21.5 vs 18.2 μg/m^3; p = 0.05) (Table 2). Logistic regression analysis revealed that the factors associated with HCC were age (odds ratio [OR]: 1.10; CI, 1.03-1.17; p = 0.01), $PM_{2.5}$ level (OR: 1.51; CI, 1.02-2.23; p = 0.04), and HBsAg seropositivity (OR: 6.60; CI, 1.51-28.85; p = 0.01). The best cutoff value for $PM_{2.5}$ level associated with HCC was 18.3 μg/m^3 (area under ROC curve (AUROC) = 0.66; p = 0.05). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the cutoff value were 83.3%, 37.4%, 4.6%, 98.4%, and 39.0%, respectively. A combined effect of $PM_{2.5}$ ≥18.3 μg/m^3 and HBsAg seropositivity was observed on the risk of HCC development (OR: 22.17; CI, 3.33-147.45; p = 0.001) (Table 4).

3.3. Factors associated with different year of birth

Taiwan launched a national program of HBV vaccination program in 1984. We compared the patients born before and after 1984. Patient born after 1984 had lower prevalence of HBsAg seropositivity (1.9% vs 8.3%; p = 0.02), HBcIgG seropositivity (2.8% vs 70.1%; $p < 0.001$), anti-HCV seropositivity (0.9% vs 19.1%; $p < 0.001$), and HCC occurrence (0% vs 5%; p = 0.02) than those born after 1984. They lived in areas with lower air pollutions, such as $PM_{2.5}$ (17.3 vs 18.8 μg/m^3; $p < 0.001$) and benzene (2.2 vs 2.5 ppbC; $p < 0.001$) (Table 5).

4. DISCUSSION

In the current study, we demonstrated that $PM_{2.5}$ and HBsAg seropositivity were associated with HCC occurrence and had synergistic effects after adjusting for confounding factors. The HBsAg and HBcIgG seropositivity rates were much lower among patients born after 1984, which was the year when the national HBV vaccination program was implemented in Taiwan.

The risk factors for HCC included chronic viral hepatitis, alcohol-induced liver damage, and MAFLD.[1,2] The HBV vaccination program was launched in 1984 in Taiwan and resulted in a dramatic reduction in HCC incidence.[21] The prevalence of HDV was relatively lower (approximately 2%-5%) in patients with chronic HBV infection in recent years.[22] HBV infection causes hepatic inflammation, which might lead to liver cirrhosis and even HCC. NA therapy improves the biomedical response, reduces fibrosis progression, and decreases the risk of cirrhosis and HCC. Although the seroprevalence of HBV has drastically decreased after the launch of HBV vaccination,[4,23,24] HBV remains rampant in East Asia and is the leading etiology of HCC in these regions.[25] There were some gray zones of HBV treatment, which might contribute to HCC if antiviral agents were not administered.[26] In this study, we did not investigate whether antiviral agents were administered to patients with HBV infections. However, only a portion of patients met the criteria for NAs under Taiwan's national health insurance.[27] We have previously demonstrated that NAs improve the levels of alanine aminotransferase in noncirrhotic, HBeAg-negative patients with a low viral load after 1 year of therapy.[28]

MAFLD has been recently discovered and does not exclude chronic HBV and HCV infections and alcohol-related liver diseases.[29] MAFLD was reported as a risk factor for HCC.[10] However, the association between MAFLD and HCC in Asian patients remains controversial. Some Taiwanese studies have shown that MAFLD or fatty liver mildly increases HBsAg seroclearance and is not associated with HCC incidence.[11,12]

While air pollution may cause MAFLD,[15] its association with HCC in Chronic hepatitis B (CHB) patients remains unclear.[30] Air pollution may trigger oxidative damage and inflammation,

Table 2

Factors affecting HCC occurrence

	HCC (n = 12)	Non-HCC (n = 336)	p
Age, y (mean [SD])	71.7 (9.6)	50.9 (21.0)	<0.001
Male, n (%)	9 (75.0)	182 (54.2)	0.24
$PM_{2.5}$, μg/m^3 (mean [SD])	21.5 (5.5)	18.2 (2.8)	0.05
Ozone, ppb (mean [SD])	38.0 (3.9)	36.0 (5.9)	0.44
NO_2, ppb (mean [SD])	11.9 (3.1)	10.0 (2.8)	0.08
Benzene, ppbC (mean [SD])	2.6 (0.5)	2.4 (0.5)	0.05
HBsAg seropositive, n (%)	5 (41.7)	17 (5.1)	<0.001
HBcIgG seropositive, n (%)	9 (75.0)	163 (48.5)	0.08
Anti-HCV seropositive, n (%)	0 (0)	47 (14.0)	0.38

HBcIgG = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NO_2 = nitrous oxide; $PM_{2.5}$ = particulate matter 2.5.

Table 3

Multivariate analysis of factors associated with HCC occurrence

	OR	95% CI	p
$PM_{2.5}$ per 1 μg/m^3 increase	1.51	1.02-2.23	0.04
Age per 1 y increase	1.10	1.03-1.17	0.01
HBsAg seropositivity			
No	1		
Yes	6.60	1.51-28.85	0.01

We entered age, $PM_{2.5}$, NO_2, benzene, and HBcIgG seropositive into multivariate analysis.

HBcIgG = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; NO_2 = nitrous oxide; OR = odds ratio; $PM_{2.5}$ = particulate matter 2.5.

Table 4

The combined effects of $PM_{2.5}$ and HBsAg on risk of HCC development

	$PM_{2.5}$ ≥18.3 μg/m³[a]	$PM_{2.5}$ <18.3 μg/m³	*p* for interaction
HBsAg seropositivity			0.001
No	1.52 (0.27-8.49)	1 (Reference)	
Yes	22.17 (3.33-147.45)	-	

AUROC = area under ROC curve; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; $PM_{2.5}$ = particulate matter 2.5.
[a]The best cutoff value of $PM_{2.5}$ level associated with HCC was 18.3 μg/m³ (AUROC, 0.66; $p = 0.05$).

Table 5

Characteristics of the 348 chronic hepatitis patients with different born-year

	Born before year 1984 (n = 239)	Born after year 1984 (n = 107)	*p*
Age, y (mean [SD])	63.8 (11.7)	24.2 (7.0)	<0.001
Male, n (%)	139 (57.7)	52 (48.6)	0.12
$PM_{2.5}$, μg/m³ (mean [SD])	18.8 (2.3)	17.3 (3.8)	<0.001
Ozone, ppb (mean [SD])	36.0 (6.3)	36.2 (4.5)	0.78
NO_2, ppb (mean [SD])	10.3 (2.6)	9.6 (3.2)	0.06
Benzene, ppbC (mean [SD])	2.5 (0.5)	2.2 (0.5)	<0.001
HBsAg seropositive, n (%)	20 (8.3)	2 (1.9)	0.02
HBcIgG seropositive, n (%)	169 (70.1)	3 (2.8)	<0.001
Anti-HCV seropositive, n (%)	46 (19.1)	1 (0.9)	<0.001
HCC, n (%)	12 (5.0)	0 (0)	0.02

HBcIgG = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NO_2 = nitrous oxide; $PM_{2.5}$ = particulate matter 2.5.

which might be involved in the development of chronic liver disease.[16] Studies on mice have suggested that air pollution could activate Kupffer cells, produce cytokines by activating endoplasmic reticulum stress responses, promote collagen deposition and progression to fibrosis. Air pollution is also related to liver cirrhosis and HCC.[13,14] A Taiwanese study showed that $PM_{2.5}$, HBsAg, and anti-HCV seropositivity were independent risk factors for HCC development before the era of potent antiviral agents.[17] Our previous studies showed that air pollution might impede biomedical normalization and associated with advanced liver fibrosis in CHB patients.[31,32]

Globally, approximately 70 million people are infected with HCV.[6] Patients with chronic HCV infection may develop HCC and liver-related complications. Hence, HCC is indicated as one of the leading threats to public health.[7,8] In recent years, the HCV eradication program has been eagerly executed in urban and rural areas.[9] In this study, we demonstrated that $PM_{2.5}$ and HBsAg seropositivity were independent factors and had combined effects on HCC development, and anti-HCV seropositivity was not a risk factor. In addition, we considered HBcIgG seropositive patients, who accounted for 70% of patients born after 1984 in the study. HBcIgG seropositivity has been shown to contribute to non-B and non-C HCC patients.[33]

This study had some limitations. First, this was a cross-sectional study, and we only enrolled a small number of patients. Second, we recorded home addresses by postcode; however, we did not record the area of their daily activities. Additionally, the study lacked information on MAFLD, and we did not evaluate the potential influence of MAFLD on the occurrence of HCC. However, there are conflicting data on the association between MAFLD and HCC in Asian patients.[11,12] Moreover, we did not evaluate the biomedical and noninvasive markers in the study owing to lack of the information. We proposed that air pollution is the most crucial factor for HCC over chronic HBV or HCV infection. However, we did not explore whether antiviral agents were administered. Previous studies showed that air pollution was associated with liver cancer,[34,35] but they did not adjust for viral hepatitis and HBcIgG seropositivity.

In conclusion, $PM_{2.5}$ was a risk factor for HCC after adjusting for viral hepatitis. Further studies are required to determine long-term outcomes in these patients.

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