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Risk factors for the development of hepatocellular carcinoma in Chengdu: a prospective cohort study

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Abstract. – OBJECTIVE: To investigate the incidence of hepatocellular carcinoma (HCC) in Chengdu, identify the risk factors for the development of HCC in Chengdu and provide a reference for the prevention of HCC.

PATIENTS AND METHODS: The study population was recruited from Chengdu, Sichuan Province, China. The study group recruited volunteers in Chengdu from 2007 to 2012, conducted a baseline survey, and subsequently conducted long-term follow-up until December 31, 2019. A total of 22,525 study subjects were enrolled, excluding those who reported a previous history of liver disease, malignancy, and HCC within three months of enrollment. Cox proportional risk regression models were used to screen and determine the various risk factors and their hazard ratios (HR) for HCC in Chengdu, as well as to determine whether the association between other risk factors and HCC was modified by gender.

RESULTS: The study population had a median follow-up of 5.35 years, and a total of 142 people developed HCC, with an incidence rate of 0.71%. Analysis of the multifactorial Cox proportional risk regression model showed that age (age 10 years for 1 group, HR= 1.98, 95% CI: 1.86-2.11, $p<0.001$), current smoking (HR= 1.25, 95% CI: 1.07-1.31, $p=0.031$), weekly consumption of pickled vegetables (HR= 1.70, 95% CI: 1.49-1.81, $p=0.003$) and consumption of pickled vegetables daily (HR= 1.36, 95% CI: 1.21-1.42, $p=0.021$) were risk factors for HCC, and women (HR= 0.39, 95% CI: 0.28-0.55, $p=0.002$) and the use of air conditioning (10 years for 1 group, HR= 0.79, 95% CI: 0.68-0.83, $p=0.002$) were protective factors against HCC. Further analysis revealed that the association between length of time using air conditioning and HCC was heterogeneous among men and women ($p=0.007$) and that there was an interaction between sex and use of air conditioning in the association with HCC development ($p<0.001$).

CONCLUSIONS: The Chengdu population has a high incidence of HCC and numerous risk factors for HCC. There is a synergistic interaction between sex and length of time using air conditioning in their role in the development of HCC.

Key Words:
Risk factors, Hepatocellular carcinoma, Living habits, Influencing factors, Cohort study.

Introduction

Hepatocellular carcinoma (HCC) is the 6th most prevalent malignant cancer and the second leading cause of cancer-related mortality[1]. Lv et al[2] research revealed that the incidence of HCC in China has increased in recent decades. Wang et al[3] showed that the risk factors for HCC are complex and include viral infections, genetic factors, accumulation of various liver toxins, smoking, alcohol abuse and metabolic syndrome.

Previous studies[4,5] on the effect of ambient temperature on the incidence of hepatocellular carcinoma are scarce, but Basu[6] showed that a higher mortality rate in people living in high ambient temperatures than in those living in low

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ambient temperatures. Chen et al[7] demonstrated in a national cohort study that high or low ambient temperatures lead to lower life expectancy and higher risk of various diseases, Hylander et al[6] demonstrated in a mouse study that high ambient temperatures lead to an increased risk of cancer in mice. These abovementioned studies[6-8] demonstrate that environmental temperature has an impact on human health and is likely to affect the incidence of cancer (including HCC) that the use of air conditioning to regulate ambient temperatures can greatly reduce the adverse effects of high or low ambient temperatures on the human body. However, there are no studies to prove the relationship between the use of air conditioning and the development of HCC. Based on this, the length of time using air conditioning was used as one of the variables in this study and a Cox proportional risk regression model was used to screen whether the length of time using air conditioning was a risk or protective factor for the development of hepatocellular carcinoma.

The main risk factors for HCC are essentially the same across the world, but the proportion of risk attributable to them varies[9]. The high incidence of HCC in China is closely linked to the Chinese population's lifestyle[10]. There are many studies[11,12] on risk factors for HCC, but only few[13] are based on natural population cohorts in China. This study group conducted a cohort study in Chengdu, China, to describe the incidence of HCC and analyze the associated risk factors, thus improving the study of risk factors for HCC based on a natural population cohort in China.

Patients and Methods

Study Population

A baseline survey was conducted from 2007 to 2012, followed by long-term follow-up. The study excluded self-reported history of previous liver disease (1,553) and malignancy (749) and hepatocellular carcinoma (31) within three months of enrolment from the 24,858 Chengdu cohort study participants who signed an informed consent form and had complete baseline survey data. A total of 22,525 study subjects were included in the analysis after excluding unsuitable study subjects.

Evaluation of HCC Development

The participants were followed from the date they completed the baseline survey until the occurrence of HCC, death, or loss of follow-up, or until December 31, 2019. Information on HCC incidence and death was obtained from data from the Chengdu City Cause of Death Surveillance System, the universal health insurance database, and active targeted surveillance with multiple other sources, and the International Classification of Diseases, 10th Revision (ICD-10) was used to classify the disease, with a confirmed diagnosis of HCC during follow-up as the outcome.

Risk Factor Evaluation

For the baseline survey, qualified and uniformly trained enumerators administered a face-to-face questionnaire to collect information on sociodemographic characteristics (age, education level, annual household, sex, income and marital status), behavioral lifestyle (smoking, alcohol and tea consumption, dietary status and physical activity), family history of tumors, annual average air quality level in the area where the respondent usually resides and nutrient intake of the study population. Height and weight were measured using a uniformly calibrated instrument, with body mass index (BMI) being the ratio of weight to height squared. Current smoking was defined as smoking more than once every three days; having quit smoking was defined as not presently smoking but having ever smoked more than once every three days; and drinking was defined as drinking at least once per week; quit drinking was defined as basically not drinking at present, but ever drinking weekly and for at least six months. This study uses metabolic equivalents (MET) to reflect activity intensity. An individual's daily level of physical activity (MET-h/d) is the product of a person's daily MET value for each type of physical activity and the cumulative time (h/d) the individual spends doing that type of physical activity. The annual average air quality levels in residential areas are divided with reference to the Ambient Air Quality Standards (2020 Edition) and are divided into 6 levels, with level 1 representing the best air quality and level 6 being heavily polluted air quality. Residential areas are divided according to the administrative regions of Chengdu, which are divided into 21 administrative regions, of which 1 region has an annual average air quality of Class 1, 3 regions have an annual average air quality of Class 2, 13 regions have an annual average air quality of Class 3, 2 regions have an annual average air quality of

Class 4, 2 regions have an annual average air quality of Class 5 and there are no regions with an annual average air quality of Class 6. In order to prevent bias at the final count stage, respondents who had moved out of their original area of residence were excluded and only those who had lived in the same area for a long time were counted.

Statistical Analysis

The Pearson χ^2 test and the trend χ^2 test were used to examine whether there were differences in the distribution of HCC incidence between categorical and ordinal variables, and a one-way Cox proportional risk regression model was used to examine potential risk factors for HCC incidence. Factors with statistically significant differences were included in the multifactor Cox proportional risk regression model. The risk ratios and their 95% CI were calculated to analyze whether the association between each risk factor and HCC was heterogeneous across sex and whether there was a multiplicative interaction using the likelihood ratio test, $p<0.05$ is considered statistically different. R 4.2.1 software (The R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis, and all analyses were performed using a two-sided test with $\alpha=0.05$.

Results

Baseline Information

As shown in Table I, the age of the study participants was 50.21 ± 12.57 years, and 44.2% were males. Compared to males, a higher proportion of females had less than junior secondary education, never smoked, never drank alcohol, never drank tea, ate pickled vegetables daily, and did not snore, and a lower proportion of females had MET ≥ 30.00 h/d.

Incidence of HCC

As shown in Table II, 5.35 years was the median duration of follow-up for the study population, and 142 individuals developed HCC at a rate of 0.71%. Among them, there were statistically significant differences ($p<0.01$) in the incidence of HCC among the study subjects by different marital status, sex, age, residence air quality level, education level, smoking, annual household income, alcohol consumption, tea consumption, consumption of dairy and products, consumption of pickled vegetables, consumption of fresh fruits, having a family history of tumor, years of air conditioning use, snoring status, BMI and MET.

Risk Factors for the Development of HCC

As shown in Table III, the results of the one-way Cox proportional risk regression model analysis showed that age, being unmarried, smoking or having quit smoking, drinking or having quit drinking, drinking tea weekly, consumption of pickled vegetables daily or weekly, snoring and having a family history of tumors increased the risk of developing HCC ($p<0.01$), while being female, having a lower secondary education or above, having a high annual household income, consumption of fresh fruit, using air conditioning and physical activity were protective factors for the development of HCC ($p<0.01$). Further multifactorial analysis using the Cox proportional risk regression model revealed that the risk of HCC was lower in women than in men (HR=0.39, 95% CI: 0.28-0.55, $p=0.002$), the risk of HCC was 1.98 times higher for every 10 years of age (95% CI: 1.86-2.11, $p<0.001$). The risk of HCC in smokers was 1.25 times higher than in non-smokers (95% CI: 1.07-1.31, $p=0.031$), and consumption of pickled vegetables both weekly (HR=1.22, 95% CI: 1.06-1.37, $p=0.003$) and daily (HR=1.19, 95% CI: 1.08-1.21, $p=0.006$) increased the risk of HCC, being it 0.79 times higher (95% CI: 0.68-0.83, $p<0.001$) for each additional 10 years of air conditioning use. The risk of hepatocellular carcinoma increases by 36% for each increase in one air quality level of the place of residence. (HR=1.36, 95% CI: 1.30-1.48, $p<0.001$).

Effect Modification by Sex in the Association of Various Risk Factors with Hepatocellular Carcinogenesis

As shown in Table IV, stratified analysis by sex found that the consumption of pickled vegetables weekly (HR=1.70, 95% CI: 1.49-1.81, $p=0.003$) and daily (HR=1.36, 95% CI: 1.21-1.42, $p=0.021$) and having a family history of tumors (HR=1.46, 95% CI: 1.28-1.59, $p=0.019$) were all risk factors for HCC in men, but no statistically significant association was seen in women ($p>0.05$), and further heterogeneity analysis re-

Table I. Baseline characteristics of respondents.

Variables	Male	Female	Add
Total number of people	9,972	12,553	22,525
Age (years)			
≤ 30	1,417	1,989	3,406
30-40	2,015	3,017	5,032
40-50	4,021	4,235	8,256
50-60	1,602	2,526	4,128
≥ 60	917	786	1,703
Marital status			
Married	7,718	10,505	18,223
Unmarried	2,254	20,48	4,302
Education level			
Lower secondary and below	1,892	5,017	6,909
High School	3,390	4,018	7,408
Junior College	3,127	2,499	5,626
Bachelor's degree and above	1,563	1,019	2,582
Annual household income ($ 10,000)			
< 2.0	2,719	4,124	6,843
2.0-5.0	2,602	3,714	6,316
≥ 5.0	4,651	4,715	9,366
Smoking			
Never smoked	3,019	11,326	14,345
Have quit smoking	1,286	212	1,498
Current Smoking	5,667	1,015	6,682
Drinking			
Yes	5,910	1,026	6,936
No	4,062	11,527	15,589
Drinking Tea			
Yes	1,604	4,206	5,810
No	8,368	8,347	16,715
Edible dairy and dairy products			
Yes	7,801	10,187	17,988
No	2,171	2,366	4,537
Consumption of pickled vegetables			
Rarely	945	607	1,552
Monthly	1,702	2,448	4,150
Weekly	3,405	3,709	7,114
Daily	3,920	5,789	9,709
Consumption of fresh fruit			
Rarely	341	1,228	1,569
Monthly	3,017	3,426	6,443
Weekly	4,802	5,328	10,130
Daily	1,812	2,571	4,383
Family history of tumors			
No	8,731	9,417	18,148
Yes	1,241	3,136	4,377
Length of time air conditioning has been used (years)			
0	2,115	3,052	5,167
1-10	2,986	3,706	6,692
10-20	3,248	4,219	7,467
≥ 20	1,623	1,576	3,199
Snoring			
No	4,218	3,604	7,822
Yes	5,754	8,949	14,703
BMI (kg/m^2)			
< 18.5	325	851	1,176
18.5-24	3,634	5,281	8,915
24.0-28	4,241	4,943	9,184
≥ 28.0	1,772	1,478	3,250

Continued

Table I *(Continued)*. Baseline characteristics of respondents.

Variables	Male	Female	Add
MET (h/d)			
≤ 1.00	102	142	244
1.00-10.00	1,016	2,289	3,305
10.00-20.00	1,523	3,402	4,925
20.00-30.00	2,319	2,971	5,290
≥ 30.00	5,012	3,749	8,761
Residence Air Quality Level			
1	845	957	1,802
2	1,202	1,439	2,641
3	5,661	8,358	14,019
4	1,102	950	2,052
5	501	427	928

vealed that the association between the above three and HCC was not statistically significant in men and women. Length of time using air conditioning was not statistically associated with HCC in men (p=0.497), while length of time using air conditioning was a protective factor for HCC in women (HR=0.72, 95% CI: 0.64-0.88, p<0.001), and the heterogeneity test found a statistically significant difference (p=0.007) in the association between length of time using air conditioning and HCC in men and women (p=0.05).

As shown in Table V, the results of the interaction analysis showed that the risk ratio of HCC was lowest among those who used air conditioning for 10-19 years in the same sex: risk of HCC was lower among women than males for the same length of time using air conditioning, and the disparity in risk of HCC between men and women steadily increased with duration of use. The interaction analysis found that there was an interaction between sex and length of time using air conditioning and the risk of HCC (p<0.001).

Discussion

This study investigated the incidence of HCC in 22,525 Chengdu participants over a median follow-up period of 5.35 years, and the incidence rate of HCC was 0.91%[14], which was higher than the standardized incidence rate of HCC registered in 2015 among people aged 20-60 years in Chengdu[15]. Age and male sex were identified as risk factors for the development of HCC, consistent with the findings of previous literature. Torres et al[16] discovered that the risk of HCC increased with the quantity and duration of cigarettes smoked. However, a study by Fiore et al[17] did not find a dose-response relationship between smoking and the development of HCC. The association of smoking with hepatocellular carcinogenesis and its effect size need to be studied in more detail[18]. One study[19] suggested that polymorphisms in the *EPHX1*, *ENT3*, *ATP1B3* and *ENAH* genes mediate the individual susceptibility to smoking and HCC. In addition, the methylation level of the *CDH1* gene was higher in smokers with HCC than in non-smokers[20,21]. Wu et al[22] discovered no statistically significant connection between overall alcohol consumption and HCC development, but heavy drinking, more than four times a day, was significantly associated with HCC development, and Yin et al[23] found a non-linear association between alcohol consumption and HCC development, with a strong association for heavy drinking. In this study, both abstinent and current alcohol consumption increased the risk of HCC in the univariate analysis, but no association was found between alcohol consumption and HCC in the multivariate analysis, probably because the study only distinguished whether the respondents drank alcohol when collecting their drinking status, but not the different levels of alcohol consumption. This study found that the incidence of hepatocellular carcinoma was lower in respondents living in areas with good air quality than in subjects living in areas with poor air quality, consistent with the findings of Turner et al[24].

According to a cohort study by Cai et al[25], fresh fruit consumption was not associated with an increased risk of HCC, which is consistent with the results of the present study. The frequency of consumption of edible dairy and dairy products was significantly associated with the frequency of fresh fruit in this study population[26], and only the frequency of consumption

Table II. Incidence of HCC in respondents.

Variables	Number of incidences	Incidence of disease	*p*-value
Sex			< 0.001
Male	93	0.93%	
Female	49	0.42%	
Age (years)			< 0.001
≤ 30	5	0.15%	
30-40	13	0.26%	
40-50	44	0.53%	
50-60	47	1.14%	
≥ 60	33	1.94%	
Marital status			< 0.001
Married	104	0.57%	
Unmarried	38	0.88%	
Education level			< 0.001
Lower secondary and below	63	0.91%	
High School	55	0.74%	
Junior College	16	0.28%	
Bachelor's degree and above	8	0.31%	
Annual household income ($ 10,000)			< 0.001
< 2.0	76	1.11%	
2.0-5.0	19	0.30%	
≥ 5.0	47	0.50%	
Smoking			< 0.001
Never smoked	35	0.24%	
Have quit smoking	8	0.53%	
Current Smoking	99	1.48%	
Drinking			< 0.001
Yes	109	1.57%	
No	33	0.21%	
Drinking Tea			< 0.001
Yes	14	0.24%	
No	128	0.77%	
Edible dairy and dairy products			< 0.001
Yes	113	0.63%	
No	29	0.64%	
Consumption of pickled vegetables			< 0.001
Rarely	16	1.03%	
Monthly	11	0.27%	
Weekly	47	0.66%	
Daily	68	0.70%	
Consumption of fresh fruit			< 0.001
Rarely	4	0.25%	
Monthly	58	0.90%	
Weekly	57	0.56%	
Daily	23	0.52%	
Family history of tumors			0.002
No	125	0.69%	
Yes	17	0.39%	
Length of time air conditioning has been used (years)			< 0.001
0	72	1.39%	
1-10	31	0.46%	
10-20	28	0.37%	
≥ 20	11	0.34%	
Snoring			0.006
No	63	0.81%	
Yes	79	0.54%	

Continued

Table II *(Continued)*. Incidence of HCC in respondents.

Variables	Number of incidences	Incidence of disease	*p*-value
BMI (kg/m^2)			< 0.001
< 18.5	2	0.17%	
18.5-24	68	0.76%	
24.0-28	55	0.60%	
≥ 28.0	17	0.52%	
MET (h/d)			< 0.001
≤1.00	1	0.41%	
1.00-10.00	18	0.54%	
10.00-20.00	41	0.83%	
20.00-30.00	45	0.85%	
≥ 30.00	37	0.42%	
Residence air quality level	142		< 0.001
1	6	0.33%	
2	16	0.45%	
3	82	0.61%	
4	21	1.02%	
5	17	1.83%	

of fresh fruit was included in the multifactorial analysis to prevent covariates from influencing the results[27,28]. HCC is a complex condition caused by environmental and genetic factors[29]. Some studies[30,31] have demonstrated that environmental factors have a higher role in the development of HCC than genetic ones, which may explain why a family history of tumors was a risk factor for HCC in the univariate analysis, but not in the multivariate study.

Table III. Association analysis of the risk of HCC in respondents.

Variables	One-factor Cox proportional risk regression model analysis		Multi-factor Cox proportional risk regression model analysis	
	HR value (95% CI)	*p*-value	HR value (95% CI)	*p*-value
Sex				
Male	1		1	
Female	0.31 (0.22-0.40)	< 0.001	0.39 (0.28-0.55)	0.002
Age (per 10 years)[a]	2.47 (2.33-2.59)	< 0.001	1.98 (1.86-2.11)	< 0.001
Marital status				
Married	1		1	
Unmarried	1.94 (1.82-2.11)	< 0.001	1.26 (1.13-1.33)	0.073
Education level				
Lower secondary and below	1		1	
High School	1.07 (0.92-1.20)	0.261	1.07 (0.99-1.20)	0.401
Junior College	0.52 (0.39-0.62)	< 0.001	0.69 (0.51-0.92)	0.078
Bachelor's degree and above	0.57 (0.40-0.65)	< 0.001	0.66 (0.58-0.82)	0.626
Annual household income ($ 10,000)				
< 2.0	1		1	
2.0-5.0	0.45 (0.31-0.55)	< 0.001	0.60 (0.44-0.67)	0.044
≥ 5.0	0.37 (0.33-0.41)	< 0.001	0.92 (0.88-1.04)	0.858
Smoking				
Never smoked	1		1	
Have quit smoking	2.71 (2.37-2.88)	< 0.001	1.12 (0.91-1.28)	0.462
Current Smoking	2.81 (2.44-2.96)	< 0.001	1.25 (1.07-1.31)	0.031
Residence Air Quality Level (per 1 level)[a]	1.64 (1.52-1.76)	< 0.001	1.36 (1.30-1.48)	<0.001

[a]Continuous variables.

Table IV. Analysis of the interaction between respondent gender and time spent using a refrigerator on the development of HCC.

Variables	Male		Female		Heterogeneity test *p*-value
	HR value (95% CI)	*p*-value	HR value (95% CI)	*p*-value	
Consumption of pickled vegetables					
Rarely	1.00		1.00		
Weekly	1.70 (1.49-1.81)	0.003	1.49 (1.22-1.56)	0.573	0.172
Daily	1.36 (1.21-1.42)	0.021	1.53 (1.39-1.84)	0.491	0.383
Family history of tumors					
No	1.00		1.00		
Yes	1.46 (1.28-1.59)	0.019	1.06 (0.93-1.22)	0.824	0.142
Length of time air conditioning has been used (per 10 years)[a]	0.87 (0.76-1.06)	0.497	0.72 (0.64-0.88)	< 0.001	0.007

[a]Continuous variables.

A study by Manthravadi et al[32] found a negative association between air conditioning use and HCC incidence and recommended the introduction of air conditioning in developing countries to reduce the incidence of HCC, similar to the findings of the present study. The study[32] found that the use of air conditioning was a protective factor for HCC in Asia, but no statistically significant association was found in European countries[33]. Air conditioning can keep patients at colder temperatures for longer periods of time, Schneider et al[34] found that cancer cell production was inhibited when people were exposed to temperatures below 22 degrees. People who used air conditioning were exposed to colder temperatures for longer periods of time than those who did not use air conditioning, resulting in a lower risk of HCC due to the suppression of cancer cell production. Further analysis revealed that there was a synergistic interaction between sex and air conditioning use: women had a lower risk of developing HCC the longer they used air conditioning, the mechanism of which needs to be further investigated. A study by Jochen and Elike[35] showed that the incidence of viral hepatitis is higher at lower ambient temperatures, and that patients with viral hepatitis are more likely to develop hepatocellular carcinoma. The present study showed that the use of air conditioning to reduce ambient temperature was beneficial in reducing the incidence of hepatocellular carcinoma. Since self-reported liver disease patients (including self-reported viral hepatitis patients) was excluded from the baseline study, the conclusion that the use of air conditioning reduces the incidence of hepatocellular carcinoma may only apply to people who have not had liver disease, and risk factors for hepatocellular carcinoma incidence in people with liver disease or previous liver disease will be investigated in future studies.

This study explored each risk factor for HCC and its effect size comprehensively and quantitatively by means of a prospective cohort study in the Chengdu area, but some shortcomings remain. The information collected in this study was dictated by the study participants, and there may be recall bias leading to the hypothesis that

Table V. Analysis of the interaction between respondent gender and time spent using a refrigerator on the development of HCC.

Length of time air conditioning has been used (years)	Male		Female	
	HR value (95% CI)	*p*-value	HR value (95% CI)	*p*-value
0	1.00		0.82 (0.71-0.99)	0.049
1-10	0.81 (0.72-1.03)	0.096	0.50 (0.39-061)	0.003
10-20	0.76 (0.69-0.85)	0.034	0.21 (0.12-0.33)	< 0.001
≥ 20	0.92 (0.87-1.09)	0.907	0.36 (0.18-0.59)	0.006

the results tend to be invalid. Due to the fact that information on the participants was gathered only at the baseline survey, it was impossible to assess the association between changes in risk variables and the risk of HCC during the follow-up period. In future studies, the impact of changes in risk variables on the incidence of HCC will be studied.

Conclusions

Based on long-term follow-up data from 22,525 patients during the period 2012-2019, this study conducted a prospective cohort study on the incidence of HCC in the Chengdu population and found that age, current smoking, and consumption of pickled vegetables weekly or more frequently were risk factors for HCC, that female sex and length of time using air conditioning were protective factors for HCC, and that sex and air conditioning use had a synergistic effect on the synergistic interaction between sex and air conditioning use in the association with HCC incidence.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Availability of Data and Materials

The data used to support the findings of this study are included within the article.

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Informed Consent

Informed consent was obtained from all patients included in this study prior to submission of data.

Ethics Approval

This study was designed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kunming University of Science and Technology. Approval number: KUST201606451.

Authors' Contribution

Conceptualization: Qiang Cao and Qi Zhang. Methodology: Andong Fan and Xiaoling Zhang. Validation: Yuquan Chen. Formal analysis: Qi Zhang and Yuquan Chen. Investigation: Qiang Cao and Qi Zhang. Resources: Yuquan Chen and Andong Fan. Data Curation: Xiaoling Zhang. Writing - Original Draft: Qiang Cao. Writing - Review and Editing: Xiaoling Zhang. Supervision: Xiaoling Zhang. Project administration: Xiaoling Zhang and Qiang Cao.

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