Association Between Baseline C-Reactive Protein and the Risk of Lung Cancer: A Prospective Population-Based Cohort Study

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ABSTRACT

C-reactive protein (CRP), a systemic marker of diagnosing chronic inflammation, has been associated with the incidence of multiple types of cancer. However, little is known about the impact of CRP on lung cancer incidence in Chinese population. A total of 97,950 participants without cancer at baseline (2006–2007) of the Kailuan Cohort Study were followed up. The concentration of plasma high-sensitivity CRP (hsCRP) was tested for all participants at baseline interview. Multivariable Cox proportional hazards regression models were used to assess the association between levels of hsCRP and incident lung cancer. During 8.7-year follow-up, 890 incident lung cancer cases occurred and were divided into three groups according to the level of hsCRP. The risk of incident lung cancer was significantly increased with elevated levels of hsCRP [$HR_{Medium/Low}$, 1.21; 95% confidence interval (CI), 1.03–1.42; $HR_{High/Low}$, 1.42, 95% CI, 1.20–1.68; $P_{trend} < 0.001$], compared with the low group after adjusting confounders. Moreover, after stratifying by BMI, the significantly positive associations between the hsCRP level and the risk of lung cancer were found among those with BMI < 24 ($HR_{High/Low}$, 1.51; 95% CI, 1.18–1.94; $P_{trend} = 0.001$) and BMI = 24–28 ($HR_{High/Low}$, 1.47; 95% CI, 1.13–1.92; $P_{trend} = 0.003$), but not among those with BMI ≥ 28 ($HR_{High/Low}$, 1.01; 95% CI, 0.64–1.57; $P_{trend} = 0.991$). There was an antagonistic interaction between hsCRP levels and BMI that contributed to development of lung cancer ($P_{interaction} = 0.049$). In conclusion, these findings indicate a dose-dependent relationship between hsCRP and lung cancer risk among Chinese population, especially in nonobese participants, suggesting that CRP could serve as a potential biomarker for prediction of lung cancer risk and identification of high-risk population.

Prevention Relevance: In this prospective population-based cohort study, we found an association between higher plasma hsCRP and an increased risk of developing lung cancer, with stronger associations observed among nonobese participants.

Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer incidence and death in China (1). The 5-year survival rate of lung cancer in China remains only 16.1% (2). Therefore, detection of available biomarkers, especially early non-invasive, to identify the high-risk population and then performing early detection may play an important role in the prevention and treatment of lung cancer, and ultimately improve survival benefit.

Recently, chronic inflammation has been found to be associated with cancer incidence, and many inflammatory factors could serve as biomarkers for some cancer risk (3, 4). C-reactive protein (CRP), one of the most frequently used systemic markers for diagnosing chronic and acute inflammation, is known to be synthesized by liver cells in response to pro-inflammatory cytokines and plays an important role in the

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inflammatory process (5). Levels of CRP in blood are typically extremely low (the median normal concentration is 0.8 mg/L) in healthy individuals, but may be quickly increased after induction of inflammatory response associated with cancer (6). Although, the association between high-sensitivity CRP (hsCRP) and the subsequent risk of lung cancer has been investigated extensively in previous studies (7–14), the results were inconclusive. Some studies showed a positive association (9–14), whereas others showed no associations (7, 8), and acquiring further evidence is warranted.

In this study, therefore, we conducted a large population-based cohort study to prospectively evaluate whether higher levels of hsCRP at baseline are associated with the risk of lung cancer among Chinese population.

Materials and Methods

Study design and population

The Kailuan Cohort has been described in detail previously (15). Briefly, the data were obtained from a health examination of employees of the Kailuan Group in the city of Tangshan in Northern China. From May 2006 to December 2007, a total of 101,510 current and retired employees of the Kailuan Group underwent physical examinations for the first time at 11 hospitals affiliated with the Kailuan Group and all expenses were paid by the Kailuan Group. Among these subjects, we excluded subjects with a diagnosis of any prevalent cancer at baseline and those who did not provide blood samples. Finally, a total of 97,950 (96.5%) participants were included in this analysis.

Standardized questionnaires and physical examination were administered face-to-face by trained physicians at baseline interview. Information obtained from the questionnaire included assessments of demographics (age, gender, and education level), socioeconomics, behavioral factors (smoking habits and alcohol consumption), major chronic diseases (diabetes, hyperlipidemia, hypertension, and heart disease), and medical history. To standardize the measurements, height and weight were measured for all participants while they were wearing scrubs in health examination. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2). Diabetes was defined with any of the following criteria: (i) self-report of diabetes diagnosed by a physician; (ii) fasting plasma glucose ≥7.0 mmol/L or 2 hours plasma glucose ≥11.1 mmol/L; (iii) use of glucose-lowering medications during the past 2 weeks. Brisk walking, jogging, and working out were considered to be physical activity. Physical activity time was defined as longer than 30 minutes.

The study was performed according to the guidelines of the Helsinki declaration and its later amendments or comparable ethical standards and was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences, and Kailuan Group. All participants provided written informed consent.

Clinical measurements of plasma hsCRP levels

Antecubital vein blood samples were collected in the morning after overnight fasting, and transfused into EDTA-containing vacutainers. At room temperature, tubes were centrifuged for 10 minutes at 3,000 × *g* (centrifuge radius of 17 cm). Plasma samples were frozen rapidly at −80°C after separation for storage until laboratory analyses were performed. A commercial and high-sensitivity nephelometry assay (Cias Latex CRP-H, Kanto Chemical Co. Inc.) with a lower limit of detection of 0.1 mg/L was used to measured the concentration of hsCRP. In-house intra- and interassay coefficient of variations for hsCRP were 6.53% and 4.78%, respectively.

Follow-up and cancer ascertainment

Those who participated in the study were followed up until cancer, death, or December 31, 2015, whichever event came first. The mean follow-up time is 8.7 ± 1.2 years. During the study period, participants were followed up by face-to-face interviews every 2 years and given a routine medical examination by trained physicians until December 31, 2015, and the incident cancer cases in the cohort were collected by tracking subjects.

For 7355 participants without face-to-face follow-up, the information of incident lung cancer was further supplemented by interviewing discharge summaries from the 11 hospitals affiliated to Kailuan Group in which participants were diagnosed and treated, and by evaluating medical records from medicare to review diagnoses that might have been missed.

The diagnosis of incident lung cancer was confirmed by clinical experts who review the medical record. Information of imaging diagnosis (i.e., ultrasonography, computerized tomographic scanning, and magnetic resonance imaging), blood biochemical examination, and pathologic diagnosis was collected to evaluate PLC events. Lung cancer was coded as C34, according to the International Classification of Diseases, Tenth Revision (ICD-10).

Statistical analysis

We divided baseline hsCRP levels into three categories, according to American Heart Association (16, 17): low group (<1 mg/L), medium group (1–3 mg/L), and high group (>3 mg/L). Categorical variables were described as numbers (percentages, %) and compared using the Chi-square test. The cumulative incidence over time was studied with the Kaplan–Meier method, and the log-rank test was applied to assess differences between the levels of hsCRP groups using SPSS 20.0 software. Cox proportional hazards regression model was used to calculate HRs and 95% confidence intervals (CI) for baseline hsCRP levels and incident lung cancer, with adjustments for age, gender, education level (<high school or ≥high school), smoking (ever/never), alcohol consumption (ever/never), diabetes (yes/no), BMI (<24, 24–28, or ≥28 kg/m^2) for Asian population and physical activity (<3 or ≥3 times/week). We conducted the stratified analyses by age, gender, education,

smoking, alcohol drinking, diabetes, BMI, and frequency of physical activity. The *P* values for multiplicative interaction were tested by entering the cross-product of the stratifying variables and the hsCRP (three categories) exposure into the regression models and assessing whether such an inclusion improved model fit. The Cochran–Armitage test was used for trends in the association between increasing hsCRP levels and the risk of lung cancer. A two-sided *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.2.

Data availability

The data generated in this study are available upon request from the corresponding author.

Results

Baseline and demographic characteristics of the subjects in the Kailuan Cohort are listed and compared in **Table 1**. The mean age of subjects was 51.5 ± 12.4 years for all groups. Nearly 20% of participants in this study were female (19.3%), or with education level as senior high school and above (19.5%). Nearly 40% were ever cigarette smokers (38.1%) or alcohol drinkers (38.9%). One-fifth of the subjects were obese (BMI ≥ 28), and less than 16.0% practiced physical activity more than three times per week (**Table 1**). There were statistically significant differences on hsCRP levels in terms of age, gender, education, smoking, alcohol drinking, diabetes, BMI, and frequency of physical activity (all $P < 0.001$; **Table 1**).

A total of 890 incident lung cancers occurred until December 31, 2015, and new lung cancer cases were 421, 244, and 225 in the low, medium, and high groups, respectively (**Table 2**). The cumulative incidence in the medium ($1{,}125/10^5$) and high groups ($1{,}299/10^5$) were higher than that in the low group to ($899/10^5$; **Fig. 1**, log-rank test, $P < 0.001$).

Table 2 showed that compared with those in the low hsCPR group, subjects in the medium (HR, 1.21; 95% CI, 1.03–1.42) and high hsCRP group (HR, 1.42; 95% CI, 1.20–1.68) had an increased risk of lung cancer, with a dose-dependent relationship ($P_{trend} < 0.001$), after adjustments for age, gender, education, smoking, alcohol consumption, BMI, diabetes, and the frequency of physical activity. When stratified by BMI, the significantly positive associations between the hsCRP level and the risk of lung cancers were found among those with BMI < 24 (HR, 1.51; 95% CI, 1.18–1.94 for high levels of hsCRP; $P_{trend} = 0.001$) and BMI = 24–28 (HR, 1.47; 95% CI, 1.13–1.92 for high

Table 1. Baseline characteristics of participants in the Kailuan cohort 2006 to 2007 examination according to plasma levels of hsCRP ($n = 97{,}950$).

		hsCRP (mg/L)			
Characteristics	**Total (%)**	**<1** ***n* (%)**	**1–3** ***n* (%)**	**>3** ***n* (%)**	***P*[c]**
Total	97,950 (100)	53,855 (55.0)	25,014 (25.5)	19,081 (19.5)	
Age (years)					<0.0001
Mean ± SD	51.5 ±12.4 (years)				
≤52	49,659 (50.7)	30,772 (62.0)	11,912 (24.0)	6,975 (14.0)	
>52	48,291 (49.3)	23,083 (47.8)	13,102 (27.1)	12,106 (25.1)	
Gender					<0.0001
Female	19,765 (20.2)	10,532 (53.3)	5,059 (25.6)	4,174 (21.1)	
Male	78,185 (79.8)	43,323 (55.4)	19,955 (25.5)	14,907 (19.1)	
Education					<0.0001
<High school	76,850 (78.5)	43,089 (56.1)	19,637 (25.5)	14,124 (18.4)	
≥High school	19,056 (19.5)	10,596 (55.6)	5,252 (27.6)	3,208 (16.8)	
Smoking					<0.0001
Never	57,329 (58.5)	32,061 (55.9)	14,365 (25.1)	10,903 (19.0)	
Ever[a]	38,603 (39.4)	21,643 (56.1)	10,536 (27.3)	6,424 (16.6)	
Alcohol drinking					<0.0001
Never	56,544 (57.8)	31,255 (55.3)	14,273 (25.2)	11,016 (19.5)	
Ever[a]	39,419 (40.2)	22,470 (57.0)	10,641 (27.0)	6,308 (16.0)	
Diabetes					<0.0001
No	86,849 (88.7)	49,735 (57.3)	22,035 (25.4)	15,061 (17.3)	
Yes	11,101 (11.3)	4,102 (37.0)	2,979 (26.9)	4,020 (36.1)	
BMI (kg/m^2)					<0.0001
<24	37,325 (38.1)	23,544 (63.1)	7,493 (20.1)	6,288(16.8)	
24–28	41,138 (42.0)	22,033 (53.5)	11,061 (26.9)	8,044 (19.6)	
≥28	18,706 (19.1)	7,856 (42.0)	6,233 (33.3)	4,617 (24.7)	
Frequency of physical activity[b]					<0.0001
<3 times/week	80,673 (82.4)	45,817 (56.8)	20,263 (25.1)	14,593 (18.1)	
≥3 times/week	15,037 (15.4)	7,860 (52.3)	4,615 (30.7)	2,562 (17.0)	

[a]Ever means current and former.
[b]Physical activity time longer than 30 minutes.
[c]*P* values were calculated from χ^2 test.

Table 2. Association between hsCRP levels at baseline interview and risk of lung cancer in Kailuan Chort, 2006–2015.

	hsCRP (cases of incident lung cancer, mg/L)							
	<1		1–3		>3			
	Cases (*n*)	Reference	Cases (*n*)	HR (95% CI)	Cases (*n*)	HR (95% CI)	P_{trend}	$P_{interaction}$
Total ($n = 890$)	421	1.00	244	**1.27 (1.08–1.49)**	225	**1.56 (1.33–1.83)**	**<0.001**	
Total ($n = 890$)[a]	421	1.00	244	**1.21 (1.03–1.42)**	225	**1.42 (1.20–1.68)**	**<0.001**	
Age (year)[b]								0.728
≤52	126	1.00	50	1.07 (0.77–1.49)	34	1.31 (0.89–1.92)	0.195	
>52	295	1.00	194	**1.27 (1.06–1.53)**	191	**1.47 (1.22–1.78)**	<0.001	
Gender[c]								0.177
Female	44	1.00	20	0.74 (0.43–1.28)	20	0.84 (0.48–1.50)	0.456	
Male	377	1.00	224	**1.27 (1.07–1.53)**	205	**1.48 (1.24–1.77)**	**<0.001**	
Education[d]								0.583
<High school	371	1.00	211	**1.24 (1.04–1.47)**	189	**1.48 (1.24–1.77)**	**<0.001**	
≥High school	50	1.00	31	1.10 (0.70–1.74)	20	1.13 (0.67–1.92)	0.605	
Smoking[e]								0.220
Never	218	1.00	110	1.12 (0.89–1.41)	107	**1.31 (1.03–1.65)**	**0.030**	
Ever[j]	203	1.00	131	**1.31 (1.05–1.63)**	103	**1.55 (1.21–1.97)**	**<0.001**	
Alcohol drinking[f]								0.109
Never	239	1.00	121	1.09 (0.87–1.36)	119	**1.29 (1.03–1.62)**	**0.029**	
Ever[j]	182	1.00	121	**1.38 (1.09–1.74)**	91	**1.60 (1.24–2.07)**	**<0.001**	
Diabetes[g]								0.076
No	381	1.00	212	**1.23 (1.03–1.45)**	183	**1.45 (1.21–1.73)**	**<0.001**	
Yes	40	1.00	32	1.07 (0.66–1.73)	42	1.20 (0.73–1.98)	0.485	
BMI (kg/m^2)[h]								**0.049**
<24	207	1.00	91	1.23 (0.96–1.58)	99	**1.51 (1.18–1.94)**	**0.001**	
24–28	158	1.00	107	1.25 (0.98–1.60)	90	**1.47 (1.13–1.92)**	**0.003**	
≥28	53	1.00	45	0.99 (0.66–1.48)	34	1.01 (0.64–1.57)	0.991	
Frequency of physical activity[i,k]								0.648
<3 times/week	340	1.00	164	1.08 (0.89–1.30)	168	**1.39 (1.15–1.67)**	**0.001**	
≥3 times/week	80	1.00	78	**1.72 (1.25–2.36)**	40	**1.54 (1.05–2.26)**	**0.006**	

[a]Adjusted for age, gender, education, smoking, alcohol drinking, diabetes, BMI and physical activity.
[b]Adjusted for gender, education, smoking, alcohol drinking, diabetes, BMI and physical activity.
[c]Adjusted for age, education, smoking, alcohol drinking, diabetes, BMI and physical activity.
[d]Adjusted for age, gender, smoking, alcohol drinking, diabetes, BMI and physical activity.
[e]Adjusted for age, gender, education, alcohol drinking, diabetes, BMI and physical activity.
[f]Adjusted for age, gender, education, smoking, diabetes, BMI and physical activity.
[g]Adjusted for age, gender, education, smoking, alcohol drinking, BMI and physical activity.
[h]Adjusted for age, gender, education, smoking, alcohol drinking, diabetes and physical activity.
[i]Adjusted for age, gender, education, smoking, alcohol drinking, diabetes, and BMI.
[j]Ever means current and former.
[k]Physical activity time longer than 30 minutes.

levels of hsCRP; $P_{trend} = 0.003$), but there was no association with hsCRP in subjects with BMI ≥ 28 (HR, 1.01; 95% CI, 0.64–1.57 for high levels of hsCRP; $P_{trend} = 0.991$). There was evidence for a negative interaction between hsCRP levels and BMI for the risk of incident lung cancer ($P_{interaction} = 0.049$) such that there was no association with hsCRP in subjects with BMI ≥ 28.

There were differences in hsCRP levels (>10 or ≤10 mg/L) between stratification variables (Supplementary Table S1). Therefore, we conducted sensitivity analysis excluding individuals ($n = 4, 041$) with CRP more than 10 mg/L, which might be due to acute inflammations at baseline (16–18) or excluding cases that were diagnosed within the first 2 years of baseline, and there was still a positive association of between hsCRP levels and lung cancer risk (Supplementary Fig. S1).

Discussion

In this cohort study, we prospectively examined the association between the plasma levels of hsCRP and risk of incident lung cancer. The cumulative incidences went up with the increase of hsCRP Levels. Overall, we observed that elevated hsCRP levels at baseline interview had a dose–response effect on an increased risk of lung cancer among Chinese people, especially in nonobese participants.

Several possible mechanisms might explain the association between high CRP and increasing risk of lung cancer. Dysregulated chronic inflammation and ongoing inflammation can drive oncogenesis and provide angiogenic factors that enhance the subsequent cell proliferation and lead to tumor growth (19, 20). In particular, some inflammatory cells secrete chemokines and cytokines, such as IL6, IL8, and TNFα, into the blood that stimulate liver CRP production (21, 22). CRP, one of

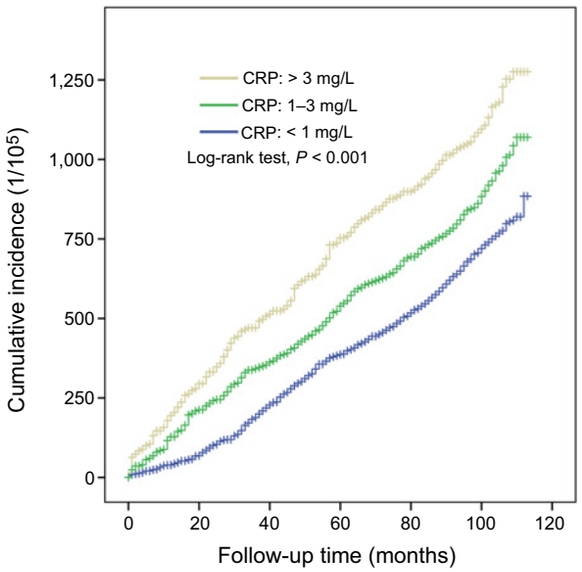

Figure 1.
The cumulative incidence of lung cancer in different hsCRP levels. The cumulative incidence in the medium (1,125/10^5) and high groups (1,299/10^5) were higher than that in the low group to (899/10^5; log-rank test, $P < 0.001$).

the most frequently used systemic markers for diagnosing chronic inflammation, is known to be synthesized by liver cells in response to pro-inflammatory cytokines and plays an important role in the inflammatory process (5, 6). Although the biological mechanisms underlying the association between CRP and cancer risk remain unresolved, a population-based cohort study of 2,276 men from eastern Finland followed a 21-year period suggested that subjects with hsCRP in the highest quartile, as compared with those in the lowest quartile, had a significantly increased risk of lung cancer (RR, 3.22; 95% CI, 1.44–7.20; ref. 23). A study conducted by Allin KH and colleagues (16), using the same categories of baseline plasma levels of hsCRP as our present study, revealed that the subjects with hsCRP 3 to 10 mg/L had 2.2-fold risk of lung cancer, comparing to those with hsCRP < 1 mg/L. A meta-analysis which included 10 studies (7 studies from the Europe, 2 from the United States, and 1 from Japan) on the CRP and lung cancer (a total of 1918 cases) demonstrated an average risk ratio of 1.33 (95% CI, 1.23–1.45) between the hsCRP levels and the risk of lung cancer (I^2 = 36.6%; ref. 24), and also emphasized that CRP was significantly associated with the lung cancer in men but not in women, which was consistent with our research. This difference may be due to the influence of female hormones (25).

Notably, in our study among younger subjects, CRP levels were not associated with lung cancer risk, but they were among older subjects. An underlying mechanism is that persistent and systemic inflammation increases with age (26). Elevated CRP levels at baseline were associated with an increased risk of lung cancer among participants with less education, but not among those with more education. Since health is thought to be affected by education (27), individuals with high levels of education tend to be more physically active and make healthy choices (28). In addition, less educated individuals could be more at risk of exposure to environmental carcinogens (such as dust, fumes, and certain chemicals; ref. 27) which could induce inflammation (29, 30), compared with more educated individuals. We also observed no association between diabetes and CRP levels on the risk of incident lung cancer. One possibility is that diabetes may not be independently associated with lung cancer risk (31, 32). Another possibility is only 11% of participants had diabetes at baseline.

Smoking is a well-known risk factor for lung cancer. In the study, although we did not found a significant interaction of the CRP and lung cancer risk associated by smoking status, there was a tendency for a larger magnitude of the association in smoker than nonsmoker. The elevated CRP levels were in relation to increased lung cancer risk in former and current smokers ($P_{trend} < 0.001$), suggesting that tobacco smoking may play a vital role in inflammatory processes, as a result of which contributed to the etiology of lung cancer (33). In the nonsmokers, we also found the significant associations between the hsCRP level and the risk of lung cancers ($P_{trend} = 0.003$). It is possible because many of people in the Kailuan group are exposed to coal dust or passive smoking, independent of smoking status.

In addition, after stratifying by BMI, a positive association between hsCRP levels and risk of incident lung cancer was observed in the BMI < 24 ($P_{trend} = 0.001$) and the BMI ($P_{trend} = 0.003$; refs. 24–28), whereas there was no association in those with higher BMI (≥28). We also found statistical evidence for an interaction between CRP and BMI ($P_{interaction} = 0.049$). A meta-analysis on the BMI and lung cancer indicated that increased BMI was negatively associated with the risk of lung cancer (0.76; 95% CI, 0.70–0.83 in men and 0.80; 95% CI, 0.66–0.97 in women; ref. 34). Moreover, BMI was associated with a diversity of circulating markers, including CRP, involved in the inflammatory response in obesity-related cancers (35, 36). Also, the inflammatory response increased the resting energy expenditure, which was maintained or increased in patients with lung cancer who subsequently lost weight. In contrast, on healthy subjects, the resting energy expenditure falls with weight loss (37). As an interesting outcome, the interaction of CRP and lung cancer risk by BMI is statistically significant, indicating those nonobese subjects with high level of hsCRP may be prone to lung cancer.

There are several strengths and limitations that should be noted when interpreting the results of our study. The most important strength of our study is that it was a large-scale population-based prospective cohort study and lung cancer diagnosis. The second strength of our study is that we also had high-quality follow-up, and the lost to follow-up rate was <1%. The third strength of the present study is the high rate of blood

samples collection among all subjects (96.5%), and the use of a highly sensitive assay which has good quality control characteristics to detect CRP.

Potential limitations in our study include confounding and selection bias. However, several potential confounders associated with CRP levels were involved in the Cox regression model, although we naturally cannot exclude all possible confounders, such as environmental pollutants and dietary habit, for lung cancer. Another limitation of our study was the relatively short follow-up time (mean = 8.7 years), but the moderate number (the minimum number of cases in subgroups was 20) of lung cancer cases allowed us to perform subgroup analyses by potential effect modifiers with sufficient statistical power. Third, we did not collect the information on smoking duration and intensity, or drinking volume and duration.

To conclude, this prospective population-based study supported a dose-dependent association between the risk of lung cancer and the levels of hsCRP. The association was the strongest among participants with higher levels of plasma CRP and lower levels of BMI status. The hsCRP may emerge as a potential marker for lung cancer risk and identification of high-risk population. The underlying biologic mechanisms of the relationship between CRP levels and increased lung cancer risk need further research.

Authors' Disclosures

No author disclosures were reported.

Authors' Contributions

J. Yin: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft. **G. Wang:** Conceptualization, resources, data curation, formal analysis, investigation, methodology, writing–review and editing. **Z. Wu:** Data curation. **Z. Lyu:** Data curation, investigation, writing–review and editing. **K. Su:** Data curation, investigation. **F. Li:** Data curation, investigation. **X. Feng:** Data curation, investigation. **L.-W. Guo:** Data curation, investigation. **Y. Chen:** Data curation, investigation. **S. Xie:** Data curation, investigation. **H. Cui:** Data curation, investigation. **J. Li:** Data curation. **J. Ren:** Data curation, investigation. **J.-F. Shi:** Data curation, investigation. **S. Chen:** Data curation, formal analysis, investigation. **S. Wu:** Conceptualization, resources. **M. Dai:** Conceptualization, resources, supervision, writing–review and editing. **N. Li:** Conceptualization, resources, supervision, funding acquisition, writing–original draft. **J. He:** Conceptualization, supervision.

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Note

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