

High sensitivity-C-reactive protein variability and risk of cancer incidence: A longitudinal prospective cohort study cancer

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Abstract. The association between inflammation and cancer has been extensively studied. However, studies examining the relationship between the magnitude of inflammatory fluctuations and cancer remain limited. Consequently, the present study aimed to explore the association between high-sensitivity C-reactive protein (hs-CRP) variability and the occurrence of cancer. A total of 42,514 participants were enrolled in the present study, with their hs-CRP levels measured over a 4-year period. The coefficient of variation (CV) of hs-CRP was used to quantify the variability in inflammatory status. Cox regression analysis was used to assess the association between hs-CRP variability and cancer risk after adjusting for potential confounding factors. The results demonstrated that a high CV of hs-CRP was significantly associated with reduced cancer risk [hazard ratio (HR), 0.84; 95% confidence interval (CI), 0.75-0.94]. Participants with high hs-CRP and low CV had a significantly increased risk of cancer (HR, 1.42; 95% CI, 1.18-1.70). In the stratified analysis of tumors at different sites, the association between hs-CRP variability and lung cancer risk was the most pronounced (HR, 0.77; 95% CI, 0.63-0.96). Sensitivity analyses confirmed the stability of the association between hs-CRP variability and cancer. In conclusion, higher hs-CRP variability was associated with lower cancer risk,

particularly for lung cancer; however, these findings provide preliminary evidence and require validation in future studies.

Introduction

Cancer is the second leading cause of death worldwide (1), and its incidence continues to rise annually (2). It is estimated that by 2040, there will be ~290,000 new cancer diagnoses and ~50,000 cancer-related deaths, with >16% of deaths occurring in low- and middle-income countries (3,4). Cancer treatment imposes substantial physical and psychological suffering on patients and places a marked financial burden on them (5,6). This multifaceted issue expands beyond individual patients, affecting families, careers and the broader society (7). Consequently, numerous studies are actively investigating risk factors associated with cancer (8). A comprehensive understanding of cancer etiology, along with effective interventions, is urgently needed.

Inflammation, particularly chronic inflammation, is a known contributor to tumor development (9-11). This association is supported by multiple mechanisms through which inflammation influences key processes in tumorigenesis, including genomic instability, DNA damage, oncogene activation and impaired tumor suppressor activity (12). Beyond contributing to the early stages of cancer development, chronic inflammation also serves a pivotal role in cancer progression (13,14); ~25% of all cancers are associated with chronic inflammation (15).

Among several peripheral inflammatory markers, high-sensitivity C reactive protein (hs-CRP) has been extensively studied due to its long plasma half-life, minimal diurnal variation and independence from age or sex (16). A previous prospective cohort study reported a notable association between elevated hs-CRP levels and cancer risk (17). Moreover, our previous studies have further supported this association, demonstrating a link between elevated hs-CRP levels and unfavorable survival outcomes across multiple cancer types (18,19). Collectively, these studies indicate a strong association between hs-CRP and cancer; however, a key limitation is that hs-CRP levels were measured only once at baseline.

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Nonetheless, cancer development is often associated with the long-term effects of risk factors. As an acute-phase response protein, hs-CRP is susceptible to fluctuations triggered by both endogenous and exogenous factors, particularly in the presence of inflammation, autoimmune disease or cancer (16). Relying solely on baseline hs-CRP levels as a predictor of cancer development has limitations. By contrast, serial measurements of hs-CRP over time, capturing both high and low levels as well as their fluctuations, provide a comprehensive reflection of peripheral inflammation and the associated inflammatory response. Variability, defined as the degree of fluctuation in a biomarker over time, constitutes a critical metric. Commonly used variability indicators include the coefficient of variation (CV) and the variation independent of the mean (VIM). Therefore, the present study aimed to assess changes in hs-CRP over time, expressing variability using the CV, and incorporating VIM as a complementary indicator to explore the association between hs-CRP variability and cancer incidence. The Kailuan cohort has previously been used to examine CRP trajectories and cancer risk (20). The present study uses the same source cohort and the same 2006-2010 CRP measurement period but addresses a different scientific question. It focuses on CRP variability rather than trajectory patterns.

Materials and methods

Study design and population. Data for the present study were obtained from the Kailuan cohort, a prospective cohort located in northern China. In 2006, employees of the Kailuan Group, including retirees, were invited to participate. A total of 101,510 employees agreed to take part and provided signed informed consent. Participants underwent questionnaire interviews, health examinations and laboratory assessments at Kailuan Hospital (Tangshan, China). Follow-up medical examinations and questionnaires were administered every 2 years. Participants who underwent <3 medical examinations between 2006-2010 were excluded. The present analysis was conducted using the Kailuan cohort, the same source population used in the previous CRP trajectory study by Liu *et al* (20). However, since the exposure definition differed, the inclusion and exclusion criteria and the final analytical sample were not identical. All personal information of the participants included in the final analysis was kept confidential. The study protocol adhered to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Kailuan Medical Group, Kailuan Company, which has direct oversight over Kailuan General Hospital, our participating clinical site (ChiCTR-TNRC-11001489).

Variable evaluation. Fasting blood samples were collected and analyzed for glucose, hs-CRP and triglyceride levels using a Hitachi 747 auto-analyzer (Hitachi, Ltd.) at the Kailuan General Hospital central laboratory. Serum hs-CRP was measured by immunoturbidimetry (detection limit, 0.1 mg/l) (21). To ensure data stability and scientific rigor, participants with hs-CRP levels of >15 mg/l were excluded, as the mean hs-CRP value is far lower than this threshold, and values above it may stem from detection errors or special physiological conditions.

Blood measurements were performed using automated analyzers following standard procedures. Experienced nurses measured the height and weight of the participants, and the body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Demographic details included sex, age, educational level and income. Educational attainment of high school was classified as 'high', while lower levels were categorized as 'low'. A monthly family income of >1,000 yuan per capita was classified as 'high income', with lower incomes categorized as 'low income'. Lifestyle information, including smoking, alcohol consumption and physical exercise, was obtained from participant responses to the lifestyle questionnaire.

The primary outcome of the present study was cancer incidence, with mortality as the secondary outcome. A prospective follow-up design was employed, tracking all participants from the baseline assessment performed in 2010-2011 until the occurrence of cancer or death. Death data were retrieved from the death certificates issued by the National Vital Statistics Bureau. The follow-up period extended from the baseline assessment to 2021, during which all outcome events were meticulously recorded.

Calculation of hs-CRP variability. hs-CRP was measured during three distinct periods: 2006-2007, 2008-2009 and 2010-2011. To quantify the hs-CRP variability, the CV was calculated as the standard deviation (SD) divided by the mean hs-CRP level across the three measurements for each participant ($CV = SD / \text{mean}$). This measure is widely used to assess variability independent of the absolute level (22); however, it is acknowledged that CV may be less stable when mean hs-CRP levels are low or when the distribution is skewed. Therefore, to enhance the robustness of the findings, the present study additionally employed the VIM as a complementary measure. Unlike CV, VIM is designed to be uncorrelated with the mean and thus provides a more stable estimate of variability across different mean levels. Both CV and VIM were categorized into tertiles (low, moderate and high) for analysis: $VIM = k \times SD(\text{hs-CRP}) / \text{mean}(\text{hs-CRP})^x$; $SD(\text{hs-CRP}) = \text{constant} \times \text{mean}(\text{hs-CRP})$; and $k = \text{Mean}[\text{Mean}(\text{hs-CRP})]^x$. This variability measure was then treated as a fixed covariate in the Cox proportional hazards models to assess its association with the risk of incident cancer during the subsequent follow-up period.

Statistical analysis. Normally distributed continuous variables were summarized using the mean and SD and analyzed using unpaired t-tests. Non-normally distributed continuous variables were analyzed using the Wilcoxon rank-sum test. Categorical variables were analyzed using the χ^2 test. This approach ensured the appropriate analysis of different variable types.

Moreover, Cox regression analysis was utilized to explore the relationship between hs-CRP variability and cancer risk. Model A was unadjusted, whereas Model B was adjusted for sex, age, education and income. Besides the adjustments in Model B, Model C was further adjusted for BMI, smoking, alcohol consumption and physical exercise. The proportional hazards assumption was tested using Schoenfeld residuals.

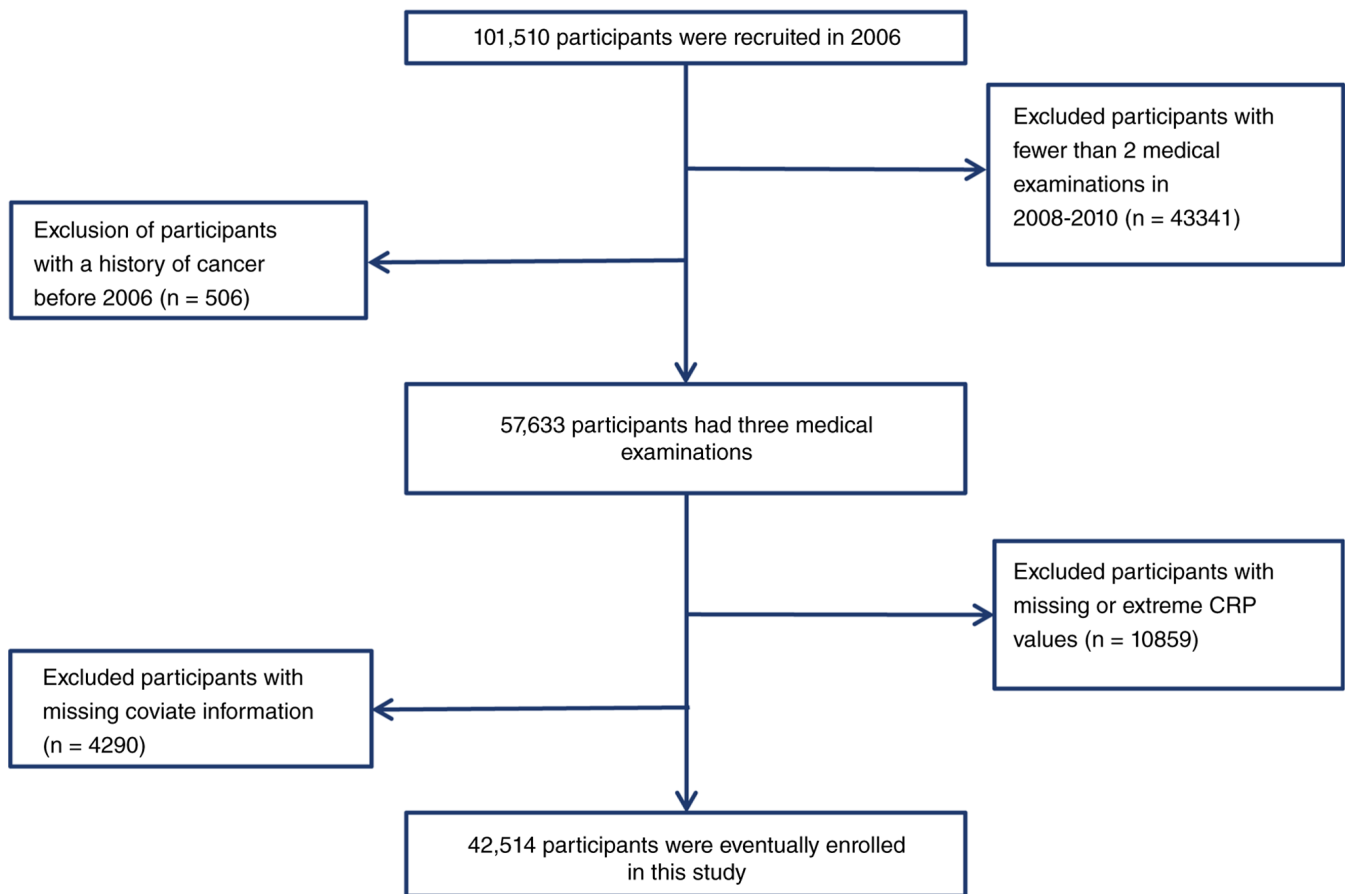


Figure 1. Flow diagram of participant selection. A total of 42,514 participants were included in the final analysis. CRP, C reactive protein.

The global tests were non-significant ($P>0.05$), indicating that the assumption was not violated. Restricted Cubic Spline (RCS) plots were generated to visually illustrate the complex relationship between continuous CV of hs-CRP and cancer risk. Additionally, the model was fitted using the 'TRAJ' program in SAS version 9.4 (SAS Institute, Inc.) to group individuals with similar patterns of hs-CRP change between 2006-2010. Subsequently, the association between hs-CRP variability and incident cancer in the overall cohort was examined within subgroups defined by distinct hs-CRP trajectories. The incidence of site-specific cancers during follow-up period was estimated and their association with the CV of hs-CRP was explored. Several sensitivity analyses were performed to assess the robustness of the findings and to address potential confounding. To minimize the influence of preclinical or undiagnosed cancer, participants who developed cancer within the initial 2-year follow-up period were excluded. To reduce the impact of acute inflammatory conditions, participants with hs-CRP levels of >10 mg/l were also excluded. Given the potential influence of metabolic factors in cancer, fasting blood glucose and lipid levels were additionally adjusted for. Moreover, to ensure that the observed association reflected hs-CRP variability rather than baseline inflammation, baseline hs-CRP levels were further adjusted for. Aspirin use was also included as a covariate in additional analyses.

Using VIM as a complementary indicator of variability, Cox regression analyses and RCS plots were additionally used

to explore the association between VIM of hs-CRP and cancer incidence. In addition, Cox regression analysis was used to assess the association between the CV and death, as well as cancer-specific mortality. The competing risk plots illustrated the relationships between different levels of hs-CRP variability and the occurrence of cancer and death.

All statistical tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using SAS (version 9.4; SAS Institute, Inc.) and R version 4.2.3 (RStudio, Inc.).

Results

The present study included 42,514 participants from the Kailuan cohort. The detailed process of participant inclusion and exclusion is shown in Fig. 1. Among the included participants, 24% were women and 76% were men, with an average age of 53.24 (11.69) years and a median follow-up duration of 10.98 years. Participants with higher hs-CRP variability tended to be men, younger and have lower BMIs (Table I). Mean hs-CRP was categorized as high (≥ 3 mg/l) or low (<3 mg/l) based on clinical experience (23), and participants were stratified according to present baseline information. The results revealed that participants with higher hs-CRP were more likely to be women, older and have higher BMIs (Table SI).

Cox regression analysis was then performed to evaluate the association between hs-CRP variability and cancer

Table I. Baseline characteristics of participants, stratified by the coefficient of variation of hs-CRP (n=42,514).

Characteristic	CV of hs-CRP			P-value
	Lowest tertile (<53.07)	Middle tertile (53.07~84.05)	Highest tertile (≥84.05)	
N	14,173	14,172	14,169	
Sex, n (%)				
Woman	3,622 (25.6)	3,504 (24.7)	3,093 (21.8)	<0.001
Man	10,551 (74.4)	10,668 (75.3)	11,076 (78.2)	
Age, years	54.56 (11.82)	53.55 (11.77)	51.62 (11.47)	<0.001
Education, n (%)				<0.001
Low	10,336 (72.9)	11,040 (77.8)	10,991 (77.6)	<0.001
High	3,837 (27.1)	3,132 (22.1)	3,178 (22.4)	
Income, n (%)				<0.001
Low	12,832 (90.5)	13,207 (93.2)	13,355 (94.3)	<0.001
High	13,41 (9.5)	965 (6.8)	814 (5.7)	
Smoke, n (%)				<0.001
No	8,880 (62.7)	9,223 (65.1)	9,088 (64.1)	<0.001
Current and past	5,293 (37.3)	4,949 (34.9)	5,081 (35.9)	
Alcohol intake, n (%)				<0.001
No	7,951 (56.1)	8,606 (60.7)	8,458 (59.7)	<0.001
Yes	62,22 (43.9)	5,566 (39.3)	5,711 (40.3)	
Physical exercise, n (%)				<0.001
No	1,204 (8.5)	1,301 (9.2)	1,465 (10.3)	<0.001
Yes	12,969 (91.5)	12,871 (90.8)	12,704 (89.7)	
BMI, kg/m ²	25.47±3.39	25.23±3.38	24.79±3.29	<0.001
FBG, mmol/l	5.75±1.67	5.68±1.76	5.58±1.59	<0.001
TG, mmol/l	1.36 (0.93,2.06)	1.28 (0.88,1.91)	1.26 (0.90,1.85)	<0.001
hs-CRP (2010)	1.27 (0.70,2.50)	1.21 (0.68,2.43)	1.00 (0.50,2.70)	<0.001
hs-CRP (2008)	1.33 (0.80,2.70)	1.60 (0.81,3.03)	1.60 (0.70,3.20)	<0.001
hs-CRP (2006)	1.10 (0.60,2.30)	0.70 (0.29,1.80)	0.33 (0.11,1.08)	<0.001
Mean hs-CRP	1.30 (0.75,2.52)	1.40 (0.77,2.50)	1.57 (0.95,2.60)	<0.001

Continuous variables are presented as mean ± standard deviation. Continuous variables that are not normally distributed were expressed as the median (interquartile range). Categorical variables were presented as numbers and percentages. Differences in normally and non-normally distributed baseline characteristics were compared using the chi-square test or t-test and Wilcoxon rank sum test, respectively. CV, coefficient of variation; hs-CRP, high sensitivity C reactive protein; BMI, body mass index; FBG, fasting blood-glucose; TG, triglyceride.

occurrence. The high hs-CRP group had a ~20% higher risk of cancer than the low hs-CRP group [hazard ratio (HR), 1.20; 95% confidence interval (CI), 1.07-1.33; $P<0.001$]. RCS was then used to observe the association between continuous CV of hs-CRP and cancer risk, and the results demonstrated that as CV increased, HR decreased, suggesting that higher visit-to-visit variability of hs-CRP was associated with lower cancer risk (Fig. 2A). Subsequently, hs-CRP variability was stratified into three groups based on the tertile intervals of CV of hs-CRP: Low, medium and high. Moderate hs-CRP variability did not show a significant association with cancer risk compared with low variability (adjusted HR, 0.93; 95% CI, 0.84-1.04; $P=0.205$), but high variability exhibited a notable protective effect against cancer (adjusted HR, 0.84; 95% CI, 0.75-0.94; $P=0.003$). To further assess the influence of hs-CRP levels on the relationship between variability and cancer risk, an additional Cox regression analysis was performed

by cross-classifying hs-CRP levels and variability. Using individuals with low hs-CRP levels and high variability as the reference group, all other groups showed elevated cancer risk compared with the reference (HR >1 for each group), indicating that the reference group had the lowest cancer risk. Compared with that of the reference group, the group with low hs-CRP level and low variability had a ~20% increased risk of cancer (adjusted HR, 1.20; 95% CI, 1.06-1.37; $P=0.05$), and the group with low hs-CRP levels and moderate variability did not have a significantly different cancer risk (adjusted HR, 1.12; 95% CI, 0.99-1.28; $P=0.079$). High hs-CRP levels were associated with a higher risk of cancer occurrence regardless of variability, with the group exhibiting the lowest variability showing the highest risk (adjusted HR, 1.42; 95% CI, 1.18-1.70; $P<0.001$; model C; Table II).

Subsequently, participants were categorized into three distinct long-term hs-CRP change patterns: Stable, increasing

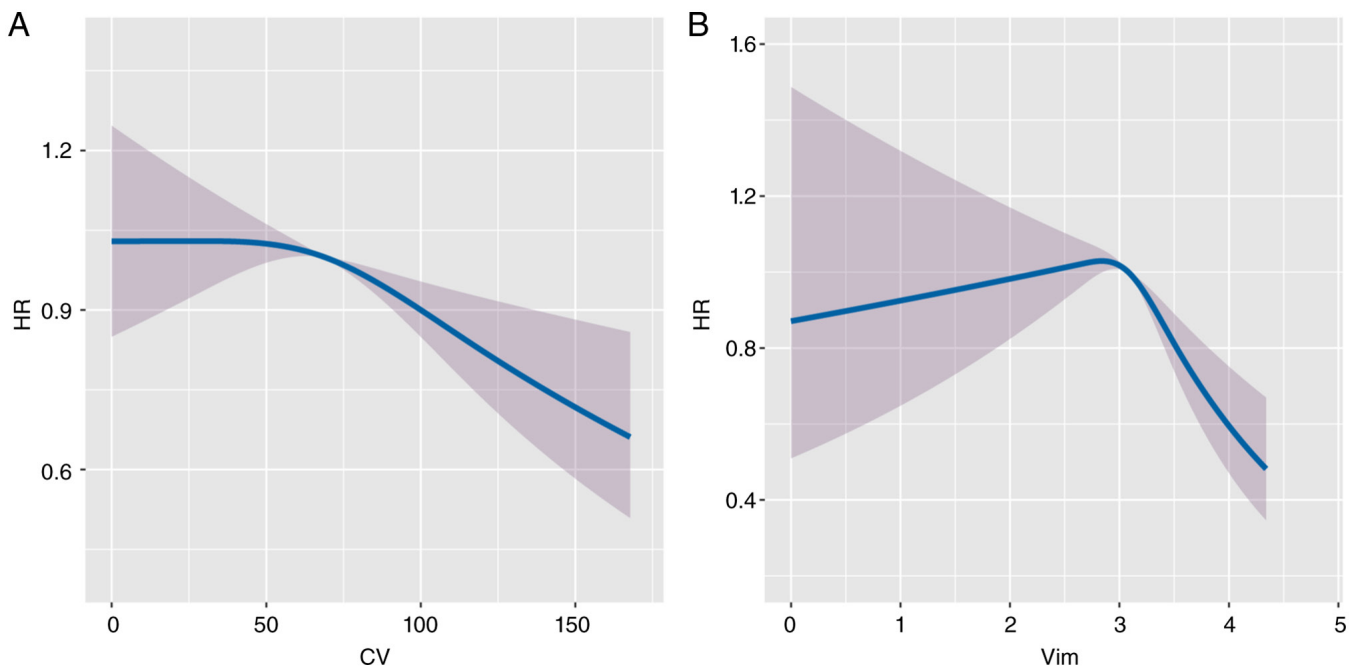


Figure 2. Association between CV and VIM of hs-CRP and risk of cancer occurrence. (A) Association between CV of hs-CRP and risk of cancer occurrence. (B) Association between VIM of hs-CRP and risk of cancer occurrence. HR, hazard ratio; CV, coefficient of variability; VIM, variation independent of the mean.

and decreasing (Fig. S1). The association between hs-CRP variability and cancer risk in participants with each of these three different patterns was then assessed. The results indicated that only in the stable group, hs-CRP variability was significantly associated with the risk of cancer (high variability in stable-pattern: HR, 0.81; 95% CI, 0.72-0.92; $P=0.001$; Table III).

Furthermore, the association between hs-CRP variability and cancer at different specific sites was evaluated. The incidence of cancer at several specific sites during the follow-up period is presented in Table SII. Among all participants, a total of 502 incident lung cancer cases occurred during the follow-up period (Table SII). Table IV indicated a significant association between CV of hs-CRP and the incidence of lung cancer (HR, 0.77; 95% CI, 0.63-0.96; $P=0.018$; Table IV).

To explore whether the association between hs-CRP variability and cancer exists in populations with different characteristics, subgroup analyses were performed. In most subgroups, high variability was associated with an elevated cancer risk. However, the P -values for interaction were not significant (all $P>0.05$), suggesting no significant heterogeneity across subgroups. Moreover, high variability was more protective against cancer than moderate variability (Fig. 3).

Additionally, sensitivity analyses were performed to ensure the stability of the findings and to rule out other factors. To minimize the possibility of reverse causation, lag analyses were performed by excluding participants who developed cancer within the first 2 years after the exposure assessment period. The results remained consistent with the main findings. The adjusted HR for the highest vs. lowest tertile of hs-CRP-CV was 0.84 (95% CI, 0.75-0.94) in the primary analysis and 0.79 (95% CI, 0.70-0.90) after excluding early cancer cases in the

highest tertile group. Second, participants with markedly large values of hs-CRP were excluded. In addition, blood glucose and lipids were corrected for separately from Model C, as well as hs-CRP at baseline and aspirin use. After these exclusions and additional adjustments, the association remained significant in the highest tertile of hs-CRP variability but was attenuated and no longer significant in the middle tertile, suggesting that the effect was robust in the highest tertile but not in the middle tertile (Table V).

Moreover, VIM was used as a complementary measure of variability. The RCS plot showed a decrease in HR for cancer risk with increasing VIM of hs-CRP (Fig. 2B). Cox regression analysis was used to explore the association between VIM of hs-CRP and cancer risk. The results revealed that VIM demonstrated a similar association with cancer as CV. Furthermore, there was a significant association between higher VIM of hs-CRP and reduced cancer risk (Fig. S2).

Finally, the association between hs-CRP variability and the risk of mortality was assessed. In model A, high hs-CRP variability was significantly associated with an increased risk of death (HR, 0.81; 95% CI, 0.75-0.88; $P<0.001$). However, after adjustment for potential confounders in model C, the association was attenuated and no longer statistically significant (HR, 0.92; 95% CI, 0.85-1.00; $P=0.056$), suggesting that the association observed in model A was largely explained by confounding factors (Table SIII). Nonetheless, competing risk plots suggest that high hs-CRP variability had a lower risk of cancer development and death than low variability (Fig. S3).

Discussion

The findings of the present study indicate a significant association between high hs-CRP variability and a reduced cancer risk.

Table II. Association between serum hs-CRP levels and variability and cancer incidence.

Hs-CRP	Case/n	Model A		Model B		Model C	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
hs-CRP levels							
Low (<3 mg/l)	1,445/34,118	ref.	ref.	ref.	ref.	ref.	ref.
High (≥3 mg/l)	457/8,396	1.33 (1.19-1.47)	<0.001	1.22 (1.09-1.35)	<0.001	1.20 (1.07-1.33)	<0.001
hs-CRP variability							
Low	689/14,173	ref.	ref.	ref.	ref.	ref.	ref.
Moderate	645/14,172	0.93 (0.83-1.03)	0.181	0.93 (0.83-1.04)	0.183	0.93 (0.84-1.04)	0.205
High	568/14,169	0.81 (0.72-0.90)	<0.001	0.83 (0.75-0.93)	0.002	0.84 (0.75-0.94)	0.003
P for trend			<0.001		0.001		0.003
hs-CRP levels and variability							
Low hs-CRP with high variability	428/11,322	ref.	ref.	ref.	ref.	ref.	ref.
Low hs-CRP with moderate variability	497/11,495	1.16 (1.02-1.32)	0.026	1.13 (0.99-1.29)	0.062	1.12 (0.99-1.28)	0.079
Low hs-CRP with low variability	520/11,301	1.24 (1.09-1.41)	<0.001	1.22 (1.07-1.38)	0.003	1.20 (1.06-1.37)	0.005
High hs-CRP with high variability	140/2,847	1.33 (1.10-1.61)	0.003	1.27 (1.05-1.53)	0.015	1.25 (1.03-1.51)	0.025
High hs-CRP with moderate variability	148/2,677	1.52 (1.26-1.84)	<0.001	1.36 (1.13-1.64)	<0.001	1.33 (1.10-1.61)	0.003
High hs-CRP with low variability	169/2,872	1.65 (1.38-1.97)	<0.001	1.45 (1.21-1.73)	<0.001	1.42 (1.18-1.70)	<0.001
P for trend			<0.001		<0.001		<0.001

The 'case' indicates the number of incident cancer cases, and 'n' represents the total number of participants in the corresponding group. Model A: unadjusted; Model B: adjusted for sex, age, education, income; Model C: additionally adjusted for BMI, smoke, alcohol intake, physical exercise based on Model B. Variability was categorized into three groups based on the tertile intervals of CV of hs-CRP: Low, medium, and high. hs-CRP, high sensitivity C reactive protein; HR, hazard ratio; CI, confidence interval.

Table III. Association between hs-CRP variability and cancer incidence in different hs-CRP trajectories (2006-2010).

Comparison	Case/N	HR (95% CI)	P-value
Continuous CV of hs-CRP (per_SD)			
Overall	1,902/42,514	0.95 (0.90-0.99)	0.013
Track 1 (stable)	1,607/36,579	0.95 (0.90-1.00)	0.032
Track 2 (increase)	138/2,792	0.93 (0.79-1.08)	0.335
Track 3 (decrease)	157/3,143	0.89 (0.76-1.03)	0.122
CV tertile interval of hs-CRP			
Lowest tertile	585/12,394	ref.	
Middle tertile	555/12,255	0.95 (0.85-1.07)	0.426
Highest tertile	467/11,930	0.81 (0.72-0.92)	0.001
Track 1 (stable-pattern)			
Lowest tertile	585/12394	ref.	
Middle tertile	555/12255	0.95 (0.85-1.07)	0.426
Highest tertile	467/11930	0.81 (0.72-0.92)	0.001
Track 2 (increase-pattern)			
Lowest tertile	45/701	ref.	
Middle tertile	35/889	0.59 (0.38-0.93)	0.021
Highest tertile	58/1,202	0.71 (0.48-1.05)	0.083
Track 3 (decrease-pattern)			
Lowest tertile	59/1,078	ref.	
Middle tertile	55/1,028	0.96 (0.67-1.39)	0.848
Highest tertile	43/1,037	0.74 (0.51-1.09)	0.127

The 'case' indicates the number of incident cancer cases, and 'n' represents the total number of participants in the corresponding group. COX regression model adjusted for sex, age, education, income, BMI, smoke, alcohol intake and physical exercise. CV, coefficient of variation; hs-CRP, high sensitivity C reactive protein; HR, hazard ratio; CI, confidence interval.

Maintaining a low inflammatory state in the body is of notable importance for cancer prevention. Participants with high hs-CRP levels coupled with low variability exhibited a significantly increased risk of developing cancer, in the present study.

Previous studies have reported that hs-CRP serves not only as a prognostic factor for patients with cancer, but it is also associated with an increased risk of future cancer in seemingly healthy individuals (24). Suthahar *et al* (17) suggested that baseline hs-CRP was associated with a ~17% increase in cancer risk, and elevated hs-CRP over time was associated with an ~8% increase in cancer risk. Moreover, a study on the trajectory of hs-CRP changes suggested that maintaining a long-term, stable and low level of hs-CRP is positively meaningful for cancer prevention (20,25). The results of the present study are in line with this conclusion. Participants in a low inflammatory state (hs-CRP of <3 mg/l, or with a trajectory of low-stable) exhibited a significantly lower risk of developing cancer compared with that of participants in a high inflammatory state (hs-CRP of ≥3 mg/l). On the one hand, chronic hyperinflammatory states leads to cellular damage and DNA injury; on the other hand, the activation of pro-inflammatory pathways, such as the NF-κB pathway, may excessively inhibit surveillance by the immune system and clearance of malignant cells (26). These factors could potentially contribute to the eventual presence and growth of cancer.

Chronic inflammation is the result of incomplete resolution of acute inflammation and has long been considered one of the causes of cancer (27). Chronic inflammation can persist for several years or even throughout the lifetime of an individual, and in the long term, non-steroidal anti-inflammatory drugs are ineffective (28). One hypothesis is rooted in the concept of 'unalamation' proposed by Maddipati (29), which posits that inflammation in the absence of injury may arise from a reduction in anti-inflammatory mediators rather than an increase in pro-inflammatory mediators. In the present study, participants with consistently high hs-CRP levels exhibited the highest risk of developing cancer. Although the observational data lack direct immunological measurements to substantiate mechanistic claims, a notably speculative hypothesis is that a reduction in anti-inflammatory mediators may induce a state of immune dysregulation, manifesting as chronically stable, elevated hs-CRP. Consequently, the observed association should be considered exploratory, and residual confounding cannot be excluded. Future research incorporating specific biomarkers of immune function is essential to elucidate the underlying mechanisms and verify this speculation.

Previous studies exploring the association between hs-CRP and cancer have primarily focused on static hs-CRP levels, often overlooking its longitudinal variability. In response to inflammation or infection, the immune system activates the liver to release hs-CRP (30), resulting in a certain

Table IV. Association between hs-CRP coefficient of variation and site-specific cancer incidence.

Cancer site	Lowest tertile	Middle tertile		Highest tertile	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Head and neck	ref.	1.68 (1.09-2.59)	0.018	1.32 (0.84-2.08)	0.236
Esophagus	ref.	1.98 (1.04-3.77)	0.037	1.30 (0.65-2.60)	0.463
Gastrointestinal	ref.	1.22 (0.82-1.82)	0.318	1.13 (0.75-1.71)	0.546
Colorectal	ref.	0.81 (0.61-1.09)	0.161	0.78 (0.58-1.05)	0.100
Liver and gallbladder	ref.	1.36 (0.93-1.96)	0.109	0.81 (0.53-1.24)	0.328
Pancreatic	ref.	1.63 (0.67-3.93)	0.280	1.36 (0.72-2.48)	0.245
Lung	ref.	0.74 (0.59-0.91)	0.005	0.77 (0.63-0.96)	0.018
Breast	ref.	0.90 (0.62-1.32)	0.587	0.71 (0.47-1.09)	0.117
Uterus and ovaries	ref.	1.08 (0.56-2.06)	0.825	1.18 (0.61-2.28)	0.626
Prostate	ref.	0.58 (0.32-1.03)	0.063	0.81 (0.47-1.40)	0.448
Kidney	ref.	1.14 (0.67-1.95)	0.631	0.78 (0.43-1.42)	0.422
Urinary bladder	ref.	0.97 (0.53-1.80)	0.935	0.79 (0.40-1.54)	0.488
Hematology	ref.	0.81 (0.44-1.51)	0.511	0.63 (0.32-1.26)	0.191

Cox regression model adjusted for sex, age, education, income, BMI, smoke, alcohol intake, physical activity. Tumors of the hematology include lymphoma and leukemia. HR, hazard ratio; CI, confidence interval.

Table V. Sensitivity analyses.

CV of hs-CRP	HR (95% CI)	P-value
Exclude cancer occurrence within first 2 years (n=41,948)		
Lowest tertile	ref.	
Middle tertile	0.89 (0.80-1.00)	0.059
Highest tertile	0.79 (0.70-0.90)	<0.001
Exclude hs-CRP maxima (hs-CRP >10 mg/l) (n=40,412)		
Lowest tertile	ref.	
Middle tertile	0.94 (0.84-1.05)	0.283
Highest tertile	0.86 (0.77-0.97)	0.014
Additionally adjusted for blood glucose and lipid		
Lowest tertile	ref.	
Middle tertile	0.93 (0.84-1.04)	0.201
Highest tertile	0.84 (0.75-0.94)	0.003
Additionally adjusted for basic hs-CRP		
Lowest tertile	ref.	
Middle tertile	0.93 (0.84-1.04)	0.209
Highest tertile	0.84 (0.75-0.94)	0.002
Additionally adjusted for taking aspirin		
Lowest tertile	ref.	
Middle tertile	0.93 (0.84-1.04)	0.212
Highest tertile	0.85 (0.76-0.95)	0.003

Cox regression model adjusted for sex, age, education, income, BMI, smoke, alcohol intake, physical activity. CV, coefficient of variation; HR, hazard ratio; CI, confidence interval.

degree of physiological fluctuation, even in relatively healthy populations. Furthermore, adverse lifestyle factors such as smoking, obesity and chronic psychological stress are known

to contribute to elevated hs-CRP levels (31,32). Therefore, predicting future cancer risk based solely on a single-point hs-CRP measurement is susceptible to confounding. The

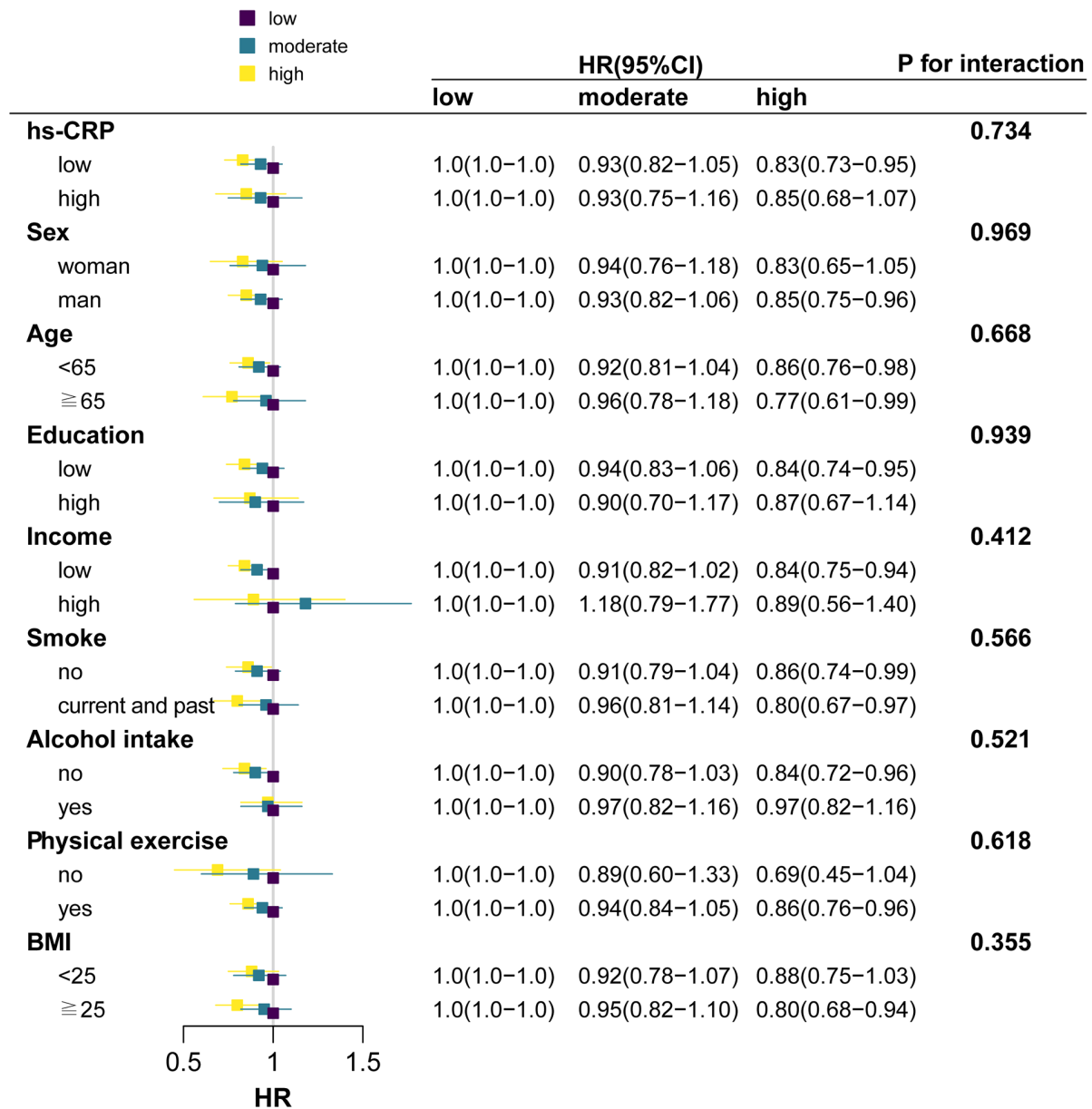


Figure 3. Association of hs-CRP coefficient of variation and cancer occurrence in participants with different characteristics. BMI, body mass index; HR, hazard ratio; 95%CI, 95% confidence interval.

present study explored the association between hs-CRP variability and cancer incidence, and a notable observation was that higher hs-CRP variability was associated with a reduced risk of cancer. In an exploratory cross-classification analysis, participants exhibiting a 'high' hs-CRP level and low 'variability' profile had a ~42% higher observed risk of developing cancer compared with those with a 'low' hs-CRP level and high 'variability' profile. This phenomenon corroborates previous epidemiological meta-analyses indicating a notable positive association between chronic inflammation, as characterized by elevated hs-CRP, and cancer incidence (33). In exploratory trajectory-stratified analyses, the inverse association between high hs-CRP variability and cancer risk was predominantly observed among individuals with a low-stable hs-CRP pattern. By contrast, no significant protective effect was detected in populations with decreasing or increasing hs-CRP trajectories; this may be due to sample size limitations, as the sample size

for decreasing or increasing hs-CRP patterns were much lower than that of populations with low stable hs-CRP pattern.

Furthermore, the findings of the present study revealed a significant association between hs-CRP variability and the incidence of lung cancer. Compared with that of individuals with low hs-CRP variability, those with high hs-CRP variability exhibited a ~23% reduced risk of developing lung cancer. While elevated hs-CRP levels have been widely recognized as a relevant prognostic factor in patients with non-small cell lung cancer (32–34). In the context of immunotherapy for non-small cell lung cancer, hs-CRP has been identified as an independent prognostic marker, with a proposed mechanism involving its association with the immunosuppressive adenosine signature pathway (34). Furthermore, Feng *et al* (35) reported that hs-CRP inhibited the activation of lung macrophages induced by commensal bacteria in an FcγR2B-dependent manner, thereby impairing

macrophage-mediated immune surveillance and facilitating the formation of the pre-metastatic niche in the lungs of tumor-bearing mice. Peripheral inflammation may influence the prognosis of patients with cancer by altering and shaping the tumor microenvironment (36). Hsu *et al* (37) reported that hs-CRP contributes to lung cancer development within the tumor microenvironment. However, research on the association between hs-CRP levels and the risk of lung cancer remains limited to date. The German Randomized Lung Cancer Screening Intervention trial reported that elevated hs-CRP levels were markedly associated with an increased risk of developing lung cancer (38). Moreover, the Kailuan Cohort Study also previously reported a notable association between high baseline hs-CRP levels and the occurrence of lung cancer (39). The findings of the present study further identified a significant association between hs-CRP variability and lung cancer. Additionally, a study assessing longitudinal changes in hs-CRP reported that participants with consistently low hs-CRP levels exhibited the lowest risk of developing cancer, whereas those with consistently high hs-CRP levels had the highest risk (17). Regarding potential mechanism underlying the association between hs-CRP and lung cancer incidence, systemic inflammation-reflected by elevated hs-CRP levels-may be associated with alterations in independent differentially methylated CpG loci, potentially contributing to lung carcinogenesis (40,41). However, given the observational nature of the present study and the absence of direct epigenetic or mechanistic measurements, these interpretations remain speculative. Further mechanistic research is warranted to substantiate the causal association between hs-CRP and lung cancer risk.

In subgroup analyses, the present study demonstrated that the inverse association between high hs-CRP variability and cancer incidence was more pronounced in older patients compared with that of middle-aged individuals, in smokers compared with that of non-smokers and in obese patients compared with that of non-obese participants. Both smoking and obesity are well-established inducers of a chronic systemic inflammatory state. As a marker of chronic inflammation, hs-CRP also reflects the biological aging status of the organism (42,43). A previous prospective cohort study reported that biological aging is frequently accompanied by low-grade inflammation, with aging of the immune system paralleled by elevated levels of pro-inflammatory markers such as hs-CRP (44). Previous reports have also proposed that biomarkers of immunosenescence may follow different age-related trajectories: Certain biomarkers increase progressively, while others remain relatively stable (45,46). hs-CRP is among the most commonly used markers of immune aging (47). In the present observational study, we hypothesize that stable hs-CRP levels may represent one manifestations of immunosenescence, whereas greater hs-CRP variability might reflect a more dynamic inflammatory state. Given that cancer is an age-related disease closely associated with aging, smoking and obesity (48), and that immunosenescence has been proposed as a key biological mechanism linking aging to cancer, we further hypothesized that hs-CRP variability, as a potential indicator of immune aging, may be associated with cancer risk. The findings of the present study demonstrated that higher hs-CRP

variability was associated with lower cancer risk within these higher-risk groups; however, this inverse association should not be interpreted as causal or as evidence of a protective effect. As no direct measures of immunosenescence were available in the cohort, further exploration of whether hs-CRP variability is associated with immune aging was not possible. Future large-scale prospective studies could examine the relationships between hs-CRP variability and aging biomarkers or DNA methylation patterns and assess whether hs-CRP variability itself could serve as a marker of biological aging.

Furthermore, in the present observational study, an association between hs-CRP variability and cancer risk was identified. Although the present research does allow the elucidation of the biological mechanisms underlying this association, it may generate hypotheses for future research on inflammation dynamics and cancer prevention. The findings suggest that lower mean hs-CRP levels were associated with reduced cancer risk, which is consistent with prior evidence linking chronic inflammation to carcinogenesis.

A strength of the present study is the examination of longitudinal hs-CRP fluctuations in relation to cancer risk, an aspect that has received limited attention in previous research. To the best of our knowledge, few studies have directly evaluated the association between the magnitude of hs-CRP variability and incident cancer using repeated measurements over time. Treating variability as a fixed exposure is consistent with the study design and with previous research examining biomarker variability in relation to long-term health outcomes. However, the present study did not formally test whether CRP variability improves risk prediction beyond mean CRP or CRP trajectories. The cross-classification and trajectory-stratified analyses were exploratory and should be considered hypothesis-generating. While a time-dependent approach could theoretically capture changes in variability over time, it would require repeated recalculation of variability within moving time windows throughout the follow-up period. This approach is methodologically complex and may introduce instability, particularly when the number of hs-CRP measurements varies across individuals. Therefore, we consider the fixed-exposure approach is appropriate and aligns with the present research question. In addition, multiple potential confounders were adjusted for, including obesity and lifestyle factors, which strengthens the internal validity of the observed associations, although residual confounding cannot be fully excluded.

Nevertheless, the present study has several limitations. First, the sex distribution in the cohort is imbalanced, with a higher proportion of men than women. Although sex-stratified analyses were performed, residual confounding or selection bias associated with sex cannot be fully excluded. This concern is, however, partially mitigated by prior studies that did not observe effect modification by sex in the association between hs-CRP and cancer risk. Second, cancer development is multifactorial, and metabolic factors may partly confound the observed association. Although total cholesterol and triglycerides were adjusted for in sensitivity analyses, residual confounding by unmeasured or imperfectly measured metabolic factors remains possible.

Third, inflammatory status may be influenced by conditions such as in autoimmune diseases. A cohort study on biological or targeted synthetic antirheumatic drugs and cancer reported that patients taking such drugs had an increased risk of developing cancer (49). However, information on autoimmune diseases was not available in the dataset used in the present study, precluding adjustment for this potential confounder. Fourth, as with any coefficient of variation, hs-CRP CV is mathematically dependent on the mean, which may introduce coupling between mean hs-CRP and its variability. To address this, trajectory-stratified analyses were performed and VIM was used, a variability metric less influenced by the mean. Nevertheless, a degree of residual dependence may persist, which is a recognized limitation of CV-based variability measures. Finally, the present study could not directly assess whether low hs-CRP variability reflects immunosenescence, as validated biomarkers or diagnostic criteria for immune aging were not measured in the cohort. As this was an observational cohort study, causality between hs-CRP variability and cancer risk cannot be established. Future studies incorporating biomarkers of immune aging and repeated inflammatory measures are warranted to clarify the relationships among hs-CRP variability, immunosenescence and cancer risk.

In conclusion, the present prospective cohort study demonstrated an inverse association between hs-CRP variability and the risk of cancer, particularly lung cancer. Participants with high hs-CRP levels and low variability demonstrated a higher cancer risk compared with those with low hs-CRP levels and high variability. However, due to the observational nature of the present study, causal inferences cannot be drawn. Further studies are needed to confirm these findings and to explore the underlying mechanisms.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

GSX wrote the manuscript. GSX, RJC, YMW, XMM and QSZ analyzed and interpreted the patient data, JQ and WQL made substantial contributions to the conception, design and intellectual content of the studies. WQL and QSZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study followed the Helsinki declaration. All participants signed an informed consent form. This study was approved by the Ethics Committee of Kailuan Medical Group, Kailuan Company. Trial registration: Kailuan study, ChiCTR-TNRC-11001489 (<http://www.chictr.org.cn/showproj.aspx?proj=8050>).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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