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Association between periodontitis and gastrointestinal cancer risk and prognosis: evidence from a nested case–control study in Southwest China

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Abstract

Background With low early detection rates and high incidence and mortality, Gastrointestinal cancer (GIC) imposes a significant global health burden. Emerging evidence indicates that periodontitis may be a potential risk factor for GIC development; however, epidemiological data remains inconclusive.

Objective This study aimed to examine the impact of periodontitis on the incidence, recurrence, and metastasis of GIC in Southwest China, thereby offering epidemiological evidence to support GIC prevention and management.

Methods Between September 2022 and August 2024, a case–control study was conducted at the Affiliated Hospital of North Sichuan Medical College. Five hundred GIC patients were included as the case group based on the predefined inclusion and exclusion criteria, while 1005 healthy individuals were recruited for the control group. Multivariate analyses were performed to examine the associations between periodontitis and GIC incidence, recurrence, and metastasis while controlling for potential confounding factors.

Results The results of this study demonstrated that periodontitis was significantly associated with the incidence of esophageal, gastric, and colorectal cancer. Even after adjusting for potential confounders, it remained a significant risk factor for esophageal cancer (OR = 2.810, 95% CI 1.032–7.649, P = 0.043), colon cancer (OR = 2.330, 95% CI 1.072–5.067, P = 0.033), and rectal cancer (OR = 2.730, 95% CI 1.247–5.379, P = 0.012). Compared to non-periodontitis subjects, periodontitis showed a significant association with distant metastasis of rectal cancer (aHR = 5.332, 95% CI 1.406–20.220, P = 0.014). Moreover, severe periodontitis was identified as an risk factor for distant metastasis in rectal cancer (aHR = 10.138, 95% CI 1.824–56.354, P = 0.008).

Conclusion This study highlights significant associations between periodontitis and an increased risk of esophageal and colorectal cancers. Additionally, patients with rectal cancer and periodontitis exhibited an increased risk of distant metastasis compared to those without periodontitis.

Keywords Periodontitis, Gastrointestinal cancer, Nested case–control study

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Introduction

Periodontitis is a widespread chronic inflammatory disease, affecting nearly 60% of the global adult population [1]. It is marked by the progressive loss of periodontal attachment, including gingival tissue, periodontal ligament fibers, and alveolar bone. Clinical manifestations of the condition include gingival inflammation, periodontal pocket formation, alveolar bone resorption, and gingival recession. In severe cases, disease progression can lead to tooth loss [2]. For these reasons, periodontal disease is ranked among the top ten most prevalent human diseases worldwide, contributing to a significant global health problem [3, 4]. Several reports have established strong associations between periodontitis and various systemic chronic diseases, including cardiovascular diseases, type 2 diabetes mellitus, and malignancies [4, 5]. These findings have driven extensive research into the role of periodontitis in systemic disease risk.

Ranking second in incidence and first in mortality, Gastrointestinal cancer (GIC) is among the most prevalent malignancies worldwide, with both rates continuing to rise. Global statistics from 2020 reported 5,142,192 new GIC cases and 3,628,920 related deaths [6]. GIC has also been reported to include various malignancies, such as esophageal, gastric, colorectal, hepatic and Pancreatic cancers [7]. According to 2023 Chinese statistics, the incidence rates per 100,000 population were 43.09 for gastric cancer, 42.74 for colorectal cancer, 19.55 for esophageal cancer, and 14.80 for hepatic cancer. The corresponding mortality rates were 29.04 for gastric cancer, 18.40 for colorectal cancer, 18.09 for esophageal cancer, and 13.20 for hepatic cancer, significantly surpassing those of the other malignancies in China [8]. Some of the established risk factors for GIC include genetic predisposition, lifestyle choices, nutritional status, microbial influences, and environmental exposures [9–11].

The critical role of systemic chronic inflammation in gastrointestinal carcinogenesis has been increasingly emphasized in recent studies [12, 13]. Through periodontal pathogen proliferation and dissemination via hematogenous spread and saliva swallowing, periodontitis may contribute to systemic chronic inflammation. As a result, periodontitis may act as an independent risk factor for GIC [4, 14, 15]. Comparative analyses have identified significant differences in periodontal microbiota composition between patients with GIC and healthy individuals [16, 17]. Furthermore, periodontal preventive interventions have been associated with a significant reduction in GIC incidence, although the underlying mechanisms remain unclear [18]. For these reasons, periodontitis may serve as a key health indicator influencing GIC development [19].

While existing research has linked periodontitis and GIC risk, few reports have examined the relationship between periodontitis severity and site-specific GIC. This study analyzed clinical data from the Affiliated Hospital of North Sichuan Medical College between September 2022 and August 2024 to examine the associations between periodontitis, its severity, and site-specific GIC outcomes. The findings of this study aim to provide valuable insights for periodontal management into GIC prevention and treatment strategies.

Materials and methods

Study population

This study enrolled patients diagnosed with GIC at the Affiliated Hospital of North Sichuan Medical College between September 2022 and August 2024. The inclusion criteria were as follows: (1) The diagnosis of esophageal carcinoma, gastric cancer, hepatocellular carcinoma, colorectal carcinoma, or pancreatic carcinoma was confirmed through the histopathological analysis of the tissue specimens obtained from endoscopic or surgical procedures [20]; (2) Absence of any gastrointestinal inflammatory diseases, autoimmune disorders, or infectious diseases. The exclusion criteria were as follows: (1) Patients with incomplete data; (2) Patients with a history of cancer in other anatomical areas or those who had undergone cancer-related treatment before the current visit; (3) Patients with a prior confirmed diagnosis of GIC. Based on the above criteria, 1,505 participants were enrolled in the study. The case group included 500 patients newly diagnosed with gastrointestinal tumors. Meanwhile, the control group comprised 1,005 patients selected at a 1:2 ratio from those undergoing routine health check-ups at the Affiliated Hospital of North Sichuan Medical College. This study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (No. 2024ER485-1). The flowchart of the study design is shown in Fig. 1.

Exposure assessment and classification

Standard questionnaires were administered by certified reviewers to assess periodontal status during clinical visits for both case and control groups [21, 22]. After receiving a cancer diagnosis, the case group underwent structured interviews that focused on their oral health status before the diagnosis. Self-reported oral health parameters gathered through these interviews were as follows: (1) A history of gingival bleeding, pain, sensitivity, and trauma; (2) Previous tooth mobility or "loose teeth" due to pathological conditions; and (3) A previous professional diagnosis of periodontitis. Due to its strongest association with elevated tumor incidence rates among oral health variables, a previous diagnosis

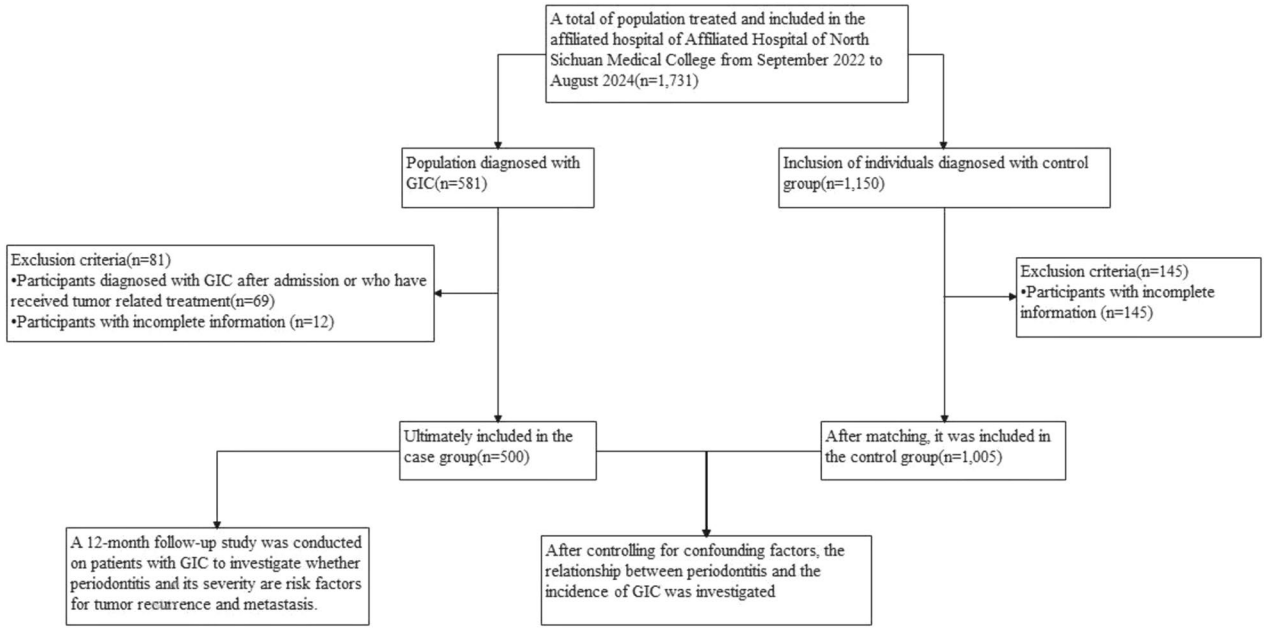

Fig. 1 The flowchart of the study design

of periodontitis was designated as the primary indicator. This parameter served as the most reliable oral health metric that could be consistently assessed by trained interviewers.

The diagnosis and classification of periodontitis were conducted by trained dental professionals through clinical examinations. According to the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) classification [23, 24], periodontal health is defined by the absence of clinical signs indicative of mild, moderate, or severe periodontitis. Mild periodontitis is defined by the presence of at least two interproximal sites with clinical attachment loss (CAL) of ≥ 3 mm and at least two interproximal sites with probing depth (PD) ≥ 4 mm (not on the same tooth), or one site with PD ≥ 5 mm. Moderate periodontitis is defined by at least two interproximal sites with CAL ≥ 4 mm (not on the same tooth) or at least two interproximal sites with PD ≥ 5 mm (not on the same tooth). Severe periodontitis is classified by at least two interproximal sites with CAL ≥ 6 mm (not on the same tooth) and at least one interproximal site with PD ≥ 5 mm. This classification system was used for comparative analysis as it comprehensively encompasses various aspects of periodontal disease and its severity levels.

Measurement of covariates

Structured interviews were used to systematically collect information on demographic characteristics, including gender, age, education, income, health insurance coverage, and residential location. During clinical visits at the Affiliated Hospital of North Sichuan Medical College, anthropometric measurements and clinical parameters—such as height, weight, blood pressure, fasting blood glucose or glycated hemoglobin (HbA1c), and lipid profiles. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and categorized into the following four groups: (1) < 20 kg/m^2; (2) 20–24.9 kg/m^2; (3) 25–29.9 kg/m^2; and (4) ≥ 30 kg/m^2. All participants were of Han Chinese ethnicity, with marital status classified as married, divorced, or widowed. Educational qualification was categorized into four levels: (1) junior high school or below; (2) partial high school education; (3) high school graduate; and (4) university degree or higher. Monthly income was divided into the following five tiers: (1) < 500 RMB; (2) 500–1000 RMB; (3) 1000–2000 RMB; (4) 2000–3000 RMB; and (5) > 3000 RMB [25]. Health insurance status was categorized as insured or uninsured, while residential locations were classified as rural or urban. Smoking status was divided into the following three groups: (1) never smokers, defined as individuals who had smoked fewer than 100 cigarettes in their lifetime; (2) former smokers, referring to those who had smoked at least 100 cigarettes but had completely quit; and (3) current smokers, defined as individuals who had smoked at least 100 cigarettes and were continuing smoking. Alcohol consumption was categorized into three groups: (1) never drinkers; (2) former drinkers; and (3)

current drinkers. Hypertension status was classified into the following: (1) non-hypertensive, defined as the absence of a physician-diagnosed hypertension; or (2) hypertensive, characterized by a physician-confirmed hypertension diagnosis or blood pressure readings of ≥ 140/90 mmHg on three separate measurements. Diabetes status was classified as follows: (1) non-diabetic, defined as the absence of a physician-diagnosed diabetes diagnosis; and (2) diabetic, characterized by a physician-diagnosed diabetes, with fasting blood glucose levels exceeding 125 mg/dL, or HbA1c > 6.4%. Meanwhile, Hyperlipidemia status was categorized as follows: (1) non-hyperlipidemic, indicating no physician-diagnosed hyperlipidemia; and (2) hyperlipidemic, defined by a physician-diagnosed hyperlipidemia or serum cholesterol levels exceeding 5.72 mmol/L or triglycerides levels exceeding 1.70 mmol/L. Family history of malignancies was recorded as present or absent.

Outcome evaluation

This study defined primary outcome parameters and applied the following statistical models: (1) Presence of GIC as a categorical outcome; (2) region-specific and site-specific malignancies as categorical variables; (3) tumor recurrence within the past 12 months as a categorical variable; and (4) tumor metastasis within the preceding 12 months as a categorical variable.

Statistical methods

IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) was used to conduct all statistical analyses. The Kolmogorov–Smirnov test was used to assess the normality of variable distribution. Continuous variables, such as age exhibited a non-normal distribution and were reported as median values with interquartile ranges [M (Q1, Q3)]. Intergroup comparisons were conducted using nonparametric tests, particularly the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages [n (%)], with between-group differences evaluated using Pearson's chi-square test or Fisher's exact test. These variables encompassed demographic characteristics, anthropometric measures, lifestyle factors, and comorbidities. Binary logistic regression analyses were performed to examine odds ratio (OR) and corresponding 95% confidence interval (CI) for the associations between periodontitis and tumors incidence. Additionally, cox regression models were utilized to assess hazard ratio (HR) and CI for the relationship between periodontitis severity and distant metastasis in colorectal cancer, with adjustments for potential confounding factors. A two-tailed P-value < 0.05 was regarded as statistically significant.

Results

Baseline data and clinical characteristics of the study population

Between September 2022 and August 2024, 500 patients with diagnosed gastrointestinal cancers were recruited from the Affiliated Hospital of North Sichuan Medical College. The case group consisted of patients with esophageal cancer (n = 138), gastric cancer (n = 79), hepatocellular carcinoma (n = 51), colon cancer (n = 83), rectal cancer (n = 124), and pancreatic cancer (n = 25). By using a 1:2 matching protocol, a control group of 1,005 tumor-free individuals was established. The study population was stratified into periodontitis (n = 635) and non-periodontitis groups (n = 870) following standardized diagnostic criteria for periodontitis. The baseline demographic and the clinical characteristics of the study population are summarized in Table 1. In terms of gender distribution, age, body mass index (BMI), marital status, insurance coverage, smoking status, hypertension, hyperlipidemia, or family history of malignancies, no statistically significant differences were observed between the case and control groups (all P > 0.05). Both groups met the predefined inclusion criteria appropriately.

The influence of periodontal condition indicators on the incidence of GIC

The analysis of periodontal indicators (Fig. 2) showed that, compared to periodontally healthy controls, individuals with gingival pain (OR = 1.805, 95% CI 1.394–2.337, P < 0.001), tooth mobility (OR = 1.376, 95% CI 1.054–1.797, P = 0.019), and history of periodontitis (OR = 2.071, 95% CI 1.569–2.735, P < 0.001) demonstrated a significantly increased risk of GIC. However, no statistically significant associations were found for gingival bleeding, gingival sensitivity, or gingival trauma (all P > 0.05).

Risk of periodontitis and specific gastrointestinal tumors after adjusting confounding factors

Furthermore, as detailed in Table 2, the association between periodontitis and GIC incidence was examined by conducting logistic regression analyses, adjusting for potential confounding factors. Periodontitis was significantly associated with increased risks of esophageal cancer (OR = 2.991, 95% CI 2.069–4.325, P < 0.001), gastric cancer (OR = 2.094, 95% CI 1.321–3.321, P = 0.002), colon cancer (OR = 1.712, 95% CI 1.092–2.682, P = 0.019), and rectal cancer (OR = 1.811, 95% CI 1.245–2.634, P = 0.002) in the unadjusted model. Notably, periodontitis remained significantly associated with esophageal and

Table 1 Baseline data and clinical characteristics of tumor group and control group

	Total population(n = 1505)	Control group(n = 1005)	Case group(n = 500)	P-value
Sex				0.150
Male	752(50.0)	489(48.7)	263(52.6)	
Female	753(50.0)	516(51.3)	237(47.4)	
Age	61(56,67)	61(57,66)	62(55,68)	0.210
BMI				0.097
< 20	244(16.2)	176(17.5)	68(13.6)	
20–25	735(48.8)	482(48.0)	253(50.6)	
25–30	494(32.8)	330(32.8)	164(32.8)	
≥ 30	32(2.1)	17(1.7)	15(3.0)	
Education				< 0.001
Not exceeding junior high school	586(38.9)	199(19.8)	387(77.4)	
Having attended high school	427(28.4)	361(35.9)	66(13.2)	
High school graduation	321(21.3)	279(27.8)	42(8.4)	
University and above	171(11.4)	166(16.5)	5(1.0)	
Income (yuan/month)				< 0.001
< 500	241(16.0)	7(0.7)	234(46.8)	
500–1000	125(8.3)	52(5.2)	73(14.6)	
1000–2000	246(16.3)	178(17.7)	68(13.6)	
2000–3000	328(21.8)	275(27.4)	53(10.6)	
> 3000	565(37.5)	493(49.1)	72(14.4)	
Marital status				0.385
Divorce	119(7.9)	81(8.1)	38(7.6)	
Widowed	166(11.0)	103(10.2)	65(12.6)	
Married	1220(81.1)	821(81.7)	399(79.8)	
Insurance				0.170
No	166(11.0)	103(10.2)	63(12.6)	
Yes	1339(89.0)	902(89.8)	437(87.4)	
Habitation				< 0.001
Rural	472(31.4)	95(9.5)	377(75.4)	
Urban	1033(68.6)	910(90.5)	123(24.6)	
Smoke				0.687
Never smoked	849(56.4)	573(57.0)	276(55.2)	
Former smokers	199(13.2)	128(12.7)	71(14.2)	
Current smokers	457(30.4)	304(30.2)	153(30.6)	
Alcohol				< 0.001
Never	765(50.8)	543(54.0)	222(44.4)	
Former drinkers	233(15.5)	119(11.8)	114(22.8)	
Current drinkers	507(33.7)	343(34.1)	164(32.8)	
Hypertension				0.165
No	1073(71.3)	728(72.4)	345(69.0)	
Yes	432(28.7)	277(27.6)	155(31.0)	
Diabetes				< 0.001
No	1391(92.4)	958(95.3)	433(86.6)	
Yes	114(7.6)	47(4.7)	67(13.4)	
Hyperlipidemia				0.629
No	1256(83.5)	842(83.8)	414(82.8)	
Yes	249(16.5)	163(16.2)	86(17.2)	
Family history of malignancies				0.593
No	1404(93.3)	940(93.5)	464(92.8)	

Table 1 (continued)

	Total population(n = 1505)	Control group(n = 1005)	Case group(n = 500)	P-value
Yes	101(6.7)	65(6.5)	36(7.2)	
Periodontitis Severity				< 0.001
No periodontitis	870(57.8)	640(63.7)	230(46.0)	
Mild periodontitis	318(21.1)	230(22.9)	88(17.6)	
Moderate periodontitis	178(11.8)	96(9.6)	82(16.4)	
Severe periodontitis	139(9.2)	39(3.9)	100(20.0)	

Age is expressed as median and quartiles M (Q1,Q3), and categorical variables are expressed as frequency and ratio [n(%)]

BMI: Body mass index

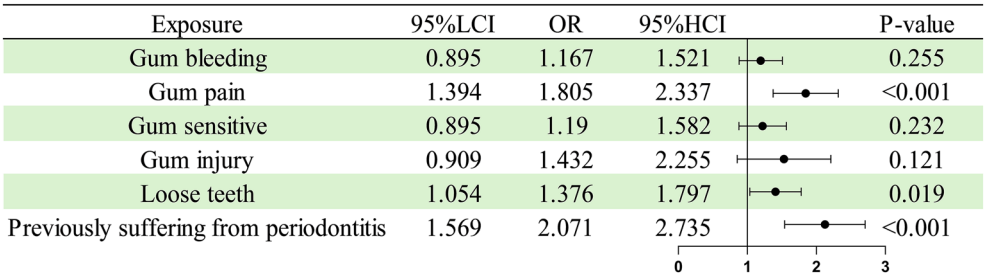

Fig. 2 Binary logistic regression analysis of factors influencing tumor occurrence. OR, odds ratio; CI, confidence interval

colorectal cancer incidence (P < 0.05) even after adjusting for gender, age, education level, income, insurance status, residential area, body mass index (BMI), marital status, smoking history, and alcohol consumption. Additionally, in Model 2, periodontitis continued to be a significant risk factor for the development of esophageal and colorectal cancer (P < 0.05).

The impact of periodontitis on tumor recurrence and metastasis

Table 3 summarizes further analysis of the relationship between periodontitis and GIC recurrence and metastasis. The data revealed that periodontitis was significantly associated with both GIC and colorectal cancer distant metastasis in the unadjusted model. Even after adjusting for gender, age, education level, income, insurance status, residential area, BMI, marital status, smoking history, and alcohol consumption, periodontitis was identified as a significant risk factor for distant metastasis in rectal cancer (HR = 4.498, 95% CI 1.253–16.152, P = 0.021). In Model 2, the adjusted HR remained consistent with the previous estimate, indicating a stable link between periodontitis and distant metastasis in rectal cancer.

The relationship between the severity of periodontitis and the recurrence and metastasis of colorectal cancer

Building on the findings from Table 3, additional analyses were performed to explore the relationship between periodontitis severity and colorectal cancer distant metastasis (See Table 4). In the unadjusted model, periodontitis was significantly associated with distant metastasis in colorectal cancer. However, no significant association was observed between periodontitis and distant metastasis in colon cancer after adjustment for gender, age, education level, income, insurance status, residential area, BMI, marital status, smoking history, and alcohol intake. Even after adjusting for potential confounders, severe periodontitis continued to be a significant risk factor for distant metastasis in rectal cancer (P < 0.05).

Discussion

China is a high-incidence region for GIC, with both incidence and mortality rates steadily increasing. As a common oral disease, periodontitis has been strongly linked to various systemic conditions. In fact, past research has indicated an elevated overall risk of GIC among individuals with periodontitis [26]. The findings of this study were consistent with these observations, revealing that people with periodontitis have a 1.886-fold increased risk of GIC compared to those without periodontitis (OR = 1.886, 95% CI 1.160–3.066). Furthermore, several studies have reported a significantly elevated risk of esophageal, gastric, hepatic, colorectal, and pancreatic cancers among patients with periodontitis [26–30]. However, some conflicting evidence suggests that periodontitis may not

Table 2 Logistic Regression Analysis of the Association between Periodontitis and GIC Incidence after Adjustment for Confounding Factors

	No. of subjects	No. of periodontitis	Unadjusted model		Model1		Model2	
			OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value
Gastrointestinal cancer (n = 500)								
No	1005	365	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	500	270	2.058(1.655–2.559)	< 0.001	1.834(1.134–2.968)	0.013	1.886(1.160–3.066)	0.011
Esophageal cancer (n = 138)								
No	1005	365	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	138	87	2.991(2.069–2.325)	< 0.001	2.765(1.022–7.483)	0.045	2.810(1.032–7.649)	0.043
Gastric cancer (n = 79)								
No	1005	365	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	79	43	2.094(1.321–3.321)	0.002	1.700(0.647–4.466)	0.282	1.503(0.533–4.233)	0.441
Liver cancer (n = 51)								
No	1005	365	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	51	24	1.559(0.886–2.741)	0.123	2.169(0.601–7.833)	0.237	2.202(0.585–8.287)	0.243
Colon cancer (n = 83)								
No	1005	365	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	83	41	1.712(1.092–2.682)	0.019	2.350(1.095–5.046)	0.028	2.330(1.072–5.067)	0.033
Rectal cancer (n = 124)								
No	1005	365	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	124	63	1.811(1.245–2.634)	0.002	2.665(1.230–5.773)	0.013	2.730(1.247–5.979)	0.012
Pancreatic cancer (n = 25)								
No	1005	365	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	25	12	1.619(0.731–3.584)	0.235	1.181(0.268–5.212)	0.826	0.887(0.146–5.397)	0.896

Model 1: Adjusting for gender, age, BMI, education, income, marriage, insurance, place of residence, smoking, and alcohol consumption

Model 2: adjust gender, age, BMI, education, income, marriage, insurance, residence, smoking, drinking, hypertension, diabetes, hyperlipidemia, and family history

HR, hazard ratio; CI, confidence interval

significantly increase the risk of gastric, hepatic, colorectal, or pancreatic cancers [31, 32].These discrepancies highlight the need for further research to clarify the association between periodontitis and site-specific gastrointestinal cancer risks.

After adjusting for multiple confounders, such as gender, age, BMI, education level, income, marital status, insurance coverage, residential area, smoking status, alcohol consumption, hypertension, diabetes, hyperlipidemia, and family history of malignancies, the results of this study suggested that periodontitis was significantly associated with an increased risk of esophageal cancer (OR = 2.810, 95% CI 1.032–7.649), colon cancer (OR = 2.330, 95% CI 1.072–5.067), and rectal cancer (OR = 2.730, 95% CI 1.247–5.979). These results suggested that periodontitis may elevate the risk of both overall and site-specific GIC.

Meanwhile, the findings of this study also revealed that colorectal cancer patients with periodontitis had significantly higher risks of distant metastasis compared to those without periodontitis ($P < 0.05$). Particularly, patients with rectal cancer and severe periodontitis demonstrated elevated risks of distant metastasis ($P < 0.05$). These findings are consistent with those of Tamaki's study, which reported that cancer patients with periodontitis tended to present higher tumor staging than those without [33]. In another study, Sung et al. reported significant associations between periodontitis and elevated mortality risks in gastric and colorectal cancers among individuals infected with *Helicobacter pylori* [28]. Similarly, in a prospective study of Japanese octogenarians, Ansai et al. found that the association between tooth loss and gastrointestinal cancer mortality remained significant even after adjusting for gender, smoking, and residential area. However, subgroup analyses did not reveal any significant correlation between periodontitis and prognosis in gastric, hepatic, colon, or pancreatic cancers ($P > 0.05$). This lack of significance could be attributed to limited sample sizes and differential confounding factors across cancer types, such as the influence of *Helicobacter pylori* in gastric cancer [32]. Meanwhile, Heikkilä et al. reported a correlation between periodontitis and increased pancreatic cancer mortality in

Table 3 Cox regression analysis of periodontitis and tumor metastasis and recurrence in different locations after adjusting for confounding factors

	NO.of subjects	Unadjusted model		Model1		Model2	
		HR(95%CI)	P-value	HR(95%CI)	P-value	HR(95%CI)	P-value
Gastrointestinal cancer (n = 500)							
Recurrence	165	1.211(0.886–1.656)	0.229	1.139(0.735–1.765)	0.559	1.043(0.669–1.625)	0.854
LNM	363	1.225(0.940–1.595)	0.133	1.163(0.808–1.672)	0.416	1.187(0.823–1.711)	0.360
Distant metastasis	153	1.584(1.117–2.244)	0.010	1.411(0.871–2.285)	0.162	1.444(0.880–2.369)	0.146
Esophageal cancer (n = 138)							
Recurrence	47	1.126(0.620–2.043)	0.697	1.282(0.492,3.338)	0.611	1.409(0.472,4.211)	0.539
LNM	105	1.273(0.785–2.065)	0.327	1.464(0.697,3.074)	0.314	1.443(0.664–3.138)	0.354
Distant metastasis	28	1.092(0.475–2.513)	0.836	3.237(0.533–19.653)	0.202	9.246(0.965–88.621)	0.054
Gastric cancer (n = 79)							
Recurrence	19	0.961(0.372–2.480)	0.934	1.747(0.367–8.312)	0.483	77.318(0.761–7854.474)	0.065
LNM	68	1.153(0.626–2.124)	0.647	1.187(0.500–2.821)	0.697	1.240(0.521–2.950)	0.627
Distant metastasis	21	1.500(0.563–3.997)	0.417	3.864(0.500–29.859)	0.195	16.827(0.447–633.406)	0.127
Liver cancer (n = 51)							
Recurrence	23	0.763(0.333–1.750)	0.524	4.549(0.726–28.498)	0.106	5.179(0.386–69.477)	0.214
LNM	19	1.206(0.430–3.380)	0.722	3.262(0.189–56.224)	0.416	3.165(0.069–145.557)	0.555
Distant metastasis	24	1.092(0.480–2.482)	0.834	0.919(0.279–3.026)	0.889	0.891(0.237–3.344)	0.864
Colon cancer(n = 83)							
Recurrence	19	1.696(0.633,4.541)	0.293	0.421(0.010–17.425)	0.648	81.588(0.274–24,303.387)	0.130
LNM	53	1.559(0.731–3.325)	0.251	0.500(0.110–2.279)	0.370	0.537(0.093–3.095)	0.486
Distant metastasis	33	3.291(1.167–9.279)	0.024	2.597(0.544–12.387)	0.231	3.123(0.477–20.446)	0.235
Rectal cancer (n = 124)							
Recurrence	41	1.618(0.839–3.121)	0.151	1.130(0.432–2.954)	0.804	1.061(0.391–2.879)	0.908
LNM	104	1.130(0.637–2.004)	0.677	1.218(0.518–2.863)	0.652	1.349(0.557–3.267)	0.507
Distant metastasis	38	2.680(1.217–5.900)	0.014	4.498(1.253–16.152)	0.021	5.332(1.406–20.220)	0.014

Model 1: Adjusting for gender, age, BMI, education, income, marriage, insurance, place of residence, smoking, and alcohol consumption

Model 2: adjust gender, age, BMI, education, income, marriage, insurance, residence, smoking, drinking, hypertension, diabetes, hyperlipidemia, and family history

LNM, lymph node metastasis; HR, hazard ratio; CI, confidence interval

Table 4 Cox regression analysis of periodontitis severity and distant metastasis of colorectal cancer after adjusting for confounding factors

	No. of subjects	Unadjusted model		Model1		Model2	
		HR(95%*CI*)	P-value	*HR*(95%*CI*)	P-value	*HR*(95%*CI*)	P-value
Colon cancer (n = 83)							
No periodontitis	11	1.00 (ref.)		1.00(ref.)		1.00(ref.)	
Mild periodontitis	8	3.053(0.974–9.576)	0.056	2.006(0.381,10.554)	0.411	2.317(0.288,18.666)	0.430
Moderate periodontitis	5	3.543(0.935–13.418)	0.063	2.889(0.417,20.042)	0.283	3.127(0.413,23.654)	0.269
Severe periodontitis	9	3.543(1.071–11.723)	0.038	3.394(0.654,17.612)	0.146	3.831(0.503,29.185)	0.195
Rectal cancer (n = 124)							
No periodontitis	12	1.00(ref.)		1.00(ref.)		1.00(ref.)	
Mild periodontitis	6	2.250(0.792–6.393)	0.128	3.510(0.840,14.663)	0.085	4.161(0.953,18.169)	0.058
Moderate periodontitis	10	2.512(0.982–6.429)	0.055	4.510(0.832,24.447)	0.081	5.571(0.952,32.579)	0.057
Severe periodontitis	10	3.351(1.303–8.617)	0.012	6.994(1.460,33.512)	0.015	10.138(1.824,56.354)	0.008

Model 1: Adjusting for gender, age, BMI, education, income, marriage, insurance, place of residence, smoking, and alcohol consumption

Model 2: adjust gender, age, BMI, education, income, marriage, insurance, residence, smoking, drinking, hypertension, diabetes, hyperlipidemia, and family history

HR, hazard ratio; CI, confidence interval

the Finnish population [34]. However, due to the limited sample size for pancreatic cancer recurrence and metastasis in the current study, definitive conclusions could not be drawn. Taken together, these findings indicate that periodontitis may significantly contribute to the development, progression, and prognosis of GIC.

Several mechanisms have been proposed to explain the association between periodontitis and GIC, with systemic inflammation and periodontal pathogens being the most widely supported. Evidence suggests that periodontitis-induced neutrophil hyperactivity promotes the hematogenous spread of oral pathogens through the release of inflammatory mediators, thereby contributing to systemic inflammation [35, 36]. This inflammatory state induces genomic instability, leading to genetic alterations in cancer cells that drive proliferation, survival, angiogenesis, and metastasis [37]. Along with periodontal pathogens, chronic systemic inflammation impairs immune cell cytotoxicity, facilitating the further spread of inflammation and pathogens. Repeated cycles of tissue damage and repair trigger DNA translocations, resulting in DNA damage and mutations that promote tumorigenesis [38]. Furthermore, periodontal pathogens, such as *Porphyromonas gingivalis* produce virulence factors like lipopolysaccharides, which enhance bacterial-host cell interactions, trigger chronic systemic inflammation, weaken host immunity, and contribute to tumorigenesis through DNA aberrations [39]. Additionally, *P. gingivalis* infection upregulates B7-H1 receptor expression, promoting tumor cell nuclear grading and distant metastasis. On the other hand, B7-H1-mediated apoptosis of activated T cells further facilitates tumor progression and metastasis [40–43].

The understanding of the relationship between periodontitis and GIC risk continues to evolve. However, establishing definitive causal associations between the two remains challenging. Therefore, well-designed randomized controlled trials and large-scale prospective studies are necessary to further clarify the nature of this association and provide stronger evidence supporting causal relationships between periodontal disease and GIC risk. While the periodontitis-GIC association is supported by substantial epidemiological evidence from cohort and case–control studies, this link may be indirect, since there is limited direct experimental evidence confirming the role of periodontitis in GIC development and progression [44].

This study offers some notable advantages, including detailed anatomical site-specific subgroup analyses of GIC, providing precise insights into incidence, recurrence, and metastasis risks across different cancer types. Additionally, by investigating periodontitis severity and its association with metastasis, the findings of this study indicated the potential benefits of early intervention in improving cancer prognosis.

This study has some limitations. First, although rigorous quality control measures were implemented, the reliance on questionnaires to assess periodontal health status may have introduced recall bias, given the multifactorial nature of GIC development. Second, the study did not examine the potential impact of periodontal treatments, such as non-surgical or surgical periodontal therapy on cancer outcomes, which could represent important intervention factors. Third, the study design does not allow for causal inference between periodontitis and cancer incidence or mortality, highlighting the need for prospective studies to comprehensively evaluate the impact of periodontitis exposure on GIC.

Conclusion

The findings of this study demonstrate a positive association between periodontitis exposure and the risk of esophageal and colorectal cancer development, as well as a significant link between periodontitis and distant metastasis in patients with rectal cancer. Notably, patients with rectal cancer and severe periodontitis show a significantly higher risk of distant tumor metastasis. These findings indicate that preventing periodontitis exposure may have important implications for reducing both the incidence and metastasis of GIC. These results could help shape public oral health initiatives aimed at promoting optimal oral health, potentially contributing to the prevention of GIC development and metastasis.

Author contributions

(I) T Luo was responsible for the conceptualization and design of the research, statistical processing, drawing and presentation of graphs and tables, implementation of the research, and writing the paper; (II) J Li collects and organizes data; (III) K Pu proposed the main research objectives and revised the paper; (IV) G Yang is responsible for the quality control and review of the article, overall responsibility for the article, and supervision and management; (V) Final approval of manuscript: All authors.

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Data Availability

All data generated or analysed during this study are included in this published article, the dataset is available upon request.

Declarations

Ethics approval and consent to participate

The participants of this study signed an informed consent form and agreed to publication, which was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College(No. 2024ER485-1).

Competing interests

The authors declare no competing interests.

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