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The association between appendectomy and increased invasion of ascending colon cancer: a retrospective study involving 880 patients

Xu Sun[1,2,3†], Rui Li[1,2,3†], Wen Zhao[1,2,3], Dingchang Li[1,2] and Guanglong Dong[1,2,3*]

Abstract

Background Ascending colon cancer is a subtype of colorectal cancer (CRC), the most common malignant tumor globally. The appendix has been considered to be a vestigial organ and appendectomy is the most routine management of acute appendicitis. However, limited studies have examined the association between appendectomy and the invasion of ascending colon cancer.

Methods In this retrospective study, 880 cases of ascending colon cancer were selected. The preoperative and postoperative clinicopathological features were retrospectively studied. Logistic regression was performed and the propensity score matching (PSM) method was used to adjust for confounding factors.

Results In total of 880 patients, 133 patients had a history of appendectomy. Patients with a history of appendectomy exhibited a higher proportion of number of lymph node metastasis (LNM) ($P=0.047$), T4 stage ($P=0.025$), N1 stage ($P=0.037$), N2 stage ($P=0.045$), M1 stage ($P=0.008$), stage III ($P=0.047$), and stage IV ($P=0.003$). The model following PSM revealed that a history of appendectomy was associated with an increased risk of LNM and M1. In 747 patients without a history of appendectomy, 568 patients (76.0%) were diagnosed with chronic appendicitis pathologically. Patients with chronic appendicitis had significantly smaller tumor sizes ($P=0.012$), reduced lymphovascular invasion (LVI) ($P=0.001$), fewer poorly differentiated tumors ($P=0.012$,), a lower number of LNM ($P=0.020$), less frequent T4 stage tumors ($P=0.023$), and a decreased incidence of N2 stage disease ($P=0.035$).

Conclusions Appendectomy is associated with a higher aggressiveness of subsequent ascending colon cancer, particularly regarding LNM. Chronic appendicitis has been linked to a decrease in tumor invasion of ascending colon cancer.

Keywords Colorectal cancer, Ascending colon cancer, Appendix, Appendectomy, Tumor invasion

†Xu Sun and Rui Li contributed equally to this work.

*Correspondence:
Guanglong Dong
dongguanglong@301hospital.com.cn
[1]Medical School of Chinese PLA, Beijing, China
[2]Department of General Surgery, The First Medical Center, Chinese PLA General Hospital, Beijing, China
[3]School of Medicine, Nankai University, Tianjin, China

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors globally, ranking third in incidence and second in mortality [1, 2]. The intestinal immune system and intestinal microbiota play a role in the tumorigenesis of CRC [3]. The appendix, often considered to be a vestigial organ, consists of dense lymphoid tissue. Participating in the regulation of the intestinal immune system and intestinal microbiota are the main functions of the appendix, which is closely related to intestinal diseases, such as ulcerative colitis, Crohn's disease, and CRC [4, 5]. Appendectomy, the most routine management of acute appendicitis, changes the intestinal immune system and microorganism balance of the human body. However, the influence of appendectomy on CRC is still controversial.

Since the appendix of the intestinal immune regulation, appendectomy might damage the immune balance and influence the occurrence of CRC. Several studies have suggested appendectomy would increase the risk of CRC [6–8]. While Rothwell et al. recommended that appendectomy was robustly and consistently associated with a lower risk of colon cancer, both overall and at the distal subsite [9]. From an anatomical perspective, the ascending colon is the segment of the large intestine that is closest to the appendix. Appendectomy appears to have a more pronounced impact on the gut microbiota and immune response in this region, potentially influencing the extent of invasion associated with ascending colon cancer. However, limited studies examined the association between appendectomy and the invasion of ascending colon cancer.

In this study, we investigated the association between clinicopathological characteristics and the history of appendectomy in ascending colon cancer patients. The TNM staging was the main comparison indicator. Our comprehensive findings may provide new insights into selecting the appropriate management for patients following appendectomy.

Materials and methods

Patients' selection

Consecutive patients with ascending colon cancer undergoing surgical resection for treatment at the First Medical Center of the Chinese People's Liberation Army (PLA) General Hospital from January 2018 to June 2023 were included in the study. The inclusion criteria were as follows: (1) The diagnosis of ascending colon cancer was validated through postoperative pathological examination (pathological reports were generated by two highly experienced pathologists); (2) patients without neoadjuvant therapy; (3) patients without history of other CRCs; (4) patients without inflammatory bowel disease; (5) patients accepted radical surgery treatment without tumor residual; (6) the appendectomy data were complete; (7) patients without appendiceal tumor. This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Medical Center of the Chinese PLA General Hospital.

Data collection

The preoperative and postoperative clinicopathological features were retrospectively studied and included the following variables: gender, age at diagnosis, body mass index (BMI), history of appendectomy, hypertension, diabetes, cardia-cerebrovascular disease, smoking, drinking, family history, intestinal obstruction, anaemia, hypoalbuminemia. The preoperative laboratory examination included Neutrophil-to-Lymphocyte Ratio (NLR), Platelets-Lymphocyte-Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR), carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), carbohydrate antigen 125 (CA125), 19 – 9 (CA19-9), 153 (CA153), 724 (CA724). The operation data included operative duration, operative approach, and intraoperative blood loss. The postoperative clinicopathological features included the tumor size, number of tumors, nerve invasion, lymphovascular invasion (LVI), histological types, number of lymph node metastasis (LNM), number of lymph node dissection (LND), TNM stage, and chronic appendicitis. The gene mutation including KRAS, BRAF, NRAS, PIK3CA were tested.

In particular, the history of appendectomy was verified through preoperative medical records and confirmed by the absence of an appendix in postoperative pathology reports. In cases where these two sources did not align, we obtained this information through follow-up telephone calls. Similarly, we measured the time interval between appendectomy and subsequent colon cancer surgery.

In addition, the diagnosis of chronic appendicitis was established based on postoperative pathological findings. After removal of ascending colon cancer, tissue samples were immediately fixed. Sections were stained with hematoxylin and eosin and independently evaluated by two experienced gastrointestinal pathologists blinded to clinical data. Chronic appendicitis was defined as fibrous tissue hyperplasia and infiltration of lymphocytes, plasma cells and eosinophils in all layers of the appendix. Cases were excluded if any of the following were present: acute inflammation, granulomas, dysplasia, or neoplastic changes [10]– [11].

Follow-up

The follow-up was conducted through telephone interviews and outpatient visits at specific intervals: 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months after surgery. The primary outcome measure was disease-free survival (DFS).

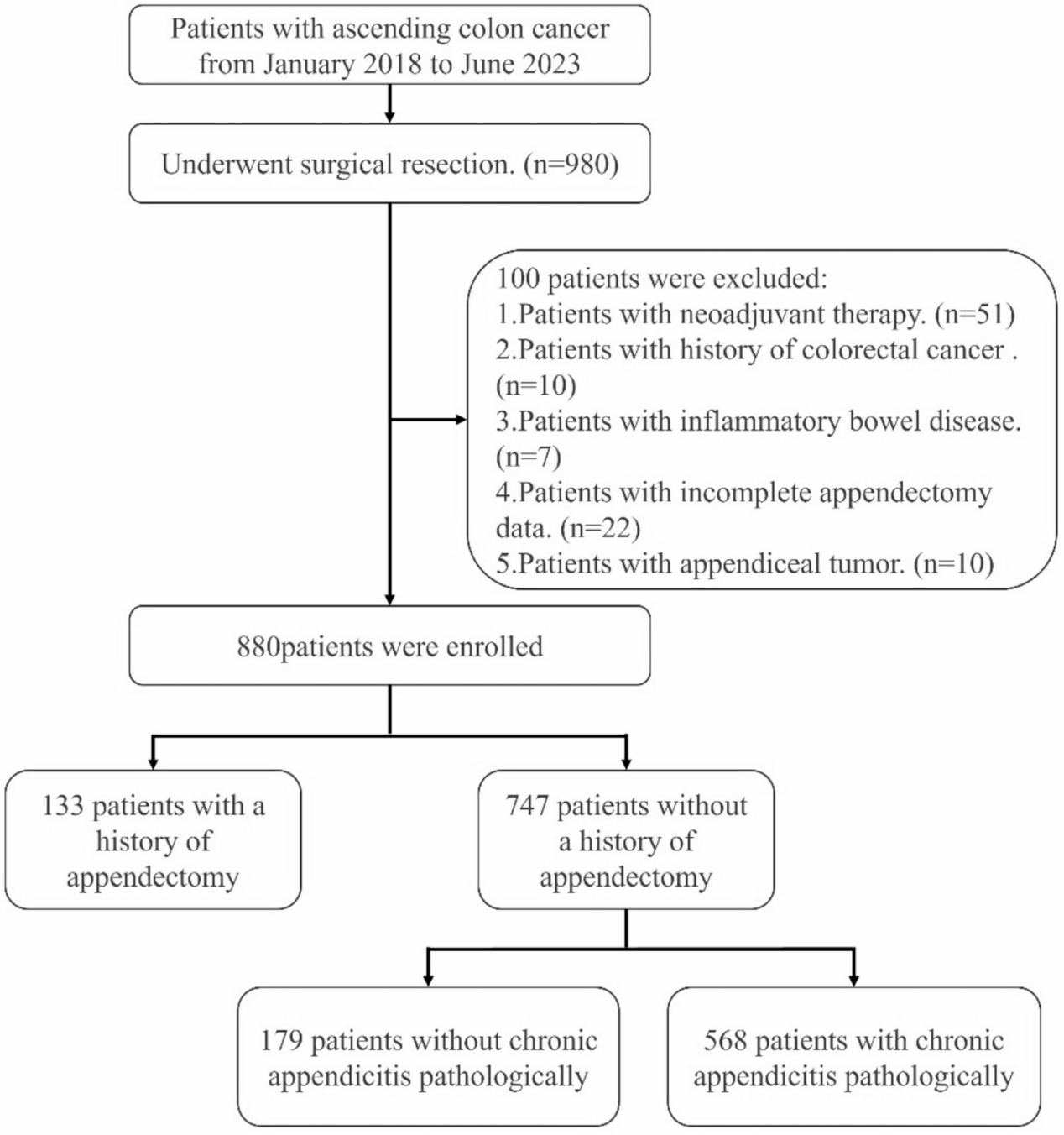

Fig. 1 The flow chart for patient selection

Patients were categorized into two groups based on the history of appendectomy. DFS curves were generated utilizing the Kaplan-Meier method and Log-Rank analysis.

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics 26.0 software (SPSS Inc, Chicago, IL, USA). Numerical data with normal distribution were expressed as the mean ± standard deviation (SD) and numerical data without normal distribution were expressed as median (interquartile range, IQR). Categorical data are presented as absolute numbers and percentages. Binary logistic regression weas used to investigate the association of clinicopathological features with LNM risk and M1 risk. Propensity score matching (PSM) method was used to adjust for confounding factors. Odds ratio (OR) and 95% confidence interval (CI) were conducted. *P*-values were two-tailed, and $P < 0.05$

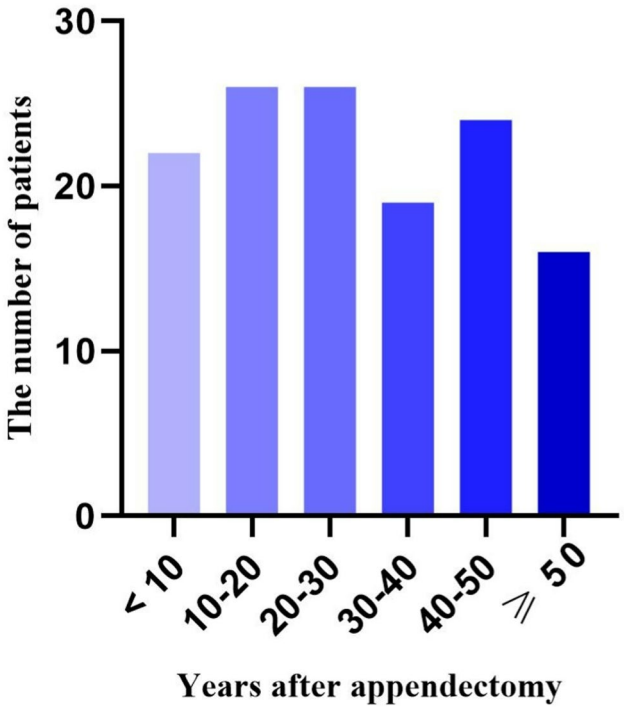

Fig. 2 Patients with different time interval following appendectomy

was accepted as statistically significant. The production of DFS curves was based on GraphPad Prism 8 software.

Results

Patients' characteristics

After rigorous screening, a total of 880 patients with ascending colon cancer were enrolled, who have undergone radical operation between January 2018 and June 2023 in our medical center. 133 (15.1%) patients had previously undergone appendectomy due to appendicitis, while an additional 747 (84.9%) patients had not received this surgical intervention. The patient selection flow chart was shown in Fig. 1. Among 133 patients with the history of appendectomy, the average time interval between appendectomy and subsequent colon cancer surgery was 25.44 years. Furthermore, the distribution of cases based on the time interval was shown in Fig. 2.

Clinicopathological features among 880 patients

Firstly, a total of 880 patients diagnosed with ascending colon cancer were classified into two groups according to their history of appendectomy (Table 1). By gender, the male to female ratio in patients with a history of appendectomy was significantly lower than that in the other group (0.82: 1 vs. 1.24: 1, $P = 0.029$, OR = 0.661). For age at diagnose, the median age of patients with a history of appendectomy was 67 years old, which was significant older than that of the other group ($P = 0.015$, OR = 1.020). The prevalence of smoking history was notably lower among patients with a history of appendectomy ($P = 0.014$, OR = 0.542). Regarding serum tumor markers, patients with a history of appendectomy exhibited elevated serum levels of CA125 ($P = 0.003$, OR = 2.374) and CA724 ($P = 0.015$, OR = 1.614). For postoperative pathology and tumor staging, patients with a history of appendectomy exhibited higher proportion of number of LNM ($P = 0.047$, OR = 1.057), T4 stage ($P = 0.025$, OR = 10.274), N1 stage ($P = 0.037$, OR = 1.566), N2 stage ($P = 0.045$, OR = 1.706), M1 stage ($P = 0.008$, OR = 2.097), stage III ($P = 0.047$, OR = 2.324), and stage IV ($P = 0.003$, OR = 4.047).

507 patients have received postoperative genetic testing, including KRAS, BRAF, NRAS, and PIK3CA. Among these patients, 226 exhibited mutations in the KRAS gene specifically located in exon 2 (Table 2).

To further investigate the association between a history of appendectomy and the pathological characteristics of ascending colon cancer, we conducted subgroup analyses based on varying T stages. In patients with T3 stage ($n = 679$), a history of appendectomy was association with older age, elevated serum levels of CA724, a greater number of positive lymph nodes, more advanced N and M staging (Fig. 3). Whereas, in patients with T4 stage ($n = 98$), only gender was found to be correlated with a history of appendectomy (Fig. 4).

The history of appendectomy with LNM risk and M1 risk

In Table 1, we discovered that a history of appendectomy was associated with LNM (both stage N1 and N2). Subsequently, we further investigate the relationship between each variable and LNM. Smoking history, intestinal obstruction, serum CEA, serum CA125, serum CA19-9, nerve invasion, LVI, poorly differentiated, T3 stage, T4 stage, and appendectomy history were associated with LNM (Table 3 and Supplemental Table 1). In model 2 (adjust for smoking history and intestinal obstruction) and model 3 (adjust for smoking history, intestinal obstruction, serum CEA, serum CA125 and serum CA19-9), the history of appendectomy was associated with LNM. However, in model 4, we adjusted the smoking history, intestinal obstruction, serum CEA, serum CA125, serum CA19-9, nerve invasion, LVI. Only T stage was associated with LNM.

Similarly, we further investigate the relationship between each variable and M1 stage. Cardia-cerebrovascular disease, intestinal obstruction, NLR, LMR, serum CEA, serum CA125, serum CA19-9, serum CA153, T3 stage, T4 stage, N stage, number of LNM, and the history of appendectomy were associated with M1 stage (Table 4 and Supplemental Table 1). In model 2 (adjusted for cardia-cerebrovascular disease and intestinal obstruction), the history of appendectomy was associated with M1

Table 1 Comparison of clinicopathological features among 880 patients with ascending colon cancer

	Total ***N*** **= 880**	**Without appendectomy** ***N*** **= 747**	**After appendectomy** ***N*** **= 133**	***P***	**OR (95%CI)**
Gender, *n* (%)				0.029	1.513 (1.044–2.192)
Male	474 (53.9)	414 (55.4)	60 (45.1)		
Female	406 (46.1)	333 (44.6)	73 (54.9)		
Age [a], years	63 (16)	63 (16)	67 (17)	0.015	1.020 (1.004–1.036)
BMI [a], kg/m^2	23.59 (4.20)	23.60 (4.25)	23.53 (3.84)	0.207	
Hypertension, *n* (%)				0.665	
Absence	603 (68.5)	514 (68.8)	89 (66.9)		
Presence	277 (31.5)	233 (31.2)	44 (33.1)		
Diabetes, *n* (%)				0.312	
Absence	722 (82.0)	617 (82.6)	105 (78.9)		
Presence	158 (18.0)	130 (17.4)	28 (21.1)		
Cardia-cerebrovascular disease, *n* (%)				0.938	
Absence	779 (88.5)	661 (88.5)	118 (88.7)		
Presence	101 (11.5)	86 (11.5)	15 (11.3)		
Smoking history, *n* (%)				0.014	0.542 (0.331–0.888)
Absence	667 (75.8)	555 (74.3)	112 (84.2)		
Presence	213 (24.2)	192 (25.7)	21 (15.8)		
Drinking history, *n* (%)				0.141	
Absence	692 (78.6)	581 (77.8)	111 (83.5)		
Presence	166 (22.2)	166 (22.2)	22 (16.5)		
Family history, *n* (%)				0.732	
Absence	835 (94.9)	708 (94.8)	127 (95.5)		
Presence	45 (5.1)	39 (5.2)	6 (4.5)		
Intestinal obstruction, *n* (%)				0.674	
Absence	583 (66.3)	497 (66.5)	86 (64.7)		
Presence	297 (33.8)	250 (33.5)	47 (35.3)		
Anaemia, *n* (%)				0.554	
Absence	431 (49.0)	369 (49.4)	62 (46.6)		
Presence	449 (51.0)	378 (50.6)	71 (53.4)		
Hypoalbuminemia, *n* (%)				0.795	
Absence	741 (84.2)	628 (84.1)	113 (85.0)		
Presence	139 (15.8)	119 (15.9)	20 (15.0)		
NLR [a]	2.22 (1.51)	2.20 (1.47)	2.43 (1.70)	0.280	
PLR [a]	162.07 (94.09)	162.83 (92.08)	153.62 (97.72)	0.186	
LMR [a]	3.87 (2.19)	3.93 (2.22)	3.71 (1.96)	0.616	
Serum CEA, *n* (%)				0.701	
Normal range	503 (57.2)	429 (57.4)	74 (55.6)		
Elevated	377 (42.8)	318 (42.6)	59 (44.4)		
Serum AFP, *n* (%)				0.674	
Normal range	879 (99.9)	746 (99.9)	133 (100)		
Elevated	1 (0.1)	1 (0.1)	0		
Serum CA125, *n* (%)				0.003	2.374 (1.349–4.179)
Normal range	812 (92.3)	698 (93.4)	114 (85.7)		
Elevated	68 (7.7)	49 (6.6)	19 (14.3)		
Serum CA19-9, *n* (%)				0.242	
Normal range	689 (78.3)	590 (79.0)	99 (74.4)		
Elevated	191 (21.7)	157 (21.0)	34 (25.6)		
Serum CA153, *n* (%)				0.653	
Normal range	870 (98.9)	738 (98.8)	132 (99.2)		
Elevated	10 (1.1)	9 (1.2)	1 (0.8)		
Serum CA724, *n* (%)				0.015	1.614 (1.097–2.375)
Normal range	627 (71.3)	544 (72.8)	83 (62.4)		

Table 1 (continued)

	Total ***N*** **= 880**	**Without appendectomy** ***N*** **= 747**	**After appendectomy** ***N*** **= 133**	***P***	**OR (95%CI)**
Elevated	253 (28.7)	203 (27.2)	50 (37.6)		
Operative duration [a], min	160 (65)	160 (66)	160 (62.5)	0.759	
Operative approach, *n* (%)				0.026	1.655 (1.063–2.578)
Laparoscopic	728 (82.7)	627 (83.9)	101 (75.9)		
Open	152 (17.3)	120 (16.1)	32 (24.1)		
Intraoperative blood loss [a], ml	50 (50)	50 (50)	50 (50)	0.531	
Tumor size [a], cm	5.00 (2.50)	5.00 (2.50)	5.00 (3.00)	0.213	
Number of tumors, *n* (%)				0.257	
Single	869 (98.8)	739 (98.9)	130 (97.7)		
Multiple (≥ 2)	11 (1.3)	8 (1.1)	3 (2.3)		
Nerve invasion, *n* (%)				0.964	
Absence	813 (92.4)	690 (92.4)	123 (92.5)		
Presence	67 (7.6)	57 (7.6)	10 (7.5)		
LVI, *n* (%)				0.128	
Absence	764 (86.8)	654 (87.6)	110 (82.7)		
Presence	116 (13.2)	93 (12.4)	23 (17.3)		
Histological types, *n* (%)				0.421	
Well differentiated	46 (5.2)	36 (4.8)	10 (7.5)		
Moderately differentiated	625 (71)	534 (71.5)	91 (68.4)		
Poorly differentiated	209 (23.8)	177 (23.7)	32 (24.1)		
Number of LNM [b]	1.40 ± 2.87	1.32 ± 2.77	1.87 ± 3.39	0.047	1.057 (1.001–1.117)
Number of LND [b]	19.58 ± 6.91	19.83 ± 7.08	18.19 ± 5.72	0.012	0.961 (0.932–0.991)
T stage, *n* (%)				0.006	
T1	31 (3.5)	30 (4.0)	1 (0.8)		
T2	72 (8.2)	63 (8.4)	9 (6.8)	0.177	
T3	679 (77.2)	581 (77.8)	98 (73.7)	0.113	
T4	98 (11.1)	73 (9.8)	25 (18.8)	0.025	10.274 (1.331–79.288)
N stage, *n* (%)				0.038	
N0	537 (61.0)	469 (62.8)	68 (51.1)		
N1	227 (25.8)	185 (24.8)	42 (31.6)	0.037	1.566 (1.028–2.385)
N2	116 (13.2)	93 (12.4)	23 (17.3)	0.045	1.706 (1.012–2.876)
M stage, *n* (%)				0.008	2.097 (1.200-3.663)
M0	806 (91.6)	692 (92.6)	114 (85.7)		
M1	74 (8.4)	55 (7.4)	19 (14.3)		
Stage (pathological), *n* (%)				0.011	
I	89 (10.1)	82 (11.0)	7 (5.3)		
II	421 (47.8)	363 (48.6)	58 (43.6)	0.134	
III	296 (33.6)	247 (33.1)	49 (36.8)	0.047	2.324 (1.013–5.332)
IV	74 (8.4)	55 (7.4)	19 (14.3)	0.003	4.047 (1.594–10.272)

[a] Values are presented as median (IQR)

[b] Values are presented as mean ± SD

BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelets-lymphocyte-ratio; LMR, lymphocyte-to-monocyte ratio, CEA, carcinoembryonic antigen; AFP, alpha fetoprotein, CA, carbohydrate antigen; LVI, lymphovascular invasion; LNM, lymph node metastasis; LND, lymph node dissection; OR, Odds ratio; CI, confidence interval

stage. However, in model 3 and model 4, there were no statistically significant associations.

Clinicopathological features among 747 patients without a history of appendectomy

In 747 patients with ascending colon cancer patients who have no history of appendectomy, we observe that 568 patients (76.0%) were diagnosed with chronic appendicitis pathologically. When compared to patients without chronic appendicitis, those with chronic appendicitis exhibited several notable differences: smaller tumor sizes ($P = 0.012$, OR = 0.912), reduced LVI ($P = 0.001$, OR = 0.468), fewer poorly differentiated tumors ($P = 0.012$, OR = 0.250), a lower number of LNM

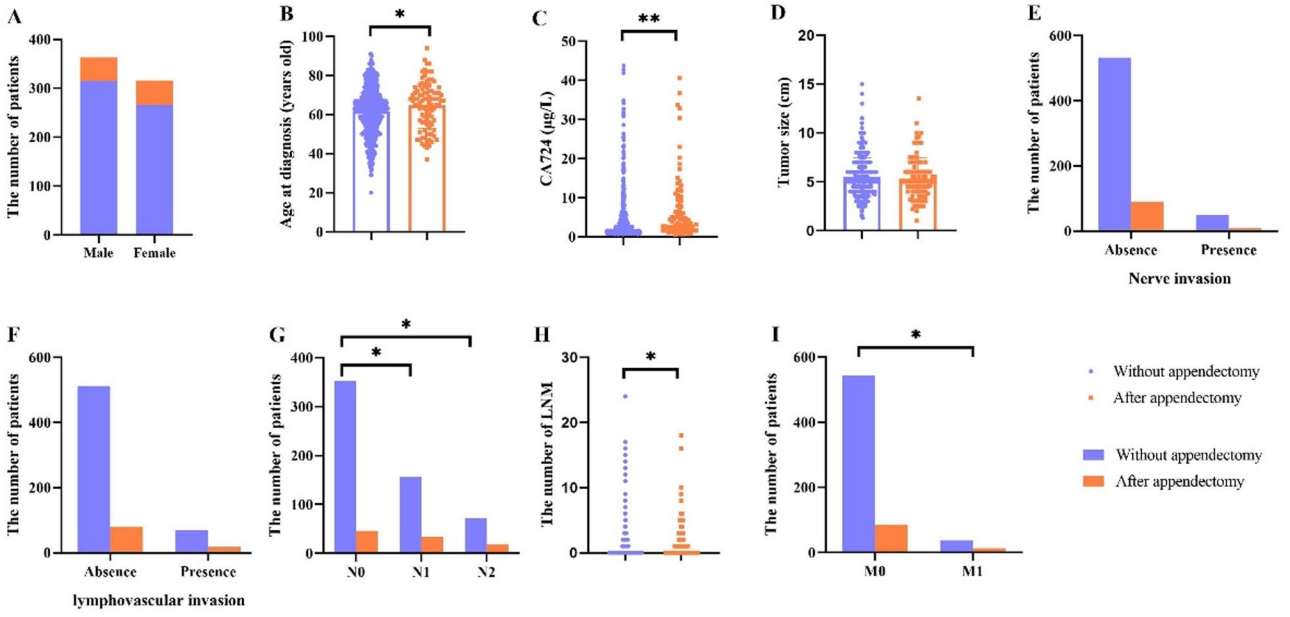

Fig. 3 Comparison of clinicopathological features among patients with T3 stage. ✱,$p < 0.05$; ✱✱,$p < 0.01$; ✱✱✱,$p < 0.001$

($P = 0.020$, OR = 0.937), less frequent T4 stage tumors ($P = 0.023$, OR = 0.262), and a decreased incidence of N2 stage disease ($P = 0.035$, OR = 0.598)(Table 5).

Disease-free survival

Among 806 patients without distant metastasis, follow-up information was available for 779 patients, with a median follow-up duration of 49 months. The DFS probability among these patients was shown in Fig. 5, stratified by the history of appendectomy (Fig. 5A) and the chronic appendicitis (Fig. 5B). The history of appendectomy corresponded to worse DFS ($P = 0.022$).

Table 2 Comparison of gene mutation among 507 patients with ascending colon cancer

	Total *N* = 507	Without appendectomy *N* = 429	After appendectomy *N* = 78
KRAS mutation, *n* (%)			
Absence	249 (49.1)	215 (50.1)	34 (43.6)
Exon 2	226 (44.6)	182 (42.4)	44 (56.4)
Exon 3	2 (0.4)	2 (0.5)	0
Exon 4	30 (5.9)	30 (7.0)	0
BRAF mutation, *n* (%)			
Absence	467 (92.1)	397 (92.5)	70 (89.7)
Exon 2	1 (0.2)	0	1 (1.3)
Exon 15	39 (7.7)	32 (7.5)	7 (0.9)
NRAS mutation, *n* (%)			
Absence	492 (97.0)	417 (97.2)	75 (96.2)
Exon 2	10 (2.0)	7 (1.6)	3 (3.8)
Exon 3	5 (1.0)	5 (1.2)	0
PIK3CA mutation, *n* (%)			
Absence	471 (92.9)	397 (92.5)	74 (94.9)
Exon 20	36 (7.1)	32 (7.5)	4 (5.1)

Discussion

The appendix was generally considered a vestigial organ, and appendectomy has not received significant attention from surgeons for many years. Several studies found an increased risk of developing CRC following an appendectomy. However, the association of appendectomy and the invasion of CRC was rarely reported. To the best of our knowledge, apart from one article that found a significant left-to-right side shift in CRC with a history of appendectomy [12], our study was the first to reveal the association between appendectomy and the invasion of ascending colon cancer. According to the high-volume cohort, we demonstrated that appendectomy was associated with a higher degree of invasion of ascending colon cancer.

The ascending colon is derived from the midgut, differing from the left-sided colon and rectum [13]. Since the different embryology, epidemiology, and pathology, ascending colon cancer often exhibits diverse disease processes, metastatic features, and prognosis. More advanced tumor stage, larger tumor size, and more lymph node metastases were observed in ascending colon cancer, compared to left-sided colon cancer. Yang et al. [14] and Lee et al. [15] reported ascending colon cancer was an independent risk factor for recurrence in stage II and stage III colon cancer. Lee et al. [15] also recommended ascending colon cancer was correlated with worse cancer-specific survival and recurrence-free survival. In this study, LNM was observed in 39% of patients diagnosed with ascending colon cancer, while distant metastasis

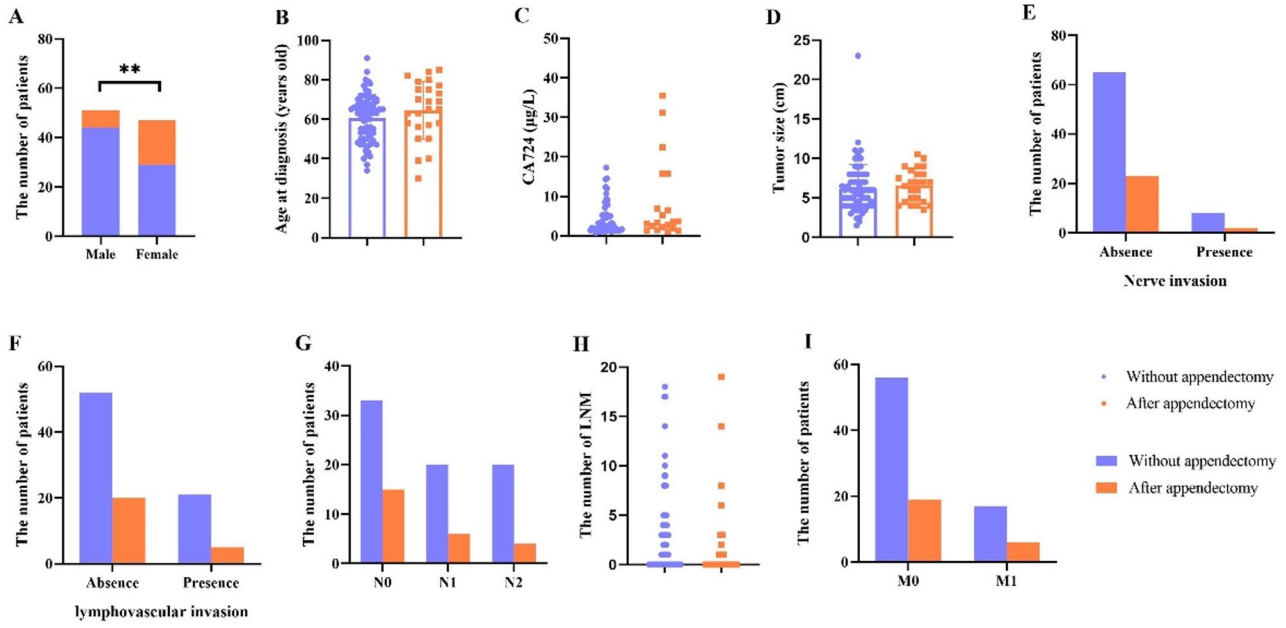

Fig. 4 Comparison of clinicopathological features among patients with T4 stage. ✱,$p < 0.05$; ✱✱,$p < 0.01$; ✱✱✱,$p < 0.001$

occurred in 8.4% of cases. Furthermore, we have developed a statistical model indicating that appendectomy was correlated with the occurrence of LNM and distant metastasis in right-sided colon cancer.

Possible reasons for increased aggressiveness of ascending colon cancer following appendectomy might include the following factors. Firstly, the right sided colon referred to the proximal end of the large intestine, which included the ascending and transverse colon. It was the section of the colon that was closest in proximity to the appendix. Various physiological and pathological changes in the appendix were more likely to impact the right colon, including inflammation, tumors, and surgical interventions. Secondly, the appendix served as an immune organ and performed immune defense functions. The intraepithelial lymphocytes, presenting in the mucous membrane layer of the appendix, were consisted of CD8 + regulatory T cells. In the submucosa of appendix, numerous lymphoid follicles were exhibited with a mixed zone consisting of T cells, B cells, and macrophages. Surrounding this was the mantle zone primarily composed of B cells, followed by the germinal center which contained B cells, follicular dendritic cells, and macrophages. Additionally, there was a T-cell area that also houses macrophages. Furthermore, IgA generated in the appendix, existed in the gastrointestinal tract,

Table 3 Odds ratios for the association of clinicopathological features with LNM risk

	Model 1		**Model 2**		**Model 3**		**Model 4**	
Variable	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Smoking history (%)	0.687 (0.496–0.952)	0.024	-	-	-	-	-	-
Intestinal obstruction (%)	1.352 (1.017–1.797)	0.038	-	-	-	-	-	-
Serum CEA (%)	2.371 (1.797–3.130)	< 0.001	2.459 (1.806–3.349)	< 0.001	-	-	-	-
Serum CA125 (%)	1.851 (1.126–3.042)	0.015	1.631 (0.945–2.817)	0.079	-	-	-	-
Serum CA19-9 (%)	3.744 (2.676–5.238)	< 0.001	4.182 (2.812–6.219)	< 0.001	-	-	-	-
Nerve invasion (%)	2.332 (1.406–3.868)	0.001	2.316 (1.297–4.137)	0.005	1.858 (0.999–3.453)	0.050	-	-
Lymphovascular invasion (%)	3.865 (2.551–5.855)	< 0.001	3.445 (2.159–5.496)	< 0.001	3.663 (2.166–6.194)	< 0.001	-	-
Poorly differentiated (%)	3.088 (1.516–6.293)	0.002	1.992 (1.400-2.835)	< 0.001	1.568 (1.070–2.297)	0.021	1.342 (0.897–2.009)	0.152
T stage								
T3 (%)	6.550 (1.972–21.755)	0.002	4.574 (2.442–8.567)	< 0.001	2.761 (1.419–5.372)	0.003	2.672 (1.329–5.371)	0.006
T4 (%)	9.722 (2.772–34.097)	< 0.001	7.294 (3.418–15.567)	< 0.001	3.487 (1.550–7.845)	0.003	3.000 (1.277–7.049)	0.012
Appendectomy history (%)	1.613 (1.113–2.337)	0.012	1.823 (1.187–2.799)	0.006	1.652 (1.034–2.640)	0.036	1.566 (0.911–2.692)	0.105

Model 1 was unadjusted. Model 2 was adjusted for smoking history and intestinal obstruction. Model 3 was adjusted for smoking history, intestinal obstruction, serum CEA, serum CA125, serum CA19-9. Model 4 was adjusted for smoking history, intestinal obstruction, serum CEA, serum CA125, serum CA19-9, nerve invasion, lymphovascular invasion

Abbreviations: OR, odds ratio; CI, confidence interval; CA, carbohydrate antigen; LNM, lymph node metatasis

Table 4 Odds ratios for the association of clinicopathological features with M1 risk

	Model 1		Model 2		Model 3		Model 4	
Variable	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Cardia-cerebrovascular disease (%)	0.305 (0.094–0.988)	0.048	-	-	-		-	-
Intestinal obstruction (%)	2.367 (1.465–3.824)	< 0.001	-	-	-		-	-
NLR	1.164 (1.067–1.270)	< 0.001	1.180 (1.072–1.299))	< 0.001	-		-	-
LMR	0.762 (0.645–0.901)	< 0.001	0.735 (0.621–0.869)	< 0.001	-		-	-
Serum CEA (%)	5.092 (2.910–8.912)	< 0.001	4.721 (2.681–8.314)	< 0.001	4.006 (2.198–7.301)	< 0.001	-	-
Serum CA125 (%)	5.849 (3.242–10.553)	< 0.001	5.700 (3.085–10.531)	< 0.001	3.162 (1.552–6.441)	0.002	-	-
Serum CA19-9 (%)	3.739 (2.294–6.096)	< 0.001	3.552 (2.157–5.849)	< 0.001	2.681 (1.542–4.667)	< 0.001	-	-
Serum CA153 (%)	4.823 (1.221–19.058)	0.025	4.113 (1.006–16.805)	0.049	4.323 (0.267–70.026)	0.303	-	-
T stage								
T3 (%)	8.108 (1.108–59.344)	0.039	6.618 (0.898–48.743)	0.064	7.167 (0.957–53.689)	0.055	4.995 (0.658–37.899)	0.120
T4 (%)	31.280 (4.132–236.790)	0.001	28.412 (3.710–217.604)	0.001	26.400 (3.359–207.497)	0.002	19.000 (2.366–152.551)	0.006
N1/2 (%)	2.999 (1.829–4.918)	< 0.001	3.014 (1.824–4.980)	< 0.001	2.674 (1.542–4.634)	< 0.001	1.953 (1.098–3.474)	0.023
Number of LNM	1.133 (1.070–1.200)	< 0.001	1.136 (1.069–1.207)	< 0.001	1.142 (1.053–1.237)	0.001	1.110 (1.024–1.203)	0.011
Appendectomy history (%)	2.097 (1.200-3.663)	0.009	2.409 (1.355–4.284)	0.003	1.779 (0.914–3.463)	0.090	1.327 (0.614–2.865)	0.472

Model 1 was unadjusted. Model 2 was adjusted for cardia-cerebrovascular disease and intestinal obstruction. Model 3 was adjusted for cardia-cerebrovascular disease, intestinal obstruction, NLR, LMR, serum CEA, serum CA125, serum CA19-9, serum CA153 adjusted for cardia-cerebrovascular disease, intestinal obstruction, NLR, LMR, serum CEA, serum CA125, serum CA19-9, serum CA153

Abbreviations: OR, odds ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio, CA, carbohydrate antigen, LNM, lymph node metatasis

and direct contact with noninvasive antigen, participate in the immune-isolation of antigens [16, 17]. Therefore, the removal of the appendix resulted in impaired or even diminished intestinal immune defense function, leading to increased vulnerability of the intestinal mucosa to toxins, inflammation, and potentially even cancer. Conversely, tumor-induced mechanical stress or immune microenvironment remodeling may alter appendiceal biology, complicating causal inference. Our data suggest an inverse association between chronic appendicitis and tumor invasion in ascending colon cancer. However, this observation may reflect either a protective immune interaction mediated by the appendix or reverse causality, wherein advanced tumors disrupt appendiceal function and mask preexisting chronic inflammation. This bidirectional interplay underscores the need for mechanistic studies to disentangle temporal and biological relationships.

The gut microbiota played a crucial role in the tumor microenvironment of CRC, as it regulated CRC development by releasing a variety of metabolites and proteins interacting with the colonic epithelium and immune cells of the host. This interaction was essential for understanding the pathogenesis of CRC and had significant implications for potential therapeutic interventions [18]. The 'pathogenic' gut colonizers, such as *Enterococcus faecalis* and adherent-invasive *Escherichia coli* were shown to promote chromosomal instability and the production of a polyketide-peptide genotoxin, colibactin, which promotes p53 expression and tumor cell proliferation [19]. Cai et al. [20] founded the bacterial and fungal gut microbiota were altered after appendectomy, with the intra fungal and bacteria–fungi interactions also changed. This alteration would impact normal functioning, leading to immune regulation failure and CRC tumorigenesis.

The influence of different interval following appendectomy for CRC was still controversial. In a study of 707,633 patients followed for an average of 13.66 years, it was found that the risk for CRC was significantly higher in the first 3 years following appendectomy [21]. The conclusion was consistent with the study by Wu et al. [22]. However, Song et al. [23] founded Increased risk of CRC was observed in patients 5 to 14 years after appendectomy, while no elevated risk of CRC was found in the subset of patients 1 to 4 years after appendectomy. In our study, 18 patients developed ascending colon cancer within 5 years after undergoing appendectomy. The highest rate of ascending colon cancer diagnosis was observed between 10 and 20 years and 20–30 years post-appendectomy. However, during the subgroup analysis, we observed that there was no significantly higher incidence of ascending colon cancer with invasive ability in patients with different intervals.

Table 5 Comparison of pathological features among 747 patients without appendectomy

	Total *N* = 747	Without chronic appendicitis *N* = 179	With chronic appendicitis *N* = 568	*P*	OR (95%CI)
Tumor size [a], cm	5.00 (2.50)	5.00 (3.00)	5.00 (2.70)	0.012	0.912 (0.849–0.980)
Number of tumors, *n* (%)				0.445	
Single	739 (98.9)	178 (99.4)	561 (98.8)		
Multiple (≥ 2)	8 (1.1)	1 (0.6)	7 (1.2)		
Nerve invasion, *n* (%)				0.281	
Absence	690 (92.4)	162 (90.5)	528 (93.0)		
Presence	57 (7.6)	17 (9.5)	40 (7.0)		
LVI, *n* (%)				0.001	0.468 (0.296–0.740)
Absence	654 (87.6)	144 (80.4)	510 (89.8)		
Presence	93 (12.4)	35 (19.6)	58 (10.2)		
Histological types, *n* (%)				0.001	
Well differentiated	36 (4.8)	4 (2.2)	32 (5.6)		
Moderately differentiated	534 (71.5)	116 (64.8)	418 (73.6)	0.140	
Poorly differentiated	177 (23.7)	59 (33.0)	118 (20.8)	0.012	0.250 (0.084–0.740)
Number of LNM [b]	1.32 ± 2.77	1.75 ± 3.47	1.18 ± 2.49	0.020	0.937 (0.887–0.990)
Number of LND [b]	19.83 ± 7.08	19.97 ± 7.15	19.79 ± 7.06	0.767	
T stage, *n* (%)				0.017	
T1	30 (4.0)	4 (2.2)	26 (4.6)		
T2	63 (8.4)	18 (10.1)	45 (7.9)	0.114	
T3	581 (77.8)	130 (72.6)	451 (79.4)	0.250	
T4	73 (9.8)	27 (15.1)	46 (8.1)	0.023	0.262 (0.083–0.832)
N stage, *n* (%)				0.018	
N0	469 (62.8)	112 (62.6)	357 (62.9)		
N1	185 (24.8)	35 (19.6)	150 (26.4)	0.172	
N2	93 (12.4)	32 (17.9)	61 (10.7)	0.035	0.598 (0.371–0.964)
M stage, *n* (%)				0.355	
M0	692 (92.6)	163 (91.1)	529 (93.1)		
M1	55 (7.4)	16 (8.9)	39 (6.9)		
Stage (pathological), *n* (%)				0.781	
I	82 (11.0)	21 (11.7)	61 (10.7)		
II	363 (48.6)	84 (46.9)	279 (49.1)		
III	247 (33.1)	58 (32.4)	189 (33.3)		
IV	55 (7.4)	16 (8.9)	39 (6.9)		

[a] Values are presented as median (IQR)

[b] Values are presented as mean ± SD

LVI, lymphovascular invasion; LNM, lymph node metastasis; LND, lymph node dissection; OR, Odds ratio; CI, confidence interval

Interestingly, we observed in ascending colon cancer patients without prior appendectomy, most patients had chronic appendicitis without any clinical symptoms, a condition that was only confirmed by postoperative pathology. The logistic regression indicated these patients suffered from a decreased degree of tumor cancer invasion, with smaller tumor sizes, reduced LVI, fewer poorly differentiated tumors, a lower number of LNM, less frequent T4 stage tumors, and a decreased incidence of N2 stage disease. Our finding provided clinical evidence that the appendix had a protective effect on the intestine.

Generally, our study offered a perspective for the pre- and post-operative management of appendectomy. Firstly, for uncomplicated appendicitis (without phlegmon, abscess, perforation, or appendicolith), the role of conservative medical management with antibiotics needed more clinical evidence to evaluate, which could avoid the complications caused by appendectomy and intestinal dysfunction [24]. Secondly, regular colonoscopy, the gold standard for diagnosing CRC, should be given careful consideration for patients following appendectomy. Especially for individuals who underwent appendectomy 10 to 30 years ago, considering the age effect on the incidence of CRC in itself, a colonoscopy was imperative. Finally, due to an increased risk of invasive in ascending colon cancer after appendectomy, it was crucial to accurately detect the right side of the colon when performing a colonoscopy, for preventing potential diagnoses from being overlooked.

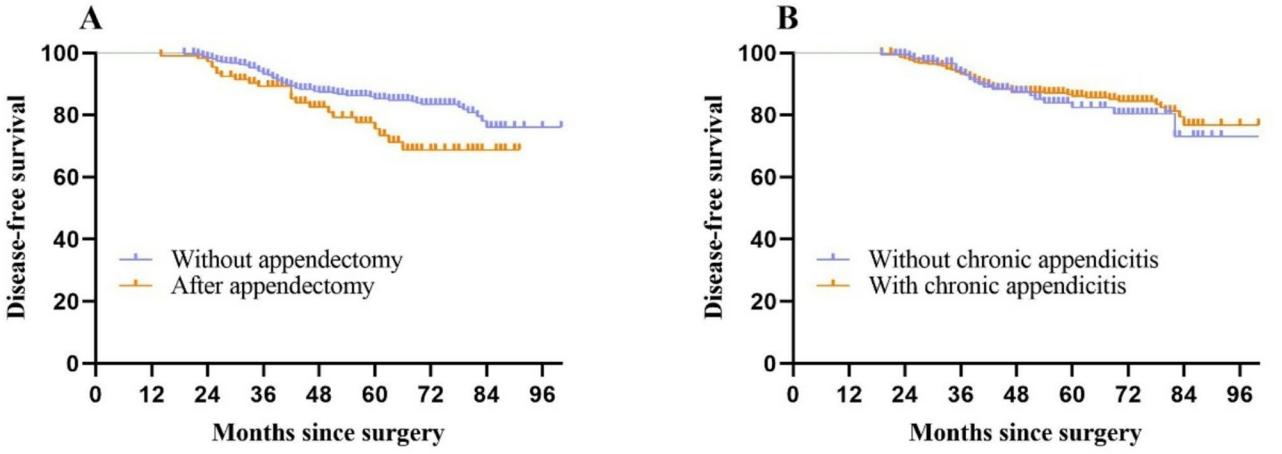

Fig. 5 Disease-free survival probabilities among patients without distant metastasis. **A**, stratified by the history of appendectomy; **B**, stratified by the chronic appendicitis among patients without history of appendectomy

Our study has several limitations. First, the sample size was relatively small, which may limit the statistical power to detect subtle associations. Second, as a retrospective analysis of clinicopathological data, our findings are susceptible to selection bias and unmeasured confounding factors despite rigorous PSM. Third, while we identified appendectomy as a potential risk factor for aggressive tumor behavior, the lack of mechanistic data precludes definitive conclusions about causality. Most critically, the retrospective design inherently cannot distinguish whether the observed association stems from appendectomy itself or underlying biological traits in patients predisposed to appendicitis and subsequent colon carcinogenesis. Therefore, large-scale prospective cohort studies with integrated biospecimen analysis are urgently needed to validate these findings and elucidate the biological mechanisms. Fourth, our findings are specific to ascending colon cancers, and the generalizability to transverse colon or other right-sided tumors remains uncertain.

Conclusion

Appendectomy is associated with a higher aggressiveness of subsequent ascending colon cancer, particularly regarding LNM. Chronic appendicitis has been linked to a decrease in tumor invasion of ascending colon cancer.

Abbreviations

CRC	Colorectal cancer
PLA	People's Liberation Army
BMI	Body mass index
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelets-lymphocyte-ratio
LMR	Lymphocyte-to-monocyte ratio
CEA	Carcinoembryonic antigen
AFP	Alpha fetoprotein
CA	Carbohydrate antigen
LVI	Lymphovascular invasion
LNM	Lymph node metastasis
LND	Lymph node dissection
DFS	Disease-free survival
SD	Standard deviation
IQR	Interquartile range
PSM	Propensity score matching
OR	Odds ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

Xu Sun: Data curation, Methodology, Formal analysis, Writing - original draft. Rui Li: Data curation, Formal analysis, Investigation, Writing-review & editing. Wen Zhao: Methodology, Visualization. Dingchang Li: Conceptualization, Supervision, Methodology. Guanglong Dong: Conceptualization, Project administration, Writing-review & editing. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the First Medical Center of the Chinese PLA General Hospital. All methods were carried out in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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