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Original Article

Biomarkers and long-term prognosis of colorectal schistosomiasis-associated rectosigmoid cancer: a retrospective study

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Abstract: Aim: This study is to assess the association between the potential long-term effects of previous schistosoma infection and rectosigmoid cancer. Methods: From November 2006 to May 2011, 25patients who had rectosigmoid carcinoma combined with colorectal schistosomiasis (SSC), 217patients with non-schistosomiasis rectosigmoid carcinoma (NSC), 19 colorectal schistosomiasis (CS) were included. Tumor characteristics, pre-operative investigations, tumor pathological examinations and postoperative courses were evaluated. Results: There was no significant difference in overall survival rate between the SSC and NSC groups. Levels of CEA, AFP and CA19-9 did not differ among three groups; CA19-9 values were significantly larger in SSC group than those in NSC group. Levels of CA-125 were significantly higher ($P<0.0001$) in CS group compared to the other two groups, but no significant difference could be observed between NSC and SSC groups. Concerning the biopsy staining, CA125 was upregulated in CS and SSC group, significantly stronger staining was observed. Conclusions: For those who travelled from or lived in endemic areas, elevated serum CA19-9 and CA-125 may be signals for those who have colorectal lesions and infested water contact history to go through the circumival precipintin test (COPT), for rectosigmoid cancer patients whose biopsy is CA-125 positive, rectosigmoid carcinoma combined with colorectal schistosomiasis (SSC) should be considered. However, schistosomiasis was not statistically significantly correlated with overall survival in patients suffering rectosigmoid cancer.

Keywords: Schistosomiasis, colorectal carcinoma, biomarker, prognosis, diagnosis

Introduction

Human schistosomiasis was first described by German tropical disease specialist Theodor Bilharz in 1851 [1]. Schistosomiasis could cause acute and long-term clinical syndromes [2], including permanent scarring of the bladder [3, 4], liver, urogenital system, small bowel [5, 6] and colon [7-9].

Regarding the colonic schistosomiasis, the adult worms of the main intestinal species, *Schistosoma mansoni* and *Schistosoma japonicum*, lay their eggs in the colonic mesenteric vessels. Then these ova penetrate the intestinal wall and are shed in the faeces (**Figure 1**). All segments of the colon may be affected, yet the rectum, sigmoid, descending colon and the domain of the inferior mesenteric vein, are the main sites of pathology. In chronic disease, the schistosoma ova are calcified and deposited with infiltration of lymphocytes and plasma cells in the submucosa and lamina propria, with giant cell reaction.

It is important to acknowledge that, because of the climate warning [8], schistosomiasis is now also becoming a cause for concern in Europe, especially in south Europe. Schistosomiasis infection in returning travelers is also one of the most common reasons. At present, due to the fact that clinical symptoms [9] and laboratory tests are nonspecific [10, 11] as well as the geographic distribution of the disease, colorec-

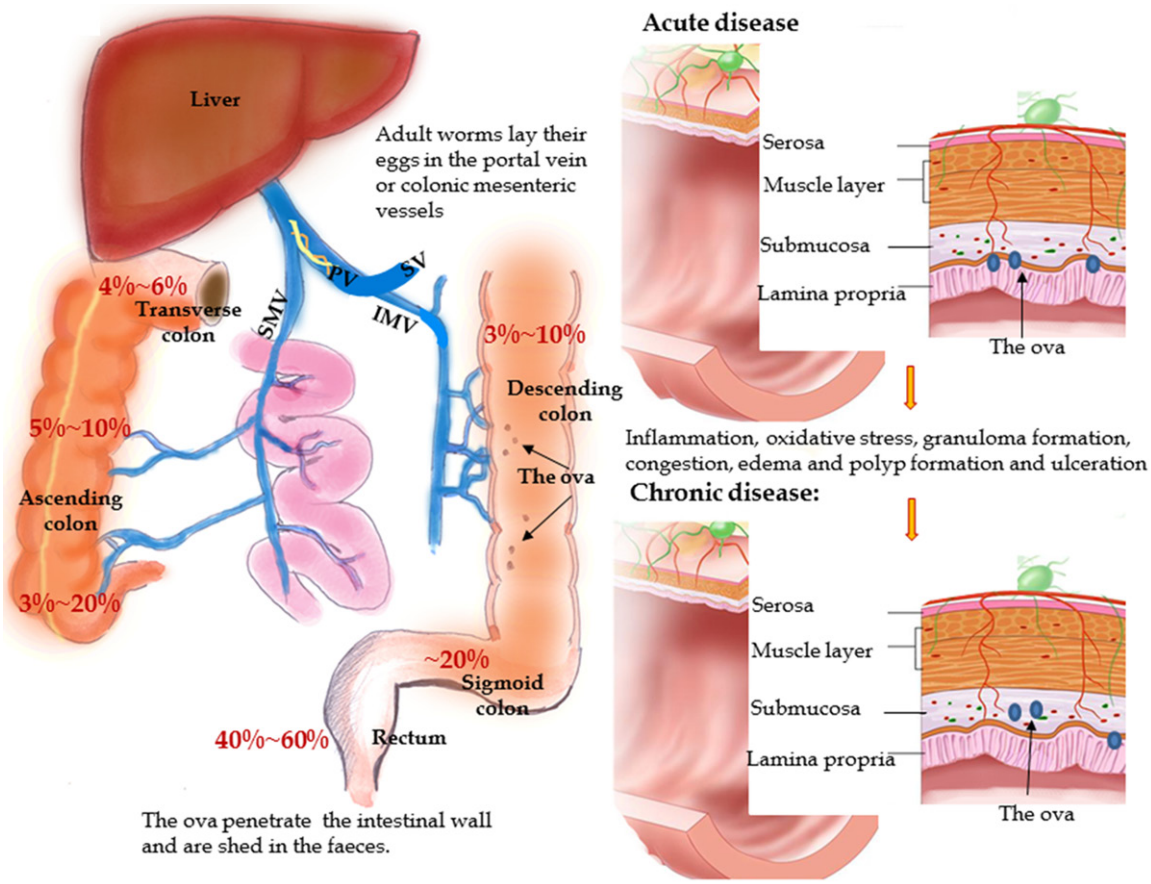

Figure 1. Schematic diagram showed adult schistosoma worms lay their eggs in the colonic mesenteric vessels, notably the inferior mesenteric vein. Then these ova penetrate the intestinal wall and are shed in the faeces. All segments of the colon may be affected, especially the rectum, sigmoid and descending colon. In acute disease, the ova are deposited in the lamina propria. In chronic disease, the schistosoma ova are calcified and deposited with infiltration of lymphocytes and plasma cells in the submucosa and lamina propria. Chronic inflammatory changes, antioxidant and fulcose status make it a precancerous condition for development of colorectal cancer. SMV, superior mesenteric vein; IMV, inferior mesenteric vein; SV, splenic vein; PV, hepatic portal vein.

tal changes as a result of schistosomiasis are generally unsure to clinicians from non-endemic areas.

Asian and African reports have proposed the biomarker and a causal relationship between chronic inflammatory changes of colonic mucosa and colorectal carcinogenesis [12, 13]. It was reported that intestinal schistosomiasis should be considered as a precancerous condition for development of colonic dysplasia and cancer as a consequence of chronic inflammation that altered inflammatory, antioxidant and fulcose status [14]. This study conducted a retrospective study, comparing the expression of antioxidant associated biomarkers, endoscopic findings, laboratory tests and prognosis in schistosomal and non-schistosomal rectosigmoid carcinoma.

Patients and methods

Histopathology and diagnoses

For histological examinations, colon tissue samples were fixed in 4% paraformaldehyde, and sections were stained with hematoxylin and eosin (H&E) by the Ruijin Hospital, Department of Pathology. The pathological TNM stages were determined according to the classification established by the American Joint Committee on Cancer. 25 patients were postoperatively histologically diagnosed with rectosigmoid carcinoma combined with colorectal schistosomiasis (SSC). 217 patients who were diagnosed with rectosigmoid carcinoma only (without colorectal schistosomiasis) were selected as a control group (NSC). Retrospective analysis was also conducted in 19 consecutive

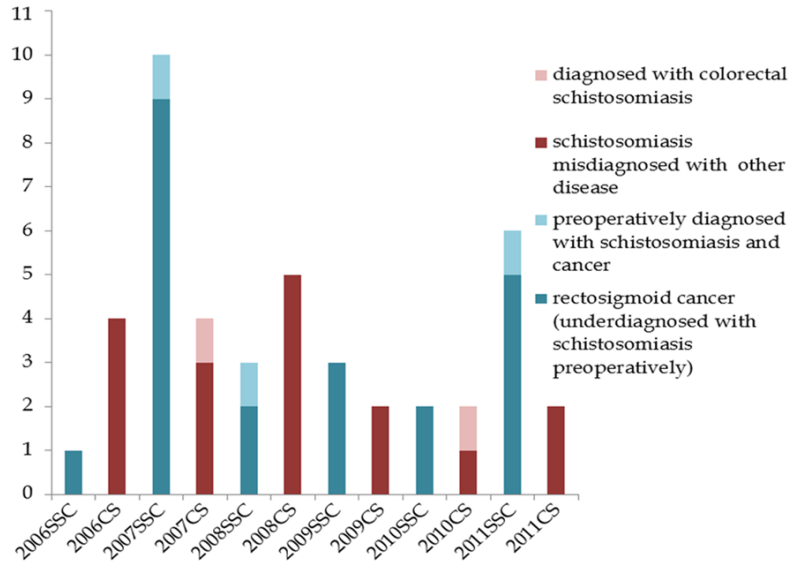

Figure 2. The rate of accurate diagnosis with colorectal schistosomiasis. SSC, rectosigmoid carcinoma combined with colorectal schistosomiasis; CS, colorectal schistosomiasis.

cases in the same period which were histologically diagnosed with colorectal schistosomiasis alone (CS).

Immunohistochemistry (IHC) procedure

IHC was performed on tissues from 83 patients (CS group: 15 cases, SSC group: 12 patients, NSC group: 56 patients). The procedure of IHC was conducted according to the manufacturer instructions (Vectastain Universal anti-mouse IgG/rabbit IgG elite ABC kit, Vector Laboratories, Inc. CA, USA). After baking slides in oven at 65°C overnight, slides were deparaffinized by applying sequential immersion for 5 min in xylene, 95% ethanol, 70% ethanol, and distilled water. Immunohistochemistry was performed on de-paraffinized formalin-fixed sections after antigen retrieval with boiling citrate buffer. IHC staining was conducted using CEA (Anti-Carcino Embryonic Antigen CEA antibody, ab4451, Abcam, England), AFP (Anti-alpha 1 Fetoprotein antibody, ab46799, Abcam), GFER (growth factor, also known as augmenter of liver regeneration) rabbit polyclonal antibody (1:600, ab36376, Abcam, England), CA19-9 (Anti-CA19-9 antibody, ab15146, Abcam), CA125 (Anti-MUC16 antibody, ab10033) and Bcl-xL rabbit monoclonal antibody (54H6, #2764, 1:300, Cell Signaling Technology, US). The primary antibodies were detected utilizing a biotinylated goat anti-rabbit/mouse antibody and Vectastain Elite ABC kit and DAB substrate (Vector Laboratories, Burlingame, CA, US). The qu antitative scoring method was reported previously by McDonald JW *et al*, in brief, the results were scored by multiplying the percentage of positive cells by the intensity.

Patient selection

Eligibility criteria included patients with histologically confirmed rectosigmoid carcinoma located up to 55 cm from the anal verge. Patients who underwent emergency surgical procedures were excluded. Preoperative staging included blood analyses with carcinoembryonic antigen serum concentration (CEA), Cancer Antigen 125 (CA-125), Cancer Antigen 19-9 (CA19-9), alpha-fetoprotein (AFP), total colonoscopy, transanal ultrasonography, abdominal magnetic resonance imaging (MRI) and thorax and abdominal computed tomography (CT). Between November 2006 and May 2011, all these patients above who underwent laparoscopic resection in the Shanghai Minimally Invasive Surgical Center at Ruijin Hospital, affiliated to Shanghai Jiao-Tong University were prospectively enrolled. Data collection included patient and tumor characteristics, pre-operative investigations, tumor pathological examination and postoperative course. Clinical laboratory tests including CEA, CA-125, CA19-9, AFP, hemoglobin collected before treatment (pre-Hb) and pre-treatment total bilirubin (pre-TBil) were performed on admission. The blood samples were collected and analyzed by experienced technicians and doctors from Laboratory Medicine Department.

Ethics statement

Protocol approval for all researches performed was obtained from the medical ethical committee of Shanghai Ruijin Hospital according to the Helsinki Declaration.

Long-term follow-up

Patients who were diagnosed with carcinoma were followed up every 6-month. The examina-

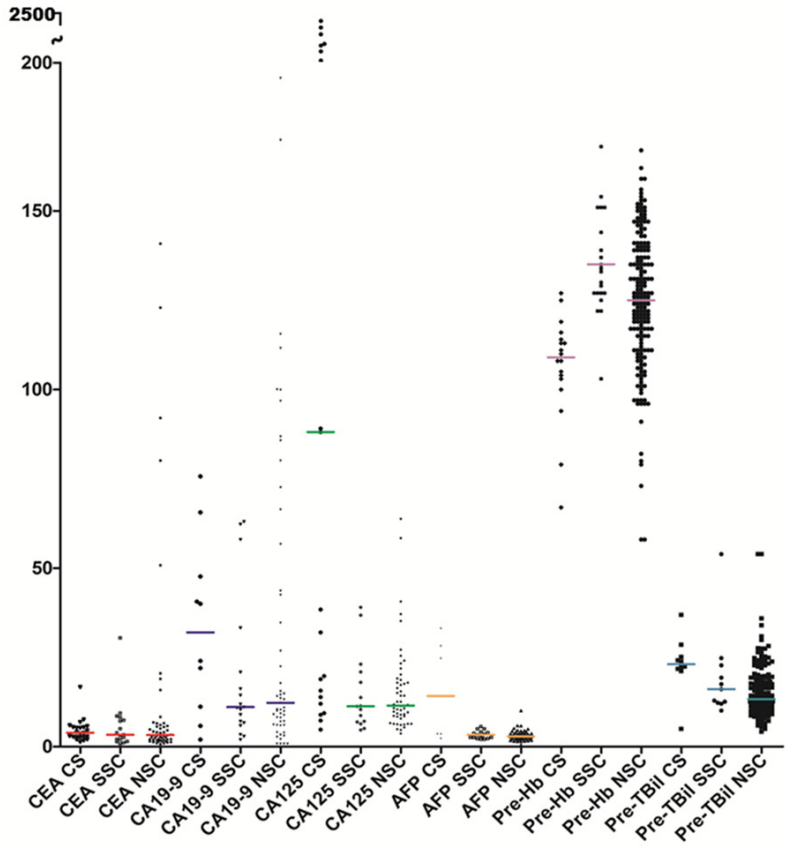

Figure 3. Laboratory examinations among three groups of patients. SSC, rectosigmoid carcinoma combined with colorectal schistosomiasis; CS, colorectal schistosomiasis. NSC, rectosigmoid carcinoma (without colorectal schistosomiasis).

tions included colonoscopic examinations, abdominal ultrasound, CT of abdominal and pelvic parts and laboratory examinations (CEA, CA19-9 and CA-125). Overall survival was calculated from surgery to death induced by all causes or end of follow up.

Statistical analysis

All measurements were expressed as means ± SD (the bar of **Figure 3** was expressed as medians), whereas count data was expressed as numbers (proportions). Differences in proportions were tested for statistical significance using the χ^2 test, and a Student's t-test was used to compare the means between groups. Categorical variables were compared using the Fisher's exact test. Continuous variables were presented as mean ± SD and compared using the Mann-Whitney U test. Kaplan Meier was performed to draw the survival curve. All statistical analyses were performed with the statistical software Stat View 5.0 for Windows (SAS Institute Inc., Cary, NC, USA), and a *P* value <0.05 was considered statistically significant.

Results

Colorectal schistosomiasis was easily underdiagnosed in patients with or without rectosigmoid carcinoma

In these 19 patients who had colorectal schistosomiasis (CS), 5 patients were underdiagnosed with ulcerative colitis, 3 patients were diagnosed with Crohn disease, 1 was diagnosed with intestinal tuberculosis, 6 patients were diagnosed with colonic polyps, 2 patients were diagnosed with rectosigmoid carcinoma. Only 2 patients (11%) were diagnosed with colorectal schistosomiasis before histologically confirmation, high-grade intraepithelial neoplasia was confirmed in 3 patients in this group. In these 25 patients who were diagnosed with sigmoid or rectal carcinoma combined with rectosigmoid schistosomiasis (SSC) by postoperative pathology, 21 were preoperative diagnosed with rectosigmoid carcinoma alone, only 3 patients got the accurate diagnoses (**Figure 2**).

Comparison of serum biomarkers in rectosigmoid carcinoma complicated with schistosomiasis

Levels of CEA, AFP and CA19-9 did not differ among three groups (CEA: *P*=0.4833, AFP: *P*=0.1108, CA19-9: *P*=0.2719). In contrast, levels of CA-125 were significantly higher (*P*<0.0001) in CS group, however, no statistical difference was found between SSC group and NSC group. When comparing the pre-Hb and pre-TBil, we found that patients in CS group produced significantly lower Hb levels (*P*<0.0001), they also produced higher TBil levels, although

Table 1. Patient characteristics and colonoscopic findings

	CS (n=19)	SCC (n=25)	NSC (n=217)	*P*-value
Gender (male/female)	13/6	20/5	143/74	0.36
Age	52±11	66±9	70±12	ns
Tumor size (cm)	-	3.5±1.1	3.6±1.2	ns
pT stage				
T1	-	0	10 (4.6%)	
T2	-	11 (44%)	66 (30.4%)	0.89
T3	-	8 (32%)	93 (42.9%)	
T4	-	6 (24%)	48 (22.1%)	
TNM stage				
I	-	10 (40%)	67 (30.9%)	
II	-	5 (20%)	65 (30%)	0.84
III	-	7 (28%)	68 (31.3%)	
IV	-	3 (12%)	17 (7.8%)	
Syndrome				
Mucosanguineous feces	3	5	12	
Diarrhoea	5	4	76	
Bowel habits changing	6	7	63	0.02
Abdominal pain	1	6	31	
Obstruction	1	2	22	
Others	4	2	13	
CEA	4.6±3.2	3.4±7.0	3.3±331.3	0.48
CA19-9	33.5±24.9	11.1±771.8	12.3±57.8	0.27
CA-125	333.5±524.3	11.3±10.9	11.5±12.2	<0.0001
AFP	16±14.3	3.2±470.7	2.9±1.5	0.1108
Pre-Hb	106.4±14.8	133±14.3	124.9±12.9	<0.001
Pre-TBil	23.1±7.9	16.1±12.4	15.4±7.2	0.1064
Preoperative biopsy	10	8	116	
Carcinoma	0	2	83	
Hyperplastic polyps	2	2	28	
Villous adenoma	1	1	11	0.0001
Tubular adenoma	5	3	17	
Others	2	0	1	
Postoperative pathology				
Well differentiated	-	3 (12%)	16 (7%)	
Moderately differentiated	-	18 (72%)	118 (54%)	0.03
Poorly differentiated	-	4 (16%)	83 (38%)	
Signet-ring cell carcinoma	-	1 (4%)	14 (6.4%)	ns
Mucinous adenocarcinoma	-	3 (12%)	42 (19.4%)	ns

CEA, carcinoembryonic antigen serum concentration; CA-125, Cancer Antigen 125; CA19-9, Cancer Antigen 19-9; AFP, alpha-fetoprotein; pre-Hb, pre-treatment hemoglobin; pre-TBil, pre-treatment total bilirubin. SSC, rectosigmoid carcinoma combined with colorectal schistosomiasis; CS, colorectal schistosomiasis; ns, not significantly different.

the difference was not significant (*P*=0.1064). Unpaired t test was performed to compare the differences between subgroups, AFP levels were significantly elevated in CS group than in the NSC group, CA19-9 levels were significantly higher in SSC group than those in NSC group (**Table 1**; **Figure 3**).

Comparison of in situ tumor biomarkers expression in schistosomiasis associated rectosigmoid carcinoma

Fifty-six formalin-fixed and paraffin-embedded samples of histologically confirmed non-schistosomiasis rectosigmoid carcinoma (NSC),

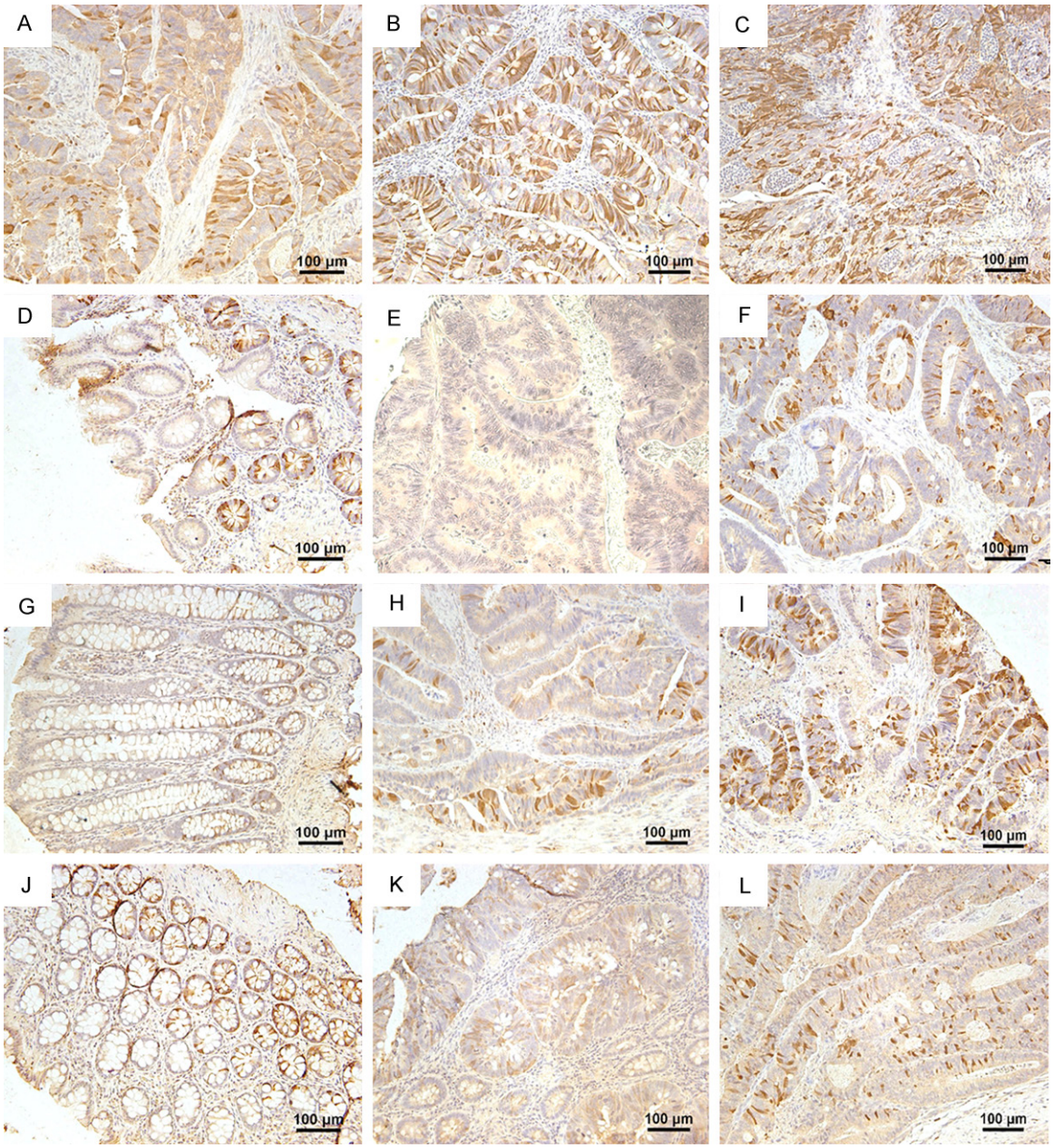

Figure 4. Representative immunohistochemistry staining of CEA, AFP, CA19-9 and CA125 in paraffin-embedded samples of histologically confirmed schistosomiasis-associated rectosigmoid carcinoma or non-schistosomiasis rectosigmoid carcinoma. (A-C) showed CEA expression in the tissues collected from rectosigmoid schistosomiasis (A); non-schistosomiasis rectosigmoid carcinoma (B); schistosomiasis-associated rectosigmoid carcinoma (C). (D-F) showed AFP expression in the tissues collected from rectosigmoid schistosomiasis (D); non-schistosomiasis rectosigmoid carcinoma (E); schistosomiasis-associated rectosigmoid carcinoma (F). (G-I) showed the expression of CA19-9 in those three groups, respectively; (J-L) showed the expression of CA125 in those three groups, respectively (400×).

twelve schistosomiasis-associated rectosigmoid carcinoma (SSC) and fifteen rectosigmoid schistosomiasis (CS) samples were assessed with CEA, CA19-9, CA125, AFP, Bcl-xL and GFER (ALR) protein expression. Immunoreactivity for CEA was present in forty samples in NSC group (71.4%), nine in SSC group (75%) and nine in CS group (60%). The positive rate and levels of AFP protein expression in the CS group (34%) were higher than those in other groups (NSC 19%,

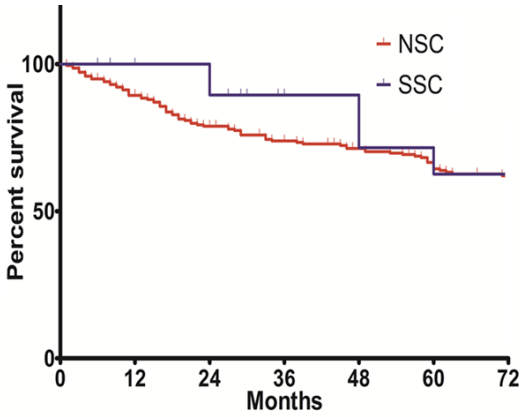

Figure 5. The 5-year overall survival rate of the patients in NSC and SSC groups. SSC, rectosigmoid carcinoma combined with colorectal schistosomiasis; NSC, rectosigmoid carcinoma (without colorectal schistosomiasis).

SSC 26%), but there was no significant difference. The positive rate of CA19-9 protein was higher in SSC and NSC groups (83.3% *vs* 77.5%). CA125 was upregulated in CS and SSC group, significantly stronger staining was observed. 7/12 SSC tissues and 36/56 NSC tissues showed GFER cytoplasm immunoreactivity. In addition, Bcl-xL has significantly elevated expression level in SSC group (**Figure 4**).

The prognosis of rectosigmoid carcinoma complicated with schistosomiasis

Median follow-up duration was 39.4 months (range from 6 to 72 months). The five-year overall survival rate in NSC and SSC groups were 72% and 69%, respectively. The survival curves were showed in **Figure 2**. There was no significant difference in overall survival rate between the two groups. Univariate analysis showed that schistosomiasis was not statistically significantly correlated with overall survival (*P*=0.3657, Hazard Ratio 0.7184, 95% CI of ratio 0.351~1.471) (**Figure 5**).

Discussion

Colon and rectum are targeted in *S. japonicum* and *S.masoni,* Adult worms live in the portal vein and its tributaries, notably the inferior mesenteric vein, to which they migrate against the blood stream after prior maturation in the hepatic sinusoids. The worms choose the portal rather than systemic veins owing to the former's higher content of oxygen and nutrients. The female worms then travel further against the blood stream towards the distal colon and rectum, driven by an oxygen gradient, to lay their ova. In the cases of intestinal cancer associated with schistosomiasis, the location of the cancer was predominately seen in the rectum [15], followed by the sigmoid colon, and then the other parts of the colon [16, 17]. Ileum and duodenal involvements have also been reported [6]. Egg deposition in the submucosa leads to granuloma formation [18], congestion, edema and polyp formation [19] and ulceration [20], the endoscopic findings of schistosomal rectosigmoid carcinoma were nonspecific [21]. These may lead to abdominal cramping, diarrhea which may be bloody, and dysentery. The diagnosis is made by finding schistosoma ova in stools, rectal scrapings, or rectal snips (**Figure 1**). Bcl-xL can prevent apoptosis by its direct pore-forming effect on the outer membrane of mitochondria to help maintain a normal membrane state under stress conditions. GFER, also called ALR, is a chaperone essential for disulfide bond formation and protein folding in the mitochondrial intermembrane space [22], it was reported [23] and our preliminary result also showed that GFER (ALR) might be a potential biomarker for colorectal cancers, however in this study, we haven't saw the difference between each group.

To evaluate the prognosis of patients with schistosomal rectosigmoid cancer, Kaplan Meier method was performed to draw the survival curves. This study reported the similar prognosis of patients in SSC and NSC, which was different from previous ones. Wang M *et al* [24] performed case-control study and showed that with/without schistosomiasis was statistically significantly correlated with overall survival and it was the only independent prognostic factor for both disease free survival and overall survival. It might be because that, patients in Wang's research were similar in pathologic tumor stage in two groups. On the contrast, some of the researches [25] including ours [26] found that schistosomal rectosigmoid cancer was normally relevant with an early tumor stage or moderate differentiated adenocarcinoma (**Table 1**, P=0.03).

In this retrospective cross-sectional study, all of the enrolled subjects with CS and SSC group resided in suburbs of the East China, which

used to be heavily endemic for *S. japonicum* and men worked more in the infested water [27]. That may be the reason why in this study the CS and SSC group contained high proportions of men.

In this study, TBil and AFP were significantly elevated while Hb had a significantly less level in CS group, which may be explained as follows: though most of the advanced schistosomiasis patients have received schistosomicides, but before the development of praziquantel, patients who received other schistosomicides might not complete the whole therapeutic process because of side effects. Thus, some of the advanced schistosomiasis patients still have live schistosomes in their portal veins. Meanwhile, there are many reports about relationship between the clinical liver fibrosis diagnosis and histopathology in advanced schistosomiasis. In addition, the tumor biochemical markers CA19-9 and CA-125 [28], which were routinely tested in gastrointestinal or ovarian cancers, were significantly higher in schistosomiasis patients (SSC and CS group respectively) than in NSC group. Therefore, elevated CA19-9 and CA-125 levels, as well as reduced Hb may be signals for those who have colorectal lesions, especially for those who have infested water contact history and gastrointestinal syndromes, to go through the circumival precipintin test (COPT).

Conclusions

Colorectal schistosomiasis is still easily underdiagnosed in patients with or without rectosigmoid carcinoma. For those who travelled from or lived in endemic areas, elevated serum CA19-9 and CA-125 may be signals for those who have colorectal lesions and infested water contact history to go through the circumival precipintin test (COPT), for rectosigmoid cancer patients whose biopsy is CA-125 positive, rectosigmoid carcinoma combined with colorectal schistosomiasis (SSC) should be considered. This study reported the similar 5-year overall survival rate of patients in SSC and NSC groups, which may be because that schistosomal rectosigmoid cancers are normally relevant with early tumor stages and moderate differentiation.

Disclosure of conflict of interest

None.

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