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Meta-Analysis

Levels of peripheral Th17 cells and serum Th17-related cytokines in patients with colorectal cancer: a meta-analysis

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Abstract: Studies suggest that inflammation is involved in the colorectal cancer (CRC) pathology and symptoms. This study sought to quantitatively summarize the clinical cytokine data. Multiple reports have described the proportion of Th17 cells in peripheral blood and serum levels of Th17-related cytokines in patients with colorectal cancer (CRC). To clarify the status of Th17 cells and Th17-related cytokines in CRC patients, we did a meta-analysis of the results published previously to quantitatively assess the levels of peripheral Th17 cells and serum Th17-related cytokines in patients with CRC. We searched PubMed, Embase, web of Science, Cochrane Library and China National Knowledge Infrastructure (CNKI) systematically for studies reporting the proportion of Th17 cells and the serum levels of Th17-related cytokines (IL-17, IL-17A, IL-6, IL-22, IL-23) in CRC patients. Studies measuring the proportion of Th17 cells and the serum levels of Th17-related cytokines (IL-17, IL-17A, IL-6, IL-22, IL-23) in CRC and healthy control subjects were included. Mean (standard deviation) proportion of Th17 cells and cytokine concentrations for CRC and control subjects were extracted. We assessed pooled data by using a random-effects model. We identified 1276 studies, of which 24 studies were included in the final meta-analytical processes. The quality was reliable according to the Newcastle–Ottawa Quality Assessment Scale (Case Control Studies). Compared with control subjects, CRC patients had a higher proportion of Th17 cells [2.37%, (0.53, 2.21)]; an elevated levels of serum IL-17A 1.11 pg./ml, 95%CI (0.16-2.07); an elevated levels of serum IL-6 3.42 pg/ml, 95%CI (3.14-3.70); an elevated levels of serum IL-22 1.32 pg/ml, 95%CI (0.94-1.70); an elevated levels of serum IL-23 0.16pg/ml, 95%CI(1.94-5.39). After sensitivity analysis, an elevated level of serum IL-17 was showed. The data showed that the proportion of Th17 cells in PB and levels of serum IL-17, IL-17A, IL-6, IL-22, IL-23 increased among CRC patients compared to control subjects. This result demonstrated that Th17 cells and Th17-related cytokines may be involved in the pathogenic mechanisms of CRC.

Key words: TH 17 cells; cytokines; Colorectal cancer; IL 17.

Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the digestive system, and its incidence is increasing year by year(1). The causes of the disease are complex and may be related to geography, diet, smoking, genetic factors, colon polyps, and chronic inflammatory stimulation (2). Early studies have found that there are many inflammatory cells in the colon cancer tumor microenvironment, such as lymphocytes, macrophages, etc. These inflammatory cells have a close relationship with the occurrence and development of colon cancer (2). Therefore, colorectal cancer is an inflammation-related tumor. A large number of studies have shown that the human immune system plays an important role in the pathogenesis of malignant tumors, but the exact mechanism in tumorigenesis and development is not yet clear. Therefore, exploring the pathogenesis from the perspective of immunology and finding new targets for immunotherapy will be the great significance to the development of biological therapy. Th17 cells are one of the components of the immune system and can produce a variety of cytokines, such as IL-17, IL-17A, IL-6, IL-23, IL-22, IL-1β, etc. Th17 cells and their secretion Cytokines are involved in the development of tumors, inflammation, and autoimmune diseases(3) At present, several cytokines have been thought to be involved in the chronic inflammation of the colorectal. Th17 cells are a major source of IL-17 in CD4+ T cell subsets(4, 5). Currently, studies have revealed that Th17 cells and IL-17 secreted by them are highly expressed in colorectal cancer tissues and peripheral blood(6). Guo et al. (7) found that cytokine IL-6 increased with the progression of CRC, and the Dukes' D phase had the highest concentration, which led to changes in the microenvironment of CRC patients and promoted the progression of CRC.

To the best of our knowledge, there has been no systematic review or meta-analysis of the associations between the Th17 Cells, or the Th17-related cytokines and Colorectal cancer to date. The present report is the first meta-analysis, based on existing reports in the literature, of the relationship between the Levels of peripheral Th17 Cells, or the serum Th17-related cytokines and Colorectal cancer. Therefore, this study reports the results of a meta-analysis conducted to determine whether the percentage of Th17 cells and the concentrations of specific cytokines differ quantitatively between patients diagnosed with CRC and healthy control subjects.

Materials and Methods

Search strategy and selection criteria

This meta-analysis was reported based on the Sys-

Table 1. Search strategy.

Data base	Search	Hits
PubMed	((colorectal OR rectal OR colonic) AND (cancer OR tumor OR neoplasms OR carcinoma)) AND (th17 OR (T helper 17 cells) OR IL-17 OR IL17)	488
EMBASE	((colorectal OR rectal OR colonic) AND ('cancer'/exp OR cancer OR 'tumor'/exp OR tumor OR 'neoplasms'/exp OR neoplasms OR 'carcinoma'/exp OR carcinoma)) AND (th17 OR (t AND helper AND 17 AND cells) OR 'il 17' OR il17)	815
Web of Science	TI= ((colorectal OR rectal OR colonic) AND (cancer OR tumor OR neoplasms OR carcinoma)) AND TS= (th17 OR (T helper 17 cells) OR IL-17 OR IL17)	116
CNKI	(TI=' Colon cancer 'or TI=' Rectal cancer ' or TI=' Colorectal cancer ‘) and (AB='Th17' or AB='Th17 cell 'or AB=' Interleukin -17' or AB='IL-17')	91
Cochrane Library	(colorectal or rectal or colonic) and (cancer or tumor or neoplasms or carcinoma): ti, ab, kw and th17 or (T helper 17 cells) or IL-17 or IL17: ti, ab, kw (Word variations have been searched)	9

tematic Review and Meta-analyses (PRISMA) Statement(8). We searched PubMed, Embase, web of science, Cochrane Library, and China Knowledge Infrastructure (CNKI) and selected eligible studies record the proportion of peripheral Th17 cells and Th17 cytokine-related cytokines in CRC patients up to March 10, 2018. In the article we used the following keywords: ‘colorectal cancer’, ‘Th17 cells’, and ‘IL-17’. Reference lists of relevant studies were searched for additional reports. The details of Search strategy were showed in table 1.

Study selection and data extraction

Inclusion criteria

1) original research (not reviews); 2) human studies; 3) reports of Th17 cell or Th17 related cytokine serum levels in CRC patients; 4) full-text studies can be found on the search website; 5) Studies using standardized histopathological examination confirmed the diagnosis of colorectal cancer. There are no restrictions on the subtype of colorectal cancer, the severity of the disease, the degree of disability, or the sex and race of the subject.

Exclusion criteria

1) studies that provided no raw data regarding the mean and standard deviation (SD) of the proportion of Th17 cells or the levels of Th17-related cytokines in serum; 2) studies with no comparison group; 3) repetitive researches (individual studies were counted only once in the analysis).

Two independent investigators reviewed the title and abstract and assessed the full text of the studies that met the inclusion criteria. Two researchers analyzed the trials selected for detailed analysis and data extraction; the third investigator resolved the differences. We validated and conducted a systematic review of quality assessments based on the Newcastle-Ottawa Quality Assessment Scale (Case-Control Study) (9) as a tool to assess the quality of non-randomized studies in meta-analyses. The case-control study literature quality evaluation mainly includes the selection of the study population, the comparability of the population and the exposure factors, a total of 8 evaluation items, each item has 1 to 2 points, and the total score is 10 points. If NOS ≥ 5 points, quality is reliable.

We extracted the following data from all included studies: author, year of publication, country, number of CRC patients and healthy persons as control subjects, mean and SD of the proportion of Th17 cells among CD4+ T cells in PB and Th17-related cytokines serum levels of CRC patients and control subjects (Table 2).

Statistical analysis

We evaluated two main results: the proportion of Th17 cells in CD4+ T cells and the level of serum Th17-related cytokines in PB. The standard mean difference (SMD) and 95% confidence interval(10)for each outcome between CRC patients and healthy controls were calculated by using a random effects model (REM). If significant heterogeneity is expected, REM is preferable because they assume and take into account the variable potential impact of uncertainty estimates, including differences between researches.

In the meta-analysis of each outcome, we performed a sensitivity analysis to evaluate the final results through impact analysis and did not change the combined results by omitting a single study. In the results display, the middle vertical line represents the total combined effect amount, and the left and right vertical lines represent the upper and lower limits of the 95% confidence interval for the total combined effect amount; the horizontal line for each study indicates that the remaining studies after the study was deleted. The amount of consolidation effect. To identify potential sources of heterogeneity, planned study level meta-regression analyses were conducted comparing SMDs to public year, ethnicity, TNM or dukes stage, specimen numbers, using meta-regression.

We assessed the likelihood of publication bias by constructing a funnel plot of the effect of each trial for standard error. We used the Begg and Egger tests to evaluate the funnel plot asymmetry and defined the publication bias of significance for p values < 0.1. The Cochran Q test and the I^2 test were used to assess the degree of heterogeneity between studies. I^2 values greater than 50% were considered indicators of moderate to high heterogeneity. A Q statistic was calculated in chi-square analysis to quantify heterogeneity among combined results. A significant Q statistic indicates diversity in the characteristics of the combined trials. Inconsistency was calculated using an I^2 index to determine the impact of heterogeneity (11). Analyses were conducted using Stata (version 12.0).

Results

Literature Search Findings

Study characteristics

We identified 1276 studies, of which 24 studies were

Table 2. Characteristics of included studies.

Author	year	country	ethnicity	control			case			TNM stage (I-II/III-IV)	Dukes stage (A/B/C/D)	Test method	index
				n	male/female	age	n	male/female	age				
Li et al	2017	China	Asian	50	23/27	57(40~75)	53	33/20	60(38~81)	23/30	-	ELISA	IL17A IL22
Cheng et al	2016	China	Asian	60	32/28	76(64~85)	76	42/34	74(61~83)	28/48	-	ELISA	IL17
Zhang et al	2016	China	Asian	78	44/34	76.21±4.44	78	47/31	75.48±4.35	25/53	-	Flow Cytometric Detection	Th17
Han et al	2015											ELISA	IL17A IL6
Zhang et al	2015	China	Asian	15			56			-	-	ELISA	IL17
Wang et al	2014	China	Asian	17	9/8	65(44~83)	54	27/27	65(43~86)	25/29	-	ELISA	IL17A IL6, IL23
Wang et al	2014	China	Asian	24	12/12	63.3±11.9	56	28/28	65.1±11.6	25/31	-	ELISA	IL17 IL23
Zhang et al	2014	China	Asian	35	18/17	49(29~64)	40	20/20	52(33~63)	24/16	-	Flow Cytometric Detection	Th17
Wang et al	2014											ELISA	IL17 IL6, IL23
Liu et al	2014	China	Asian	17	10/7	63.6±9.4	42	20/22	64.5±11.9	-	-	ELISA	IL17A IL23
Hu et al	2013	China	Asian	25	14/11	63(38~78)	33	19/14	65(42~83)	-	17/16a	Flow Cytometric Detection	Th17
Zhang et al	2013	China	Asian	10	6/4	53(20~66)	43	26/17	56(39~63)	-	25/18b	ELISA	IL17
Huang et al	2012	China	Asian	30	20/10	56(20~76)	56	36/20	62(32~81)	-	8/12/24/12	ELISA	IL17 IL6
Wen et al	2011	China	Asian	6			7			-	Yes	ELISA	IL17
Yuan et al	2016	China	Asian	15	7/8	60±9.7	30	17/13	65±13.2	12/18	-	Flow Cytometric Detection	Th17
Fang et al	2015											ELISA	IL17 IL23
Zhang et al	2014	China	Asian	50	27/23	59.5±14.7	110	61/49	58.1±15.8	38/72	-	ELISA	IL17
Li et al	2014	China	Asian	20	9/11	39(22~66)	55	28/27	63(15~84)	31/24	-	ELISA	IL17
Wang et al	2013	China	Asian	32	17/15	74(69~90)	40	24/16	75(65~93)	12/28	-	Flow Cytometric Detection	Th17
Huang et al	2012											ELISA	IL17A IL6
Mao et al	2016	China	Asian	30	17/13	53.8±20.8	103	55/48	62.9±13.6	38/65	-	ELISA	IL17
Stanilov et al	2016	China	Asian	30	18/12	53.24±12.46	43	24/19	58.2(40~86)	-	13/10/14/6	Flow Cytometric Detection	Th17
Radosavljevic et al	2010											ELISA	IL17 IL6
Adamo et al	2011	China	Asian	13	8/5	57(49~71)	17	9/8	56(48~70)	8/9	-	Luminex assay	IL17 IL22
Li et al	2017	Montenegro	Eurobaal	37			40			Yes	-	ELISA	IL17
Cheng et al	2016	Italy	Caucasian	20			25	17/8	53(29~78)	-	-	ELISA	IL23

a: 17 cases of early stage A colorectal cancer; 16 cases of advanced stage colon cancer B+C+D stage. b: 25 cases were in the A+B stage; 18 cases were in the C+D stage. Yes: use TNM stage or Dukes stage, but no detail data.

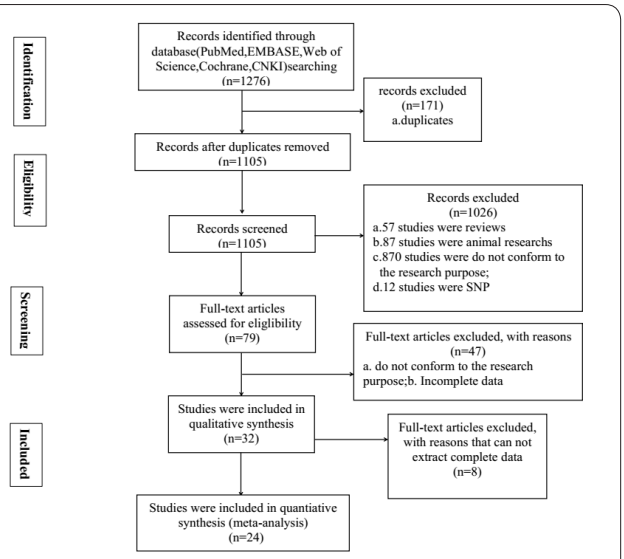

Figure 1. Flow chart.

included in the final meta-analytical processes. The study selection process was detailed in Fig. 1. In addition, we provided the details of the selected studies in Table 1. We extracted clinical data from selected studies, and the ranges were as follows: the range of case number was 7-110, the range of case mean age was 52–75 years, the range of control mean age was 39–76 years in Table 2. The range of the Newcastle–Ottawa Quality Assessment Scale (Case Control Studies) was 6 to 8 in Table 3, NOS ≥ 5 points, the quality was reliable.

The proportion of Th17 cells in peripheral blood of CRC patients

The six inclusion trials of TH-17(12-17), the results showed that the proportion of TH17 cells in CRC patients was increased by 2.37% (95% CI, 1.81-2.93) compared with the control subjects, P = 0.00. The hete-

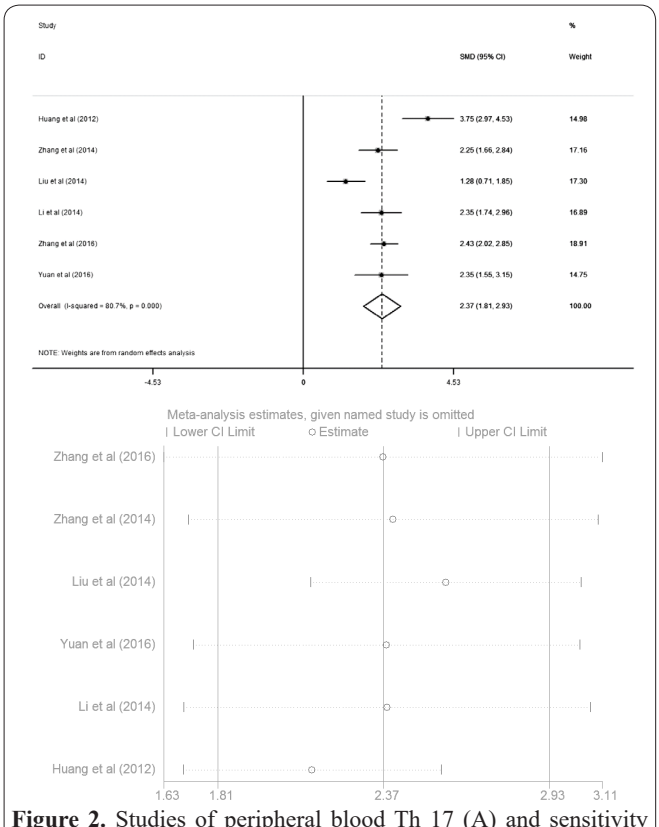

Figure 2. Studies of peripheral blood Th 17 (A) and sensitivity analysis of TH17 cells (B).

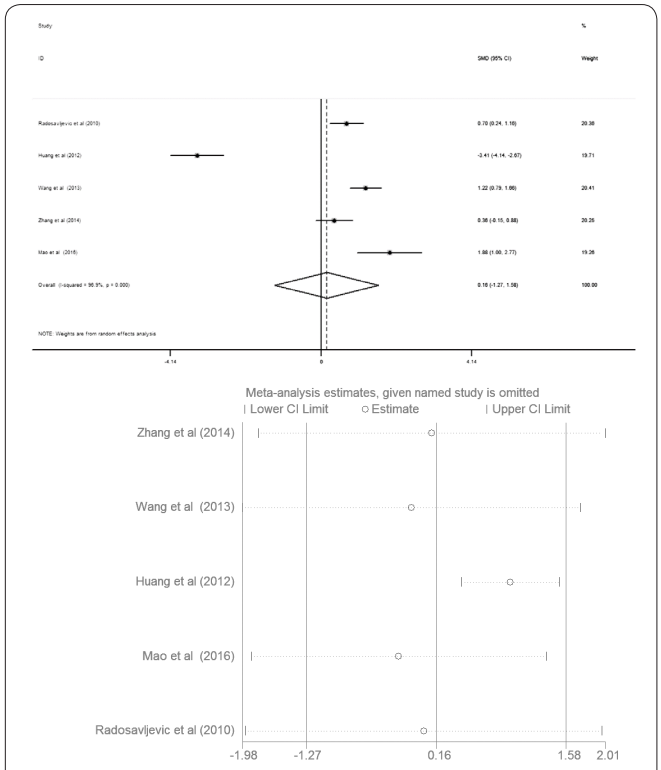

Figure 3. Studies of serum levels of IL-17 (A) and sensitivity analysis of IL 17 (B).

rogeneity test found significant heterogeneity among the studies (P = 0.00, I2 = 80.7%). The results are shown in Fig. 2A and Table 4. Sensitivity analysis found that Liu et al (2014) (14) and Huang et al(2012) (17)had the greatest impact on the overall effect, while other studies had little effect. The results were shown in Fig. 2B.

The serum levels of Th17-related cytokines in CRC patients

The five inclusion trials of TH-17-related cytokine IL-17 (17-21) showed no difference in serum IL-17 levels in CRC patients compared with the control group (0.16 pg/ml, 95% CI (-1.27-1.58).), P=0.83. However, heterogeneity test found significant heterogeneity between studies (P = 0.00, I2 = 96.9%). The results are shown in Fig. 3A and Table 4. The sensitivity analysis found that Huang et al. (2012) (17) had the greatest impact on the overall integrated effect, while other studies had little impact. The results were shown in Fig.3B.

The five inclusion trials of TH-17-related cytokine IL-17A (12, 16, 22-24), the results showed that the serum IL-17A levels in CRC patients increased 1.11 pg/ml 95% CI (0.16). , 2.07), P = 0.02) compared with the control group.However, heterogeneity test found significant heterogeneity between studies (P = 0.00, I2 = 94.9%). The results were shown in Fig. 4A and Table 4. The sensitivity analysis found that Li et al. (2017) (22) and Wang et al. (2014) (23) have the greatest impact on the overall comprehensive effect. The results were shown in Fig. 4B.

The five inclusion trials of TH-17-related cytokine IL-6 (12, 13, 16, 17, 23, 25), the results showed that the serum IL-6 levels in CRC patients increased 3.42 pg/ml, 95%CI(3.14-3.70), P =0.00) compared with the control group. However, heterogeneity test found significant heterogeneity between studies (P=0.00, I2=81.8%). The results were shown in Fig. 5A and Table 4. The sensiti-

Table 3. the Newcastle–Ottawa Quality Assessment Scale (Case Control Studies).

study	year	Selection				Comparability	Exposure			Total
		Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Li et al	2017	1	1	0	0	2	1	1	0	6
Cheng et al	2016	1	1	0	0	2	1	1	0	6
Zhang et al	2016	1	1	0	0	2	1	1	0	6
Han et al	2015	1	1	0	0	2	1	1	0	6
Zhang et al	2015	1	1	0	0	2	1	1	0	6
Wang et al	2014	1	1	1	0	2	1	1	0	7
Wang et al	2014	1	1	1	0	2	1	1	0	7
Zhang et al	2014	1	1	0	1	2	1	1	0	7
Wang et al	2014	1	1	0	0	2	1	1	0	6
Liu et al	2014	1	1	1	0	2	1	1	0	7
Hu et al	2013	1	1	1	0	2	1	1	0	7
Zhang et al	2013	1	1	1	0	2	1	1	0	7
Huang et al	2012	1	1	1	1	2	1	1	0	8
Wen et al	2011	1	1	1	0	2	1	1	0	7
Yuan et al	2016	1	1	1	1	2	1	1	0	8
Fang et al	2015	1	1	1	0	2	1	1	0	7
Zhang et al	2014	1	1	1	0	2	1	1	0	7
Li et al	2014	1	1	1	1	2	1	1	0	8
Wang et al	2013	1	1	1	1	2	1	1	0	8
Huang et al	2012	1	1	0	0	2	1	1	0	6
Mao et al	2016	1	1	1	1	2	1	1	0	8
Stanilov et al	2016	1	1	1	1	2	1	1	0	8
Radosavljevic et al	2010	1	1	1	0	2	1	1	0	7
Adamo et al	2011	1	1	1	0	2	1	1	0	7

Table 4. Summary of Comparative Outcomes for the proportion of Th17 cells and serum levels of Th17-related cytokines Measurements.

			Main Effect				Heterogeneity			
Items	**Studies numbers**	**N(CRC/HC)**	**SMD**	**95%CI**	**Z**	**P**	**Chi2**	**df**	**P**	**I2**
Th17 Cells	6	264/215	2.37	1.81,2.93	8.30	0.00	25.87	5	0.00	80.7%
IL-17	5	732/375	0.16	-1.27,1.58	0.21	0.83	129.30	4	0.00	96.9%
IL-17A	5	267/194	1.11	0.16,2.07	2.28	0.02	78.67	4	0.00	94.9%
IL-6	6	311/222	3.42	3.14,3.70	24.15	0.00	27.51	5	0.00	81.8%
IL-23	6	247/128	3.66	1.94,5.39	4.16	0.00	141.50	5	0.00	96.5%
IL-22	2	70/63	1.32	0.94,1.70	6.81	0.00	1.55	1	0.21	35.7%

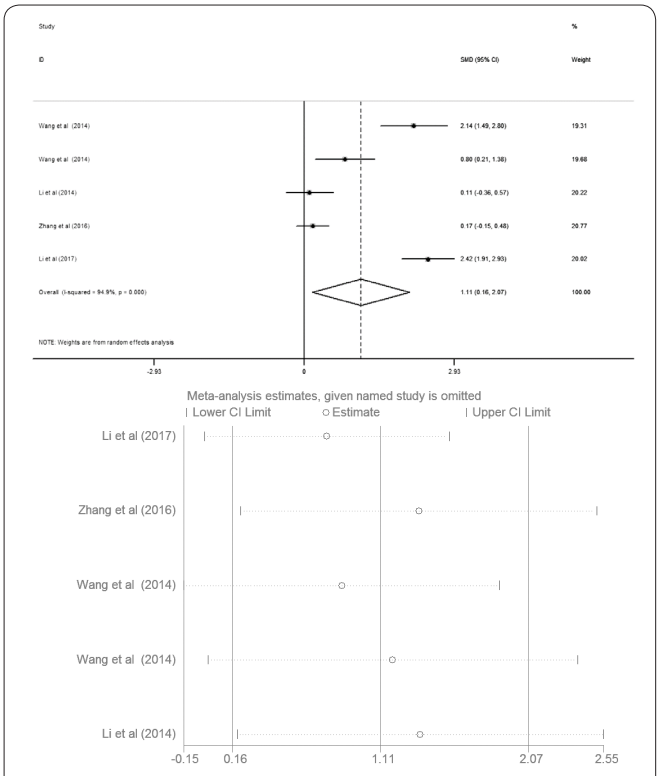

Figure 4. Studies of serum levels of IL-17A (A) and sensitivity analysis of IL 17A (B).

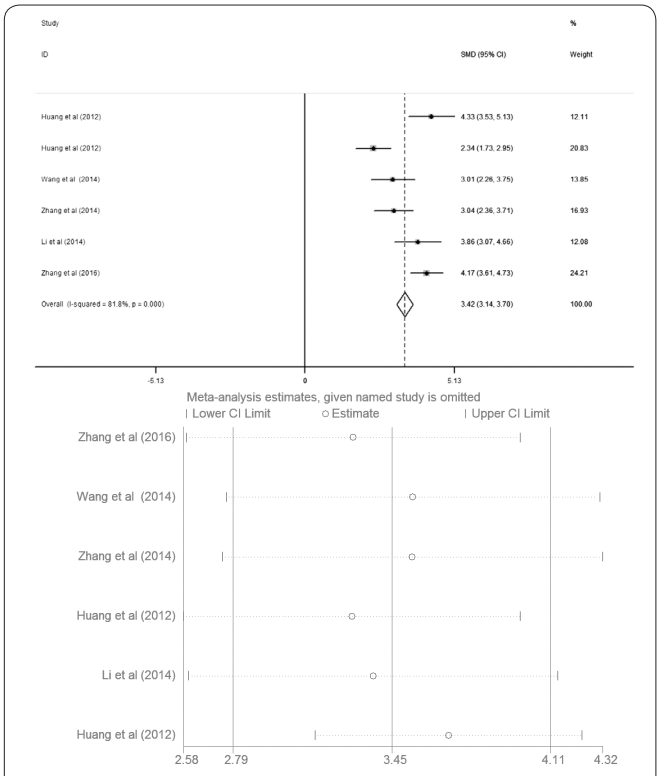

Figure 5. Studies of serum levels of IL-6 (A) and sensitivity analysis of IL 6 (B).

vity analysis found that Zhang et al(2016)(12),Huang et al(2012)(17) and Huang et al(2012)(25) had the greatest impact on the overall comprehensive effect. The results were shown in Fig. 5B.

The two inclusion trials of TH-17-related cytokine IL-22 (20, 22), the results showed that the serum IL-22 levels in CRC patients increased 1.32 pg/ml, 95%CI(0.94, 1.70), P =0.00) compared with the control group. Heterogeneity test found no heterogeneity between studies (P=0.21, I^2=35.7%). The results were shown in Fig. 6 and Table 4.

The six inclusion trials of TH-17-related cytokine IL-23 (13, 15, 23, 24, 26, 27), the results showed that the serum IL-23 levels in CRC patients increased 3.66 pg/ml, 95%CI(1.94-5.39), P =0.00) compared with the control group. However, heterogeneity test found significant heterogeneity between studies(P=0.00, I^2=96.5%). The results were shown in Fig. 7A and Table 4. The sensitivity analysis found that Li et al. (2017) (22) and Wang et al. (2014) (23)have the greatest impact on the overall comprehensive effect. The results were shown in Fig. 7B.

Meta-regression

We attempted to explain this heterogeneity by exploring the study characteristics, such as public year, ethnicity, TNM or dukes stage, specimen numbers, using meta-regression. Unfortunately, no satisfactory clues were found.

Publication Bias

The publication bias is recognized as another influent factor to the diagnosis accuracy (28). The Begg's test and Egger's test were used in this meta-analysis. Which is more than 0.05 and suggests no publication bias exist among these included studies. However, concluding whether or not publication bias exists is difficult due to the limited number of studies involved in the current meta-analysis. The data were showed in table 5.

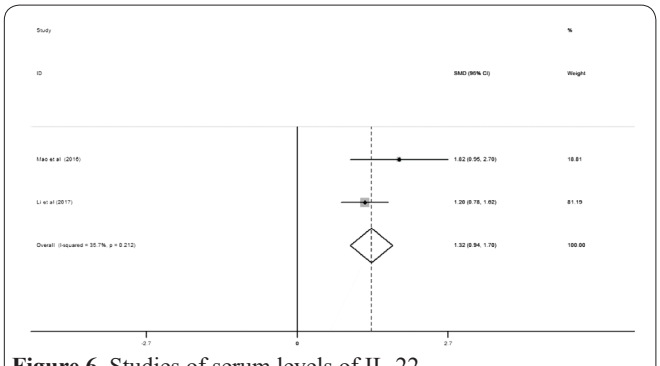

Figure 6. Studies of serum levels of IL-22.

Table 5. The *p* value of Begg's test and Egger's test.

	Begg's test	Egger's test
Th 17	0.707	0.592
IL 17	0.462	0.506
IL 17A	0.221	0.198
IL 6	0.707	0.757
IL 22	-	-
IL 23	0.133	0.009

Discussion

In the present meta-analysis, we evaluated the proportion of Th17 cells and the serum levels of Th17-related cytokines (IL-17A, IL-6, IL-23, IL-22) increased in CRC patients.Th17 cells belong to T cell subsets and secrete cytokines such as IL-6 and IL-17A (28). IL-6 cytokines have multiple functions and are involved in tumor and inflammation(29). IL-17 was the major effector factors of Th17 cells(30). Th17 cells and the secreted IL-6 and IL-17A cytokines were involved in cancer-related immune responses. IL-17A is an important proinflammatory cytokine that is secreted mainly by Th17 cells(31). However, studies have revealed that the expression of IL17A gradually increases with the progression of colorectal cancer staging and differentiation. IL-17A high rises may be one of the indicators of poor prognosis in patients with colorectal cancer(32, 33). Both M1 and M2 macrophages possess the ability to produce IL-6, a key cytokine in promoting Th17 differentiation and IL-17 and IL-22 production(34, 35), but their interaction with Th17 cells in CRC patients has not been examined. IL-23 and IL-6 promote the differentiation of Th17(34, 36-40). Th17 cells secrete IL-17 characteristically, and also secrete IL-6 and IL-22 and other inflammatory cytokines, which have a strong proinflammatory effect. IL-23 is mainly involved in the expansion and maintenance of memory Th17 cells(41). Since the discovery of Th17 cells, numerous studies have shown that Th17 cells are of great significance in autoimmune diseases, chronic inflammation, acute inflammatory initial stages, and neoplastic diseases.

The colorectal cancer in elderly patients is relatively high, which may be due to the accumulation of certain molecular changes and gene mutations in the elderly. As the age increases, the structure and function of the immune system will undergo certain changes, and there will be some pro-anti-inflammatory imbalances in the body. To put elderly people in a long-term chronic low-grade inflammation and promote the development of inflammation-related cancers (42, 43).The elderly have the characteristics of aging changes such as inflammatory aging and immune aging. The inflammatory aging characteristics of the elderly make the elderly in a chronic low-grade inflammation state, increasing the risk of tumors in the elderly.

To the best of our knowledge, the present work is the first to evaluate the proportion of Th17 cells and the serum levels of Th17-related cytokines in CRC patients via a meta-analysis. Our meta-analysis has several strengths. We did not limit in addition to the results of NOS, the methodological quality of the study was high. Also, we identified the main source of heterogeneity via sensitivity analysis. Finally, no publication bias

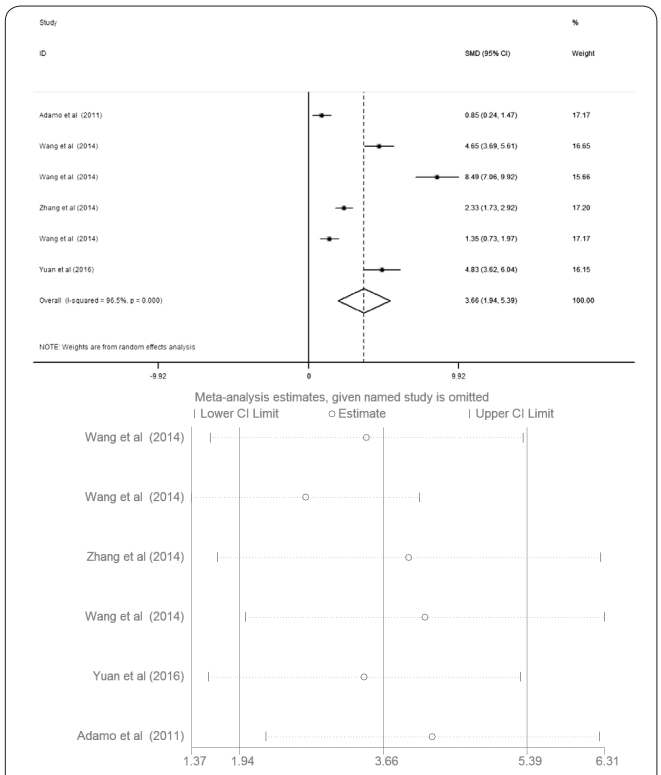

Figure 7. Studies of serum levels of IL-23 (A) and sensitivity analysis of IL 23 (B). Forest plot displaying random-effects meta-analysis results of the association between the serum levels of IL-23 and CRC. Standard mean difference (pg/ml) on horizontal axis; positive values denote higher in CRC patients; negative values denote higher in healthy control subjects. Hashed line at the overall standard mean difference. CI, confidence interval; SMD, standard mean difference.

was identified by either Begg's funnel plot or Egger's regression test, except in the case of IL-23. In the meta-analyses of each outcome, we did sensitivity analysis to evaluate the ultimate outcome by using influence analysis, and no combined outcomes were changed by omitting a single study. To identify potential sources of heterogeneity, we tried to use regression analysis and conducted a regression analysis of public year, ethnicity, TNM or dukes stage, specimen numbers. No sources of heterogeneity were found.

The present study also has several limitations. For instance, the number of included studies was very low for IL-22, which limited further analysis. Second, we were unable to extract sufficient adjustment data for certain factors, such as the clinical subtypes in CRC, Patients, the different of cancer stage and the disease duration. Finally, CRC treatments were not included. These treatments may have influence on the proportion of Th17 cells and the serum levels of Th17-related cytokines. It is difficult to exclude the influence of CRC Treatments on our results.

In summary, our meta-analysis comprehensively and systematically evaluated the proportion of Th17 cells and the serum levels of Th17-related cytokines. The results suggested that the proportion of Th17 cells and the serum levels of Th17-related cytokines (IL-17A, IL -6, IL-23, IL-22) increased in CRC patients. The result of IL-17 also showed an increase when omit the greatest effect on the main effects study. Given the limited sample size, the conclusions of this study should be treated with caution, and large sample studies are neces-

sary in the future. The clinical courses, our expression clearly lend support to the theory that Th17 cells may be involved in the pathogenic mechanism of CRC. Th17 cells and Th17-related cytokines may become new therapeutic targets for CRC treatment.

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