Research article

# An exploratory study on TCM syndrome differentiation in preoperative patients with colorectal cancer assisted by laboratory indicators

Ya-nan Wang [a], Min Zou [b], Dou Wang [c], Zhi-kuan Zhang [a], Lian-ping Qu [a], Jing Xu [a], Cai-dong Shi [a], Feng Gao [b],*

[a] Clinical College of Chinese Medicine, Gansu University of Chinese Medicine, Lanzhou 730000, China
[b] Department of Colorectal & Anal Surgery, The 940th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army, Lanzhou 730050, China
[c] Xinjiang Medical University, Urumqi 830000, China

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ABSTRACT

*Objective:* This paper aims to explore the relationship between the syndrome differentiation of traditional Chinese medicine (TCM) in colorectal cancer and the clinical laboratory indicators of patients, and to further seek the laboratory indicators to assist TCM syndrome differentiation.
*Methods:* From May 2020 to June 2021, 122 colorectal cancer patients with a clear pathological diagnosis who had not undergone surgery or chemotherapy were classified according to the TCM syndrome classification. The clinical laboratory indicators of 122 patients with preoperative colorectal cancer were collected, and the correlation between preoperative colorectal cancer TCM syndromes and Karnofsky score and clinical laboratory indicators was analyzed. The indicators affecting TCM syndromes were included in the disordered multivariate logistic regression analysis model to analyze the relative risk of the influencing factors.
*Results:* The syndromes of colorectal cancer patients were classified into excess syndrome, deficiency syndrome, and syndrome of intermingled deficiency & excess. The differences in total bilirubin (TBIL), hemoglobin (HB), uric acid (UA), and hematocrit (HCT) between the three groups were statistically significant ($P < 0.05$). The indexes such as TBIL, HB, UA, and HCT in preoperative patients with excess syndrome of colorectal cancer were higher than those in patients with syndrome of intermingled deficiency & excess and deficiency syndrome, and the comparison between groups using the LSD method showed that UA and HCT were different between the excess syndrome and deficiency syndrome groups ($P < 0.05$). Multivariate logistic regression analysis indicated that Gender, Tumor location, TNM stage, Total protein (TP), Red blood cell (RBC), HB, HCT, Platelet (PLT) and Fibrinogen (FIB) were all risk factors affecting TCM syndromes of preoperative colorectal cancer ($P < 0.05$).
*Conclusion:* There is a correlation between the TCM syndromes of colorectal cancer and the clinical laboratory indicators of the patients. Gender, Tumor location, TNM stage, TP, RBC, HB, HCT, PLT and FIB are the risk factors of TCM syndrome differentiation in preoperative patients with colorectal cancer. TBIL, UA, HB, and HCT may be the four relevant indicators of TCM syndrome differentiation in colorectal cancer.

## 1. Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors, and its incidence ranks third among malignant tumors and the mortality rate ranks second worldwide [1]. In 2020, the number of newly diagnosed colorectal cancer cases in China accounted for 28.8% of the new cases of colorectal cancer worldwide, and colorectal cancer-related deaths accounted for 30.6% of colorectal cancer-related deaths worldwide [2]. With the change of economy and dietary habits, the incidence of colorectal

cancer in China is increasing year by year. The standard treatment for colorectal cancer has been a combination of surgery, radiotherapy and chemotherapy. However, these treatments have obvious limitations. So far, the treatment effect is still unsatisfactory, which also prompts researchers to shift their treatment ideas to explore newer and more comprehensive treatments, such as immunotherapy and integrated Chinese and Western medicine treatment, etc. [3, 4].

In the treatment of colorectal cancer, TCM can help enhance the patients' immunity, and revere drug resistance, reduce toxicity and side

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* Corresponding author.
  *E-mail address:* gaof968@163.com (F. Gao).

effects of chemoradiotherapy, as well as improve the patients' sensitivity to chemoradiotherapy [5, 6]. TCM has also been widely used as adjuvant therapy in clinical practice. Under the guidance of the basic theory of TCM, the core principles of TCM treatment are syndrome differentiation and holistic concept, with syndrome differentiation as the first priority. TCM syndrome types are pathological generalizations of a certain stage of the disease, and the different syndrome types also reflect the different pathological generalizations of the current stage (including etiology, disease nature, physical factors, etc.). TCM physicians use the four diagnostic methods (observing, listening, inquiring and pulse feeling) to distinguish and analyze the stage of the patient's condition and identify patient's TCM syndrome. This process is known as syndrome differentiation. According to TCM theory, patients of excess syndrome (ES) are always vigorous in vital Qi, thus having a better ability in resisting disease, enduring treatment and resulting in a better prognosis. On the contrary, due to the lack of vital Qi, patients of deficiency syndrome (DS) have a worse ability in resisting disease, enduring treatment and their prognosis are not as good as that of the patients of ES. The syndrome of intermingled deficiency & excess (SIDE) is between ES and DS. In clinical diagnosis and treatment, different TCM syndromes always imply the progression and prognosis of a disease. Therefore, the key to curing a disease is to differentiate TCM syndromes precisely. However, how to objectively classify colorectal cancer by TCM syndrome is the focus and difficulty of integration of traditional Chinese and Western medicine. The TCM individualized treatment relies on the subjective judgment, analysis and experience of a TCM doctor, which needs more objective indicators.

A series of studies have confirmed that there is a certain correlation between TCM syndrome types and pathological tissue, tumor index [7] and hemorheology [8] in postoperative colorectal cancer patients. However, there are few studies trying to demonstrate the correlation among Karnofsky score (KPS), liver and kidney function, routine blood tests and TCM syndrome types in preoperative patients with colorectal cancer. The KPS score reflects the patient's health status and ability to receive treatment. The higher the KPS score, the better the prognosis. Conversely, the lower the KPS score, the worse the patient's ability to receive treatment and prognosis. In brief, the KPS score reflects, in part, the clinical prognosis of patients with colorectal cancer. The research on TCM syndrome types after colorectal cancer surgery showed that the corresponding TCM DS is significantly increased, while the ES is significantly reduced [9, 10]. Therefore, in this study, the effect of surgery and chemotherapy on TCM syndrome types was excluded. Different preoperative TCM syndromes and some clinical laboratory indicators at the same period of 122 cases of colorectal cancer were analyzed to seek the relationship between TCM syndrome types and clinical laboratory indicators, aiming to carry out more accurate TCM clinical syndrome differentiation assisted by laboratory indicators.

## 2. Data and methods

### 2.1. Clinical data

From May 2020 to June 2021, 122 patients with a definite pathological diagnosis of colorectal cancer who visited the Department of Colorectal and Anal Surgery of the 940th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army were collected. Among them, there were 39 cases of colon cancer and 83 cases of rectal cancer. There were 74 males and 48 females, aged 33–89 years, with an average age of 66 years (Figure 1. A). Liver function, renal function, blood routine test and tumor indicators of the patients were as follows: fasting whole blood samples were taken in the morning of the second day after admission, which were sent to the Laboratory Department of the hospital for routine examination and submission. This research plan has been reviewed and approved by the Clinical Research Ethics Committee of the hospital (No.2020KYLL075).

### 2.2. Criteria inclusion and exclusion

#### 2.2.1. Criteria for inclusion

(1) Patients with primary colorectal cancer confirmed by pathological diagnosis.
(2) Patients who live in Northwest China for a long time.
(3) Patients who have not undergone surgery, neoadjuvant chemoradiotherapy, targeted therapy, etc.
(4) Patients who have been informed and have signed informed consent form.

#### 2.2.2. Criteria for exclusion

(1) Patients whose dialectical results could not be unified by three TCM physicians.
(2) Patients with severe chronic diseases.
(3) Patients who have used drugs affecting liver and kidney function in the past week.
(4) Patients undergoing blood transfusion therapy.

### 2.3. TCM syndrome differentiation

According to The Guidelines for TCM Diagnosis and Treatment of Tumor issued by China in 2008 [11], colorectal cancer is divided into six types of TCM syndromes: liver and kidney Yin deficiency syndrome (LKYDS), spleen deficiency and Qi stagnation syndrome (SDQSS), stasis and poison obstruction syndrome (SPOS), damp-heat syndrome (DHS),
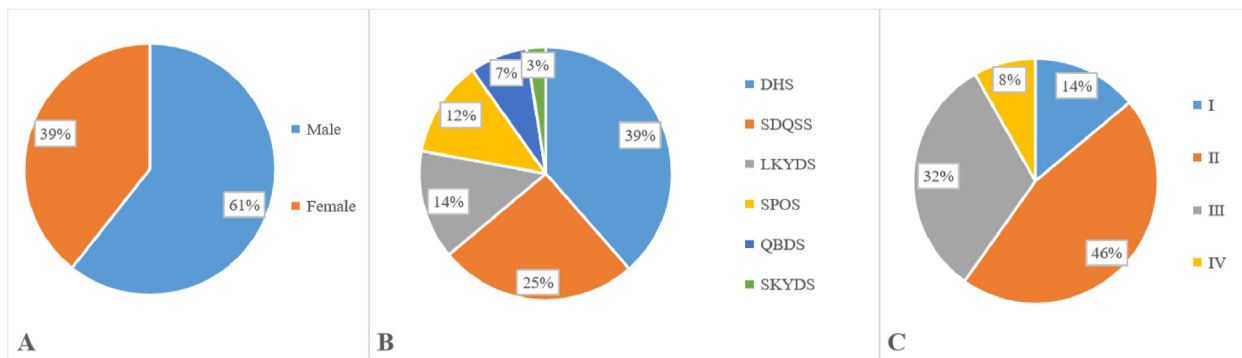


**Figure 1.** Basic data of 122 patients with preoperative colorectal cancer. Note: A shows the gender distribution of 122 patients with preoperative CRC, B shows the distribution of six types of traditional Chinese medicine in 122 patients with preoperative CRC, and C shows the TNM stage distribution of 122 patients with preoperative CRC. Abbreviation:LKYDS:liver-kidney Yin deficiency syndrome. SDQSS:spleen deficiency and Qi stagnation syndrome. SPOS:stasis and poison obstruction syndrome. DHS:damp-heat syndrome. QBDS:Qi and Blood deficiency syndrome. SKYDS:spleen-kidney Yang deficiency syndrome.

Qi and Blood deficiency syndrome (QBDS), and spleen-kidney Yang deficiency syndrome (SKYDS).

The TCM syndrome differentiation of all the included cases were identified by two associate chief physicians or above from the Department of TCM of the hospital. If their diagnoses were inconsistent, the TCM syndrome differentiation of the included cases was determined by another associate chief physician or above. In this way the TCM syndrome differentiation of the included cases was determined.

### 2.4. TCM syndrome grouping

According to the characteristics of TCM syndrome differentiation, 122 preoperative cases of colorectal cancer were divided into three groups: ES group (SPOS+DHS, 62 case), DS group (LKYDS+QBDS+-SKYDS, 29 cases), and SIDE group (SDQSS, 31 cases).

### 2.5. KPS grading

The patients' KPS was graded according to their physical health status: 100 to 80 points for grade 1 (n = 79), 70 to 50 points for grade 2 (n = 41), 40 to 30 points for grade 3 (n = 2) and ≤20 points for grade 4 (n = 0).

### 2.6. Statistical analysis

All the data were analyzed by SPSS 25.0. Kruskal-Wallis H test was used for analysis between KPS grade and three groups of syndromes. Analysis of variance was used when measurement data met normal distribution, and the rank-sum test was used when they did not meet normal distribution. The $\chi^2$ test was used for statistical analysis of enumeration data. The indicators with statistical differences in univariate analysis and the indicators affecting TCM syndrome were included in multivariate analysis, and disordered multi-classification logistic regression analysis was also performed. DS and SIDE was set as the reference term, with an adjusted entry probability of 0.10 and a removal probability of 0.15. $P <$ 0.05 was considered statistically significant.

## 3. Results

### 3.1. TCM syndrome distribution of preoperative colorectal cancer

Among 122 patients with colorectal cancer, DHS patients accounted for the highest proportion (39%, n = 47), followed by SDQSS and LKYDS (25%, n = 31) and (14%, n = 17). SPOS and QBDS patients accounted for a lower proportion (12%, n = 15) and (7%, n = 9). SKYDS patients accounted for the lowest proportion (3%, n = 3) (Figure 1B). Among all groups, ES accounted for the highest proportion (51%, n = 62), followed by SIDE (25%, n = 31) and DS (24%, n = 29).

### 3.2. Relationship between TCM syndrome types of preoperative colorectal cancer and KPS grading

The results showed that the Kruskal-Wallis H value was 47.752, $p <$ 0.001, indicating that the KPS score was significantly different among the three groups. When the KPS score of patients ranged from 100 to 80, ES was predominant, and when the KPS score of patients ranged from 70 to 50, SIDE was predominant. When the KPS score of the patients ranged from 40 to 30, DS was predominant (Table 1). The results showed that when patients physical health status was better, their TCM syndrome types tended to be ES.

### 3.3. Relationship between TCM syndrome of preoperative patients with colorectal cancer and clinical data and laboratory parameters

According to the above analysis, 122 patients with colorectal cancer were divided into three groups: ES group (n = 62), DS group (n = 29) and SIDE group (n = 31). The analysis results showed that there was no significant difference in tumor location, pathological type, presence of metastasis, and TNM stage among the three groups ($p >$ 0.05). The distribution of the TNM stage was most in stage II, accounting for 46%. This was followed by stage III, accounting for 32% (Figure 1C). It is worth noting that in the comparative analysis of gender among the three groups, there was a significant difference in gender distribution among ES, DS, and SIDE ($\chi2$ = 11.476, $p$ = 0.003) (Table 2).

The overall distribution of tumor biomarkers AFP, CEA, as well as CA-199, was not significantly different among the three groups ($p >$ 0.05). Coagulation parameters such as FIB and D-dimer were not significantly different among the three groups ($p >$ 0.05) (Table 3).

Secondly, the relationship between different TCM syndrome differentiation of colorectal cancer patients and clinical parameters such as liver and kidney function as well as blood routine was further explored (Table 4). The values of AST, ALT, ALP, UREA and PLT in liver and kidney function and blood routine were distributed as DS group > SIDE group > ES group, but the differences were not statistically significant ($p >$ 0.05). The overall distribution of TBIL and HB was significantly different among the three groups ($p <$ 0.05), and the distribution of both TBIL and HB among the three groups was ES group > SIDE group > DS group. We used HB levels (<135 g/L in men and <120 g/L in women) to determine the preoperative anemia of patients, 26 (42%) in the ES group, 15 (51%) in the DS group, and 13 (42%) in the SIDE group with preoperative anemia. Analysis of variance was performed for UA in the three groups. The results showed that F = 4.504, $p$ = 0.013, and the difference had statistical significance. The LSD method was used to compare the UA distribution between the ES group and the DS group ($p$ = 0.003). Analysis of variance was performed for HCT in the three groups. The results showed that F = 3.269, $p$ = 0.041, and the difference had statistical significance. The LSD method was used for comparison between the two groups, and the ES DS group had statistical significance compared with HCT ($p$ = 0.012). The distribution of UA and HCT among the three groups was ES group > SIDE group > DS group, and their differences between the ES and DS groups were statistically significant ($p <$ 0.05).

### 3.4. Multivariate logistic regression analysis

Finally, the laboratory indicators with statistical differences in univariate analysis and the laboratory indicators affecting TCM syndrome in the multivariate analysis equation were used for disordered multivariate logistic regression analysis. The included indexes included sex, tumor location, TNM stage, TP, RBC, HB, HCT, PLT and FIB. In regression analysis DS was set as the reference term and regression analysis between ES and DS revealed that gender, left colon cancer, TNM stage III and FIB became risk factors affecting TCM syndrome (Figure 2). Male patients

**Table 1.** Comparison of TCM KPS scores among three groups of colorectal cancer.

| KPS Grade | | TCM syndrome | | | H | P |
|---|---|---|---|---|---|---|
| | | Excess syndrome (n = 62) | Deficiency syndrome (n = 29) | Syndrome of intermingled deficiency & excess (n = 31) | | |
| KPS scores | Grade 1 | 46 (74.19%) | 19 (65.52%) | 14 (45.16%) | 47.752 | <0.001[a] |
| | Grade 2 | 16 (25.81%) | 8 (27.59%) | 17 (54.84%) | | |
| | Grade 3 | 0 (0%) | 2 (6.89%) | 0 (0%) | | |

[a] Kruskal-Wallis H test.

**Table 2.** Comparison of Clinical features of TCM syndromes among three groups of Colorectal Cancer.

| Clinical features | Clinical classification | Excess syndrome (n = 62) | Deficiency syndrome (n = 29) | Syndrome of intermingled deficiency & excess (n = 31) | P |
|---|---|---|---|---|---|
| Gender | Male (%) | 46 (74.19%) | 11 (37.93%) | 17 (54.84%) | 0.003[#] |
| | Female (%) | 16 (25.81%) | 18 (62.07%) | 14 (45.16%) | |
| Age | | 64.56 ± 11.32 | 64.97 ± 14.17 | 65.42 ± 11.90 | 0.888 |
| Lesion site | Left colon (%) | 9 (14.52%) | 3 (10.34%) | 10 (32.26%) | 0.125 |
| | Rectum (%) | 42 (67.74%) | 22 (75.86%) | 19 (61.29%) | |
| | Right colon (%) | 11 (17.74%) | 4 (13.80%) | 2 (6.45%) | |
| Pathological type | Medium differentiation (%) | 51 (82.26%) | 26 (89.66%) | 27 (87.09%) | 0.521 |
| | High differentiation (%) | 7 (11.29%) | 1 (3.44%) | 2 (6,45%) | |
| | Villous adenocarcinoma (%) | 0 (0%) | 0 (0%) | 1 (3.23%) | |
| | Low differentiation (%) | 4 (6.45%) | 2 (6.90%) | 1 (3.23%) | |
| TNM stage | I (%) | 11 (17.74%) | 4 (13.79%) | 2 (6.45%) | 0.411 |
| | II (%) | 25 (40.32%) | 12 (41.39%) | 19 (61.29%) | |
| | III (%) | 22 (35.49%) | 9 (31.03%) | 8 (25.81%) | |
| | IV (%) | 4 (6.45%) | 4 (13.79%) | 2 (6.45%) | |
| Metastasis | Y (%) | 26 (41.94%) | 13 (44.83%) | 10 (32.26%) | 0.563 |
| | N (%) | 36 (58.06%) | 16 (55.17%) | 21 (67.74%) | |

#: $\chi^2$ test.

(OR = 14.722), TNM stage III (OR = 19.098) and FIB (OR = 8.662) within the normal range were risk factors for increasing the ES. Left colon cancer (OR = 0.021) were the risk factor to increase DS.

Regression analysis between SIDE and DS revealed that gender and RBC became risk factors in TCM syndrome (Figure 3). Compared with female patients, male patients (OR = 9.504) were the risk factor to increase SIDE, and compared with RBC abnormalities, RBC (OR = 70.026) within the normal range was the risk factor to increase SIDE.

With SIDE as the reference term, regression analysis between ES and SIDE revealed that tumor location, TNM stage, TP, RBC, HB, HCT and PLT became risk factors affecting TCM syndrome (Figure 4). Left colon cancer (OR = 0.002) and laboratory parameters TP (OR = 0.095), RBC (OR = 0.011), and HCT (OR = 0.037) within the normal range were risk factors for increasing the SIDE, while TNM stage I (OR = 613.391), II (OR = 28.531), and III (OR = 28.314) and HB (OR = 15.782) and PLT (OR = 52.708) within the normal range were risk factors for increasing the ES.

## 4. Discussion

Syndrome differentiation is the primary principle in the diagnosis and treatment of diseases in TCM, and accurate syndrome differentiation is the basis of all treatments. The distribution of TCM syndromes of colorectal cancer is dominated by evidences such as blood stasis and dampness and heat in the early stage, both phlegm-dampness and qi deficiency in the middle stage, and DS in the late stage, including qi deficiency and blood deficiency [12]. In this study, we collected the clinical laboratory parameters and KPS score of 122 patients with preoperative colorectal cancer of different TCM syndromes and explored the relationship between the clinical parameters of preoperative patients with colorectal cancer and TCM syndrome.

**Table 3.** Comparison of tumor biomarkers and coagulation index of TCM syndromes among three groups of Colorectal Cancer.

| Clinical features | Excess syndrome | Deficiency syndrome | Syndrome of intermingled deficiency & excess | P |
|---|---|---|---|---|
| AFP | 2.50 ± 1.52 | 2.95 ± 1.68 | 2.86 ± 1.38 | 0.347 |
| CEA | 12.95 ± 27.62 | 35.84 ± 109.17 | 5.90 ± 8.00 | 0.621 |
| CA-199 | 303.20 ± 1495.71 | 24.27 ± 60.76 | 21.52 ± 46.68 | 0.521 |
| FIB | 3.14 ± 1.08 | 3.06 ± 0.74 | 3.50 ± 1.48 | 0.410 |
| D-Dimer | 0.69 ± 1.02 | 1.19 ± 2.23 | 0.44 ± 0.48 | 0.554 |

The results between TCM syndrome and KPS scores in the three groups of this study confirmed that when the KPS score is higher, the TCM syndrome types of patients tend to be ES. This result showed that patients may receive more thorough treatment and have a relatively better prognosis. When the KPS score is lower, the TCM syndrome types of patients tend to be DS, and their tolerance to treatment and prognosis may be poor. According to TCM theory, patients with DS have poor resistance to disease and prognosis due to the decline of vital Qi in the body, which is consistent with the statistical results between the three groups of syndromes and KPS scores.

The preliminary results showed that AST, ALT, ALP, and UREA had the highest distribution in DS, followed by the SIDE group, and ES had the lowest distribution. These results suggested that patients in the DS

**Table 4.** Comparison of the biochemical indicators of TCM syndromes among three groups of Colorectal Cancer.

| Clinical features | Excess syndrome (n = 62) | Deficiency syndrome (n = 29) | Syndrome of intermingled deficiency & excess (n = 31) | P |
|---|---|---|---|---|
| AST | 16.21 ± 4.46 | 22.83 ± 26.77 | 16.42 ± 7.92 | 0.647 |
| ALT | 15.56 ± 8.13 | 20.86 ± 25.38 | 16.35 ± 18.94 | 0.498 |
| TP | 63.55 ± 6.60 | 62.46 ± 6.93 | 64.41 ± 4.71 | 0.487 |
| ALB | 37.85 ± 3.34 | 36.34 ± 4.92 | 38.12 ± 3.06 | 0.125 |
| TBIL | 11.24 ± 5.17 | 8.40 ± 3.44 | 9.58 ± 4.39 | 0.023[b] |
| DBIL | 3.74 ± 1.90 | 3.03 ± 1.15 | 3.01 ± 1.36 | 0.099 |
| ALP | 73.85 ± 21.26 | 75.24 ± 24.63 | 80.41 ± 27.07 | 0.236 |
| GGT | 28.69 ± 28.34 | 30.17 ± 29.83 | 28.65 ± 31.36 | 0.660 |
| UREA | 5.73 ± 1.90 | 6.00 ± 2.69 | 5.77 ± 2.33 | 0.758 |
| CRE | 71.16 ± 14.90 | 65.28 ± 14.34 | 68.23 ± 11.90 | 0.147 |
| UA | 291.60 ± 79.13 | 243.17 ± 53.52 | 270.97 ± 72.60 | 0.013[c] |
| GFR | 90.22 ± 13.66 | 90.62 ± 13.23 | 90.03 ± 13.57 | 0.782 |
| WBC | 6.05 ± 1.87 | 5.91 ± 2.14 | 6.11 ± 2.12 | 0.657 |
| NEU% | 61.32 ± 11.43 | 60.34 ± 13.04 | 63.70 ± 14.08 | 0.138 |
| RBC | 4.44 ± 0.54 | 4.16 ± 0.60 | 4.38 ± 0.36 | 0.061 |
| HB | 130.80 ± 26.07 | 118.76 ± 21.77 | 126.71 ± 20.18 | 0.043[b] |
| HCT | 40.66 ± 7.01 | 36.99 ± 6.24 | 39.48 ± 5.06 | 0.041[c] |
| PLT | 198.68 ± 72.93 | 211.34 ± 71.37 | 216.77 ± 89.31 | 0.537 |

[b] The rank-sum test.
[c] Analysis of variance.
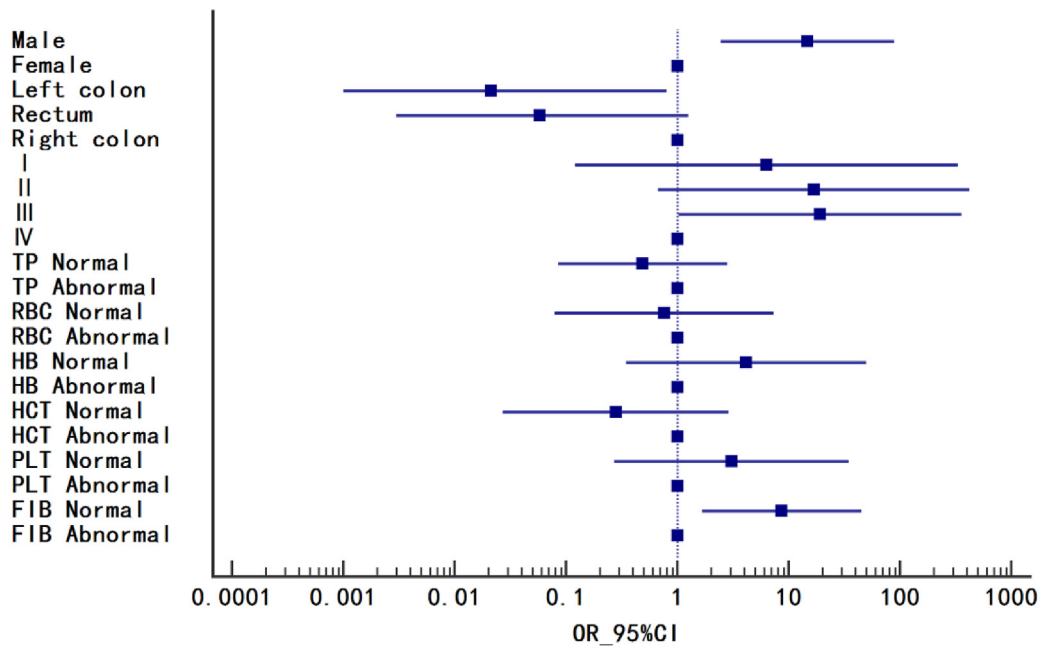
**Figure 2.** Forest Plot for ES *vs* DS Multivariate Regression Analysis. Abbreviation: ES:Excess Syndrome. DS:Deficiency Syndrome. I: TNM stage I. II: TNM stage II. III: TNM stage III. IV: TNM stage IV. TP: Total protein. RBC: Red blood cell. HB: hemoglobin. HCT: hematocrit. PLT: Platelet. FIB: Fibrinogen.
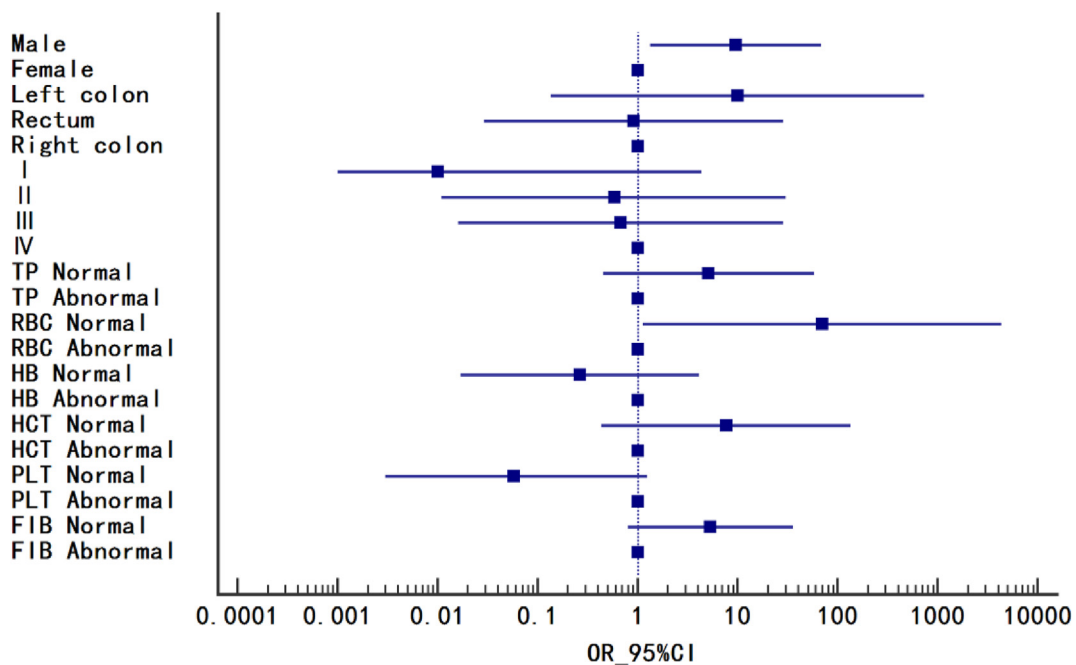


**Figure 3.** Forest Plot for SIDE *vs* DS Multivariate Regression Analysis. Abbreviation: SIDE:Syndrome of Intermingled deficiency & excess. DS:Deficiency Syndrome. I: TNM stage I. II: TNM stage II. III: TNM stage III. IV: TNM stage IV. TP: Total protein. RBC: Red blood cell. HB: hemoglobin. HCT: hematocrit. PLT: Platelet. FIB: Fibrinogen.

group might have poorer hepatic and renal function than those in the SIDE group and ES group.

Reports have confirmed that bilirubin has the properties of anti-inflammatory [13], anti-oxidation [14], and may prevent cancer and inhibit the proliferation of tumor cells by interfering with the extracellular signal-regulated kinase (ERK) pathway [15]. Studies on bilirubin and colorectal cancer have also confirmed that serum bilirubin levels are associated with the risk of colorectal cancer [16], risk of disease progression [17], postoperative complications and overall survival [18], and

clinical prognosis [19]. UA is the end product of the nucleotide metabolic cycle and has an antioxidant effect [20, 23]. A series of studies have shown that UA levels in patients are associated with the metastasis of colorectal cancer [20, 21], and UA could be used as a marker to assess tumor metastasis in patients with colorectal cancer [22]. Some reports have confirmed that high levels of UA are positively associated with the risk of colorectal cancer in men [23]. However, the effect of UA levels on colorectal cancer mortality have inconsistent results in relevant reports. Taghizadeh et al [24]. found that in a long-term study the level of UA was
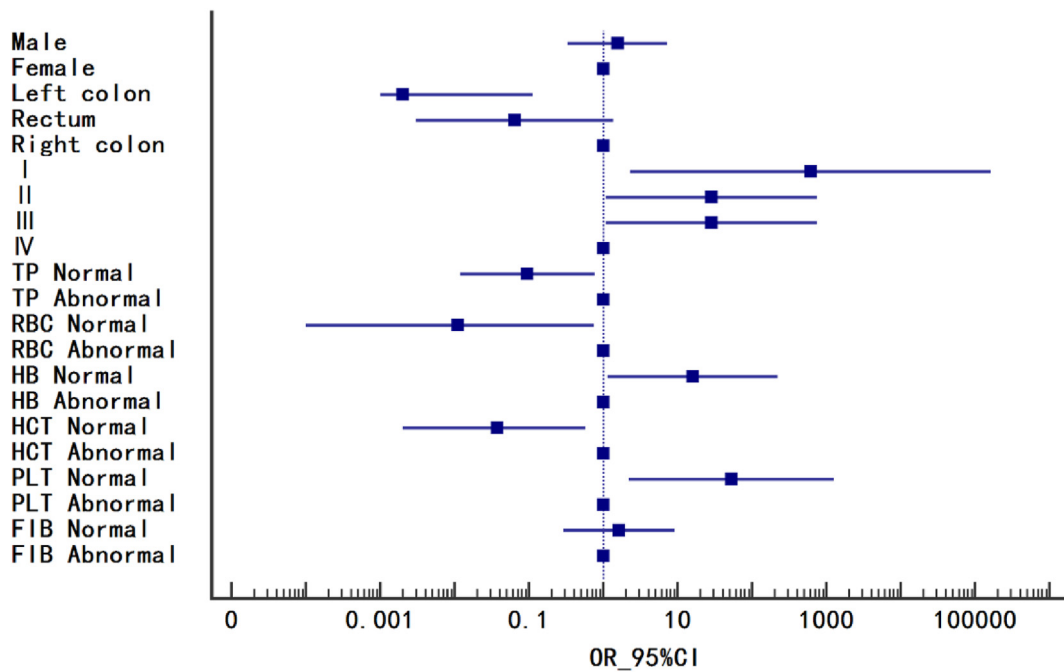
**Figure 4.** Forest Plot for ES *vs* SIDE Multivariate Regression Analysis. Abbreviation: ES:Excess Syndrome. SIDE:Syndrome of Intermingled deficiency & excess. I: TNM stage I. II: TNM stage II. III: TNM stage III. IV: TNM stage IV. TP: Total protein. RBC: Red blood cell. HB: hemoglobin. HCT: hematocrit. PLT: Platelet. FIB: Fibrinogen.

associated with a lower risk of death from colorectal cancer, and elevated serum uric acid levels might have a protective effect on patients with colorectal cancer. While studies by Üstüner et al [25]. showed that high levels of UA increased the mortality of colorectal cancer. Relevant literature has confirmed that TBIL is negatively correlated with the risk of colorectal cancer, but positively correlated with the risk of colorectal cancer progression [13, 16, 17]. The consistency results on the role of UA in the relevant literature suggest that UA is positively correlated with the risk of metastasis of colorectal cancer [20, 21, 22]. The high level distribution of TBIL and UA is associated with the early stage of colorectal cancer progression and easily promotes tumor metastasis. This result is similar to the understanding of colorectal cancer in TCM, and the distribution rule of TCM syndrome types of colorectal cancer confirms that the early TCM syndrome of colorectal cancer is mainly ES. Therefore, the high level distribution of TBIL and UA indicators may suggest that TCM syndromes in preoperative patients with colorectal cancer tend to be ES.

The occurrence of colorectal cancer is usually accompanied by varying degrees of anemia symptoms, and the incidence of anemia reaches 39.3% in newly diagnosed cases [26]. However, in this study, the preoperative anemia rate in patients with colorectal cancer was 44%. HB and HCT, as indicators to assess anemia in patients, have been reported to confirm that HB levels in patients with colorectal cancer are related to morbidity and mortality [27, 28], and can significantly improve the life quality of patients after surgery by iron supplementation [29]. The study by Cao et al [30]. found a significant correlation between HB and HCT parameters and KRAS gene mutations, and the HB and HCT parameters in the mutant group were lower than those in the wild-type group.

In this study, logistic regression analysis model was further used to explore the influencing indicators of preoperative TCM syndrome of colorectal cancer. The DS was set as the reference term. Compared with female patients, the risk of male patients suffering from ES and SIDE was 14.722 times and 9.504 times higher than that of female patients. The ES risk of patients with FIB indicators in the normal range was 8.622 times higher than that of patients with abnormal FIB indicators. Fib can be considered as a key determinant of tumor metastasis potential. The high level of Fib in peripheral blood pre-surgery predicts a poor prognosis for CRC patients [31, 32]. Compared with right colon cancer, patients with left colon cancer are more likely to be DS and SIDE. The SIDE was set as

the reference term. The results showed that the ES risk of colorectal cancer patients with TNM stage I, II and III was 613.391, 28.531 and 28.314 times of patients with TNM stage IV. The results are consistent with the development of colorectal cancer from ES to DS. TCM believes that the disease process of colorectal cancer develops from ES to DS [12]. The ES risk of patients with HB and PLT indicators in the normal range was 15.782 times and 52.708 times higher than that of patients with abnormal HB and PLT indicators. HB and PLT are used as indicators of anemia. Du [33] et al. have shown that with the progression of cancer, the spread of cancer cells can affect the production and growth of red blood cells in the body leading to anemia. The results showed that with the progression of the disease and the progression of TCM syndrome types from ES to SIDE or DS, the indicators of HB, PLT, RBC and other anemia ones will be reduced. In addition, the analysis revealed that TP, RBC and HCT parameters at normal values were ES protective factors. Zhang et al [34]. found that the incidence of anemia in patients with hypoproteinemia was significantly higher than that in patients with normal protein levels, and the occurrence of anemia in hypoproteinemia may be related to the poor nutritional status of patients. In the comparative analysis of DS and SIDE, it is found that the risk of SIDE was significantly higher in men than in women, and the risk of SIDE was significantly higher in RBC within the normal range than in RBC abnormalities. This is consistent with the results of studies by Du et al [33]. that is, female, clinical stage, low protein level and anti-tumor therapy were factors associated with the occurrence of anemia in solid tumors of the digestive tract. As indicators for evaluating anemia in patients, HB and HCT were statistically different in the correlation analysis between TCM syndrome and laboratory indicators and multivariate logistic regression analysis. In addition, the distribution of HB and HCT indicators in preoperative patients with colorectal cancer was consistent with the development rule of TCM syndrome. The results of multiple analyses confirmed that the decrease of HB and HCT indicators may make preoperative patients with colorectal cancer more likely to be with SIDE and DS.

Syndrome differentiation is not only the primary principle in TCM diagnosis and treatment of diseases, but also the premise of individualized TCM treatment. However, there is still a lack of TCM syndrome markers that can accurately differentiate syndromes In recent years,

more and more studies have made attempts to seek TCM syndrome differentiation markers. Lu et al [35]. found that there were significant differences in the distribution of cell subsets in the tumor microenvironment of colorectal cancer patients with different TCM syndromes. Goblet cells and fibroblasts subpopulations were the most distributed in ES, myeloid-monomacrophages, KRT 18 + cells, dendritic cells and MUC1+ cells subpopulations were the most distributed in DS, while CEACAM5 + cells subpopulation were mainly distributed in SIDE. Wang et al [36] found that there are significant differences in intestinal flora between patients with colorectal cancer of different TCM syndromes and healthy individuals. Compared with the healthy control group, Erysipelothrixd decreased and Lactobacillaceae increased in abundance in DS group. As a painless way of analysis, the results of gut microbiota analysis may be able to increase the accuracy of syndrome differentiation for TCM physicians. Sui et al [37] found that compared with DS, the high expression of mutant TP53, PCNA, PD-L1, Ki-67, CCL-2, IL-1a and COX-2 may be used as potential biomarkers for the diagnosis and prognosis of DHS colorectal cancer patients. The above findings may provide a basis for accurate TCM syndrome differentiation.

In this study, there was a statistically significant difference between the genders of patients with colorectal cancer, which may be related to the higher incidence of colorectal cancer in men than in women worldwide. The numerical distributions of TBIL, UA, HB, and HCT were statistically different, and their distributions among the three groups were all ES group > SIDE group > DS group. The results of multiple analyses confirmed that male patients, KPS score and TBIL, the increase of UA may make preoperative patients with colorectal cancer tend to be ES, while female patients, left colon cancer patients and KPS score and the decrease of HB and HCT may make preoperative patients with colorectal cancer tend to be SIDE and DS.

## 5. Conclusion

The aim of this study was to investigate the relationship between clinical indicators and TCM syndrome in preoperative patients with colorectal cancer. In this study, it is found that male patients, patients with high KPS scores, and the high-level distribution of TBIL and UA indicators in serum may be correlative indicators of TCM ES. It is also found that female patients, patients with low KPS score, left colon cancer patients, and the low-level distribution of HB and HCT indicators in serum may be correlative indicators of TCM SIDE or DS. These results are expected to provide a reference for accurate syndrome differentiation of clinical TCM physicians.

It has been reported that due to the effect of estrogen, the total bilirubin level in women is lower than that in men [15]. However, due to the small sample size and the number of ES male cases being much more than that of female cases, the results may be biased. In this study, in order to exclude the influence of regional diet and living habits on TCM syndrome, the collection of case sources is limited to Northwest China and does not exclude the influence of tumor metastasis on clinical laboratory parameters. In the future study, a larger sample size in different regions and multiple centers will be chosen and the influence of preoperative metastasis on clinical laboratory parameters will be excluded, which may more accurately reflect the relationship between clinical laboratory parameters and different TCM syndrome parameters in preoperative patients with colorectal cancer.

## Declarations

### Author contribution statement

Ya-nan Wang; Min Zou; Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Dou Wang: Conceived and designed the experiments; Analyzed and interpreted the data.

Zhi-kuan Zhang; Lian-ping Qu; Jing Xu; Cai-dong Shi: Performed the experiments.

Feng Gao: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

### Data availability statement

Data included in article/supp. material/referenced in article.

### Declaration of interest's statement

The authors declare no conflict of interest.

### Additional information

No additional information is available for this paper.

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