Original Article

# The association of serum folate and homocysteine on venous thromboembolism in patients with colorectal cancer: a cross-sectional study

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**Background:** Venous thromboembolism is a common complication in patients with colorectal cancer who exhibit high homocysteine and low folate levels. However, whether venous thrombosis is the result of a direct effect of folic acid or the presence of a homocysteine-mediated mediating effect cannot be determined. This study aimed to explore the association and mediating effects of serum folate and homocysteine on venous thromboembolism in patients with colorectal cancer.

**Methods:** This study included patients with colorectal cancer who were admitted to the First Hospital of Shanxi Medical University from May 2020 to May 2022. The patients' medical records were reviewed to collect information on general demographic characteristics, the prevalence of venous thromboembolism on admission, laboratory blood indices, serum folate, and serum homocysteine. SPSS 26.0 software was used for data collation and statistical analysis; the $\chi^2$ test was utilized for univariate analysis and unconditional logistic regression was applied for multivariate analysis. R 4.1.2 was used to perform the mediating effect test.

**Results:** A total of 236 colorectal cancer patients were investigated. The prevalence of colorectal cancer combined with venous thromboembolism was 15.3%; serum folate was <10.75 nmol/L in 25.4% of patients; and serum homocysteine was ≥22 μmol/L in 30.5% of patients. After controlling for confounding factors, the risk of venous thromboembolism was 2.48 times greater [95% confidence interval (CI): 1.04 to 5.94] in patients with low serum folate (<10.75 nmol/L) than in those with high serum folate (≥10.75 nmol/L). Also, the risk of venous thromboembolism was greater in those with high serum homocysteine (≥22 μmol/L) [odds ratio (OR) =2.99. 95% CI: 1.11 to 8.08]. The mediating effect test showed no direct effect of serum folate on venous thromboembolism combined with colorectal cancer, and a full mediating effect of serum homocysteine between serum folate and venous thromboembolism combined with colorectal cancer, with a mediating effect value of 0.002 and a total effect value of 0.0054.

**Conclusions:** Serum folate influences the formation of venous thromboembolism through serum homocysteine. It is recommended that the nutritional supplementation of patients be enhanced to control serum folate and serum homocysteine levels.

**Keywords:** Colorectal cancer; venous thromboembolism; folic acid; homocysteine; influencing factors

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## Introduction

There is a strong relationship between venous thromboembolism and tumours; it is a common complication in patients with tumours and an important predictor of death within 1 year of diagnosis (1). A study based on a large population sample showed that 20% of new cases of venous thromboembolism were associated with malignancy (2). In a prospective study, venous thromboembolism was also found to occur in approximately 8% of patients diagnosed with malignancy (3). Tumour type has a significant impact on the incidence of venous thromboembolism, with cancers of the gastrointestinal tract (such as colorectal cancer) having a greater risk of thrombosis than other slower-growing tumours (4-8).

Patients with colorectal cancer exhibit high serum homocysteine and low serum folate compared to the healthy population (9). A case-control study of colorectal cancer from New York University showed (10) that compared to the control group, serum folate was lower and serum homocysteine was higher in the case group. Homocysteine increases the production of reactive oxygen species, which form hydroxyl radicals that remove electrons from other molecules and induce subsequent oxidation of lipids, proteins, carbohydrates, and nucleic acids, leading to endothelial dysfunction and vascular wall damage, and eventually to platelet activation and thrombus formation (11-15).

### Highlight box

**Key findings**

- This cross-sectional study assessed the differences between patients with colorectal cancer combined with venous thromboembolism and those without. We found that folic acid influences the formation of venous thromboembolism via homocysteine and has a fully mediated effect.

**What is known and what is new?**

- Homocysteine is a risk factor for venous thrombosis and folic acid is a key factor in the homocysteine metabolic pathway.
- In this study, the effect of folic acid on venous thromboembolism was combined with the effect of homocysteine on venous thromboembolism, and a mediating effect of folic acid on venous thromboembolism was observed.

**What is the implication, and what should change now?**

- This study showed that there was a significant difference between folic acid and homocysteine in patients with and without venous thromboembolism and that folic acid mediated the effect of homocysteine on venous thromboembolism in patients with colorectal cancer.

Folic acid deficiency prevents the re-production of methionine, resulting in homocysteine accumulation in the body, and is a sensitive indicator of elevated homocysteine. As a link in the metabolic pathway of homocysteine methylation, approximately 50% of homocysteine is remethylated to form methionine, and folic acid completes the methyl cycle by providing methyl to homocysteine in the form of the coenzyme N-5-methyltetrahydrofolate catalyzed by vitamin B12-dependent enzymes and methionine synthase (16). In a case-control study of venous thromboembolism, plasma homocysteine concentrations were significantly different between the two groups and there was also a strong concentration-dependent association between folic acid and the risk of venous thromboembolism (17). However, whether venous thrombosis is the result of a direct effect of folic acid or the presence of a homocysteine-mediated mediating effect cannot be determined.

Previous studies (2-9) have focused on the incidence of venous thromboembolism in patients with multiple tumours or the difference between homocysteine in patients with venous thromboembolism and without tumours. However, reports on the difference in serum homocysteine and folic acid concentrations and their mediating effects in patients with colorectal cancer combined with venous thromboembolism are lacking. The current data supplement the research gap on the difference between folic acid and homocysteine in patients with venous thromboembolism with colorectal cancer, and provide a basis for folic acid supplementation in patients with clinical colorectal cancer complicated with venous thromboembolism. In this study, we investigated the differences between serum folate and homocysteine in patients with colorectal cancer combined with venous thromboembolism and in patients with colorectal cancer combined with homocysteine within 24 hours of admission and investigated the mediating effect of serum homocysteine and folate on colorectal cancer combined with venous thromboembolism to provide new ideas for the prevention of thrombosis in hospitalized colorectal cancer patients. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2839/rc).

## Methods

### *Study design and participants*

Data were obtained from colorectal cancer patients admitted to the Department of Gastrointestinal Surgery

of the First Hospital of Shanxi Medical University. The inclusion criteria were as follows: (I) age ≥18 years; (II) complete clinical history; (III) confirmed diagnosis of colorectal cancer on admission; (IV) diagnosis of venous thromboembolism on admission; and (V) no major surgery in the last 3 months of admission. The exclusion criteria were as follows: (I) patients with diseases related to abnormal coagulation function; (II) those taking anticoagulant drugs for a prolonged period; and (III) patients who had undergone chemotherapy.

A retrospective cross-sectional study was conducted using a highly trained investigator who reviewed the patients' medical records. The survey period was from May 2020 to May 2022. A total of 613 people were included in the study population, 377 were excluded, including 334 without folic acid or homocysteine indicators, 34 without venous thromboembolism diagnosis on admission, 4 with coagulation-related disorders, and 5 with chemotherapy. The general data collection included the following: gender, age, occupation, and family history of cancer. The patients' medical records were also collected, including the primary tumour location, tumour American Joint Committee on Cancer (AJCC) stage, tumour metastasis, combined with venous thromboembolism at 24 hours of admission (venous thromboembolism was confirmed by colour Doppler ultrasonography), combined with other chronic diseases (hypertension, hyperlipidaemia, cardiovascular disease, diabetes, anaemia, malnutrition), and nutrition-related information [nutrition risk screening-2002 (NRS-2002), body mass index (BMI)]. The following laboratory blood indicators were examined: serum folate, serum homocysteine, D-dimer, prothrombin time, activated partial thromboplastin time, thrombin time, prothrombin time activity, international standard ratio of prothrombin time, haemoglobin, platelet count, red blood cell count, white blood cell count, total protein, and albumin. Subject operating characteristic curves for the laboratory blood markers of patients at admission were plotted to determine the optimal cut-off values, which were used for grouping. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of First Hospital of Shanxi Medical University (No. SK014), and informed consent was taken from all the patients.

### *Statistical analysis*

IBM SPSS Statistics software (version 26.0) was used for data collation and statistical analysis. The $\chi^2$ test was used for one-way analysis and unconditional logistic regression was applied for multi-way analysis. The bias-corrected percentile Bootstrap method was used to test for mediating effects (1,000 replicate samples) and the mediation function of R 4.1.2 was employed to estimate the direct effect (ADE), indirect effect (ACME), and total effect (Total Effect). The test level was set to $\alpha$=0.05, and the test was two-sided. The unconditional logistics regression model was used to assess the odds ratio (OR) and 95% confidence interval (CI) for folic acid to homocysteine in patients with and without venous thromboembolic colorectal cancer.

Model included gender, age, family history of cancer, cancer stage, whether metastatic, comorbid chronic diseases (hypertension, hyperlipidaemia, sexual cerebrovascular disease, diabetes, anaemia), body mass index (BMI), nutrition risk screening-2002 (NRS-2002), D-dimer, prothrombin time, activated partial thromboplastin time, prothrombin time, haemoglobin, platelet count, red blood cell count, white blood cell count, total protein, and albumin.

## Results

A total of 236 patients with colorectal cancer were included in this study, with a male-to-female ratio of 1.11:1 and a mean age of (65.39±11.55) years. Among these patients, 40.7% (96/236) were retired; 40.7% (96/236) had a primary location in the rectum, 57.6% (136/236) had a stage III tumor; 45.8% (108/236) were combined with High blood pressure; 39.0% (92/236) were combined with anaemia; 86.4% (204/236) had an NRS-2002 ≥3; and 44.1% (104/236) had a BMI ≥24 kg/m$^2$ (see *Table 1*, *Figure 1*).

The prevalence of combined venous thromboembolism in colorectal cancer was 15.3% (36/236), serum folate was <10.75 nmol/L in 25.4% (60/236), and serum homocysteine was ≥22 μmol/L in 30.5% (72/236). Univariate analysis of colorectal cancer combined with venous thromboembolism showed that the differences in occupation, tumour stage, hypertension, diabetes mellitus, anaemia, nutrition risk screening-2002 (NRS-2002), body mass index (BMI), serum folate, serum homocysteine, D-dimer, Prothrombin time, Haemoglobin, Red blood cell count, Total protein, and White blood cell count were statistically significant (see *Table 1*).

### *Multivariate analysis*

Using colorectal cancer combined with venous

 

**Table 1** Univariate analysis of combined venous thromboembolism in patients with colorectal cancer

| Factors | Total | Combined venous thromboembolism | | $\chi^2$ value | P value |
|---|---|---|---|---|---|
| | | Yes (n=36) | No (n=200) | | |
| Gender | | | | 1.117 | 0.291 |
| Male | 124 (52.5) | 16 (44.4) | 108 (54.0) | | |
| Female | 112 (47.5) | 20 (55.6) | 92 (46.0) | | |
| Age (years) | | | | 0.230 | 0.632 |
| <60 | 60 (25.4) | 8 (22.2) | 52 (26.0) | | |
| ≥60 | 176 (74.6) | 28 (77.8) | 148 (74.0) | | |
| Occupation | | | | 15.056 | 0.001 |
| Farmers | 68 (28.8) | 20 (55.6) | 48 (24.0) | | |
| Retirement | 96 (40.7) | 8 (22.2) | 88 (44.0) | | |
| Other | 72 (30.5) | 8 (22.2) | 64 (32.0) | | |
| Family history of cancer | | | | – | 0.222[a] |
| Yes | 12 (5.1) | 0 (0.0) | 12 (6.0) | | |
| None | 224 (94.9) | 36 (100.0) | 188 (94.0) | | |
| Original location | | | | 2.280 | 0.516 |
| Rectum | 96 (40.7) | 16 (44.4) | 80 (40.0) | | |
| Left hemi-colon | 52 (22.0) | 8 (22.2) | 44 (22.0) | | |
| Right hemicolectomy | 72 (30.5) | 8 (22.2) | 64 (32.0) | | |
| Other | 16 (6.8) | 14 (11.1) | 12 (6.0) | | |
| Tumour staging | | | | – | 0.015[a] |
| Period I | 20 (8.5) | 0 (0.0) | 20 (10.0) | | |
| Period II | 64 (27.1) | 8 (22.2) | 56 (28.0) | | |
| Phase III | 136 (57.6) | 28 (77.8) | 108 (54.0) | | |
| Phase IV | 16 (6.8) | 0 (0.0) | 16 (8.0) | | |
| Transfer or not | | | | 1.595 | 0.207 |
| Yes | 36 (15.3) | 8 (22.2) | 28 (14.0) | | |
| No | 200 (84.7) | 28 (77.8) | 172 (86.0) | | |
| High blood pressure | | | | 9.484 | 0.002 |
| Yes | 108 (45.8) | 8 (22.2) | 100 (50.0) | | |
| No | 128 (54.2) | 28 (77.8) | 100 (50.0) | | |
| Hyperlipidaemia | | | | – | 0.141[a] |
| Yes | 16 (6.8) | 0 (0.0) | 16 (8.0) | | |
| No | 220 (93.2) | 36 (100.0) | 184 (92.0) | | |
| Cardiovascular diseases | | | | 0.533 | 0.465 |
| Yes | 92 (39.0) | 16 (44.4) | 76 (38.0) | | |
| No | 144 (61.0) | 20 (55.6) | 124 (62.0) | | |

**Table 1** *(continued)*

**Table 1** *(continued)*

| Factors | Total | Combined venous thromboembolism | | $\chi^2$ value | P value |
|---|---|---|---|---|---|
| | | Yes (n=36) | No (n=200) | | |
| Diabetes | | | | 7.646 | 0.006 |
| Yes | 36 (15.3) | 0 (0.0) | 36 (18.0) | | |
| No | 200 (84.7) | 36 (100.0) | 164 (82.0) | | |
| Anemia | | | | 13.687 | <0.001 |
| Yes | 92 (39.0) | 24 (66.7) | 68 (34.0) | | |
| No | 144 (61.0) | 12 (33.3) | 132 (66.0) | | |
| Malnutrition | | | | 0.002 | 0.961 |
| Yes | 104 (44.1) | 16 (44.4) | 88 (44.0) | | |
| No | 132 (55.9) | 20 (55.6) | 112 (56.0) | | |
| BMI (kg/m$^2$) | | | | 17.106 | <0.001 |
| ≤18.4 | 16 (6.7) | 8 (22.2) | 8 (4.0) | | |
| >18.4, <24 | 116 (49.2) | 12 (33.3) | 104 (52.0) | | |
| ≥24 | 104 (44.1) | 16 (44.4) | 88 (44.0) | | |
| NRS-2002(points) | | | | 6.664 | 0.010 |
| <3 | 32 (13.6) | 0 (0.0) | 32 (16.0) | | |
| ≥3 | 204 (86.4) | 32 (100.0) | 168 (84.0) | | |
| Serum folate (nmol/L) | | | | 20.342 | <0.001 |
| <10.75 | 60 (25.4) | 20 (55.6) | 40 (20.0) | | |
| ≥10.75 | 176 (74.6) | 16 (44.4) | 160 (80.0) | | |
| Serum homocysteine (μmol/L) | | | | 26.197 | <0.001 |
| <22 | 164 (69.5) | 12 (33.3) | 152 (76.0) | | |
| ≥22 | 72 (30.5) | 24 (66.7) | 48 (24.0) | | |
| D-Dimer [mg/L (FEU)] | | | | 7.064 | 0.008 |
| ≥243 | 100 (42.4) | 8 (22.2) | 92 (46.0) | | |
| <243 | 136 (57.6) | 28 (77.8) | 108 (54.0) | | |
| Prothrombin time (s) | | | | – | 0.006[a] |
| ≤11.5 | 32 (13.6) | 0 (0.0) | 32 (16.0) | | |
| >11.5 | 204 (86.4) | 36 (100.0) | 168 (84.0) | | |
| Activated partial thromboplastin time (s) | | | | 2.165 | 0.141 |
| ≤25.1 | 56 (23.7) | 12 (33.3) | 44 (22.0) | | |
| >25.1 | 180 (76.3) | 24 (66.7) | 156 (78.0) | | |
| Prothrombin time (s) | | | | 2.109 | 0.146 |
| ≥16.6 | 80 (33.9) | 16 (44.4) | 64 (32.0) | | |
| <16.6 | 156 (66.1) | 20 (55.6) | 136 (68.0) | | |

**Table 1** *(continued)*

**Table 1** *(continued)*

| Factors | Total | Combined venous thromboembolism | | $\chi^2$ value | P value |
|---|---|---|---|---|---|
| | | Yes (n=36) | No (n=200) | | |
| Prothrombin time activity (%) | | | | – | 0.769 |
| ≥130 | 24 (10.2) | 4 (11.1) | 20 (10.0) | | |
| <130 | 212 (89.8) | 32 (88.9) | 180 (90.0) | | |
| International standard ratio for prothrombin time | | | | – | 0.222[a] |
| ≤0.85 | 12 (5.1) | 0 (0.0) | 12 (6.0) | | |
| >0.85 | 224 (94.9) | 36 (100.0) | 188 (94.0) | | |
| Haemoglobin (g/L) | | | | 6.490 | 0.011 |
| <130 | 168 (71.2) | 32 (88.9) | 136 (68.0) | | |
| >130 | 68 (28.8) | 4 (11.1) | 64 (32.0) | | |
| Platelet count ($10^9$/L) | | | | 1.589 | 0.207 |
| >350 | 44 (18.6) | 4 (11.1) | 40 (20.0) | | |
| <350 | 192 (81.4) | 32 (88.9) | 160 (80.0) | | |
| Red blood cell count ($10^{12}$/L) | | | | 4.590 | 0.032 |
| <4.3 | 176 (74.6) | 32 (88.9) | 144 (72.0) | | |
| >4.3 | 60 (25.4) | 4 (11.1) | 56 (28.0) | | |
| Total protein (g/L) | | | | 8.106 | 0.004 |
| <60 | 60 (25.4) | 16 (44.4) | 44 (22.0) | | |
| >60 | 176 (74.6) | 20 (55.6) | 156 (78.0) | | |
| Albumin (g/L) | | | | 2.950 | 0.086 |
| ≤40 | 184 (78.0) | 32 (88.9) | 152 (76.0) | | |
| >40 | 52 (22.0) | 4 (11.1) | 48 (24.0) | | |
| White blood cell count ($10^9$/L) | | | | 32.516 | <0.001 |
| ≥4.25 | 188 (79.7) | 16 (44.4) | 172 (86.0) | | |
| <4.25 | 48 (20.3) | 20 (55.6) | 28 (14.0) | | |

Data are shown as n (%). [a], Calculated using Fisher's exact probability method. BMI, body mass index; NRS-2002, nutrition risk screening-2002. In parentheses is the percentage of the value.

thromboembolism as the dependent variable, an unconditional logistic regression model was established, and univariate analysis was performed to screen statistically significant independent variables and to aggregate experience with relevant literature. The results showed that the risk of combined venous thromboembolism in patients with serum folate <10.75 nmol/L was 2.48 times higher [95% confidence interval (CI): 1.04 to 5.94] and the risk of combined venous thromboembolism was 2.99 times higher (95% CI: 1.11 to 8.08) in patients with serum homocysteine ≥22 μmol/L than in patients with serum homocysteine <22 μmol/L (see *Table 2*).

### *Mediating effects analysis*

Mediating effects were tested using the bias-corrected percentile Bootstrap method (1,000 replicate samples), with the 95% CI not including 0 indicating a significant mediating effect. The results showed that there was no direct effect of serum folate on the occurrence of venous thromboembolism in colorectal cancer, and there was a full mediating effect of serum homocysteine between folate and

 

venous thromboembolism combined with colorectal cancer, with a mediating effect value of 0.002 and a total effect value of 0.0054. Also, the mediating effect accounted for 37.0% of the total effect (see *Table 3*, *Figure 2*).

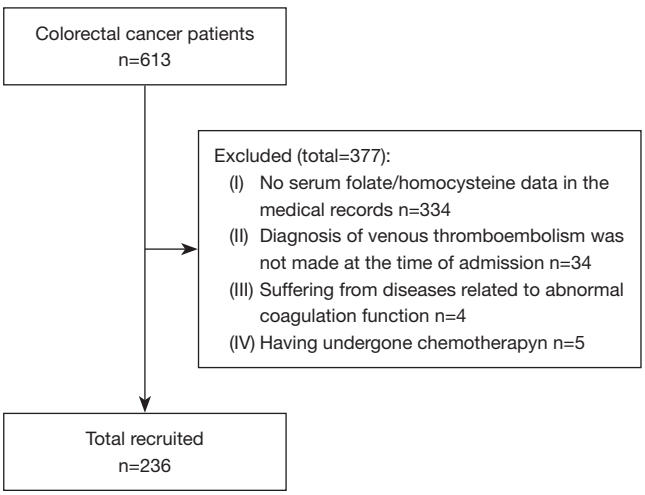


**Figure 1** Study participants.

## Discussion

Patients with colorectal cancer combined with venous thromboembolism often have lower serum folate and higher homocysteine. A study (18) evaluating hyperhomocysteinemia combined with deep vein thrombosis showed that 15.0% of patients had hyperhomocysteinemia and 43.3% had low folic acid levels. A case-control study (9) of colorectal cancer showed that there were significant differences in serum folate and serum homocysteine in both case groups. In this study, 55.6% (20/36) of patients with combined venous thromboembolism had low serum folate, 66.7% (24/36) had high homocysteine levels, and 33.3% (12/36) had both serum folate and homocysteine outside the normal range, suggesting that patients with colorectal cancer combined with venous thromboembolism are more likely to be folate deficient and have high serum homocysteine. The tumour-related features included tumour-related characteristics that were significantly different between the two groups, with stage III patients being more likely to have venous thromboembolism, which is a previous retrospective study (19). Also, blood

**Table 2** Multi-factor logistic regression analysis of combined venous thrombosis in patients with colorectal cancer

| Variables | β | $S_{\bar{\chi}}$ | Wald $\chi^2$ | P value | OR (95% CI) | aOR value (95% CI)[a] |
|---|---|---|---|---|---|---|
| Serum folate (nmol/L) | | | | | | |
| <10.75 | 1.372 | 0.401 | 11.717 | 0.001 | 3.95 (1.80–8.66) | 2.48 (1.04–5.94) |
| ≥10.75 | | | | | 1.00 | |
| Serum homocysteine (μmol/L) | | | | | | |
| ≥22 | 1.659 | 0.404 | 16.870 | 0.000 | 5.25 (2.38–11.59) | 2.99 (1.11–8.08) |
| <22 | | | | | 1.00 | |
| Constant term | –2.954 | 0.349 | 71.745 | 0.000 | | |

Only variables with statistically significant results are listed in the table; Adjustment factors included gender, age, family history of cancer, cancer stage, whether metastatic, comorbid chronic diseases (hypertension, hyperlipidaemia, sexual cerebrovascular disease, diabetes, anaemia), body mass index (BMI), nutrition risk screening-2002 (NRS-2002), D-dimer, prothrombin time, activated partial thromboplastin time, prothrombin time, haemoglobin, platelet count, red blood cell count, white blood cell count, total protein, and albumin. aOR, adjustment odds ratio; CI, confidence intervals; OR, odds ratio.

**Table 3** Analysis of serum homocysteine in serum folate and the mediating effect of combined venous thromboembolism in colorectal cancer

| Effect | Effect value | Boot 95% CI | P value |
|---|---|---|---|
| Direct effects | –0.0034 | –0.011–0.000 | 0.18 |
| Indirect effects | –0.0020 | –0.0037–0.0000 | <0.001 |
| Total effect | –0.0054 | –0.0142–0.0000 | 0.02 |

CI, confidence intervals.

 

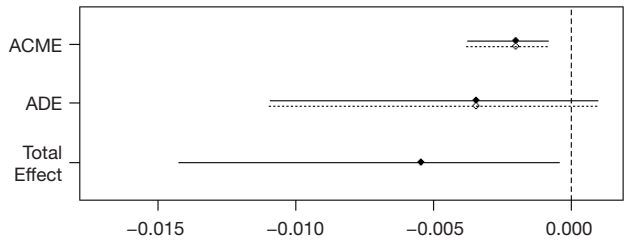


**Figure 2** The mediated effect and 95% CI test results of homocysteine in folic acid and combined thromboembolism with rectal cancer. ACME, indirect effect; ADE, direct effect; Total Effect, total effect in the graph; CI, confidence intervals.

parameters such as D-dimer and leukocyte count were markedly different between the two groups, and D-dimer and leukocyte count were included in the risk model to predict the risk of combined venous thromboembolism in oncology patients (20).

Homocysteine is a sulphur-containing amino acid that is used in the remethylation pathway to produce methionine (21). Folic acid, as part of the remethylation pathway, provides sufficient N-5-methyltetrahydrofolate to ensure the smooth production of methionine from homocysteine (22). If folate levels are too low, homocysteine can accumulate and increase in the body, and the free thiol group of homocysteine produces oxidative stress and activates platelets. This leads to endothelial dysfunction and vessel wall damage, resulting in thrombosis. Homocysteine can also cause protein homocysteinylation by forming amine bonds with lysine residues, altering the structure and function of proteins, and causing protein damage through thiol radical mechanisms, leading to thrombosis (23-26). The logistic regression results from this study showed that, after adjustment, the risk of combined venous thromboembolism was 2.99 times higher in patients with serum homocysteine ≥22 μmol/L than in those with serum homocysteine <22 μmol/L (95% CI: 1.11 to 8.08). A previous French case-control study (27) showed that patients with hyperhomocysteine (>15 μmol/L) had a 1.48 times higher risk of venous thromboembolism compared with normal homocysteine patients. Another meta-study showed that hyperhomocysteine with low serum folate (≤4.9 nmol/L) (OR =3.14) was a risk factor for venous thromboembolism formation (28). The risk of combined venous thromboembolism in colorectal cancer patients with serum folate <10.75 nmol/L in this study was 2.48 times (95% CI: 1.04–5.94) higher than in patients with serum folate ≥10.75 nmol/L, indicating that homocysteine and low serum folate are independent risk factors for combined venous thromboembolism in colorectal cancer.

The results of this study also showed that folic acid did not directly affect venous thromboembolism in patients with colorectal cancer but indirectly affected venous thromboembolism through a homocysteine-mediated full mediating effect. It is suggested that the effect of folic acid on venous thromboembolism is mediated through the homocysteine remethylation pathway to achieve the effect on venous thromboembolism (29,30). Moreover, our findings demonstrated that the prevalence of venous thromboembolism combined with colorectal cancer was 15.3% (36/236), with 33.3% (12/36) of patients with combined venous thromboembolism having both high homocysteine and low folate. Furthermore, we observed that the prevalence of venous thrombosis was slightly higher than in previous studies (31,32), possibly due to the indirect effect of folate on venous thromboembolism through a homocysteine-mediated fully mediated effect. The prevalence of venous thrombosis in colorectal cancer patients was increased due to the indirect effect of folic acid on the occurrence of venous thrombosis through homocysteine-mediated complete mediation.

In summary, serum folate and serum homocysteine are independent risk factors for venous thromboembolism combined with colorectal cancer, and folate affects venous thromboembolism through a fully mediated effect (via homocysteine). Therefore, it is recommended that clinicians strengthen patients' nutritional supplementation, control serum folate and serum homocysteine levels, or administer appropriate folate supplementation and observe changes in homocysteine levels. This study provides further theoretical support for the application of folate in the prevention and treatment of venous thromboembolism.

### *Limitations*

This was is a single-center study and there are limitations in terms of the representativeness of the population. Also, the possible role of vitamin B12 as a coenzyme of the homocysteine metabolic pathway in modulating the mediating effect was not addressed in this study. In future studies, the relationship between serum folate and homocysteine and preoperative/postoperative venous thromboembolism in patients with colorectal cancer will be further investigated in a large multicenter sample.

 

## Conclusions

There are differences in serum folic acid and homocysteine between patients with colorectal cancer complicated with venous thromboembolism and those without concomitant, and the complete mediating effect of folic acid mediated by homocysteine affects venous thromboembolism. This may be more conducive to reducing the complications of venous thromboembolism in colorectal cancer patients, and provide a basis for the use of folic acid in venous thrombosis in colorectal cancer patients in the future.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2839/rc

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of First Hospital of Shanxi Medical University (No. SK014), and informed consent was taken from all the patients.



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