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Original Article

Clinical and prognostic significance of hypercoagulability in patients with metastatic colorectal cancer

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Abstract: The relationship between hypercoagulation and malignant solid tumors has been reported in previous studies. The current study aimed to explore association between hypercoagulation, clinicopathological features, and prognosis in metastatic colorectal cancer (mCRC) patients. Coagulation index data was collected from 153 metastatic colorectal cancer patients. Of these patients, 113 cases (73.86%) were detected with blood hypercoagulation. Hypercoagulation was much more frequent in patients aged ≥ 60 years, ECOG=2 points, those that smoked and drank, and number of metastatic sites > 2 ($P < 0.01$). Survival analysis suggested hypercoagulation as a significant prognostic factor in both overall survival (OS, P=0.0291) and time to recurrence (TTR, P=0.0305). After adjusting for competing risk factors, hypercoagulation and number of metastatic sites > 2 remained independent predictors of OS (HR: 1.621, 95% CI: 1.167-3.158, P=0.021) and time to recurrence (HR: 1.486, 95% CI: 1.294-3.627, P=0.015). In conclusion, results showed that blood hypercoagulation was frequent in patients with mCRC. Different clinical features were associated with hypercoagulation. Moreover, hypercoagulation was shown to be an independent predictor of OS and TTR.

Keywords: Hypercoagulability, colorectal cancer, tumor metastasis

Introduction

Hypercoagulation and increased risks of venous thromboembolic events (VTE) in cancer patients have been reported in previous studies [1, 2]. Since the 1980s, the phenomenon of a comorbidity between blood hypercoagulation and malignant solid tumors has been increasingly investigated [3-5]. Although specific mechanisms remain elusive, the association between tumor characteristics and hypercoagulation has been reported. Prospective clinical studies have shown that patients with cancers have a 4.1-fold risk of thrombosis, compared to healthy patients [6]. Based on the results of "Khorana scores", developed to assess the risk of VTE in cancer patients, pancreatic, gastric, and brain cancers, many tumors have been categorized with very high risk of VTE. Lung, lymphomas, and gynecologic cancers have shown a high risk. Breast and colorectal cancers have shown the lowest risk of VTE [7, 8].

Several mechanisms have been reported to contribute to cancer-associated hypercoagulation, including overexpression of mucins by tumor cells and the activation of some oncogenes [9, 10]. However, results have suggested that cancer-associated hypercoagulation was dependent on immune cells, such as tumor associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and tumor related neutrophils in the tumor microenvironment (TME). More recently, neutrophil extracellular traps (NETs) released from activated neutrophils were found to be closely related to hypercoagulation [11-13]. Moreover, previous studies have suggested that another potential modulator of the coagulation cascade was the key sentinel of innate immunity [14, 15]. Although much progress has been made in understanding the causes of cancer-associated hypercoagulation, the heterogeneity of causative mechanisms still poses a considerable challenge to the application of effective preventive and therapeutic strategies.

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in the world [16, 17]. Colorectal cancer mortality has decreased by 39% in United States in the past two decades. This is due to early detection of the disease, as well as better access to colonoscopy procedures and new treatments [18]. Approximately 50% of patients with CRC will develop liver metastases during their lifetime. This is the most insidious aspect of cancer and the leading cause of CRC-related deaths [19]. The mechanisms behind cancer cell metastasis remain unclear. However, accumulating data has suggested that increased expression of adhesion molecules are critical components of tumor cells spreading to distant organs [20]. The present study explored association between hypercoagulation, clinicopathological features, and prognosis in metastatic colorectal cancer (mCRC) patients. This study aimed to provide new approaches for diagnostic and prognostic evaluation of mCRC.

Patients and methods

Patients

A total of 153 patients, diagnosed with mCRC, were collected in the General Hospital of the Beijing Military Region, from September 2012 to December 2016. Recorded data included gender, age, pathology, tumor stage, alcohol and tobacco habits, complications (high blood pressure, coronary heart disease, diabetes, hyperlipidemia), coagulation index, plasma prothrombin time (PT), activated partial thromboplastin time (activated partial thromboplastin time, APTT), platelets (PLT), fibrinogen (FIB), and D-dimer (D-dimmer, DD). For the 153 patients with mCRC, treatment response was evaluated after 4 cycles of chemotherapy. This study was approved by the Regional Ethical Review Boards for General Hospital of the Beijing Military Region. Patients were treated according to principles of the Declaration of Helsinki for medical research involving human subjects. All patients provided informed written consent prior to study entry.

Coagulation index determination

Fasting venous blood was collected 3-5 mL in the morning. Next, 10^9 mol/L sodium citrate 0.3 mL was mixed thoroughly and centrifuged at 3,000 r/min for 15 minutes. The plasma was ready for use. An ACL TOP automatic coagulation analyzer was used within 2 hours (US Instrumentation Laboratory Company). PT, APTT, FIB, and DD indicators were also used (United States Instrumentation Laboratory Company company).

Determination of platelet parameters

The patients were enrolled in the morning and fasted. Next, 3-5 mL of venous blood was collected and mixed well with the EDTA-K anticoagulant tube. It was applied using the XE-2100 automatic blood analyzer within 2 hours (SYSMEX CORPORATION, USA), detecting PLT indicators.

Criteria for determination of hypercoagulability

PT: 11.8~17.6 seconds, shortening > 3 seconds was abnormal; APTT: 25.1~36.5 seconds, shortening > 3 seconds was abnormal; PLT: (100~300) * 10^9/L, > 300 * 10^9/L was abnormal; FIB: 2~4 g/L, > 4 g/L was abnormal; DD: 0~0.3 mg/L, > 0.3 mg/L was abnormal. One or more abnormalities indicated hypercoagulation.

Statistical analysis

Student's t-tests were used for comparison of variables showing normal distribution. Mann Whitney U-tests were employed for comparisons of variables not showing normal distribution within qualitative data. Pearson's Chi-Square tests, Fisher's exact tests, and Yates Continuity Correction tests were used for comparisons of qualitative data. Kaplan-Meier survival analysis and log-rank tests were used for evaluation of survival. Overall survival (OS) and time to recurrence (TTR) were chosen as the primary end points. Potential prognostic variables were analyzed univariately, with one factor taken at a time, as well as in a multivariate model combining all factors. Results are reported as hazard ratios (HR) and 95% confidence intervals (CI). Statistical evaluations were carried out using SPSS software (Statistical Package for the Social Science, version 15.0, SPSS Inc, Chicago, IL). $P < 0.05$ indicates statistical significance.

Results

Characteristics of hypercoagulable states in patients diagnosed with metastatic colorectal cancer

Of the 153 patients with mCRC, 113 (73.86%) had hypercoagulation. Of these, DD increased

Table 1. Demographics and baseline characteristics of patients with associated coagulation index (N=153)

Variable	PT (S)	APTT (S)	PLT (10^9/L)	FIB (g/L)	D-D (mg/L)
Age					
< 60 years (*n*=81)	11.00±1.23	31.15±3.30	271.96±57.79	3.48±0.81	0.43±0.37
≥ 60 years (*n*=72)	10.67±0.91	30.50±4.46	303.35±77.43	3.75±0.76	0.57±0.53
t	1.89	1.02	-2.86	-2.05	-1.91
P	0.06	0.31	0.01	0.04	0.06
Gender					
Male (*n*=87)	10.94±1.16	30.80±3.60	286.40±71.42	3.60±0.79	0.50±0.50
Female (*n*=66)	10.72±1.01	30.90±4.36	287.17±67.00	3.61±0.80	0.48±0.40
t	1.19	-0.28	-0.06	-0.03	0.22
P	0.24	0.78	0.95	0.98	0.83
ECOG scores					
0-1 (*n*=86)	10.93±1.14	31.04±3.44	260.14±52.36	3.42±0.67	0.42±0.36
2 (*n*=67)	10.74±1.04	30.60±4.41	320.87±73.71	3.84±0.88	0.59±0.55
t	1.05	0.69	-5.95	-3.37	-2.27
P	0.30	0.49	< 0.01	< 0.01	0.025
Alcohol and tobacco habits					
Both (*n*=12)	10.48±0.66	30.46±2.65	326.08±60.70	4.02±0.70	0.84±1.0
Alcohol or tobacco (*n*=19)	10.80±1.10	30.33±4.45	292.84±58.10	3.80±1.16	0.65±0.52
Neither (*n*=122)	10.89±1.13	30.96±3.92	281.91±70.83	3.54±0.72	0.44±0.34
F	0.76	0.28	2.34	2.67	5.78
P	0.47	0.76	0.10	0.07	< 0.01
Comorbidities					
More than two (*n*=19)	10.73±0.72	30.64±2.93	323.63±62.15	3.91±0.51	0.73±0.54
One (*n*=48)	10.79±1.18	31.64±4.91	310.42±74.71	3.69±0.88	0.60±0.54
none (*n*=86)	10.90±1.23	30.45±3.37	265.36±60.05	3.50±0.78	0.38±0.35
F	0.28	1.49	10.82	2.56	6.78
P	0.76	0.23	< 0.01	0.08	< 0.01
Metastatic sites, N					
1 (*n*=59)	10.71±1.13	30.85±3.52	270.55±64.70	3.31±0.54	0.37±0.28
2 (*n*=73)	10.87±1.09	30.87±4.04	291.30±68.74	3.70±0.87	0.53±0.38
> 2 (*n*=21)	11.13±1.00	30.76±4.46	314.23±75.07	4.10±0.79	0.73±0.83
F	1.24	0.01	3.59	10.04	5.85
P	0.29	0.99	0.03	< 0.01	< 0.01

in 98 cases (86.72%), PLT increased in 58 cases (51.33%), FIB increased 34 in cases (30.09%), APTT shortened 6 in cases (5.31%), and PT shortened in 4 cases (3.54%). Moreover, 32 cases (28.32%) were elevated in PLT and DD, 18 cases (15.66%) were abnormal with PLT and FIB. and DD increased in 15 cases (13.27%) (**Table 1**).

Comparison of the hypercoagulability group with the control group according to different clinical features in patients with mCRC

Hypercoagulation was much more frequent in patients aged ≥ 60 years, compared to those < 60 years ($P < 0.05$), as well as in patients with ECOG=2 points ($P < 0.01$). Moreover, those that smoked and drank had more hypercoagulation, compared with those with no tobacco and alcohol addictions ($P < 0.01$). There were significant differences between the hypercoagulation group and control group divided by the number of metastatic sites ($P < 0.05$). Results are shown in **Table 2**.

Survival descriptions of different subgroups divided by hypercoagulable state

Descriptive survival statistics and Kaplan-Meier curves suggested that the variable of hyper-

Table 2. Comparison between the hypercoagulation group and control group

Variable	Hypercoagulation group (*n*=113)	Control group (*n*=40)	χ^2	*P*
Age			13.11	< 0.01
< 60 years (*n*=81)	50 (44.24%)	31 (77.50%)		
≥ 60 years (*n*=72)	63 (55.76%)	9 (22.50%)		
Gender			1.94	0.16
Male (*n*=87)	68 (60.18%)	19 (47.50%)		
Female (*n*=66)	45 (39.82%)	21 (52.50%)		
ECOG scores			18.24	< 0.01
0-1 (*n*=86)	52 (46.02%)	34 (85.00%)		
2 (*n*=67)	61 (53.98%)	6 (15.00%)		
Alcohol and tobacco habits			7.81	< 0.01
Yes	29 (25.66%)	2 (5.00%)		
No	84 (74.34%)	38 (95.00%)		
Comorbidities			15.21	< 0.01
Yea	60 (53.10%)	7 (17.50%)		
No	53 (46.90%)	33 (82.50%)		
Metastatic sites, N (%)			3.87	0.01
1	45 (39.80%)	14 (35.00%)		
2	50 (44.20%)	23 (57.50%)		
> 2	18 (16.00%)	3 (7.50%)		

coagulation had prognostic significance in this relatively selected cohort. Hypercoagulation was associated with decreasing 1-, 3-, 5-year OS rates (P=0.0291, **Figure 1A**) and increasing 1-, 3-, 5-year TTR rates (P=0.0305, **Figure 1B**).

Predictors associated with prognosis of patients with mCRC

Cox's proportional hazards model was used to quantify the prognostic significance of risk factors after multivariable adjustment. Multivariable analysis was performed to assess factors that demonstrated significant effects in univariate analysis. After adjusting for competing risk factors, number of metastases > 2 and hypercoagulation remained as independent predictors of time to recurrence (HR: 1.486, 95% CI: 1.294-3.627, P=0.015 and HR: 1.621, 95% CI: 1.167-3.158, P=0.021) and overall survival (HR: 1.872, 95% CI: 1.572-4.962, P=0.001 and HR: 1.583, 95% CI: 1.325-4.721, P=0.002). Details are shown in **Table 3**.

Discussion

Hypercoagulation refers to a condition in which the body stops coagulation due to various factors. Anticoagulation and fibrinolytic systems of the body become dysfunctional. Changes in physical and chemical properties of the blood lead to high coagulability or thrombosis [21]. There are many diseases in which excessive activation of the coagulation cascade occurs, resulting in the formation and dissemination of blood clots in the circulation. Hypercoagulation has been described in association with strokes, sepsis, atherosclerosis, and many kinds of cancers [22]. Hypercoagulation has been reeatedly in patients with malignant tumors [23, 24].

Several potential mechanisms of hypercoagulation have been described. First, tumor cells could synthesize and secrete large amounts of tissue factor (TF) and cancer procoagulant (CP). This can be combined with activated FVII to form a FVIIa-TF complex that activates FX and initiates extrinsic coagulation pathways [25]. Studies have shown that proto-oncogene activation and tumor suppressor gene inactivation are underlying causes for induction of TF overexpression [26, 27]. Proto-oncogene K-ras mutations and loss of p53 proteins in colorectal cancer lead to high expression of TF. TF, the initiation factor of coagulation pathways, also plays an important role in tumor invasion and metastasis [28]. CP is a vitamin K-dependent cysteine protease involved in coagulation, without FVII directly activating FX and activating the coagulation system [29]. Second, patients with malignant solid tumors simultaneously have anticoagulation and fibrinolytic system imbalances. Expression of antithrombin (AT), protein C (PC), protein S (PS), and thrombomodulin (TM) decrease in patients with tumors. Patients with low expression of PC, PS, and TM were found to be related to the presence of PC, PS, and TM antibodies [30]. Increased levels of plasminogen activator inhibitor-1 (PAI-1) were produced by tumor cells and inhibition of tissue-type plasminogen activators (t-PA) makes the body prone to hypercoagulation [31]. Third, tumor cells present antigens that can make the

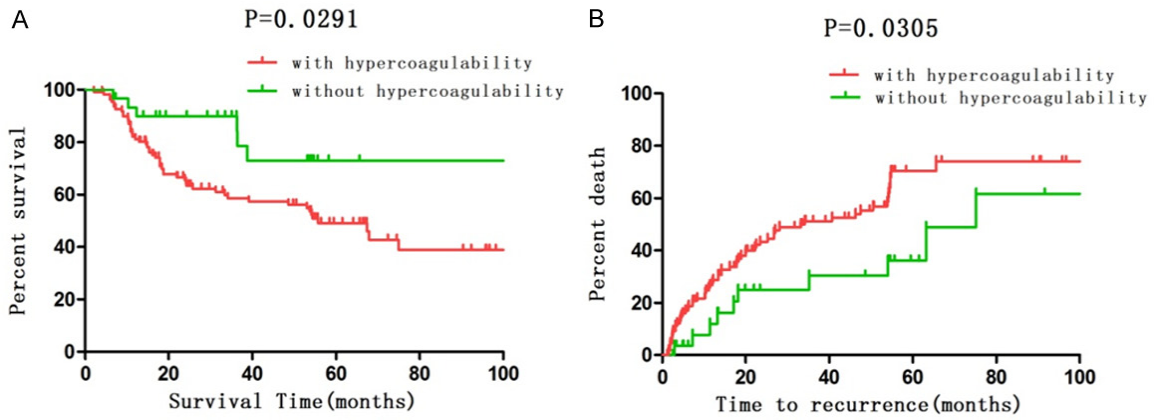

Figure 1. Overall survival and time to recurrence estimates, A: OS of patients stratified by hypercoagulation (P=0.0291; B: TTR of patients stratified by hypercoagulation (P=0.0305).

Table 3. Multivariable Cox proportional hazard regression analysis of patients demographics and survival

Variables	TTR		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.125 (0.825-1.432)	0.153	1.049 (0.945-1.121)	0.086
ECOG-PS: 2	1.019 (0.768-1.312)	0.764	1.109 (0.684-1.532)	0.186
Comorbidities: yes	1.193 (0.773-1.203)	0.621	1.054 (0.914-1.392)	0.082
No. of metastases > 2	1.486 (1.294-3.627)	0.015	1.872 (1.572-4.962)	0.001
hypercoagulation	1.621 (1.167-3.158)	0.021	1.583 (1.325-4.721)	0.002

body produce immune and inflammatory responses. The activating macrophages, T-cells that release IL-1β and TNF-α, could induce high expression of TF, activate PLT, stimulate PAI-1 pathways, and inhibit PC pathways to promote blood hypercoagulation [32].

Of the 153 patients with mCRC in this study, 113 were hypercoagulable, with a positive rate of 73.86%. D-D, PLT, and FIB were the most prominent. Activation of endogenous and exogenous coagulation pathways could increase coagulation factor activity and procoagulant and blood clot contraction. This may result in secondary hyperfibrinolysis. Age ≥ 60 years, ECOG score=2 points, alcohol and tobacco habits, combined underlying disease, and number of tumor distant metastasis were shown to be risk factors for hypercoagulation, in accord with previous studies [33]. Elderly patients are prone to have hypercoagulation and to be associated with underlying diseases, such as hypertension, hyperlipidemia, and diabetes, as well as relatively poor physical conditions and less activity [34]. Factors that cause hypercoagulation due to smoking and drinking are related to loss of vascular endothelial cells. This results in changing the coagulation system and the body into a hypercoagulable state.

There were limitations to the current study, however: (1) The sample size was too small. Larger sample studies are necessary to confirm present results; and (2) Whether hypercoagulation has the optimal specificity and sensitivity for CRC diagnosis and prognosis requires confirmation.

In conclusion, the current study found that hypercoagulation was frequent in patients with metastatic colorectal cancer. Different clinical features were associated with hypercoagulation. Moreover, hypercoagulation was shown to be an independent predictor of OS and TTR.

Disclosure of conflict of interest

None.

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