Observational Study

Medicine®

OPEN

D-Dimer level was associated with prognosis in metastatic colorectal cancer

A Chinese patients based cohort study

Chan Liu, MD[a], Yueguo Ning, MD[a], Xiaoming Chen, MD[a], Qian Zhu, MD, PhD[b,*]

Abstract

D-dimer level is a direct measure of activated coagulation and has been used as a biomarker of hypercoagulability. In this study, we aimed to explore the associations between D-dimer level and the clinicopathological features and prognosis in metastatic colorectal cancer (mCRC) patients. One hundred seventy-eight patients diagnosed with mCRC from the Department of General Surgery, Jingmen First People's Hospital from September 2014 to December 2018 were collected. Data of coagulation index was evaluated and survival analysis was performed to identify the biomarker of mCRC. Among 178 cases of colorectal cancer, we found that the value of 0.55 mg/L, 5ng/ml and 40U/ml were cut-off values of D-Dimer, CEA and CA-199 for patients survival, respectively. hypercoagulability was much more frequent in patients aged ≥60 years than <60 years ($P < .001$) and also in patients with ECOG ≥2 points ($P < .001$). Moreover, those patients who have CEA >5ng/ml and CA-199>40U/ml had hypercoagulable state ($P < .001$). There was a significant difference in D-Dimer >0.55 mg/L and D-Dimer ≤0.55 mg/L among the number of metastatic sites ($P < .01$) and patients with comorbidities ($P < .01$). Survival analysis showed that patients with D-Dimer >0.55 mg/L have significantly unfavorable overall survival ($P = .006$) and progressive free survival ($P = .011$).

Abbreviations: APTT = activated partial thromboplastin time, DD = D-Dimer, FIB = fibrinogen, mCRC = metastatic colorectal cancer, NETs = neutrophil extracellular traps, OS = overall survival, PFS = progressive free survival, PLT = platelet, PT = prothrombin time.

Keywords: D-Dimer, metastatic colorectal cancer, prognosis

1. Introduction

Colorectal cancer (CRC) represents the third most frequent neoplastic disorder worldwide and one of the main causes of tumor-related mortality.[1,2] Colorectal cancer mortality has decreased by 39% in United States in the past 2 decades due to early detection of the disease as well as better access to colonoscopy and new treatments.[3] Nevertheless, approximately 50% of patients with colorectal cancer will develop liver metastases during their lifetime. Tumor metastasis is the most insidious aspect of cancer and is the leading cause of CRC-related death.[4] The mechanism behind cancer cell metastasis is unclear but accumulating data suggest that increased expression of adhesion molecules and capacity to migrate are critical components of tumor cell spread to distant organs.[5]

D-Dimer, a stable end product of fibrin degradation, is a widely used and highly sensitive global indicator of activated coagulation and fibrinolysis.[6–8] Elevated D-dimer levels were shown in different cancer types, such as lung, colorectal, breast, ovarian and pancreatic adenocarcinoma and were identified as poor prognosis biomarkers in these patients.[9–13] Moreover, it is widely known that activated coagulation is not only representing a high risk for thrombosis, but also is implicated with tumor cell invasion, angiogenesis and metastatic tumor. Some of the mechanisms known to D-Dimer levels contribute to tumor-related factors such as the expression of mucins by tumor cells and the activation of oncogenes.[14,15] However, researchers have demonstrated that D-Dimer could play significant role in immune cells such as tissue factor on macrophages, platelets and neutrophils and, more recently, neutrophil extracellular traps (NETs) released from activated neutrophils.[16–18] Moreover, in vitro and in vivo studies suggested that another potential modulator of the coagulation cascade was the complement system, the key sentinel of innate immunity, which is also associated with D-Dimer formation.[19,20] Although much progress has been made towards understanding the causes of cancer-associated hypercoagulation, the heterogeneity of the causative mechanisms poses still a considerable challenge to the application of effective preventive and therapeutic strategies.

Our study was based on the hypothesis that tumor activity is displayed by elevated D-Dimer plasma levels and that D-Dimers

Editor: Eva Zapata.

CL and YN contributed equally to this study.

The authors who have taken part in this study declared that they have nothing to disclose regarding funding or conflict of interest with respect to this manuscript.

[a] Department of General Surgery, Jingmen First People's Hospital, Jingmen, Hubei Province, [b] Department of Hepatobiliary and Pancreatic Surgery, Zhongnan Hospital of Wuhan University, Pancreatic Surgery Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China.

[*] Correspondence: Qian Zhu, Department of Hepatobiliary and Pancreatic Surgery, Zhongnan Hospital of Wuhan University, Pancreatic Surgery Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, China (e-mail: ehbhly@sina.com).

How to cite this article: Liu C, Ning Y, Chen X, Zhu Q. D-Dimer level was associated with prognosis in metastatic colorectal cancer: A Chinese patients based cohort study. Medicine 2020;99:7(e19243).

Received: 12 September 2019 / Received in final form: 14 January 2020 / Accepted: 16 January 2020

http://dx.doi.org/10.1097/MD.0000000000019243

might be used as a prognostic marker in patients with metastatic colorectal cancer. Our aim for this study was also to provide a novel insight in the association of D-dimer levels with other tumor associated antigens in metastatic colorectal cancer patients.

2. Patients and methods

2.1. Patients

Collected 178 patients diagnosed with mCRC from the Department of General Surgery, Jingmen First People's Hospital from September 2014 to December 2018, and recorded data: gender, age, pathology, stage, alcohol and tobacco habits, complications (high blood pressure, coronary heart disease, diabetes, hyperlipidemia), ECD scores, coagulation index: plasma prothrombin time (PT), activated partial thromboplastin time (activated partial thromboplastin time, APTT), platelet (PLT), fibrinogen (FIB), D-dimer (D-dimmer, DD), and imaging data; and for all the 178 patients with mCRC. Patients with CRC were further identified as having metastatic diseases if subsequent to their first recorded CRC diagnosis they had at least one inpatient or two outpatient claims with a diagnosis of metastasis. The date of the first claim with a metastasis diagnosis was deemed the index date. Each patient was required to be continuously enrolled for at least 6 months before the index date. Patients were excluded from the study if they had a history of another primary cancer prior to the index date or if they had a diagnosis of metastasis prior to the first CRC diagnosis. The patients flow chart was shown in Figure 1. This study was approved by the Regional Ethical Review Boards for Jingmen First People's Hospital. Patients were treated according to the *Declaration of Helsinki's* ethical principles for medical research involving human subjects. All patients provided an informed written consent prior to study entry.

2.2. Treatment regimens

For each patient, first, second, and third-line treatment regimens were identified and dates of initiation and termination were determined. A treatment regimen was defined as one or more chemotherapeutic agents (5-fluorouracil, capecitabine, irinotecan, and oxaliplatin) and/or mCRC labeled biologics (bevacizumab, cetuximab) administered within a 4-day period, with the condition that all elements were administered more than once within 28 days. In the event that a new drug was added to a regimen within 28 days of the start of a line of therapy, this was considered an addition to the existing line, rather than a new line of therapy. The end of a line of therapy was defined by either a 90-day gap in treatment or initiation of a new regimen that was not merely the addition of a new drug to the existing regimen.

2.3. Quantification of D-Dimer

Sodium citrate plasma samples were analyzed for D-dimer by quantitative fully automated Innovance D-dimer immuneturbidimetric assay (Siemens Healthcare Diagnostics Products GmbH, Germany) determined on BCS (Dade-Behring Coagulation System). D-dimer measurements in plasma were performed in the routine clinical laboratory at Jingmen First People's Hospital. Plasma D-dimer levels 0.55 mg/L was used as cutoff for normal versus high D-Dimer values, according to the receiver operating characteristic (ROC) curve analyses.

2.4. Coagulation index determination

Collected and enrolled patients with fasting venous blood 3 to 5 ml in the morning and 10^9 mol/L sodium citrate 0.3 ml, mixed thoroughly, centrifuged at 3000 r/min for 15 minutes, and the plasma was ready for use. The ACL TOP automatic coagulation analyzer was used within 2 hours (US Instrumentation Laboratory Company), Test PT, APTT, FIB, DD indicators (kit manufacturers are the United States Instrumentation Laboratory Company company).

2.5. Determination of platelet parameters

The patients were enrolled in the morning and fasted with 3 to 5 ml of venous blood, mixed well with EDTA-K anticoagulant

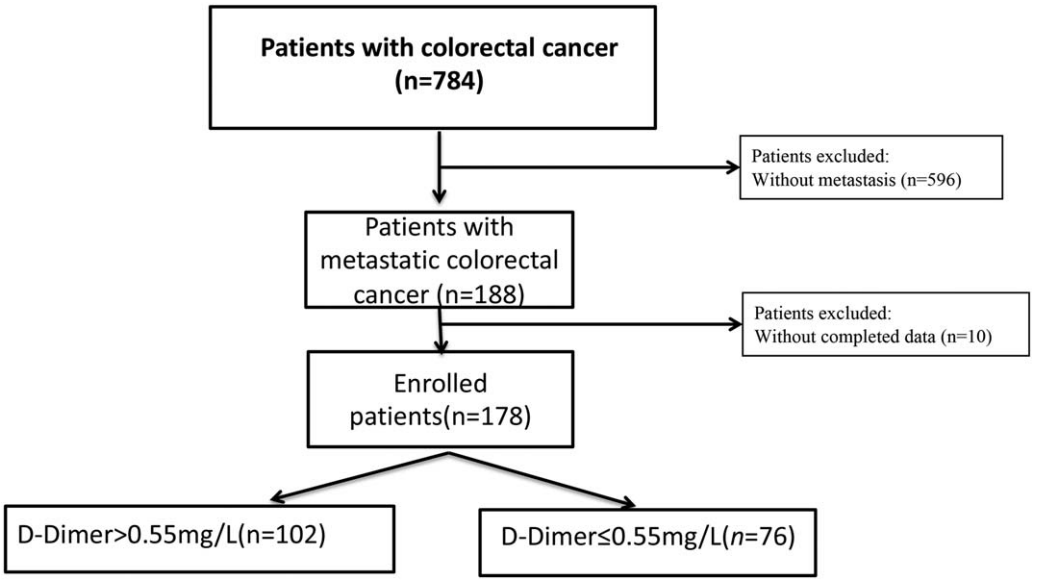

Figure 1. Flow chart of patients with mCRC.

tube, and applied XE-2100 automatic blood analyzer within 2 hours (SYSMEX Corporation, USA), detect PLT indicators.

2.6. Follow-up

Following treatment, serum D-Dimer, CEA, CA19–9 were obtained and abdominal ultrasound was performed in all patients monthly. Abdominal contrast-enhanced CT scans or MRs were performed every 3 months. Further investigations were carried out when clinically indicated or when tumor progression was suspected. Overall survival (OS) was defined as the period from the date of first treatment until death. Patients who did not experience an event were censored on the date of last contact. Progressive free survival (PFS) was defined as the period from the date of first treatment until an occurrence of an event (progressive disease, death, diagnosis of a second malignant neoplasm), whichever occurred first.

2.7. Statistical analysis

Student-t test was used for comparing variables showing normal distribution and Mann–Whitney *U* test for comparing variables not showing normal distribution within qualitative data. Pearson Chi-Square test, Fisher Exact Test and Yates Continuity Correction Test were used for comparing qualitative data. The predictive performance of D-Dimer, CEA and CA-199 were measured using the area under receiver operating characteristic (ROC) curve (AUC). AUCs were also used to compare D-Dimer, CEA and CA-199 using the Hanleyand McNeil method.[21] Kaplan–Meier survival analysis and log-rank were used for evaluating survival. OS and progressive free survival (PFS) were chosen for the evaluation as the primary end-points. Potential prognostic variables were analyzed both univariately with one factor taken at a time, and then in a multivariate model combining all factors. Results are reported as hazard ratios (HR) and their 95% confidence intervals (CI). A HR > 1 indicated an elevated risk with respect to the reference category. A confidence interval which did not include the value 1 indicated statistical significance at the 5% level. All statistical evaluations were carried out using SPSS software (Statistical Package for the Social Science, version 15.0, SPSS Inc, Chicago, IL). A value of $P < .05$ was considered to be statistically significant in all the analyses.

3. Results

3.1. Identifying cut-off values and comparison of groups divided by D-Dimer according to different clinical features in patients with mCRC

We performed ROC curves to identify the cut-off values of D-Dimer, CEA and CA-199. We found that the value of 0.55 mg/L, 5 ng/ml and 40 U/ml were cut-off values of D-Dimer, CEA and CA-199, respectively. Moreover, the predictive value was performed to compare the prognostic significance of these factors on both the overall survival and progressive free survival of patients with mCRC. The AUC of D-Dimer divided by 0.55 mg/L (AUC:0.816) was significant larger than CEA (AUC:0.638) and CA-199 (AUC:0.652) for predicting overall survival (Fig. 2A). The AUC of D-Dimer divided by 0.55 mg/L (AUC:0.781) was significant larger than CEA (AUC:0.613) and CA-199 (AUC:0.687) for predicting overall survival (Fig. 2B). We then compared the clinical features between the patients with D-Dimer >0.55 mg/L and D-Dimer ≤ 0.55 mg/L. we found that D-Dimer >0.55 mg/L was much more frequent in patients aged ≥ 60 years than <60 years ($P < .001$) and also in patients with ECOG ≥ 2 points ($P < .001$). Moreover, those who have CEA >5ng/ml and CA-199 >40U/ml had hypercoagulable

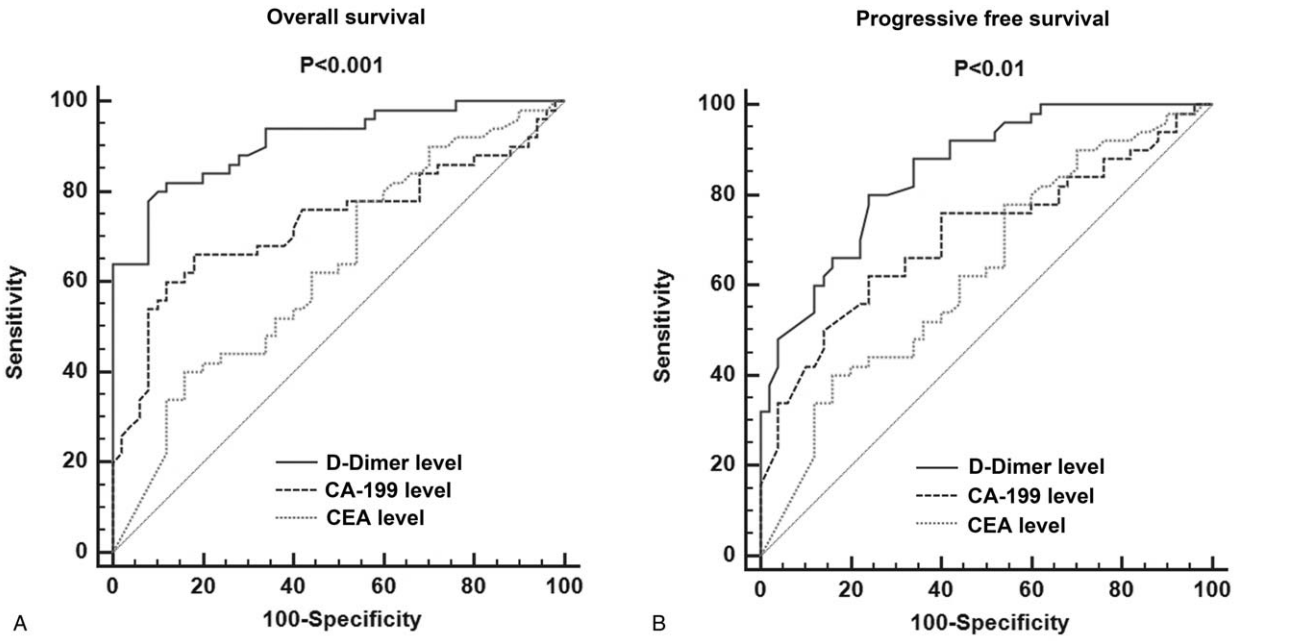

Figure 2. A: The AUC of D-Dimer divided by 0.55 mg/L was significant larger than CEA and CA-199 for predicting overall survival. B: The AUC of D-Dimer divided by 0.55 mg/L (AUC:0.781) was significant larger than CEA and CA-199 for predicting overall survival.

Table 1

The comparison between patients in D-Dimer > 0.55 mg/L group and in D-Dimer ≤0.55 mg/L group.

Variable	D-Dimer>0.55mg/L (*n*=102)	D-Dimer≤0.55mg/L (*n*=76)	χ^2	*P*
Age			18.7	<.001
<60 years	39 (38.3%)	54 (71.1%)		
≥60 years	63 (67.7%)	22 (28.9%)		
Gender			0.09	.764
Male	60 (58.8%)	43 (56.6%)		
Female	42 (41.2%)	33 (43.4%)		
ECOG scores			36.9	<.001
<2	41 (40.2%)	64 (84.2%)		
≥2	61 (59.8%)	12 (15.8%)		
CEA levels (ng/ml)			16.2	<.001
>5	66 (64.7%)	26 (34.2%)		
≤5	36 (35.3%)	50 (65.8%)		
CA-199 levels (U/ml)			29.3	<.001
>40	70 (68.6%)	21 (27.6%)		
≤40	32 (31.4%)	55 (72.4%)		
Alcohol and tobacco habits			1.25	.263
Yes	29 (28.4%)	16 (21.1%)		
No	73 (71.6%)	60 (78.9%)		
TNM stage			0.32	.583
III	12 (11.8%)	10 (13.2%)		
IV	90 (88.2%)	66 (86.8%)		
Comorbidities			18.6	<.001
Yea	60 (58.8%)	20 (26.3%)		
No	42 (41.2%)	56 (73.7%)		
Metastatic sites, N (%)			27.5	<.001
1	15 (14.7%)	34 (44.7%)		
2	50 (49.0%)	33 (43.4%)		
>2	37 (36.3%)	7 (9.2%)		
Chemotherapy			0.225	.635
Yes	56 (54.9%)	39 (51.3%)		
No	46 (46.1%)	37 (48.7%)		

state ($P < .001$). There was a significant difference in D-Dimer >0.55 mg/L and D-Dimer ≤0.55 mg/L among the number of metastatic sites ($P < .01$) and patients with comorbidities ($P < .01$). The results details were shown in Table 1.

3.2. Characteristics of hypercoagulable state in patients diagnosed with metastatic colorectal cancer

Among the 178 patients with mCRC, 102 (57.3%) had D-Dimer elevated which was associated with hypercoagulable state, among which PLT increased in 50 cases (49.1%), FIB increased 34 in cases (33.2%), APTT shortened in 28 cases (27.5%), PT shortened in 39 cases (38.2%). Of these patients, we found that PT and FIB were significantly associated with D-Dimer >0.55 mg/L (Table 2).

Table 2

Demographics and Baseline Characteristics of Patients with associated Coagulation index associated with D-Dimer (N=178).

Variable	D-Dimer > 0.55mg/L (*n*=102)	D-Dimer ≤ 0.55mg/L (*n*=76)	*P*
PT (S)	11.00 ± 1.23	12.67 ± 0.91	.012
APTT (S)	31.15 ± 3.30	30.50 ± 4.46	.254
PLT (*10^9/L)	286.40 ± 71.42	287.17 ± 67.00	.587
FIB (g/L)	3.75 ± 0.76	3.48 ± 0.81	.008

3.3. Survival descriptions of different subgroups divided by D-Dimer values

Descriptive survival statistics and Kaplan–Meier curves suggested that the variable of D-Dimer had prognostic significance in this relatively selected cohort. Patients with D-Dimer >0.55 mg/L have significantly unfavorable overall survival ($P = .006$, Fig. 3A) and progressive free survival ($P = .011$, Fig. 3B).

3.4. Predictors associated with prognosis of patients with mCRC

Cox proportional hazards models were then used to quantify the prognostic significance of risk factors after multivariable adjustment. A multivariable analysis was performed to assess the factors that demonstrated significant effects as in univariate analysis. After adjusting for competing risk factors, Number of metastases >2 and D-Dimer >0.55 mg/L remained independent predictors of progressive free survival (HR: 1.375, 95% CI: 1.189–3.382, $P = .025$ and HR: 1.621, 95% CI: 1.196–3.078, $P = .014$) and overall survival ((HR: 1.778, 95% CI: 1.506–4.187, $P = .003$ and HR: 1.694, 95% CI: 1.375–4.430, $P = .005$). The details are shown in Table 3.

4. Discussion

Activated coagulation in cancer patients is implicated both in tumor progression and in development of VTE. Hypercoagula-

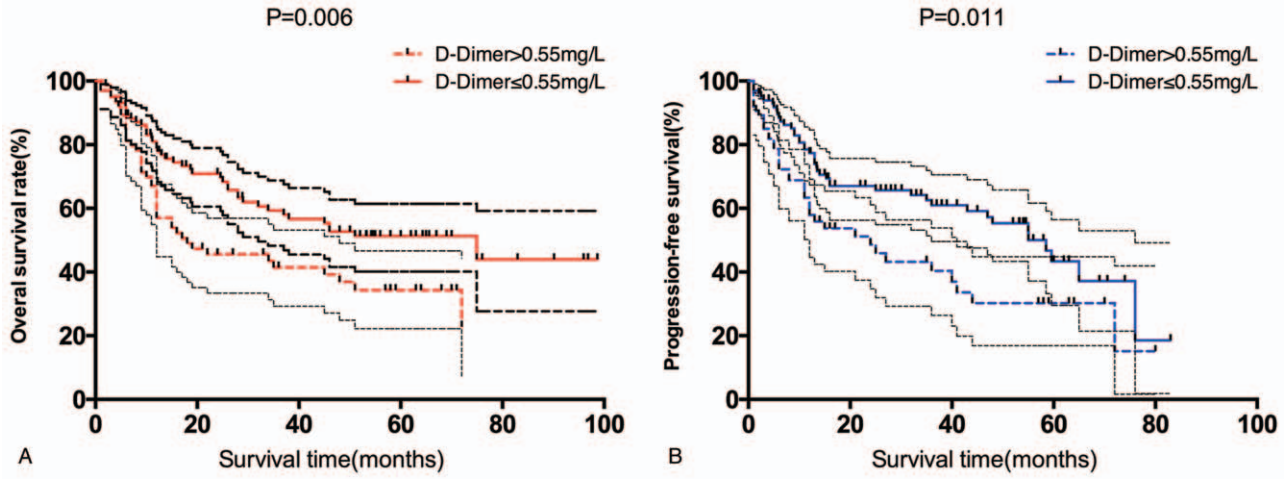

Figure 3. Overall survival and progressive free survival, A: OS of patients stratified by D-Dimer levels ($P = .006$; B: PFS of patients stratified by D-Dimer levels ($P = .011$).

bility refers to a condition in which the body stops coagulation, anticoagulation, and fibrinolytic system imbalance due to various factors. Changes in the physical and chemical properties of blood resulted in hypercoagulability or thrombosis.[22] There are many diseases where excessive activation of the coagulation cascade occurs therefore resulting in the formation and dissemination of blood clots in circulation. Thrombotic phenomena have been described in association with stroke, sepsis, and atherosclerosis and with many forms of cancer.[23] D-dimer, one of the key components in the process of embolism and fibrinolysis, has been found to be associated with the prognosis in patients with CRC Several studies have reported that plasma D-dimer levels were elevated and associated with the stage and mortality in CRC.[24,25] Moreover, the D-dimer level is a direct measure of activated coagulation and has been used as a biomarker of hypercoagulability. The elevated D-dimer level suggests that hypercoagulability plays a major role in the pathogenesis of cancer-related ischemic stroke (CRIS).[26,27] Recently, Wang and his colleagues found that the plasma D-dimer value of 2.785 μg/mL was the cutoff in identifying CRIS patients.[28] Moreover, the frequency of microembolic signals in the internal carotid arteries on transcranial Doppler images correlated linearly with D-dimer levels in patients with IS and cancer, which indicated that elevated D-dimer levels are an independent predictor for the detection of embolic signals.[29]

In the present study, we performed ROC curves to identify the cut-off values of D-Dimer, CEA and CA-199. We found that the value of 0.55 mg/L, 5 ng/ml and 40U/ml were cut-off values of D-Dimer, CEA and CA-199, respectively. Moreover, the predictive value was performed to compare the prognostic significance of these factors on both the overall survival and progressive free survival of patients with mCRC. Of the 178 patients with colorectal cancer, we found that PT and FIB were significantly associated with D-Dimer >0.55 mg/L. In this study, The study age ≥60 years, ECOG score ≥2 points, CEA and CA-199 levels, combined underlying disease and number of tumor distant metastasis are risk factors for hypercoagulability, which is consistent with previous study.[30] Elderly patients are prone to hypercoagulability and associated with underlying diseases such as hypertension, hyperlipidemia, and diabetes, as well as relatively poor physical conditions and less activity.[31] Basic diseases such as hypertension, hyperlipidemia, and diabetes are all important factors that cause vascular damage, making the blood vessels brittle and easily damaged. The factors that cause the body's hypercoagulability due to smoking and drinking are also losses to the vascular endothelial cells. All of these factors lead to changes in the coagulation system and the body is in a hypercoagulable state.

However, there are limitations of this study:

(1) the sample size is too small in this study, and further larger sample study is needed to confirm the present results;
(2) whether D-Dimer level have the optimal specificity and sensitivity for CRC diagnosis and prognosis also needs future confirmation.

Table 3

Multivariable Cox proportional hazard regression analysis of patients' demographic and survival.

Variables	PFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.114 (0.810–1.201)	.764	1.004 (0.879–1.121)	.489
ECOG-PS: 2	1.124 (0.727–1.462)	.252	1.193 (0.632–1.839)	.078
CEA levels (ng/ml)	1.136 (0.704–1.354)	.201	1.113 (0.851–1.427)	.241
CA-199 levels (U/ml)	0.869 (0.667–1.452)	.355	1.132 (0.604–1.527)	.087
Comorbidities: yes	1.102 (0.771–1.219)	.601	1.219 (0.732–1.305)	.103
No. of metastases > 2	1.375 (1.189–3.382)	.025	1.778 (1.506–4.187)	.003
D-Dimer levels (mg/L)	1.621 (1.196–3.078)	.014	1.694 (1.375–4.430)	.005

In conclusion, we found D-Dimer level was frequent in patients with metastatic colorectal cancer. Different clinical features were associated with D-Dimer level and D-Dimer >0.55 mg/L was independent predictor of overall survival and progressive free survival

Author contributions

Conceptualization: Chan Liu, Qian Zhu.
Data curation: Yueguo Ning.
Investigation: Chan Liu.
Methodology: Chan Liu, Yueguo Ning.
Project administration: Xiaoming Chen.
Software: Yueguo Ning, Xiaoming Chen.
Validation: Xiaoming Chen, Qian Zhu.
Writing–original draft: Xiaoming Chen, Qian Zhu.
Writing–review & editing: Xiaoming Chen, Qian Zhu.

References

[1] Faugeras L, Dili A, Druez A, et al. Treatment options for metastatic colorectal cancer in patients with liver dysfunction due to malignancy. Crit Rev Oncol Hematol 2017;115:59–66.
[2] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
[3] Ait Ouakrim D, Pizot C, Boniol M, et al. Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. BMJ (Clinical research ed) 2015;351:h4970.
[4] Monteiro J, Fodde R. Cancer stemness and metastasis: therapeutic consequences and perspectives. Eur J Cancer (Oxford, England: 1990) 2010;46:1198–203.
[5] Wang JM, Deng X, Gong W, et al. Chemokines and their role in tumor growth and metastasis. J Immunol Methods 1998;220:1–7.
[6] Desch A, Gebhardt C, Utikal J, et al. D-dimers in malignant melanoma: association with prognosis and dynamic variation in disease progress. Int J Cancer 2017;140:914–21.
[7] Wang Z, Qian Z, Ren J, et al. Effect of D-dimer and tissue factor-1208D/I gene polymorphism on the prognosis of patients with off-pump coronary artery bypass grafting. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2017;29:1097–101.
[8] Watanabe A, Araki K, Harimoto N, et al. D-dimer predicts postoperative recurrence and prognosis in patients with liver metastasis of colorectal cancer. Int J Clin Oncol 2018;23:689–97.
[9] Chen X, Chang Z, Liu Z. D-dimer increase: an unfavorable factor for patients with primary liver cancer treated with TACE. Cancer Chemother Pharmacol 2019;83:797–802.
[10] Ge YL, Liu CH, Wang N, et al. Elevated Plasma D-Dimer in Adult Community-Acquired Pneumonia Patients is Associated with an Increased Inflammatory Reaction and Lower Survival. Clin Lab 2019;65:
[11] Li B, Zhang H, Zhou P, et al. Prognostic significance of pretreatment plasma D-dimer levels in patients with spinal chordoma: a retrospective cohort study. Eur Spine J 2019;28:1480–90.
[12] Qi T, Zhu C, Lu G, et al. Elevated D-dimer is associated with increased 28-day mortality in acute-on-chronic liver failure in China: a retrospective study. BMC Gastroenterol 2019;19:20.
[13] Xu Y, Wang B, Jiang LJ, et al. Roles of microembolus and plasma D-dimer in evaluating the warfarin anticoagulant therapy efficacies for patients with atrial fibrillation. Heart Surg Forum 2019;22:E015–e018.
[14] Andrianifahanana M, Moniaux N, Schmied BM, et al. Mucin (MUC) gene expression in human pancreatic adenocarcinoma and chronic pancreatitis: a potential role of MUC4 as a tumor marker of diagnostic significance. Clin Cancer Res 2001;7:4033–40.
[15] Boccaccio C, Sabatino G, Medico E, et al. The MET oncogene drives a genetic programme linking cancer to haemostasis. Nature 2005;434:396–400.
[16] Darbousset R, Thomas GM, Mezouar S, et al. Tissue factor-positive neutrophils bind to injured endothelial wall and initiate thrombus formation. Blood 2012;120:2133–43.
[17] von Bruhl ML, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J Exp Med 2012;209:819–35.
[18] Demers M, Krause DS, Schatzberg D, et al. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proc Natl Acad Sci U S A 2012;109:13076–81.
[19] Amara U, Rittirsch D, Flierl M, et al. Interaction between the coagulation and complement system. Adv Exp Med Biol 2008;632:71–9.
[20] Markiewski MM, Nilsson B, Ekdahl KN, et al. Complement and coagulation: strangers or partners in crime? Trends Immunol 2007;28:184–92.
[21] Hanley JA. Receiver operating characteristic (ROC) methodology: the state of the art. Crit Rev Diagn Imaging 1989;29:307–35.
[22] Anderson JA, Weitz JI. Hypercoagulable states. Clin Chest Med 2010;31:659–73.
[23] Perre A, Markman M. Extended venous thromboembolism prophylaxis for high-risk patients undergoing surgery for malignancy. Case Rep Oncol 2011;4:115–7.
[24] Kilic L, Yildiz I, Sen FK, et al. D-dimer and international normalized ratio (INR) are correlated with tumor markers and disease stage in colorectal cancer patients. Cancer Biomark 2015;15:405–11.
[25] Yamamoto M, Yoshinaga K, Matsuyama A, et al. Plasma D-dimer level as a mortality predictor in patients with advanced or recurrent colorectal cancer. Oncology 2012;83:10–5.
[26] Guo Y, Chen F, Cui W. Usefulness of plasma D-dimer level for monitoring development of distant organ metastasis in colorectal cancer patients after curative resection. Cancer Manag Res 2018;10:4203–16.
[27] Qin QX, Cheng XM, Lu LZ, et al. Biomarkers and potential pathogenesis of colorectal cancer-related ischemic stroke. World J Gastroenterol 2018;24:4950–8.
[28] Wang JY, Zhang GJ, Zhuo SX, et al. D-dimer >2.785 mug/ml and multiple infarcts >/=3 vascular territories are two characteristics of identifying cancer-associated ischemic stroke patients. Neurolog Res 2018;40:948–54.
[29] Seok JM, Kim SG, Kim JW, et al. Coagulopathy and embolic signal in cancer patients with ischemic stroke. Ann Neurol 2010;68:213–9.
[30] Nakashima MO, Rogers HJ. Hypercoagulable states: an algorithmic approach to laboratory testing and update on monitoring of direct oral anticoagulants. Blood Res 2014;49:85–94.
[31] Kawai K, Watanabe T. Colorectal cancer and hypercoagulability. Surg Today 2014;44:797–803.