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High Preoperative Fibrinogen Level is Closely Associated with Receipt of Chemotherapy and Advanced Disease in Patients with Colorectal Cancer

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Background: There is still lack of a preoperative simple, reliable and non-invasive blood marker predicting the stage of the disease (luminal or extraluminal) and the need for chemotherapy at the time of diagnosis in patients with colorectal cancer (CRC). The study aimed to investigate any relationship between the preoperative fibrinogen level and CRC disease stage as well as the receipt of chemotherapy before surgery.

Method: A total 297 CRC patients undergoing surgical resection for any reason (curative or palliative) enrolled in this study. The serum fibrinogen level was calculated in the preoperative period. The need for chemotherapy was assessed by two different expert oncologists. Comparisons were made between the fibrinogen level with disease stage as well as the chemotherapy.

Results: The mean fibrinogen level was 455±128,5 mg/dL with high level in 77,4% of all CRC patients. The level of fibrinogen in both Duke's C and D significantly were higher than Duke's B (p<0,001). High preoperative fibrinogen level had a 27.9-fold increase the risk of receiving chemotherapy (Hazard Ratio:27.9, P<0.0001, 12.8-60.4; 95% C.I). The majority of CRC patients receiving chemotherapy (94,4%) had both high fibrinogen and CEA levels.

Conclusion: High preoperative fibrinogen is closely linked with receipt of chemotherapy and advanced disease in patients with CRC. Notable, this association is more prominent when fibrinogen and CEA are both high.

Keywords: Colorectal cancer, fibrinogen, carcinoembryonic antigen, chemotherapy

Introduction

Colorectal cancer (CRC) is still a significant clinical problem leading high cancer-related mortality in all over the world countries due to inadequate colonoscopic screening and surveillance program (1). Surgical removal of potentially resectable CRC and adjuvant chemotherapy are mainstay of curative treatment (2).

At the time of the CRC diagnosis, the current preoperative evaluators including radiologic, pathologic assessments and blood-markers are unable to measure the actual stage of disease correctly (*first*: operable or inoperable, *second*: luminal disease or extraluminal) and need for chemotherapy (pre or postoperative period), especially in a patient without radiologically ap-

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parent metastasis. The preoperative measurement of carcinoembryonic antigen (CEA) has been used for many years to predict the prognosis, survival rate, and recurrence, but is a normal range in more than half of CRC patients at the time of diagnosis and has been claimed more frequently not to be a perfect indicator in recent years (3-5). Despite these improvements concerning the host inflammatory response to tumor development and progression in recent years, there is still a lack of a simple, non-invasive and reliable method that accurately measured to disease stage and the need for chemotherapy (6, 7). Consequently, a substantial number of new research has been launched to find a new blood-marker for CRC.

In this context, the association of systemic activation of coagulation factors such as fibrinogen, d-dimer and cancer behaviors such as growth, deep invasion, and distant metastasis has been shown in recent years, mainly arising from the pathway of cancer-related thromboembolic events (8). Fibrinogen, an inflammatory featured major protein that has recently been linked frequently to tumor progression and metastasis as well as mortality in many cancers, seems to be one of the most promising markers in colorectal cancer, but few number of studies have been conducted with itself (9). In preliminary studies, elevated fibrinogen level has been associated with lymph node metastasis in advanced gastric cancer with no serosal invasion (4). Preoperative fibrinogen has been commonly studied in the field of predicting of prognosis, life expectancy and disease recurrence of CRC (9, 10).

Unlike previous studies, our purpose is to investigate any relationship between preoperative fibrinogen level and both tumor stage and the need for chemotherapy in patients with CRC. This paper is the first study to investigate whether high preoperative fibrinogen, a simple, noninvasive and reliable blood test, is associated with receipt of chemotherapy and advanced disease in patients with CRC.

Materials and Methods

A total of 5200 colonoscopic reports were investigated regarding CRC diagnosis retrospectively, from September 2010 to May 2014. Soon after, all medical documents were investigated carefully, and 55 cases with CRC excluded from this study because of insufficient information. A total of 297 patients were eligible for this study. All patients underwent a surgical operation, whether curative or palliative and curative or palliative. Tumor localization and stage were confirmed by radiological, surgical and pathological reports. In the postoperative period, detailed pathological examination, tumor cell type differentiation, depth and lymph node invasion, and immunohistochemistry examination were made by two different pathologists by using modified Astler-Coller's classification (11). The need of chemotherapy was assessed by expert oncological medical council decision via current guidelines. In preoperative period, a CT scan was performed to all patients and the puncture biopsies, if necessary, were made in case of metastatic disease suspicion.

The preoperative fibrinogen samples were taken in the early morning of surgery and were measured by the Clauss standard method with bovine thrombin. The reasons that may affect the levels of fibrinogen such as chronic inflammation, hematological diseases were also investigated by a medical report and detailed physical examination in living patients. All participants signed the informed consent form.

The local ethics committee approved this study via number 245-36589. Statical analyses were made by SPSS 15 software (SPSS, Chicago, IL), p<0,05 was accepted as statistically significant.

Results

The comprehensive demographic data of this study are shown in Table-1. Some of the most notable findings are briefly summarized as below. The mean age of CRC patients was 61.9±13.1 (24-92) with slightly male 160 (53.8%) dominant feature, and most of the patients were over the age of fifty 244 (82.2%). Anemia was seen 97.1% of all patient with most commonly as mild-type (HB:10-13 mg (44.8%) anemia. The most cited of the tumor was rectum (45.8%), and the left-side CRC (described as between rectum and splenic flexure) was significantly common than right-side CRC (described as between distal transverse colon and cecum) (78.1%/21.9%, p<0,001). The mean fibrinogen levels of Duke's C (479.7) and Duke's D (489.4) were significantly higher than Duke's B (405.2) (p<0,001) (Table-2). According to Cox logistic regression analyze, the most critical factors affecting the status of chemotherapy were tumor location (left or right), high fibrinogen and CEA leves (Table-3). The risk of receipt of chemotherapy increased 27.9 times in patients with high fibrinogen level (Hazard ratio:27.9; p<0,001; 12.8-60.4; CI 95%) (Table-3). Approximately 95% of CRC patients with high fibrinogen and CEA levels received chemotherapy (Table-4). The optimal cut-off of preoperative fibrinogen level regarding advan-ced disease stage (Duke's C and D) and the need for chemotherapy was analyzes with receiver operating characteristic (ROC) curve that demonstrated a 361.5 mg/dL level had an 88% sensitivity and 80% specificity, area under curve=0.84 (Figure-1).

Table-1: Baseline important demographic, histopathological, clinical, and laboratory features ofCRC patients who underwent a surgical operation (The data showed as a mean±standart deviation).

Patients	297
Sex	
Male	160(53.8%)
Female	137(46.1%)
Age(year)	61.9±13.1(24-92)
>50	244(82.2%)
<50	53(17.8%)
Fibrinogen level	455±128,5(164-900)
High	230(77.4%)
Normal	67(22.6%)
CEA	67.4± 239.8(0.6-2242)
Normal	152(51.2%)
High	145(48.8%)
Anemia	
None(>13 gr/dl)	71(2.9%)
Hb(10-13 gr/dl)	133(44.8%)
Hb(<10 gr/dl)	93(31.3%)
Gall Bladder	
Exist with no stone	248(83.5%)
Exist with stone	30(10.1%)
Cholecystectomy	19(6.4%)
Adjuvant Chemotherapy	
Yes	238(80.1%)
No	59(19.9%)
Colorectal Tumors features	
Age groups	
20-29	6(2%)
30-39	77(2.4%)
40-49	44(14.8%)
50-59	60(20.2%)
60-69	83(27.9%)
70-79	77(25.9%)
80-89	19(6.4%)
>90	1(0.3%)
Location	
Rectum	136(45.8%)
Sigmoid colon	63(21.2%)
Descending colon	33(11.1%)
Transvers colon	9(3%)
Ascending colon and cecum	56(18.9%)
Simple location	
Left Colon	232(78,1%)
Right Colon	65(21,9%)
Cell types	
Adenocarcinoma	280(94.3%)
Mucinous adenocarcinoma	14(4.7%)
Signet ring cell carcinoma	3(1%)
Differentiation	
Well differentiated	163(54.9%)
Moderate differentiated	113(38%)
Poor differantiated	21(7.1%)
Tumor Stages	
(To Modified Duke's classification of Astler and Coller)	
B1	18(6.1%)
B2	84(28.3%)
B3	4(1.3%)
C1	26(8.8%)
C2	94(31.6%)
D	71(23.9%)
Simple Dukes's Stage	
B	106(35.7%)
C	120(40.4%)
D	71(23.9%)

Table-2. The mean fibrinogen levels of Duke's C and D were higher than Duke's C (p<0,001).

Fibri-nogen	Duke's Stage B (405.2β ±121)	C (479.7β ±108)	D (489.4β ±147)	Total
Normal (22.6%)	50 (42.2%)	7 (5.8%)	10 (14.9%)	67 (100%)
High (77.4%)	56 (52.8%)	113 (94.2%)	61 (85.9%)	230 (100%)
Total	106 (100%)	120 (100%)	71 (100%)	297 (100%)
P value		P >0.05	P< 0.001	

β The mean fibrinogen level

Table-3. Cox regression analyses showed a significant risk for receipt of chemotherapy with elevated fibrinogen, carcinoembryonic antigen (CEA) and CRC location.

	P	OR	95% CI	
			Lower	*Upper*
CRC (Left/Right)	0,010	4,232	1,402	12,773
Fibrinogen	0,0001	27,919	12,887	60,484
CEA	0,022	2,542	1,145	5,643

CRC; colorectal cancer, *CEA*; carcinoembrionic antigen, *OR*; odd ratio, *CI*; confidential interval

Table-4. High preoperative fibrinogen and CEA are highly associated with receipt of chemotherapy

Fibrinogen (F) CEA (C)	Chemotherapy (Yes) 238 (80,1%)	(No) 59 (19,9%)	Total 292 (100%)
F^N and C^N	11 (23,4%)	36 (76,6%)	47 (100%)
F^N and C^H	12 (60%)	8 (40%)	20 (100%)
F^H and C^N	97 (92,4%)	8 (7,6%)	105 (100%)
F^H and C^H	118 (94,4%)	7 (5,6%)	125 (100%)

N Normal, H High

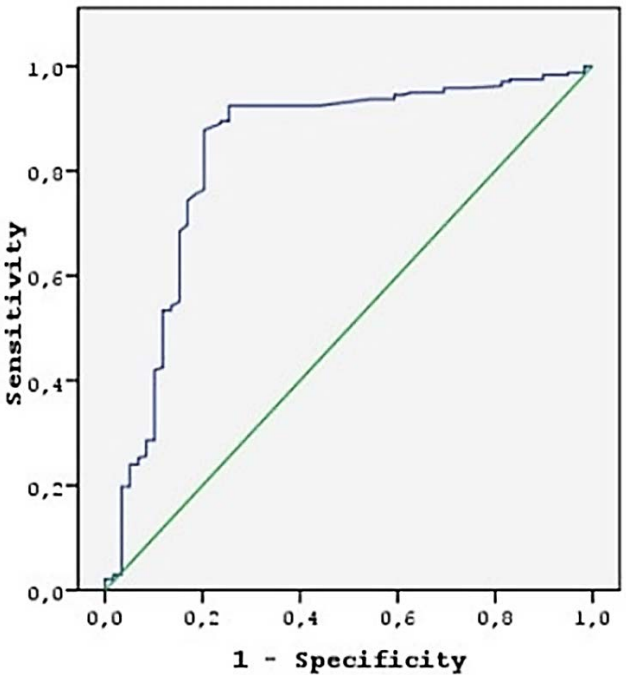

Figure-1: The receiver operating characteristic (ROC) curve analyses showed that a suitable cut-off level for poreoperative fibrinogen regarding advanced disease stage and receipt of chemotherapy as 361.5 mg/L had an 88% sensitivity and 80% specificity, area under curve=0.84.

Discussion

Unlike the previous studies, to best of our knowledge, this study is the first report to investigate the relationship between serum fibrinogen and both disease stage (limited to luminal or extra-luminal) and especially the need for chemotherapy in patients with CRC. The most critical finding we found in this study is that high preoperative fibrinogen level is greatly associated with receipt of chemotherapy and advanced disease stage. Notably, this association is more prominent when both fibrinogen and CEA are high together. Again firstly, we have found that high fibrinogen level increases 27.9 fold the risk of receiving chemotherapy with 95% confidence interval. We have also determined a cut-off level for preoperative serum fibrinogen (361.5 mg/dL) that is highly associated with advanced stage and high risk of chemotherapy.

Up to now, the pre and postoperative CEA measurements have still been used for CRC patients evaluation. However, it is detected at the normal limit in two-thirds of the patients with CRC, and also is influenced by many benign factors, such as pregnancy, smoking, and intra-abdominal inflammatory events(12). After understanding the low value of the potential use of CEA in the evaluation of colorectal cancer patients, the search for new tumor markers has begun to gain a big momentum in recent years (5, 10).

With increased knowledge about the mechanisms of molecular pathways of CRC growth, deep invasion, and extended metastasis that is commonly known as hematologic, the new relationship between coagulation factors and cancer behaviors has increasingly been the subject of lots of cornerstone manuscript in recent years (13, 14). Of these, especially fibrin-related products are frequently associated with advanced disease, prognosis and cancer-related venous thromboembolism (6, 15-17). Also, it is shown that these factors show dynamic changes during anti-tumor treatment (8, 18). The determination of the effect of these factors on colon cancer growth and spread is very striking finding. From these factors, the fibrinogen is now being considered a major determinant of colon cancer growth and dissemination (7). In all previous studies, the significance of preoperative fibrinogen is often studied mainly regarding a predictor of therapeutic response, prognostic value, and survival rate in patients with CRC (3, 18-21). High preoperative fibrinogen is often associated with advanced disease stage, poor tumor differentiation, more deep invasion and lymph node metastasis (9, 22). Up to now, there is no a unique study investigating the relationship between preoperative fibrinogen and receipt of chemotherapy.

Apart from other studies, in this paper, we studied the relationship between preoperative fibrinogen and the receipt of chemotherapy as well as disease stage. As in previous studies, we firstly found that high preoperative fibrinogen correlates with advanced stage. Our second finding, high preoperative fibrinogen is greatly associated with receipt of chemotherapy, has not been investigated before. We also determined a useful cut-off level for preoperative fibrinogen with high sensitivity and specificity.

Conclusion

Despite the improvements in the field of tumor growth, development and metastasis pathways in recent years, there is still a lack of a simple, non-invasive and reliable method that accurately measured to disease stage and the need for chemotherapy. Our study revealed some new information to clinicians and a patient who has a new CRC diagnosis at the time of diagnosis. If a patient with CRC has high preoperative fibrinogen and CEA, this patient is most probably advanced disease (extraluminal) and will high probably receipt chemotherapy.

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Abbreviations

CRC: Colorectal Carcinoma
CEA:Carcinoembrionic antigen
HB: Hemoglobin