Cite as: Wang HB, Wu W, Pu ZZ, Zhang LH, Wang YB, Xu H. Effects of laparoscopic surgery combined with intraperitoneal thermal perfusion on postoperative coagulation indicators in patients with colorectal cancer [J]. Chin J Clin Res, 2024, 37(9):1342-1346.

DOI: 10.13429/j.cnki.cjcr.2024.09.007

Effects of laparoscopic surgery combined with intraperitoneal thermal perfusion on postoperative coagulation indicators in patients with colorectal cancer

WANG Hongbing, WU Wan, PU Zhizhong, ZHANG Lihua, WANG Yubin, XU Hao

Department of Gastroenterology and Breast Surgery, The People's Hospital of Kaizhou District, Chongqing 405400, China

Corresponding author: XU Hao, E-mail: 691095612@qq.com

Abstract: Objective To observe the changes of coagulation function in patients with colorectal cancer (CRC) after laparoscopic surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC). **Methods** Sixty patients with colorectal cancer admitted to The People's Hospital of Kaizhou District, Chongqing from January to October 2023 were selected as the study subjects and randomly divided into study group and control group, with 30 cases in each group. The control group underwent laparoscopic surgery, while the study group underwent laparoscopic surgery combined with HIPEC (fluorouracil). The surgical conditions and changes in perioperative coagulation function indicators between two groups. **Results** There was no statistically significant difference between the study group and the control group in intraoperative blood loss[(84.33±40.66) mL *vs* (100.33±52.82) mL], surgical time[(174.77±31.29) min vs (167.67±28.61) min], anal exhaust time [(3.17±0.79) d *vs* (3.03±0.81) d], and postoperative hospital stay [(14.23±3.76) d *vs* (14.70±5.34) d] (P>0.05). The levels of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), and D-dimer (D-D) in the two groups showed significant fluctuations over time (P<0.05), while there was no significant difference in the above indicators between the two (P>0.05). There was no statistically significant difference between the two groups in postoperative complications (20.0% vs 13.3%, χ^2=0.481, P=0.481) such as abdominal bleeding, deep vein thrombosis, intestinal obstruction, and anastomotic fistula. **Conclusion** Although laparoscopic surgery leads to enhanced coagulation function and hypercoagulable blood in patients with colorectal cancer, the combination of postoperative intraperitoneal thermal perfusion chemotherapy does not increase the risk of postoperative DVT. Therefore, intraperitoneal thermal perfusion technology is still safe and reliable.

Keywords: Colorectal cancer; Laparoscopic surgery; Hyperthermic intraperitoneal chemotherapy; Coagulation function; Fluorouracil

Fund program: Chongqing Municipal Health Commission Project (2023WSJK080); Guiding Project of Science and Technology Bureau of Kaizhou District, Chongqing (2022-Z-01-44)

Colorectal cancer (CRC) is a common gastrointestinal tumor, and peritoneal implantation metastasis is a terminal stage for CRC patients, representing a significant cause of postoperative recurrence and mortality [1]. Hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective method for treating peritoneal implantation metastases and associated malignant ascites. It not only effectively targets peritoneal metastases but also effectively controls the production of malignant ascites, significantly improving patients' quality of life [2]. Therefore, HIPEC is widely applied in the prevention and treatment of peritoneal metastases in CRC. However, there is still some controversy regarding the impact of HIPEC on patients' coagulation function. For example, Dirkmann *et al.* [3] suggested that the high temperature of the perfusate during HIPEC caused hypercoagulation, while the absorption of the perfusate inhibited the coagulation function, ultimately leading to a high risk of thrombosis. Conversely, domestic studies showed that intra-abdominal hyperthermic perfusion improved coagulation function in patients undergoing laparoscopic gastric cancer radical surgery [4]. Therefore, the impact and mechanisms of HIPEC on coagulation function need further investigation. This study explores the effects of laparoscopic surgery combined with HIPEC on postoperative coagulation indicators in CRC patients. The findings are reported as follows.

1 Materials and methods

1.1 General information

Sixty CRC patients admitted to The People's Hospital of Kaizhou District from January to October 2023 were selected as research subjects. All patients were randomly divided into study group and control group, with 30 cases in each group, according to a random number table. This study was approved by the Medical Ethics Committee of The People's Hospital of Kaizhou District, Chongqing [Ethics Number:

202201(XP)-19].

Inclusion criteria: (1) Complete clinical data, clear surgical indications, and postoperative pathological diagnosis of CRC; (2) Good general condition without severe diseases of the heart, lungs, kidneys, or other major organs; (3) No contraindications for laparoscopic surgery and HIPEC; (4) No bleeding tendency or similar conditions; (5) Informed consent provided and signed by the patient.

Exclusion criteria: (1) Abnormalities in heart, brain, liver, or kidney function; (2) Receiving other treatments at present; (3) Presence of liver or lung distant metastases.

In the study group, there were 18 male and 12 female patients, with an average age of (55.73±10.41) years. Tumor locations included 19 rectal and 11 colonic cases; tumor T stages were T_{1-2} in 7 cases and T_{3-4} in 23 cases. In the control group, there were 21 male and 9 female patients, with an average age of (53.63±10.47) years. Tumor locations included 14 rectal and 15 colonic cases; tumor T stages were T_{1-2} in 6 cases and T_{3-4} in 24 cases. Comparisons of general data between the two groups showed no statistically significant differences (P>0.05), indicating comparability.

1.2 Methods

Both groups of patients underwent laparoscopic colorectal cancer radical resection performed by a senior associate chief physician or higher. In the control group, a conventional abdominal drainage tube was placed postoperatively. In the study group, four drainage tubes were inserted through punctures in the left and right pelvic cavities and the left and right pericolic gutters. Within 3 days postoperatively, preventive HIPEC was administered twice using the BR-TRG-1 heated perfusion machine produced by Guangzhou Baorui Medical Technology Co., Ltd. Half an hour before the perfusion, sedation and analgesia were provided using a mixture of duromorphine and phenazocine. A solution for heated perfusion chemotherapy was prepared by adding 1 g of fluorouracil to 5 000 mL of 0.9% sodium chloride injection. The solution was heated to 35°C and infused into the abdominal cavity through the water inlet at a rate of 200 – 400 mL/min. The abdominal cavity temperature was then precisely controlled at approximately 43 °C for 1 hour of heated perfusion chemotherapy. During the procedure, oxygen supplementation and electrocardiographic monitoring were provided, and prophylactic antiemetic treatment was administered with 2 mg of tropisetron via intravenous push. The infusion flow rate and volume were adjusted according to the patient' s tolerance. Throughout the procedure, the volume of perfusion fluid in the abdominal cavity was maintained above 2 000 mL, with the residual fluid at the end of the procedure controlled to be below 1,200 mL. The residual fluid was then continuously drained through a drainage bag.

1.3 Observation indicators

(1) The intraoperative bleeding, operation time, anal exhaust time and postoperative hospitalization time were recorded.

(2) The changes of coagulation function indexes of the two groups in the preoperative period, immediate postoperative period and 72 h postoperative period were recorded.

(3) Postoperative complications such as abdominal bleeding, deep vein thrombosis (DVT), intestinal obstruction and anastomotic fistula were also recorded in both groups.

1.4 Detection methods

All patients were taken 5 mL of fasting venous blood before, immediately after, and 72 h after the operation, respectively, and sent to the Laboratory Department for blood coagulation indexes [prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer(D-D)] detection using the CS2000i series of hemocoagulation of Japan's Sysmex.

1.5 Statistical methods

Data were analyzed using SPSS 20.0 software. Data with normal distribution were expressed as $\bar{x}$±s, and between-group comparisons were performed using *t*-test. Repeated measures data were analyzed using repeated measures ANOVA. Categorical data were presented as case (%), with between-group comparisons performed using the chi-square test. A *P*-value < 0.05 was considered statistically significant.

2 Results

2. 1 Comparison of the surgical conditions

The intraoperative bleeding, operation time, anal exhaustion time and postoperative hospitalization time of the two groups were compared, and the difference was not statistically significant ($P > 0.05$). **See Table 1.**

2.2 Comparison of changes in perioperative coagulation indexes

The coagulation indicators, including PT, APTT, FIB, and D-D, showed significant changes over time within each group ($P < 0.05$). However, there was no significant differences in these indicators between the two groups ($P > 0.05$). **See Table 2.**

2.3 Comparison of postoperative complications

In the study group, there were 2 cases of abdominal hemorrhage, 3 cases of intestinal obstruction, and 1 case of anastomotic leakage. In the control group, there was 1 case of abdominal hemorrhage, 1 case of deep vein thrombosis, 1 case of intestinal obstruction, and 1 case of anastomotic leakage. The difference in complication rates between the study group and control group was not statistically significant (20.00% *vs* 13.33%, χ^2=0.481, *P*=0.488).

Tab. 1 Comparison of surgical conditions between two groups of patients (n=30, $\bar{x}\pm s$)

Group	Intraoperative bleeding (mL)	Operation time (min)	Anal exhaustion time (d)	Hospitalization time (d)
Study group	84.33±40.66	174.77±31.29	3.17±0.79	14.23±3.76
Control group	100.33±52.82	167.67±28.61	3.03±0.81	14.70±5.34
***t* value**	1.315	0.917	0.645	0.391
***P* value**	0.194	0.363	0.521	0.697

Tab.2 Comparison of coagulation function indicators before and after surgery between two groups of patients (n=30, $\bar{x}\pm s$)

Group	PT (s)			APTT (s)		
	Before operation	Immediately after operation	72 h after the operation	Before operation	Immediately after operation	72 h after the operation
Study group	10.98±1.63	9.03±1.24[a]	9.74±1.08	28.74±3.62	25.11±3.54[a]	25.44±3.04
Control group	10.70±1.50	9.32±1.25[b]	9.72±1.09	27.89±2.92	26.21±3.76[b]	26.73±3.99
$F_{time}/F_{intergroup}/F_{interaction}$		28.930/0.001/0.810			9.818/1.007/1.695	
$P_{time}/P_{intergroup}/P_{interaction}$		<0.001/0.970/0.447			<0.001/0.320/0.188	

Group	FIB (g/L)			D-D (mg/L)		
	Before operation	Immediately after operation	72 h after the operation	Before operation	Immediately after operation	72 h after the operation
Study group	2.98±0.58	3.72±0.63[a]	3.61±0.48	0.44±0.21	2.02±1.19[a]	1.75±0.99
Control group	3.09±0.63	3.86±0.53[b]	3.59±0.49	0.47±0.21	2.04±1.42[b]	1.80±1.95
$F_{time}/F_{intergroup}/F_{interaction}$		27.127/1.193/0.316			39.422/0.030/0.006	
$P_{time}/P_{intergroup}/P_{interaction}$		<0.001/0.279/0.730			<0.001/0.862/0.994	

3 Discussion

The global cancer epidemiology database showed that CRC was the third most common cancer and the second leading cause of death [5]. Despite the use of various treatment modalities such as surgery, chemotherapy, targeted therapy, radiotherapy, immunotherapy, and biological therapy [6], the treatment outcomes for CRC remain suboptimal due to the occurrence of intraperitoneal implantation and metastasis [7]. Therefore, there is a need to adopt safe and effective methods to eliminate residual microlesions and free cancer cells in the abdominal cavity [8-9], in order to prolong patient survival and improve prognosis. HIPEC, as a novel and mature technique, targets the destruction of residual microlesions and free cancer cells in the peritoneal cavity and is currently considered the standard approach for the prevention and treatment of peritoneal metastasis in CRC [2,10-11].

Malignant tumor patients are prone to postoperative coagulation disorders, with a two-fold increased risk of DVT and a three-fold increased risk of pulmonary embolism (PE) compared to non-cancer patients, making venous thromboembolism one of the main causes of death among cancer patients [12]. This is because cancer cells can activate the coagulation system by producing and releasing pro-coagulant and fibrinolytic proteins, inflammatory cytokines, and pro-coagulant microparticles, leading to a hypercoagulable state or thrombotic predisposition [13]. The pathogenesis and factors associated with cancer-related thrombosis are extremely complex, including various risk factors such as clinical risk factors, fibrinolytic system, and pro-coagulant factor expression, which can activate the hemostatic system and lead to thromboembolism [14-15]. Despite extensive research on complications of HIPEC conducted domestically and internationally in the past, studies on its impact on coagulation function are scarce. Therefore, research on the effects of HIPEC on the coagulation system and thrombotic risk in cancer patients is necessary.

PT primarily reflects the status of extrinsic coagulation, while APTT mainly reflects the intrinsic coagulation status. Both PT and APTT are significantly shortened in thrombotic diseases or hypercoagulable states. FIB is a coagulation factor protein synthesized by the liver and is significantly elevated in infectious diseases, tumors, and thrombotic diseases. D-D is a product of cross-linked fibrin degradation and mainly reflects fibrinolytic function, with marked increases in diseases such as deep vein thrombosis and malignancies,

indicating a hypercoagulable state and secondary fibrinolysis. Thus, these four coagulation indicators can accurately reflect changes in the body's coagulation function [16].

Previous studies have shown that both open surgery and laparoscopic surgery result in significant prolongation of PT and increases in D-D and FIB levels postoperatively [17]. Compared to traditional surgery, laparoscopic surgery leads to a more pronounced extension of PT and further elevation of D-D and FIB levels. Our study similarly showed that, immediately after surgery and at 72 hours postoperatively, PT and APTT significantly decreased, while FIB and D-D levels markedly increased in both groups, further demonstrating that abdominal colorectal surgery activates the coagulation system, resulting in a hypercoagulable state in patients. Consequently, due to the pro-coagulant and thrombotic stimuli associated with laparoscopic surgery, patients are in a distinctly hypercoagulable state postoperatively and at risk of thrombotic diseases, warranting proactive preventive measures during the perioperative period. Currently, there is no unified conclusion on the impact of HIPEC on coagulation function both domestically and internationally.

In foreign studies, recent research by Dranichnikov *et al.* [18] showed that PT and APTT were directly elevated following HIPEC, but returned to normal levels by the fifth postoperative day, indicating an increase in bleeding factors during the initial days after surgery. In contrast, FIB, platelet count, D-D, and antithrombin levels increased on the fifth day and continued to rise until the end of the study, suggesting a potential increase in the risk of thromboembolic complications. However, a study by Kim *et al.* [19] presented different findings. They observed that platelet count, PT, and APTT decreased below preoperative levels after HIPEC, indicating a hypercoagulable state. Studies categorized the risk factors for thrombosis in cancer patients into three general categories, the first includes patient-related factors such as advanced age, immobility, obesity, previous thrombosis, genetic predispositions to thrombosis, elevated white blood cell and platelet counts, and comorbid conditions; the second encompasses cancer-related factors, such as the site and stage of cancer, inflammatory components, and necrotic tumors; the third consists of treatment-related factors, including the extent and duration of surgical trauma, blood loss, length of hospital stay, chemotherapy, reduced liver perfusion during intraperitoneal hyperthermic chemotherapy, and fluid volume, all of which may disrupt hemostatic balance and increase the risk of postoperative thromboembolic complications. Thus, it is evident that the occurrence of thromboembolic complications following HIPEC or any other major surgery largely depends on the balance between tissue damage, coagulation, and fibrinolytic system functions.

In a research conducted in China, it is believed that the coagulation function of patients during HIPEC is primarily influenced by both the intraperitoneal hyperthermia and the chemotherapy drugs [22]. On one hand, the high-temperature perfusate used in intraperitoneal hyperthermia can cause dilation of the abdominal blood vessels, leading to a large amount of perfusate being absorbed into the abdominal cavity, which dilutes the patient's blood and subsequently reduces coagulation function. Additionally, the elevated body temperature during intraperitoneal hyperthermia may also lead to increased coagulation function [2]. On the other hand, the chemotherapy drugs used during the heat perfusion period may also contribute to coagulation dysfunction in patients. Research by Pan *et al.* [23] found that gastrointestinal cancer patients were inherently in a hypercoagulable state, which was further exacerbated, especially during the stage of tumor metastasis. Chemotherapy at this stage may significantly increase the risk of thrombosis due to damage to endothelial cells caused by the chemotherapy drugs. In summary, for patients with CRC undergoing laparoscopic surgery combined with HIPEC, their coagulation function may be influenced by multiple factors including the tumor, anesthesia, laparoscopic surgery, intraperitoneal hyperthermic chemotherapy, and chemotherapy drugs. Feng *et al.* [24] found that intraperitoneal hyperthermic chemotherapy only caused short-term abnormalities in coagulation function indicators in a few cases, with no statistically significant differences in complications. Our study similarly found no statistical differences in PT, APTT, FIB, and D-D values at postoperative time points between the two groups. This indicates that the impact of HIPEC on coagulation function in patients undergoing CRC surgery is within a controllable range and does not increase the risk of postoperative DVT.

In conclusion, although laparoscopic surgery leads to enhanced coagulation function and hypercoagulable state of blood in CRC patients, their postoperative combined HIPEC does not increase the risk of postoperative DVT, so HIPEC technique is still safe and reliable.

The authors report no conflict of interest

References

[1] Yuan ZX, Lin QF, Cai J, et al. Advances in indication of cytoreductive surgery of peritoneal metastasis in gastrointestinal cancer[J]. Chin J Pract Surg, 2023, 43(8): 951-955. **[In Chinese]**

[2] Cui SZ. Progress in the research of abdominal thermal perfusion chemotherapy technology in China in the last decade[J]. Guangdong Med J, 2023, 44(6): 661-665. **[In Chinese]**

[3] Dirkmann D, Hanke AA, Görlinger K, et al. Hypothermia and acidosis synergistically impair coagulation in human whole blood[J]. Anesth Analg, 2008, 106(6): 1627-1632.

[4] Li L, Zhang JQ, Si HF, et al. Effect of hyperthermic intraperitoneal perfusion on

blood coagulation in patients undergoing laparoscope-assisted radical surgery for gastric cancer[J]. Chin J Anesthesiol, 2015, 35(11): 1328-1330. **[In Chinese]**

[5] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6): 394-424.

[6] Li P. Effect of radical resection of colorectal cancer combined with intraperitoneal hyperthermic perfusion chemotherapy on tumor markers and long-term survival of patients[J]. J Aerosp Med, 2021, 32(4): 417-418. **[In Chinese]**

[7] Lin Y, Guo XK, Shen C, et al. Safety evaluation of preventive intraperitoneal hyperthermic perfusion chemotherapy in patients with advanced colorectal cancer after radical resection[J]. Chin J Colorectal Dis Electron Ed, 2021, 10(6): 591-598. **[In Chinese]**

[8] Zhang Y. Effect and safety of laparoscopic radical resection of colon cancer combined with postoperative intraperitoneal thermoinfusion chemotherapy with Loplatin on patients with colon cancer[J]. Clin Med, 2023, 43(4): 1-4. **[In Chinese]**

[9] Yang F, Zhang YM, Zhou CP, et al. Safety and short-term efficacy of radical surgery combined with hyperthermic intraperitoneal chemotherapy for locally advanced gastric cancer[J]. Chin J Gen Surg, 2021, 30(4): 412-420. **[In Chinese]**

[10] Jiang XM, Chen W, Zheng WQ, et al. Effect of hyperthermic intraperitoneal chemotherapy on intestinal barrier function in patients with colorectal cancer[J]. Acta Med Univ Sci Technol Huazhong, 2021, 50(1): 82-85, 108. **[In Chinese]**

[11] Xu L, Sun J. Advances in treatment of peritoneal metastasis from colorectal cancer[J]. Chin Clin Oncol, 2023, 28(1): 84-89. **[In Chinese]**

[12] Falanga A, Marchetti M. Cancer-associated thrombosis: enhanced awareness and pathophysiologic complexity[J]. J Thromb Haemost, 2023, 21(6): 1397-1408.

[13] Falanga A, Schieppati F, Russo L. Pathophysiology 1. mechanisms of thrombosis in cancer patients[M]//Soff G. Thrombosis and Hemostasis in Cancer. Cham: Springer, 2019: 11-36.

[14] Schieppati F, Russo D, Falanga A. Cancer tissue procoagulant mechanisms and the hypercoagulable state of patients with cancer[J]. Semin Thromb Hemost, 2015, 41(7): 756-764.

[15] Ma YL, Wang BF, He PY, et al. Coagulation- and fibrinolysis-related genes for predicting survival and immunotherapy efficacy in colorectal cancer[J]. Front Immunol, 2022, 13: 1023908.

[16] Ma XL, Li YY, Zhang J, et al. Prognostic role of D-dimer in patients with lung cancer: a meta-analysis[J]. Tumor Biol, 2014, 35(3): 2103-2109.

[17] Xu H, Zheng LH, Zhang JY, et al. Effects of transabdominal preperitoneal prosthetic and Lichtenstein hernia repair on coagulation function in patients with inguinal hernia[J]. Chin J N Clin Med, 2020, 13(1): 64-66. **[In Chinese]**

[18] Dranichnikov P, Mahteme H, Cashin PH, et al. ASO visual abstract: coagulopathy and venous thromboembolic events following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy[J]. Ann Surg Oncol, 2021, 28(3): 440.

[19] Kim MH, Yoo YC, Bai SJ, et al. Physiologic and hemodynamic changes in patients undergoing open abdominal cytoreductive surgery with hyperthermic intraperitoneal chemotherapy[J]. J Int Med Res, 2021, 49(1): 030006052098326.

[20] Connolly GC, Khorana AA. Emerging risk stratification approaches to cancer-associated thrombosis: risk factors, biomarkers and a risk score[J]. Thromb Res, 2010, 125: S1-S7.

[21] Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects[J]. J Thromb Haemost, 2013, 11(2): 223-233.

[22] Li L, Meng FM, Sun PC. Influencing factors of perioperative coagulation function in patients with intraperitoneal hyperthermia perfusion during operation[J]. J Zunyi Med Univ, 2014, 41(8): 90-91. **[In Chinese]**

[23] Pan JL, Wang XJ, Wu P. The impact of chemotherapy on coagulation function in patients with gastrointestinal cancer[J]. Clin Med China, 2012, 28(12): 1245-1249. **[In Chinese]**

[24] Feng Q, Yuan XH, Zheng ZX, et al. Clinical trial of intra-operative hyperthermic intraperitoneal chemotherapy for advanced gastric cancer[J]. Chin J Clin Oncol Rehabil, 2011, 18(3): 238-241. **[In Chinese]**

Submission received: 2024-02-01/ **Revised:** 2024-03-30

·论　著·

腹腔镜手术联合腹腔热灌注化疗对结直肠癌患者术后凝血指标的影响

王红兵，吴万，蒲志忠，张丽华，王毓彬，徐浩
重庆市开州区人民医院胃肠乳腺外科，重庆 405400

摘要：目的　观察结直肠癌（CRC）患者腹腔镜手术后进行腹腔热灌注化疗（HIPEC）治疗后凝血功能的变化。**方法**　选取 2023 年 1 月至 10 月重庆市开州区人民医院收治的 60 例 CRC 患者作为研究对象，随机分为研究组和对照组，各 30 例。对照组采用腹腔镜手术，研究组采用腹腔镜手术联合 HIPEC（氟尿嘧啶）。观察比较两组患者手术情况及围术期凝血功能指标的变化。**结果**　研究组和对照组患者术中出血量[（84.33±40.66）mL *vs*（100.33±52.82）mL]、手术时间[（174.77±31.29）min *vs*（167.67±28.61）min]、肛门排气时间[（3.17±0.79）d *vs*（3.03±0.81）d]及术后住院时间[（14.23±3.76）d *vs*（14.70±5.34）d]比较，差异无统计学意义（$P>0.05$）。两组患者组内凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）、纤维蛋白原（FIB）、D 二聚体（D-D）水平随着时间点推移有显著变化（$P<0.05$），而两组组间上述指标比较差异无统计学意义（$P>0.05$）。两组患者术后腹腔出血、深静脉血栓、肠梗阻及吻合口瘘等并发症总发生率比较，差异无统计学意义（20.00% *vs* 13.33%，$\chi^2=0.481$，$P=0.488$）。**结论**　尽管腹腔镜手术导致结直肠癌患者凝血功能增强，血液处于高凝状态，但其术后联合 HIPEC 并不增加术后深静脉血栓形成风险，故 HIPEC 仍安全可靠。

关键词：结直肠癌；腹腔镜手术；腹腔热灌注化疗；凝血功能；深静脉血栓形成；氟尿嘧啶
中图分类号：R735.3　**文献标识码：**A　**文章编号：**1674-8182(2024)09-1342-05

Effects of laparoscopic surgery combined with hyperthermic intra peritoneal chemotherapy on postoperative coagulation indicators in patients with colorectal cancer

WANG Hongbing, WU Wan, PU Zhizhong, ZHANG Lihua, WANG Yubin, XU Hao
Department of Gastroenterology and Breast Surgery, The People's Hospital of Kaizhou District, CQ, Chongqing 405400, China
Corresponding author: XU Hao, E-mail: 691095612@qq.com

Abstract: Objective　To observe the changes of coagulation function in patients with colorectal cancer (CRC) after laparoscopic surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC). **Methods**　Sixty patients with CRC admitted to The People's Hospital of Kaizhou District, CQ from January to October 2023 were selected as the study subjects and randomly divided into study group and control group, with 30 cases in each group. The control group underwent laparoscopic surgery, while the study group underwent laparoscopic surgery combined with HIPEC (fluorouracil). The surgical conditions and changes in perioperative coagulation function indicators were observed and compared between two groups. **Results**　There was no statistically significant difference between the study group and the control group in intraoperative blood loss [(84.33±40.66) mL *vs* (100.33±52.82) mL], surgical time [(174.77±31.29) min *vs* (167.67±28.61) min], anal exhaust time [(3.17±0.79) d *vs* (3.03±0.81) d], and postoperative hospital stay [(14.23±3.76) d *vs* (14.70±5.34) d] ($P>0.05$). The levels of prothrombin time (PT), activated partial

DOI: 10.13429/j.cnki.cjcr.2024.09.007
基金项目：重庆市卫生健康委医学科研项目（2023WSJK080）；重庆市开州区科学技术局指导性项目（2022-Z-01-44）
通信作者：徐浩，E-mail：691095612@qq.com
出版日期：2024-09-20

QR code for English version

thromboplastin time (APTT), fibrinogen (FIB), and D-dimer (D-D) in the two groups showed significant fluctuations over time ($P<0.05$), while there was no significant difference in the above indicators between the two groups ($P>0.05$). There was no statistically significant difference in the total incidence of postoperative compliaticons (20.00% *vs* 13.33%, $\chi^2 = 0.481$, $P = 0.488$) such as abdominal bleeding, deep vein thrombosis, intestinal obstruction, and anastomotic fistula between the two groups. **Conclusion** Although laparoscopic surgery leads to enhanced coagulation function and hypercoagulable blood in patients with CRC, the combination of postoperative HIPEC does not increase the risk of postoperative deep vein thrombosis, therefore, HIPEC technology is still safe and reliable.

Keywords: Colorectal cancer; Laparoscopic surgery; Hyperthermic intraperitoneal chemotherapy; Coagulation function; Deep vein thrombosis; Fluorouracil

Fund program: Chongqing Municipal Health Commission Medicial Research Project (2023WSJK080); Guiding Project of Science and Technology Bureau of Kaizhou District, Chongqing (2022-Z-01-44)

结直肠癌(colorectal cancer, CRC)是一种常见的消化道肿瘤,而腹腔种植转移是 CRC 患者的终末期阶段,是导致患者术后复发和死亡的重要原因[1]。腹腔热灌注化疗(hyperthermic intraperitoneal chemotherapy, HIPEC)是一种针对腹腔种植转移及合并恶性腹腔积液治疗的有效手段,不仅能有效地靶向治疗腹腔种植转移,亦能有效控制恶性腹水的产生,使患者的生存质量显著提高[2]。因此,在预防和治疗 CRC 腹腔种植转移方面 HIPEC 应用广泛。但 HIPEC 对患者凝血功能影响与否仍存在一定争议。比如 Dirkmann 等[3]认为 HIPEC 过程中灌注液的高温能够造成患者凝血功能亢进,而腹腔灌注液的吸收又能抑制患者的凝血功能,最终导致患者血栓形成高风险。而国内有研究显示,腹腔内热灌注可改善腹腔镜胃癌根治术患者的凝血功能[4]。因此,HIPEC 对患者的凝血功能的影响及机制有待进一步研究。故本研究探讨腹腔镜手术联合 HIPEC 对 CRC 患者术后凝血指标的影响。现报道如下。

1　资料与方法

1.1　一般资料　选取 2023 年 1 月至 10 月重庆市开州区人民医院收治的 60 例 CRC 患者作为研究对象,所有患者按照随机数字表随机分为研究组和对照组,各 30 例。本研究经重庆市开州区人民医院医学伦理委员会审核批准[伦理编号:202201(XP)-19]。纳入标准:(1) 临床资料完整,手术指征明确,术后病理学确诊为 CRC;(2) 一般情况良好,无严重心、肺、肾等重要脏器疾病;(3) 无腹腔镜手术和 HIPEC 禁忌证;(4) 无出血倾向等疾病;(5) 对本研究知情,并签署了知情同意书。排除标准:(1) 心、脑、肝、肾功能异常者;(2) 现阶段行其他治疗者;(3) 出现肝、肺远处转移者。研究组男性 18 例,女性 12 例;年龄(55.73±10.41)岁;肿瘤部位,直肠 19 例,结肠 11 例;肿瘤 T 分期,$T_{1\sim2}$期 7 例,$T_{3\sim4}$期 23 例。对照组男性 21 例,女性 9 例;年龄(53.63±10.47)岁;肿瘤部位,直肠 14 例,结肠 15 例;肿瘤 T 分期,$T_{1\sim2}$期 6 例,$T_{3\sim4}$期 24 例。两组患者的一般资料比较,差异无统计学意义($P>0.05$)。

1.2　方法　两组患者均由手术熟练的副主任医师及以上职称主刀进行腹腔镜下 CRC 根治术。对照组术后常规放置腹腔引流管。研究组术后分别于左右盆腔和左右结肠旁沟经戳孔放置 4 根引流管。术后 3 d 内使用广州保瑞医疗技术生产的 BR-TRG-1 型热灌注机实施预防性 HIPEC 2 次。灌注前半小时使用杜非合剂[盐酸哌替啶(杜冷丁)+盐酸异丙嗪(非那根)]镇静止痛。采用 1 g 氟尿嘧啶加入 5 000 mL 的 0.9%氯化钠注射液配置成热灌注化疗液。将其加热至 35 ℃后以 200~400 mL/min 的速度进水管注入腹腔,然后使腹腔内温度精准控制在 43 ℃左右,进行热灌注化疗 1 h;期间予以吸氧和心电监护,并予以托烷司琼 2 mg 静脉推注预防性止吐治疗。根据患者的耐受情况来控制灌注流量和流速,整个过程维持腹腔内灌注液量在 2 000 mL 以上,结束时控制体内残留灌注液在 1 200 mL以下,残余液体灌注后接引流袋持续引流干净。

1.3　观察指标　记录两组患者术中出血量、手术时间、肛门排气时间及术后住院时间等情况。观察两组患者术前、术后即刻、术后 72 h 凝血功能指标变化。同时记录两组患者的术后腹腔出血、深静脉血栓形成(deep vein thrombosis, DVT)、肠梗阻及吻合口瘘等并发症情况。

1.4　检测方法　所有患者分别于术前、术后即刻、术后 72 h,抽取空腹静脉血 5 mL,送至检验科使用日本希森美康 CS2000i 血凝全自动血凝分析仪系列进行凝血指标[凝血酶原时间(prothrombin time, PT)、活化部分凝血活酶时间(activated partial thromboplastin

time, APTT)、纤维蛋白原(fibrinogen, FIB)、D 二聚体(D-dimer, D-D)]检测。

1.5　统计学方法　采用 SPSS 20.0 软件进行统计学分析。计量资料以 $\bar{x}\pm s$ 表示,两组间比较采用成组 t 检验,重复测量数据比较采用两因素多水平重复测量方差分析。计数资料以例(%)表示,采用 χ^2 检验。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　两组患者手术及术后情况比较　两组患者的术中出血量、手术时间、肛门排气时间及术后住院时间比较,差异无统计学意义($P>0.05$)。见表 1。

2.2　两组患者围术期凝血指标变化的比较　两组患者凝血功能各指标随着时间点推移有显著变化($P<0.05$)。而两组患者组间对应指标比较差异无统计学意义($P>0.05$)。见表 2。

2.3　两组患者术后并发症情况比较　研究组术后发生腹腔出血 2 例,肠梗阻 3 例,吻合口瘘 1 例,并发症总发生率 20.00%,对照组术后腹腔出血 1 例,深静脉血栓 1 例,肠梗阻 1 例,吻合口瘘 1 例,并发症总发生率 13.33%,两组并发症发生率比较差异无统计学意义($\chi^2=0.481$, $P=0.488$)。

表 1　两组患者手术及术后情况比较　($n=30$, $\bar{x}\pm s$)

Tab. 1　Comparison of operative and postoperative conditions between two groups of patients　($n=30$, $\bar{x}\pm s$)

组别	术中出血量(mL)	手术时间(min)	肛门排气时间(d)	术后住院时间(d)
研究组	84.33±40.66	174.77±31.29	3.17±0.79	14.23±3.76
对照组	100.33±52.82	167.67±28.61	3.03±0.81	14.70±5.34
t 值	1.315	0.917	0.645	0.391
P 值	0.194	0.363	0.521	0.697

表 2　两组患者手术前后凝血功能各指标比较　($n=30$, $\bar{x}\pm s$)

Tab. 2　Comparison of coagulation function indicators before and after surgery between two groups of patients ($n=30$, $\bar{x}\pm s$)

组别	PT(s)			APTT(s)		
	术前	术后即刻	术后 72 h	术前	术后即刻	术后 72 h
研究组	10.98±1.63	9.03±1.24[a]	9.74±1.08	28.74±3.62	25.11±3.54[a]	25.44±3.04
对照组	10.70±1.50	9.32±1.25	9.72±1.09	27.89±2.92	26.21±3.76	26.73±3.99
$F_{时间}/F_{组间}/F_{交互}$ 值		28.930/0.001/0.810			9.818/1.007/1.695	
$P_{时间}/P_{组间}/P_{交互}$ 值		<0.001/0.970/0.447			<0.001/0.320/0.188	

组别	FIB(g/L)			D-D(mg/L)		
	术前	术后即刻	术后 72 h	术前	术后即刻	术后 72 h
研究组	2.98±0.58	3.72±0.63[a]	3.61±0.48	0.44±0.21	2.02±1.19[a]	1.75±0.99
对照组	3.09±0.63	3.86±0.53	3.59±0.49	0.47±0.21	2.04±1.42	1.80±1.95
$F_{时间}/F_{组间}/F_{交互}$ 值		27.127/1.193/0.316			39.422/0.030/0.006	
$P_{时间}/P_{组间}/P_{交互}$ 值		<0.001/0.279/0.730			<0.001/0.862/0.994	

注:与本组术前时点比较,[a]$P<0.05$。

3　讨　论

全球肿瘤流行病学数据库显示,CRC 是第三大常见的肿瘤,是第二大致死原因[5]。尽管有手术、化疗、靶向、放疗、免疫以及生物治疗等各种手段的应用[6],但由于腹腔种植转移的出现,CRC 治疗效果仍不理想[7]。因此,需要采取安全而又有效的手段来清除腹腔内残留的微小肿瘤灶和游离肿瘤细胞[8-9],达到延长患者生存期,并改善其预后。而 HIPEC 作为新型又成熟的技术,它能够靶向消灭患者腹腔体内残留的微小肿瘤灶和游离肿瘤细胞,目前被认为是 CRC 腹腔种植转移预防和治疗的标准方法[2,10-12]。

恶性肿瘤患者易发生术后凝血功能障碍,其较普通手术患者,DVT 的风险升高两倍,肺栓塞(pulmonary embolism, PE)的风险升高三倍,故动静脉血栓形成是肿瘤患者死亡的主要原因之一[13]。这是因为肿瘤细胞可以通过产生并释放促凝血和纤溶蛋白、炎性细胞因子和促凝血微粒等激活凝血系统,导致恶性肿瘤的高凝状态或血栓前状态[14-16]。肿瘤相关血栓形成的发病机制和因素极其复杂,包括临床风险因素、纤溶系统和促凝血因子表达在内的各种风险因素均可激活止血系统并导致血栓栓塞[17-18]。尽管国内外在过去对 HIPEC 进行了大量并发症方面的研究,但对其凝血功能影响的研究甚少。因此,进行 HIPEC 对肿瘤患者凝血系统和血栓风险方面的研究很有必要。

PT 主要反映外源性凝血功能状况,而 APTT 则主要反映内源性凝血功能状况[14]。当出现血栓性疾病或者血液高凝状态时两者都会明显缩短。FIB 是由肝脏合成的一种具有凝血功能分子蛋白,在感染性疾病、肿瘤及血栓性疾病时会明显升高[14]。D-D 是血浆交联纤维蛋白降解的产物,主要反映纤维蛋白溶

解功能[19]，在 DVT 及恶性肿瘤等疾病时会明显升高，这时机体处于高凝状态，存在继发性纤维蛋白溶解功能亢进。因此，上述四项凝血指标均能较为准确地反映机体凝血功能的变化[19]。既往研究发现，无论是开腹手术还是腹腔镜手术，腹股沟疝患者术后 PT 均显著延长，D-D 及 FIB 均显著升高[20]，相对于传统手术，腹腔镜手术后患者 PT 时间延长更加明显，D-D 及 FIB 水平也进一步升高。本研究与之相同，两组患者凝血指标术后即刻和术后 72 h，PT 和 APTT 均明显下降，FIB 和 D-D 指标也均明显上升，这也同样证明了腹腔镜 CRC 手术导致了患者机体凝血系统激活，造成患者处于高凝状态。由此可见，腹腔镜手术由于存在促凝及血栓形成的诱因，术后患者处于明显的高凝状态，存在术后发生血栓性疾病的风险，应在围手术期采取积极预防措施。目前国内外关于 HIPEC 对患者凝血功能影响的研究尚无统一结论。

Dranichnikov 等[21]研究显示，PT 和 APTT 在 HIPEC 术后直接升高，但在术后第 5 天恢复到正常水平，表明在术后最初几天出血因素增加。相反，FIB、血小板计数、D-D 和抗凝血酶在第 5 天增加，并持续增加到研究的最后一天，这预示着血栓栓塞并发症的风险可能升高。但 Kim 等[22]的研究不一样，其发现 HIPEC 术后，患者血小板计数、PT 和 APTT 较术前水平下降，显示出高凝状态。Connolly 等[23]和 Falanga 等[24]将肿瘤患者的血栓形成危险因素一般分为三类：第一类患者相关因素，如高龄、卧床、肥胖、既往血栓形成、血栓形成的遗传、白细胞和血小板计数高以及合并症等；第二类肿瘤相关因素，如肿瘤部位和分期、炎症成分、坏死肿瘤等；第三类是治疗相关因素，如手术创伤范围与时长、失血量、住院时长、化疗、HIPEC 期间肝脏灌注减少、补液量等，均可能会使凝血失去平衡，增加术后血栓栓塞并发症的风险。由此可见，HIPEC 或任何其他大手术后血栓栓塞并发症的发生在很大程度上取决于组织损伤、凝血和溶栓-纤溶系统功能之间的平衡。

国内的研究认为，HIPEC 过程中患者的凝血功能主要受腹腔热灌注和化疗药物两个方面的影响[25]。一方面，腹腔热灌注的高温灌注液可以导致患者的腹腔血管扩张，造成大量的灌注液被腹腔吸收，继而稀释患者的血液，导致患者的凝血功能降低。同时，腹腔热灌注过程中患者的体温升高也会导致患者的凝血功能亢进[2]。另一方面，患者热灌注期间应用的化疗药物可能也会导致患者凝血功能异常。潘静玲等[26]的研究发现，胃肠道肿瘤患者本身就处于明显的高凝状态，尤其是肿瘤发生转移后的阶段，这种高凝状态会进一步加重。此时进行化疗，可能会因为化疗药物对血管内皮细胞的损伤显著增加血栓形成的风险。综上所述，对于腹腔镜手术联合 HIPEC 治疗的 CRC 患者，其凝血功能可能受肿瘤、麻醉、腹腔镜手术、HIPEC 以及化疗药物等多方面因素的影响。冯强等[27]在其研究中发现 HIPEC 后只有少数病例出现短期凝血功能指标异常，在并发症方面无显著影响。本研究发现，两组患者术后各时间点对应 PT、APTT、FIB 及 D-D 值差异无统计学意义。这也说明 HIPEC 对腹腔镜 CRC 手术患者凝血功能影响在可控范围，并不增加术后 DVT 风险。

另外，本研究发现两组患者在一般资料、术中出血量及手术时间基线一致的情况下，肛门排气时间、术后住院时间以及各并发症发生情况差异并无统计学意义，进一步证明 HIPEC 的安全性和可靠性。

综上所述，尽管腹腔镜手术可导致 CRC 患者凝血功能增强，血液处于高凝状态，但其术后联合 HIPEC 并不增加术后 DVT 风险，故 HIPEC 技术仍安全可靠。

利益冲突　无

参考文献

[1] 袁紫旭，林青锋，蔡建，等.肿瘤细胞减灭术治疗消化道肿瘤腹膜转移的适应证研究进展[J].中国实用外科杂志，2023，43(8)：951-955.
Yuan ZX, Lin QF, Cai J, et al. Advances in indication of cytoreductive surgery of peritoneal metastasis in gastrointestinal cancer[J]. Chin J Pract Surg, 2023, 43(8): 951-955.

[2] 崔书中.近 10 年中国 HIPEC 技术研究进展[J].广东医学，2023，44(6)：661-665.
Cui SZ. Progress in the research of abdominal thermal perfusion chemotherapy technology in China in the last decade[J]. Guangdong Med J, 2023, 44(6): 661-665.

[3] Dirkmann D, Hanke AA, Görlinger K, et al. Hypothermia and acidosis synergistically impair coagulation in human whole blood[J]. Anesth Analg, 2008, 106(6): 1627-1632.

[4] 李璐，张加强，司辉锋，等.腹腔内热灌注对腹腔镜胃癌根治术患者凝血功能的影响[J].中华麻醉学杂志，2015，35(11)：1328-1330.
Li L, Zhang JQ, Si HF, et al. Effect of hyperthermic intraperitoneal perfusion on blood coagulation in patients undergoing laparoscope-assisted radical surgery for gastric cancer[J]. Chin J Anesthesiol, 2015, 35(11): 1328-1330.

[5] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6): 394-424.

[6] 李萍.结直肠癌根治术联合 HIPEC 对患者肿瘤标志物、远期生存的影响[J].航空航天医学杂志,2021,32(4):417-418.
Li P. Effect of radical resection of colorectal cancer combined with intraperitoneal hyperthermic perfusion chemotherapy on tumor markers and long-term survival of patients[J]. J Aerosp Med, 2021, 32(4): 417-418.

[7] 林曜,郭熙恺,沈楚,等.进展期结直肠癌患者根治术后行预防性 HIPEC 的安全性评价[J].中华结直肠疾病电子杂志,2021,10(6):591-598.
Lin Y, Guo XK, Shen C, et al. Safety evaluation of preventive intraperitoneal hyperthermic perfusion chemotherapy in patients with advanced colorectal cancer after radical resection[J]. Chin J Colorectal Dis Electron Ed, 2021, 10(6): 591-598.

[8] 张玉.腹腔镜结肠癌根治术联合术后洛铂 HIPEC 治疗结肠癌的效果及安全性[J].临床医学,2023,43(4):1-4.
Zhang Y. Effect and safety of laparoscopic radical resection of colon cancer combined with postoperative intraperitoneal thermoinfusion chemotherapy with Loplatin on patients with colon cancer[J]. Clin Med, 2023, 43(4): 1-4.

[9] 杨飞,张亚铭,周潮平,等.局部进展期胃癌根治性手术联合 HIPEC 的安全性及近期疗效[J].中国普通外科杂志,2021,30(4):412-420.
Yang F, Zhang YM, Zhou CP, et al. Safety and short-term efficacy of radical surgery combined with hyperthermic intraperitoneal chemotherapy for locally advanced gastric cancer[J]. Chin J Gen Surg, 2021, 30(4): 412-420.

[10] 姜旭勉,陈炜,郑威强,等.HIPEC 对进展期结直肠癌患者肠黏膜屏障功能的影响[J].华中科技大学学报(医学版),2021,50(1):82-85,108.
Jiang XM, Chen W, Zheng WQ, et al. Effect of hyperthermic intraperitoneal chemotherapy on intestinal barrier function in patients with colorectal cancer[J]. Acta Med Univ Sci Technol Huazhong, 2021, 50(1): 82-85, 108.

[11] 徐璐,孙婧.结直肠癌伴腹膜转移治疗的研究进展[J].临床肿瘤学杂志,2023,28(1):84-89.
Xu L, Sun J. Advances in treatment of peritoneal metastasis from colorectal cancer[J]. Chin Clin Oncol, 2023, 28(1): 84-89.

[12] 张颖,杨波,印天,等.间歇性肿瘤细胞减灭术+腹腔热灌注化疗在晚期上皮性卵巢癌治疗中的应用[J].中华全科医学,2024,22(5):768-771.
Zhang Y, Yang B, Yin T, et al. Application of intermittent cytoreductive surgery + hyperthermic intraperitoneal chemotherapy in the treatment of advanced ovarian cancer[J]. Chin J Gen Pract, 2024, 22(5): 768-771.

[13] Falanga A, Marchetti M. Cancer-associated thrombosis: enhanced awareness and pathophysiologic complexity[J]. J Thromb Haemost, 2023, 21(6): 1397-1408.

[14] 王砚春,卢仁泉.出凝血检测在肿瘤患者中的应用价值探讨[J].诊断学理论与实践,2023,22(4):341-347.
Wang YC, Lu RQ. The application value of determination of hemostasis and thrombosis in tumor patients[J]. J Diagn Concepts Pract, 2023, 22(4): 341-347.

[15] 李莉,周培华,薛翔,等.中国肺癌术后静脉血栓栓塞发生的 Meta 分析[J].中国临床研究,2022,35(5):627-631.
Li L, Zhou PH, Xue X, et al. VTE occurrence after postoperative lung cancer in China: Meta-analysis[J]. Chin J Clin Res, 2022, 35(5): 627-631.

[16] Falanga A, Schieppati F, Russo L. Pathophysiology 1. Mechanisms of thrombosis in cancer patients[J]Cancer Treat Res, 2019, 179: 11-36.

[17] Schieppati F, Russo D, Falanga A. Cancer tissue procoagulant mechanisms and the hypercoagulable state of patients with cancer[J]. Semin Thromb Hemost, 2015, 41(7): 756-764.

[18] Ma YL, Wang BF, He PY, et al. Coagulation- and fibrinolysis-related genes for predicting survival and immunotherapy efficacy in colorectal cancer[J]. Front Immunol, 2022, 13: 1023908.

[19] Ma XL, Li YY, Zhang J, et al. Prognostic role of D-dimer in patients with lung cancer: a meta-analysis[J]. Tumor Biol, 2014, 35(3): 2103-2109.

[20] 徐浩,郑伦辉,张居易,等.腹腔镜腹膜前疝修补术与 Lichtenstein 疝修补术对腹股沟疝患者凝血功能的影响[J].中国临床新医学,2020,13(1):64-66.
Xu H, Zheng LH, Zhang JY, et al. Effects of transabdominal preperitoneal prosthetic and Lichtenstein hernia repair on coagulation function in patients with inguinal hernia[J]. Chin J N Clin Med, 2020, 13(1): 64-66.

[21] Dranichnikov P, Mahteme H, Cashin PH, et al. ASO visual abstract: coagulopathy and venous thromboembolic events following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy[J]. Ann Surg Oncol, 2021, 28(3): 440.

[22] Kim MH, Yoo YC, Bai SJ, et al. Physiologic and hemodynamic changes in patients undergoing open abdominal cytoreductive surgery with hyperthermic intraperitoneal chemotherapy[J]. J Int Med Res, 2021, 49(1): 030006052098326.

[23] Connolly GC, Khorana AA. Emerging risk stratification approaches to cancer-associated thrombosis: risk factors, biomarkers and a risk score[J]. Thromb Res, 2010, 125: S1-S7.

[24] Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects[J]. J Thromb Haemost, 2013, 11(2): 223-233.

[25] 李璐,孟凡民,孙培春.术中腹腔热灌注患者围术期凝血功能的影响因素[J].中国实用医刊,2014,41(8):90-91.
Li L, Meng FM, Sun PC. Influencing factors of perioperative coagulation function in patients with intraperitoneal hyperthermia perfusion during operation[J]. Chin J Pract Med, 2014, 41(8): 90-91.

[26] 潘静玲,王小娟,吴萍.化疗对胃肠道肿瘤患者凝血功能的影响[J].中国综合临床,2012,28(12):1245-1249.
Pan JL, Wang XJ, Wu P. The impact of chemotherapy on coagulation function in patients with gastrointestinal cancer[J]. Clin Med China, 2012, 28(12): 1245-1249.

[27] 冯强,袁兴华,郑朝旭,等.进展期胃癌术中 HIPEC 临床研究[J].中国肿瘤临床与康复,2011,18(3):238-241.
Feng Q, Yuan XH, Zheng ZX, et al. Clinical trial of intra-operative hyperthermic intraperitoneal chemotherapy for advanced gastric cancer[J]. Chin J Clin Oncol Rehabil, 2011, 18(3): 238-241.

收稿日期:2024-02-21　**修回日期**:2024-03-30　**编辑**:王海琴