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Logistic regression analysis of risk factors for abdominal adhesion during hyperthermic intraperitoneal chemotherapy for ovarian cancer

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Abstract. The present study aimed to explore the risk factors for abdominal adhesion during hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer via logistic regression analysis. The present study is a retrospective analysis involving 165 patients with ovarian cancer treated at The Department of Gynecology, Shanghai First Maternity and Infant Hospital (Shanghai, China) from February 2021 to June 2023. All patients were treated with HIPEC or adjuvant therapy. During the treatment, the patients were divided into the control (n=61) and observation (n=104) groups according to the presence of abdominal adhesion. The results of the present study highlighted the notable role of monitoring biomarkers such as C-reactive protein and plasminogen activator inhibitor-1 in predicting the risk of abdominal adhesions in patients with ovarian cancer treated with HIPEC. By optimizing surgical techniques, controlling inflammatory reactions, adopting anti-adhesion strategies and implementing detailed preoperative assessment and preventive measures for patients undergoing HIPEC, the incidence of adhesions may be effectively reduced and treatment safety improved.

Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) is an innovative treatment modality for ovarian cancer and other peritoneal metastatic tumors (1,2). This approach combines the surgical removal of the tumor (cytoreduction) and the subsequent direct injection of heated chemotherapy drugs into the abdominal cavity during the procedure, which improves the killing effect of the drug on cancer cells while reducing the toxicity to normal tissue. Although HIPEC enhances antitumor effects while increasing local drug concentration and temperature, it also increases the risk of abdominal adhesions, one of the common complications after surgery (3-5).

Abdominal adhesions are mainly a side effect of the natural healing process after surgery, in which fibrous tissue forms connections between two parts within the abdominal cavity that should be independent of each other (6). Although adhesions can be asymptomatic, in some cases they may contribute to chronic pain, intestinal obstruction and even recurrent abdominal surgery requirements (7). Therefore, abdominal adhesions not only affect the quality of life but may also increase medical costs and the complexity of subsequent treatment. Clinically, understanding and identifying factors that may increase the risk of adhesion is key to optimizing treatment outcomes and preventing surgical complications. It has been shown that the inflammatory response, surgical skills and individual patient differences (such as prior surgical history, radiotherapy history and some underlying diseases) may be associated with the development of abdominal adhesion (8-10). Studies have shown that adhesion is particularly common among patients with ovarian cancer undergoing HIPEC; 70% of these patients develop new intra-abdominal adhesions during the HIPEC perfusion process, mainly between the abdominal wall and the intestinal tract, and mostly form during the period after the abdominal cavity is closed and before the perfusion fluid fills (11,12). However, systematic studies on risk factors for abdominal adhesion after HIPEC treatment for ovarian cancer are rare. Therefore, the present study aimed to explore the risk factors associated with the development of abdominal adhesion in patients with ovarian cancer following HIPEC treatment by conducting multiple logistic regression analyses. By identifying these key factors, clinicians may be armed with more information to help them make more targeted decisions when preparing and performing such treatments, thereby optimizing patient treatment outcomes and minimizing adverse outcomes.

Materials and methods

Patients. The present study was a retrospective study. A total of 165 patients with ovarian cancer who were treated at the

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Department of Gynecology, Shanghai First Maternity and Infant Hospital (Shanghai, China) from February 2021 to June 2023 were selected as the research subjects. The data were derived from the electronic medical record system, pathological diagnosis reports and clinical follow-up records. The serum samples were from the serum specimens of patients previously frozen in the hospital's biological sample bank. The patients were aged 47-65 years (mean age, 57.33±4.65 years) and were American Society of Anesthesiologists (ASA) grade I-III (2020 Revised Edition) (13). All patients were treated with HIPEC or adjuvant therapy. During the treatment period, the patients were divided into the control (no abdominal adhesion, n=61) and observation (abdominal adhesion, n=104) groups. The sample size for the present study was calculated according to the following formula: $N=Z^2$ x [P x (1-P)]/E2, where N represents the sample size, Z the statistic (when the confidence level is 95%, Z=1.96; when the confidence level is 90%, Z=1.64), E the error value and P the probability value. It was determined that 165 samples were the minimum sample size for quantitative research.

Inclusion criteria. The inclusion criteria were as follows: i) Patients >18 years of age; ii) ovarian cancer identified by imaging and histopathological analysis; iii) patients who had undergone abdominal surgery; iv) ASA grade I to III; and v) normal routine blood results, electrolyte balance and coagulation.

Exclusion criteria. The exclusion criteria were as follows: i) Severe heart disease, liver and kidney dysfunction or other systemic disease that may affect surgical safety; ii) severe bleeding tendency or coagulation dysfunction; iii) patients known to be allergic to chemotherapy agents used in HIPEC; iv) patients who had undergone abdominal surgery within 1 year; v) patients with active infectious disease; vi) pregnant or lactating women; vii) uncontrolled mental illness or cognitive dysfunction; and viii) patients who did not follow the treatment plan.

ELISA analysis of the expression levels of inflammatory factors and fibrinolytic system-related enzymes. The biomarker levels were measured 24 h after the completion of HIPEC. Blood samples were collected from each patient, which were immediately centrifuged (250 x g for 10 min at 20-25˚C) to isolate the plasma and then stored at -80˚C. An ELISA kit was used to detect the enzymatic activities of fibrinolytic system-related enzymes such as tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), D-dimer and fibrin degradation products (FDPs), as well as the expression levels of inflammatory factors such as C-reactive protein, TNF-α, and IL-6 in the samples. The plasma samples were diluted 1:100 with physiological saline and 100 µl was added to the corresponding wells. Standard solutions of known concentrations were set up to prepare the standard curve. The samples were incubated at 37˚C for 1-2 h to promote the binding of rabbit polyclonal antibodies against human C-reactive protein (1:500; cat. no. AF6570), human TNF-α (1:500; cat. no. AF8208), human IL-6 (1:500; cat. no. AF5164), human tPA (1:500; cat. no. YT4707), human PAI-1 (1:500; cat. no. AF9017), human D-dimer (1:500; cat. no. AF10359) and FDPs (1:500; cat. no. AF6879), all purchased from Beyotime Biotechnology. The plates were washed at least three times with PBS or TBS containing 0.05% Tween-20 for 3 min each time. Then, 100 µl of biotin-labeled goat anti-rabbit IgG secondary antibody (1:500; Shanghai Byrgent Company; cat. no. 20250510) was added and incubated at 37˚C for 1 h. Next, the plates were washed again to remove the unbound second antibody. Subsequently, 100 µl TMB substrate was added for 15-30 min to produce blue products by reaction of the substrate with peroxidase. The reaction was stopped by adding 50 µl of 2N sulfuric acid and the resulting blue color changed to yellow. The optical density was measured at 450 nm using a spectrophotometer and the concentration of the target protein in the sample was calculated using the standard curve. This series of steps ensured the accuracy and reproducibility of the experiments, suitable for the assessment of fibrinolytic system activity.

Statistical analysis. The present study employed SPSS 26.0 (IBM Corp.) statistical software. Continuous data are expressed as mean ± standard deviation after confirming normal distribution, intergroup comparisons were conducted using independent sample t-test. Categorical data are expressed as percentages, and intergroup comparisons were performed using χ^2 analysis. Fisher's exact test was used when the number of cells with expected counts <20% was <5. Logistic regression was applied to analyze the correlation between two factors. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of general patient data. The mean age of the control group was 56.26±3.27 years, with a mean BMI of 22.36±2.03 kg/m^2. The control group included 7 cases with hypertension, 4 with diabetes mellitus, 6 with a smoking history and 10 with a drinking history in the past 3 years. The mean age of the observation group was 57.43±4.55 years, with a mean BMI of 23.45±1.85 kg/m^2. The observation group included 13 patients with hypertension, 6 with diabetes, 9 with a smoking history and 16 with a drinking history in the past 3 years. There were no statistically significant differences in the general patient data (P>0.05; Table I).

Analysis of plasma inflammatory cytokines. The plasma levels of inflammatory cytokine CRP, TNF-α and IL-6 were increased in the observation group compared with the control group (P<0.05; Table II).

Analysis of fibrinolytic system levels. The levels of certain fibrinolytic system-related enzymes was measured by ELISA. The levels of tPA, D-dimer and FDPs were reduced in the observation group (P<0.05) and the PAI-1 levels were increased in the observation group compared with the control group (P<0.05) (Table III).

Analysis of treatment plan and adhesion risk. The association between the previous treatment regimen and abdominal adhesion was analyzed. In the observation group (with abdominal adhesion), the proportion of patients who experienced prior abdominal surgery and abdominal radiotherapy was increased compared with the control group (P<0.05), suggesting a

Table I. General patient data.

Variable	Control group, n=61	Observation group, n=104	t-value/ χ^2 value	P-value
Mean age, years	56.26±3.27	57.43±4.55	t=2.098	0.553
Mean BMI, kg/m^2	22.36±2.03	23.45±1.85	t=1.336	0.133
Hypertension, n (%)	7 (11.48)	13 (12.50)	χ^2=4.309	0.274
Diabetes mellitus, n (%)	4 (6.56)	6 (5.77)	-[a]	0.891
Smoking history, n (%)	6 (9.83)	9 (8.65)	χ^2=0.052	0.820
Drinking history, n (%)	10 (16.39)	16 (15.38)	χ^2=3.447	0.711

[a]Diabetes mellitus data were analyzed using Fisher's exact test.

Table II. Analysis of plasma cytokine levels.

Group	CRP (mg/l)	TNF-α (pg/ml)	IL-6 (pg/ml)
Control group (n=61)	9.26±2.55	1.89±0.42	19.34±2.55
Observation group (n=104)	16.38±4.17	3.88±0.68	28.43±4.17
t-value	13.208	11.446	9.527
P-value	0.014	0.003	0.025

CRP, C-reactive protein.

Table III. Analysis of fibrinolytic system enzyme levels.

Group	tPA (ng/ml)	PAI-1 (ng/ml)	D-dimer (µg/ml)	FDPs (µg/ml)
Control group (n=61)	12.35±2.44	26.38±3.55	0.57±0.22	3.86±1.21
Observation group (n=104)	7.41±1.68	59.32±5.61	0.35±0.16	1.95±1.02
t-value	11.227	9.405	13.621	15.334
P-value	0.012	0.003	0.026	0.005

tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; FDPs, fibrin degradation products.

certain association between the treatment regimen history and abdominal adhesion (Table IV).

Risk analysis of other diseases and adhesion. The association between other diseases and abdominal adhesion was also analyzed. In the observation group (with abdominal adhesion), the proportion of patients with pelvic inflammation, peritonitis, ulcerated colitis and abdominal injury was higher compared with the control group (P<0.05), suggesting that diseases linked to abdominal inflammation may be associated with abdominal adhesion (Table V).

Multiple logistic regression analysis. Multiple logistic regression analysis showed that preoperative plasma CRP and PAI-1 increase, a history of abdominal surgery, abdominal radiotherapy and abdominal inflammatory disease were risk factors affecting the occurrence of abdominal adhesion in patients with ovarian cancer receiving peritoneal chemotherapy (P<0.05; Table VI).

Table IV. Treatment plan history and abdominal adhesion risk analysis.

Group	Abdominal operation, n (%)	Abdominal radiotherapy, n (%)
Control group, n=61	17 (27.87)	11 (18.03)
Observation group, n=104	85 (81.73)	44 (42.31)
t-value	16.224	10.531
P-value	0.012	0.003

Discussion

The present study investigated the risk factors for the development of abdominal adhesion in patients with ovarian cancer after receiving HIPEC. The results revealed that some key

Table V. Analysis of abdominal inflammation and abdominal adhesion risk.

Group	Pelvic inflammation, n (%)	Peritonitis, n (%)	Colitis gravis, n (%)	Abdominal injury, n (%)
Control group, n=61	5 (8.20)	1 (1.64)	0 (0.00)	2 (3.28)
Observation group, n=104	18 (17.31)	12 (11.54)	6 (5.77)	9 (8.65)
t-value	15.229	14.617	10.335	16.288
P-value	0.002	0.016	0.036	0.004

Table VI. Multiple logistic regression analysis.

Variable	Odds ratio	95% Confidence interval	P-value
Preoperative plasma CRP >11.32 mg/l	1.551	1.165-1.771	0.013
Preoperative PAI-1 >42.85 ng/ml	1.490	1.483-1.656	0.026
History of abdominal radiotherapy (yes)	1.635	0.981-3.623	0.006
Abdominal inflammation (yes)	1.881	1.551-2.375	0.011
PCI score >5	1.289	0.329-5.046	0.716
Integrity of cytoreductive surgery (CC score): Residual lesion diameter >2.5 mm	7.548	1.473-38.675	0.115
HIPEC regimen(+)[a]	1.120	0.851-1.486	0.095
Duration of surgery >60 min	1.042	1.019-1.083	0.126

[a]The variable 'HIPEC regimen' is determined based on the treatment plan received, and '+' indicates the use of HIPEC. CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; PCI, Percutaneous Coronary Intervention; CC, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

biomarkers and clinical conditions may have a significant effect on the risk of abdominal adhesion. The results of the present study showed that patients with HIPEC who had a high preoperative CRP level had a significantly higher incidence of postoperative abdominal adhesions. CRP is a widely used biomarker for acute and chronic inflammation. Surgeries, severe traumas and burns directly damage tissue cells, and the tissue factors and necrotic substances released at the injured site will activate the coagulation system and the immune system, prompting the secretion of inflammatory cytokines and stimulating the liver to synthesize CRP (14,15). A previous study has shown that an increase in CRP (indicating an active inflammatory response) stimulates the deposition of fibrin in the peritoneum, creating conditions for the formation of adhesions (16). However, CRP is not specific and it is difficult to directly determine its causal relationship with adhesions as CRP, an acute-phase response protein, is a downstream marker of systemic inflammation rather than a direct driving factor for adhesion formation. Therefore, it is difficult to establish a causal relationship between CRP and adhesions (17). Additionally, other studies have confirmed that an increase in PAI-1 reflects the inhibition of the fibrinolytic system, which often leads to abnormal fibrin deposition after surgery and increases the risk of adhesions (18-20). PAI-1 affects the adhesion process by regulating the fibrinolytic system; it can inhibit the activity of fibrinolytic activators, reduce fibrin degradation and promote the formation and solidification of adhesion tissues (21). The research conducted by Gao *et al* (22) revealed that an elevated preoperative PAI-1 level indicates an increased risk of postoperative adhesions. However, its expression is regulated by various factors and the increase may be a comprehensive response of the body rather than the direct cause of adhesions. The results of this study differ from those of the present study, which is due to different types of diseases being studied. Another study demonstrated that the levels of inflammatory markers in ovarian cancer patients undergoing HIPEC are significantly correlated with the formation of intra-abdominal adhesions. However, the inflammatory factors involved in this study are different from those in the present study (23).

In the present study, the levels of CRP, TNF-α and IL-6 before treatment were significantly higher in the observation group than in the control group. These findings highlight the role of chronic and acute inflammation in promoting postoperative adhesion formation. This state may lead to postoperative changes in the intraabdominal environment that increase fibrin deposition and thus promote adhesion formation. TNF-α and IL-6 are important pro-inflammatory cytokines that play key roles in the inflammatory and immune responses. TNF-α is an early inflammatory response mediator that can activate inflammatory cells, increase vascular permeability and promote the migration of inflammatory cells to the sites of inflammation (24). IL-6 participates in the stimulation of B cells and T cell activation, promoting the immune response (25). The elevation of these cytokines may have exacerbated the inflammatory response in the peritoneum, leading to more fibrous tissue deposition and adhesions to form (26,27). The inflammatory response promotes the formation of fibrous tissue by stimulating fibroblast proliferation and collagen deposition (28). The activity of the fibrinolytic system may be inhibited and the clearance of fibrin is slowed, further increasing the risk of adhesion.

Research has found that abdominal adhesions are associated with significant changes in the activity of the fibrinolytic system (29). In the present study, through ELISA detection, it was found that the tPA, D-dimer and FDP levels were reduced in the observation group patients, while the PAI-1 level was increased. This indicates that the fibrinolytic system function of the observation group was inhibited, which may be a key factor leading to the formation of postoperative adhesions. tPA is a key fibrinolytic system component and its main function is to promote the conversion of plasminogen to plasmin, which is able to degrade fibrinin blood clots. Effective fibrinolytic activity is essential to prevent fibrin accumulation from excessive disease after surgery and tissue injury (30,31). Furthermore, D-dimer, a direct product of fibrinolysis after thrombus lysis, is commonly used to assess fibrinolytic activity *in vivo* (32). In the present study, the decreased D-dimer levels implied a decrease in fibrinolytic activity. This was further confirmed by the FDPs measurements as FDPs are also products of fibrin degradation. The formation of abdominal adhesions is a complex biological process involving the interaction of the inflammatory response, tissue damage repair and the fibrinolytic system (33). Surgical trauma and the subsequent inflammatory response prompt the body to release large amounts of inflammatory mediators and growth factors that can stimulate fibroblast proliferation and accumulation of collagen, resulting in adhesions. When the fibrinolytic system activity is reduced, these fibrillins cannot be removed efficiently removed, thus forming persistent adhesions in the abdominal cavity.

In the context of HIPEC treatment, chronic abdominal inflammatory diseases, such as pelvic inflammation, peritonitis, ulcerative colitis and inflammation caused by abdominal trauma, significantly increase the risk of abdominal adhesion. These diseases cause repeated damage to the peritoneal surface through persistent or periodic inflammatory responses, which in turn promotes the formation of fibrosis and adhesions (34). As a thin membrane that covers and supports the abdominal organs, its healthy state is critical to the intra-abdominal environment. Under normal circumstances, the peritoneum is able to prevent adhesion between organs through its lubricated surfaces. However, when chronic inflammatory diseases such as pelvic inflammation or peritonitis are present, persistent inflammatory states disrupt this protective layer of the peritoneum, leading to increased collagen fiber deposition and intensification of the fibrosis process, thus significantly increasing the risk of adhesion. Ulcerative colitis not only affects the intestinal wall but also can further intensify the inflammatory response in the local area and the adjacent peritoneum by releasing inflammatory mediators and cytokines such as TNF-α and IL-6 (35). Abdominal injuries, whether caused by trauma or surgery, are also common causes of adhesion. Mechanical manipulation during surgery, such as tissue cutting or suture, and possible postoperative infection are all potential contributing factors of adhesion formation. These manipulations often result in direct damage to the peritoneum and changes in the microenvironment, triggering the activation of fibroblasts and overproduction of collagen, thus forming adhesions (36).

The limitations of the present study include its retrospective and single-center design, which restricts its external validity. In subsequent studies, multi-center prospective research should be conducted. Additionally, due to medical ethics requirements, it was not possible to perform biopsies to collect ovarian cancer samples during the treatment of patients undergoing HIPEC for ovarian cancer, thus preventing the molecular profiling of these patients. In future research, animal experiments will be used to achieve the experimental goal of collecting markers from advanced ovarian cancer that has metastasized to different parts of the body.

In conclusion, the results of the present study indicate that preoperative monitoring of biomarkers such as CRP and PAI-1 is of great value in predicting the risk of abdominal adhesion after HIPEC. It may help to reduce the incidence of abdominal adhesion by optimizing the surgical technique, controlling the inflammatory response as well as the use of anti-adhesion strategies. In addition, patients with a history of abdominal surgery or radiotherapy should be evaluated carefully preoperatively and corresponding preventive measures during surgery should be taken. Through these methods, the safety and efficacy of HIPEC treatment and the quality of life of patients can be improved.

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Availability of data and material

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JC contributed to the conception of the study. JY performed the experiments, wrote the manuscript and performed the data analyses. JC and JY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics committee of Shanghai First Maternity and Infant Hospital (approval no. KS24207). As this study involved retrospective data analysis and all patient information was anonymized, the committee waived the requirement for written informed consent. All procedures complied with the ethical norms and regulations.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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