Nomogram to Predict Tube Occlusion During Hyperthermic Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei

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ABSTRACT

Objective: To investigate the factors contributing to the blockage of perfusion tubes during hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with appendiceal pseudomyxoma peritonei (PMP) undergoing combined cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy treatment, and to construct a nomogram for predicting the risk of tube occlusion.

Study Design: Observational study.

Place and Duration of the Study: Department of Gastrointestinal Surgery, Central Hospital Affiliated to Shandong First Medical University, Jinan, China, from June 2017 to December 2023.

Methodology: Tube occlusion was defined as the inability to achieve 30 minutes of continuous unobstructed perfusion. Statistical methods such as univariate analysis, multivariate analysis, and Lasso regression were employed for data analysis.

Results: The results revealed that 27% of the 383 hyperthermic intraperitoneal chemotherapy perfusion treatments resulted in the tube occlusion events. Multivariate logistic regression analysis identified age, CA-125, CA19-9, and pathological type as the independent risk factors. A nomogram predicting the tube occlusion was constructed and validated for its predictive accuracy and clinical utility.

Conclusion: This study successfully developed a nomogram to predict the tube occlusion risk during cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy treatment for patients with pseudomyxoma peritonei, providing valuable guidance for clinical practice and aiding in personalised treatment decisions to improve patient prognosis. However, further research is needed to validate the reliability and clinical applicability of the model, as well as to investigate the impact of tube occlusion on treatment outcomes and corresponding management strategies.

Key Words: *Pseudomyxoma peritonei, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy treatment, Tube occlusion, Nomogram.*

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INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare clinical condition characterised by the accumulation of abundant mucin within the peritoneal cavity, with an annual incidence of approximately one to three per million. It is typically caused by mucinous adenomas or adenocarcinomas originating from organs such as the appendix or ovaries.[1-4] As a peritoneal disease, its progression is slow but progressive, ultimately, potentially, and severely impacting patients' quality of life and life expectancy.[5]

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In recent years, there have been significant advancements in the treatment of PMP, with cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) emerging as essential modalities for improving patient survival and quality of life.[5,6] Guidance from multiple clinical practice guidelines has led to more precise and standardised application of HIPEC.[7-9] However, tube occlusion during HIPEC procedures has emerged as a critical factor affecting treatment efficacy and patients' safety. Currently, there is limited research on the risk factors for tube occlusion during CRS followed by closed HIPEC treatment. This study aimed to develop and validate a nomogram based on the common clinical indicators to predict the risk of tube occlusion in patients with PMP undergoing CRS combined with HIPEC treatment.

METHODOLOGY

The research protocol and informed consent documentation received approval from the Ethics Committee of the Central Hospital Affiliated with Shandong First Medical University

(Approval no. 20240305004). This study was a single-centric observational study that enrolled 107 patients with appendiceal PMP treated with CRS combined with HIPEC at the Central Hospital Affiliated to Shandong First Medical University from June 2017 to December 2023. Inclusion criteria were patients aged 18 years or older with a pathologically confirmed diagnosis of PMP, those who underwent closed abdominal perfusion three to four times postoperatively, and those with complete clinical data. Exclusion criteria were perioperative death and patients who were not first-time recipients of CRS combined with HIPEC. Perfusion records were retrieved from the hospital's electronic medical record system and treatment devices, extracting essential patient information, including gender, age, body mass index (BMI), medical history (disease and surgical history), preoperative laboratory indicators for hyperthermic intraperitoneal chemotherapy (blood analysis, inflammatory markers, and tumour markers). Collected pertinent surgical details, such as peritoneal cancer index (PCI) scores, cytoreduction (CC) scores, and postoperative pathology.

PMP patients underwent laparoscopic examination under general anaesthesia, assessing PCI to determine the extent of the primary tumour invasion and peritoneal spread. Following PCI scoring, the maximum resection of visible tumours was achieved. Postoperatively, a CC score was assigned, with CC0 indicating complete eradication of visible lesions, representing CRS.

After CRS, four catheters were placed bilaterally in the pelvic cavity, spleen fossa, and diaphragmatic liver surface, using specialised hyperthermic perfusion drainage tubes, each with six side holes. Surgeons completed 3-4 cycles of HIPEC treatment within seven days, with a 24-hour interval between each cycle. Each HIPEC treatment lasted for 60 minutes. The intracavitary hyperthermic treatment system was the BR-TRG-1 model.

Tube occlusion was defined as the inability to achieve 30 minutes of continuous unobstructed perfusion. After occlusion, the main manifestations included fluctuations in the perfusion curve of the outflow tube, accompanied by the slowing of the outflow tube flow rate and a decrease in the outflow tube temperature. The HIPEC with tube occlusion was assigned to the study group and the rest of the HIPEC were assigned to the control group. To reduce error, the criteria were used by two physicians with intermediate titles, and the occurrence or absence of tube occlusion events during HIPEC treatment were recorded.

Categorical variables were presented as n (%). Single-factor analysis was conducted using the χ^2 test, and multiple-factor analysis employed a binary logistic regression model. The glmnet package was used for the Lasso regression variable selection, with the cv.glmnet function choosing λ through 10-fold cross-validation for variable screening. Statistical analyses were performed using SPSS 26.0 software (IBM, New York) and R software (version 4.3.1). A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 107 patients with PMP treated with CRS combined with HIPEC were included. Among these patients, two had peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S) from the appendix, 52 had diffuse peritoneal mucinous adenoma (DPAM) from the appendix, 45 had peritoneal mucinous carcinoma (PMCA) from the appendix, one had DPAM from the ovary, five had peritoneal mucinous carcinomatosis PMCA from the ovary, one had PMCA from the peritoneal mesothelium, and one had PMCA from the bile duct (Figure 1A).

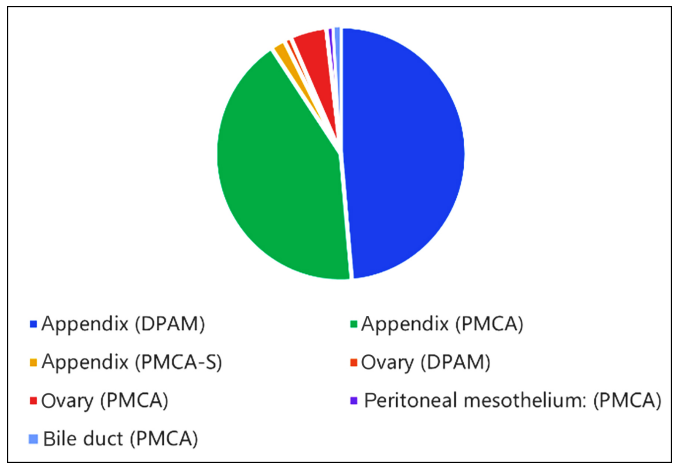

Figure 1A: Pie chart of primary sites and histological types in 107 patients with PMP.
DPAM: Diffuse peritoneal mucinous adenoma, PMCA: Peritoneal mucinous carcinoma, PMCA-S: Peritoneal mucinous carcinomatosis with signet ring cells.

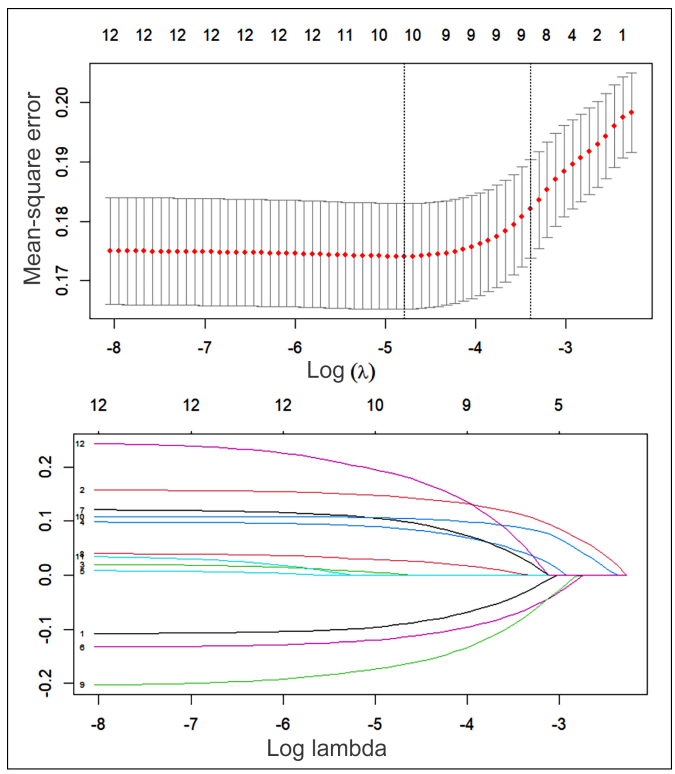

Figure 1B: Lasso regression pathway diagram and cross-validation plot.
Excluding PCI, omentectomy, Lambda = 0.008336023, remainder 10 variables

Table I: Univariate analysis of the occurrence rate and risk factors for tube occlusion during the HIPEC treatment.

Variables		Overall (n%)	Tube-blockage (n%)	Research Control (n%)	p-value
Gender	Male	155 (40.5)	34 (8.9)	121 (31.6)	0.058
	Female	228 (59.5)	70 (18.3)	158 (41.3)	
Age (years)	≤60	189 (49.3)	39 (10.2)	150 (39.2)	0.005
	>60	194 (50.7)	65 (17.0)	129 (33.7)	
BMI (kg/m²)	<28	351 (91.6)	93 (24.3)	258 (67.4)	0.337
	≥28	32 (8.4)	11 (2.9)	21 (5.5)	
Diabetes	No	330 (86.2)	96 (25.1)	237 (61.9)	0.033
	Yes	53 (13.8)	24 (6.3)	29 (7.6)	
Hypertension	No	299 (78.1)	90 (23.5)	209 (54.6)	0.014
	Yes	84 (21.9)	14 (3.7)	70 (18.3)	
Previous abdominal surgery	No	176 (46.0)	45 (11.7)	131 (34.2)	0.520
	Yes	207 (54.0)	59 (15.4)	148 (38.6)	
Ascites	No	118 (30.9)	35 (9.2)	83 (21.7)	0.475
	Yes	264 (69.1)	69 (18.1)	195 (51.0)	
CRP (mg/L)	≤10	17 (6.4)	3 (1.1)	14 (5.3)	0.240
	>10	247 (93.6)	77 (29.2)	170 (64.4)	
WBC (10^9/L)	≤10	299 (78.1)	90 (23.5)	209 (56.6)	0.014
	>10	84 (21.9)	14 (3.7)	70 (18.3)	
NE (%)	≤75	138 (36.0)	32 (8.4)	106 (27.7)	0.190
	>75	245 (64.0)	72 (18.8)	173 (45.2)	
PLT (10^9/L)	≤300	324 (84.6)	92 (24.0)	232 (60.6)	0.201
	>300	59 (15.4)	12 (3.1)	47 (12.3)	
CA125 (U/mL)	≤35	236 (71.5)	51 (15.5)	185 (56.1)	0.011
	>35	94 (28.5)	33 (10.0)	61 (18.5)	
CEA (ng/mL)	≤5	170 (47.4)	59 (16.4)	111 (30.9)	0.003
	>5	189 (52.6)	39 (10.9)	150 (41.8)	
CA199 (U/mL)	≤27	163 (46.3)	61 (17.3)	102 (29.0)	<0.000
	>27	189 (53.7)	36 (10.2)	153 (43.5)	
Visceral resection	No	22 (5.7)	1 (0.3)	21 (5.5)	0.014
	Yes	361 (94.3)	103 (26.9)	258 (67.4)	
PCI	≤20	190 (49.6)	61 (15.9)	129 (33.7)	0.031
	>20	193 (50.4)	43 (11.2)	150 (39.2)	
CC score	0, 1	211 (55.1)	63 (16.4)	148 (38.6)	0.188
	2, 3	172 (44.9)	41 (10.7)	131 (34.2)	
Stoma	No	341 (89.0)	92 (24.0)	249 (65.0)	0.827
	Yes	42 (11.0)	12 (3.1)	30 (7.8)	
Omentectomy	No	67 (17.5)	12 (3.1)	52 (13.6)	0.061
	Yes	316 (82.5)	92 (34.0)	224 (58.5)	
Pathology	DPAM	189 (49.3)	71 (18.5)	118 (30.8)	<0.000
PMCA, PMCA-S		194 (50.7)	33 (8.6)	161 (42.0)	

BMI: Body mass index, CRP: C-reactive protein, NE: Neutrophil percentage, PLT: Platelets, PCI: Peritoneal cancer index, CC: Completeness of cytoreduction.

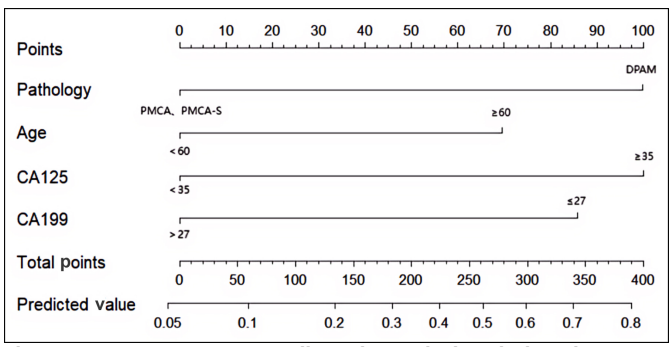

Figure 2A: Nomogram to predict tube occlusion during the HIPEC for PMP.

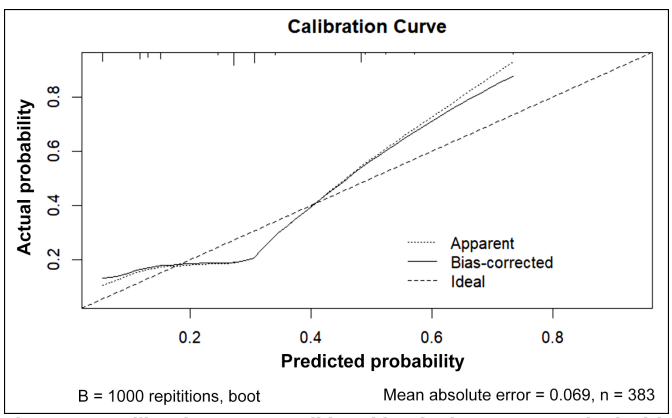

Figure 2B: Calibration curves validated by the bootstrap method with 1,000 clinical predictions.

Table II: Tube occlusion multifactorial logistic regression analysis.

Variable	Overall (n%)	OR (95% CI)	p-value
Age (years)			0.001
≤60	189 (49.3)	1	
>60	194 (50.7)	2.676 (1.501, 4.771)	
Diabetes			0.565
No	330 (86.2)	1	
Yes	53 (13.8)	1.383 (0.458, 4.170)	
Hypertension			0.178
No	299 (78.1)	1	
Yes	84 (21.9)	1.747 (0.776, 3.9330	
CEA (ng/mL)			0.793
≤5	170 (47.4)	1	
>5	189 (52.6)	0.924 (0.511, 1.670)	
CA199 (U/mL)			0.049
≤27	163 (46.3)	1	
>27	189 (53.7)	0.542 (0.294, 0.999)	
CA125 (U/mL)			0.001
≤35	236 (71.5)	1	
>35	94 (28.5)	2.930 (1.551, 5.537)	
Visceral resection			0.062
No	22 (5.7)	1	
Yes	361 (94.3)	7.432 (0.920, 61.218)	
Gender			0.129
Male	155 (40.5)	1	
Female	228 (59.5)	1.588 (0.875, 2.883)	
WBC (10^9/L)			0.089
≤10	299 (78.1)	1	
>10	84 (21.9)	0.488 (0.214, 1.115)	
Pathology			0.003
PMCA, PMCA-S	194 (50.7)	1	
DPAM	189 (49.3)	2.484 (1.364, 4.523)	

Following CRS, a total of 383 closed HIPEC procedures were performed on 107 patients. Among them, there were 104 (27%) cases in the study group and 279 (73%) cases in the control group. Conducting single-factor analysis on the clinical data of the study group and the control group using the $\chi 2$ test showed that age, gender, diabetes, hypertension, carcinoembryonic antigen (CEA), CA19-9, CA-125, visceral resection, PCI, omentectomy, pathology, and white blood cell count were significantly associated with tube occlusion during the HIPEC treatment ($p < 0.1$, Table I).

Lasso regression analysis and cross-validation were performed to prevent overfitting of the model, excluding two variables: Omentectomy and PCI. Eventually, 10 variables including age, gender, diabetes, hypertension, CEA, CA19-9, CA-125, visceral resection, pathology, and white blood cell count were retained (Figure 1B).

Multivariate binary logistic regression analysis identified age (OR = 2.676; p = 0.001), CA-125 (OR = 2.930; p = 0.001), CA19-9 (OR = 0.542; p = 0.049), and pathology type (OR = 2.484; p = 0.003) as independent risk factors ($p < 0.05$, Table II).

Based on the logistic analysis results, four variables (age, CA-125, CA19-9, and pathology type) were selected to construct a nomogram predictive model for tube occlusion during the HIPEC treatment (Figure 2A). The model calculates the total score of different factors, with higher scores indicating a greater risk of tube occlusion occurrence. For instance, for a patient with the following model variables: 50 years old, CA-125 <35 U/ml, CA19-9 <27 U/ml, and pathology indicating

DPAM, the total score calculated through the tube occlusion risk nomogram analysis was 185 points. By extrapolating from the obtained results the probability of tube occlusion occurrence for that patient was 30%.

Calibration curves, validated by the bootstrap method with 1,000 clinical predictions, demonstrated close alignment between the observed and predicted curves, indicating a close approximation of the predicted tube occlusion cases to actual occurrences (Figure 2B).

DISCUSSION

Currently, there is a scarcity of research on tube occlusion during closed HIPEC treatment. To the best of the authors' knowledge, this study is the first to explore tube occlusion in PMP patients undergoing HIPEC therapy. To enhance the clinical relevance of study, the investigation defined tube occlusion as the inability to achieve continuous perfusion for less than 30 minutes. This definition was informed by previous researches which indicate that cancer cells undergo time-dependent exponential death after receiving heat for 30 to 40 minutes at 43 degrees celsius.[10,11] A study involving 214 patients undergoing CRS-HIPEC showed that body temperature could not be maintained above 38°C for 30 minutes during perfusion, indicating a declining trend in survival rates.[12]

This study successfully constructed a nomogram predictive model for assessing the risk of tube occlusion in patients with PMP undergoing CRS combined with HIPEC treatment. Through detailed analysis of data from 107 patients, the study identified several risk factors, including advanced age, histological subtype of DPAM, decreased CA19-9 levels, and elevated CA-125 levels.

Due to the lack of prior relevant research, explanations regarding the causes of tube occlusion in this study can only be speculative. The analysis is as follows.

Advanced age contributes to vascular ageing, resulting in diminished vascular elasticity[13] and impaired blood flow, which couples with the naturally elevated viscosity of secretions in older individuals, exacerbating the risk of drainage tube obstruction. Additionally, malignancies promote a hypercoagulable state, further increasing this risk.[14]

Low-grade PMP is more prone to the tube occlusion possibly due to its higher mucin content in ascitic fluid. In a study of 75 PMP patients undergoing enhanced CT, thinner mucin deposition was observed in high-grade PMP compared to low-grade PMP.[15] Additionally, research suggests that low-grade PMP has significantly higher mucin content in ascites compared to high-grade PMP, contributing to the formation of gelatinous or jelly-like ascites, which are more likely to cause obstructions. Conversely, high-grade PMP is associated with haemorrhagic ascites and lower mucin content.[16] In pathology, low-grade PMP is characterised by band-like or island-like tumour morphology, sparse cell distribution, and mild dysplasia often showing increased mucus production during cell division.[17] In contrast, high-grade PMP exhibits irregular glandular structures, strong heterogeneity, and relatively lower mucin secretion capability.[18]

Elevated CA-125 levels may be attributed to inflammatory reactions caused by peritoneal implants possibly reflecting disease extension, indicating broader peritoneal involvement. Higher CA-125 levels suggest wider tumour involvement, more free-tumour cells, and residual tumour tissue leading to luminal obstruction.[19,20] CA19-9 production is associated with tumour cell growth and spread, reflecting abnormal proliferation and infiltration of cancer cells.[21] Compared to PMCA and PMCA-S, DPAM typically exhibits decreased CA19-9 levels. However, due to the increased content of mucin in DPAM, the probability of tube occlusion is often elevated.

This study has some limitations inherent to its retrospective design. Firstly, selection bias is a concern as the inclusion criteria and patient selection were not randomised. Additionally, the relatively small number of patients may limit the generalisability of the findings and reduce the statistical power to detect significant differences. Moreover, after tube blockage, the fluctuating temperature during abdominal perfusion may affect postoperative physiological processes such as gastrointestinal emptying, gastrointestinal decompression, and defaecation, leading to postoperative gastrointestinal dysfunction. This requires further research and observation.

CONCLUSION

In patients with pseudomyxoma peritonei, tube occlusion during postoperative HIPEC is a frequent occurrence. This study developed a predictive nomogram model using clinical indicators to anticipate this risk, incorporating factors like age, CA-125, CA19-9, and pathology type. Validation showed high predictive accuracy and clinical relevance.

ETHICAL APPROVAL:

Ethical approval for this study was secured prior to the initiation of the research from the Ethics Committee of the Central Hospital Affiliated with Shandong First Medical University, Jinan, China (Approval no. 20240305004).

PATIENTS' CONSENT:

Verbal consent was obtained from all individual participants included in the study to publish the data concerning their cases.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

QL, CL: Study design and data collection.
BW: Data analysis.
QL: Wrote the manuscript.
GY: Supervised the overall research process.
All authors approved the final version of the manuscript to be published.

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