

World Journal of *Clinical Cases*

World J Clin Cases 2021 June 26; 9(18): 4460-4880



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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Lin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

June 26, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Observational Study

Risk factors for postoperative delayed gastric emptying in ovarian cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Supported by Beijing Natural Science Foundation, No. 7202075 and "Beijing Hospitals Authority" Ascent Plan, No. DFL20190701.

Institutional review board statement: All the patients provided written informed consent

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Abstract

BACKGROUND

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) has shown promising results in improving the survival of ovarian cancer patients. Although the safety profiles of CRS-HIPEC exist, more attention should be paid to gastrointestinal complications, as the procedure involves a considerable proportion of bowel resection and anastomosis.

AIM

To identify the risk factors for delayed gastric emptying in ovarian cancer treated with CRS-HIPEC.

METHODS

A cross-sectional study was conducted. According to the inclusion and exclusion criteria, we retrospectively analyzed 77 patients admitted between March 2014 and April 2018 with advanced and recurrent ovarian cancer treated with CRS-HIPEC in Beijing Shijitan Hospital of Capital Medical University. Risk factors for delayed gastric emptying were analyzed using univariate analysis. All of the statistically significant variables in the univariate analysis were entered into the multivariable logistic regression model to determine factors independently associated with delayed gastric emptying.

RESULTS

Among the 77 included patients, 36.4% (28/77) had delayed gastric emptying

before enrollment and the study was reviewed and approved by the ethics committee and institutional review board of Beijing Shijitan Hospital, Capital Medical University.

Informed consent statement: All the patients provided written informed consent before enrollment.

Conflict-of-interest statement: Neither the submitted paper nor any similar paper, in whole or in part, has been submitted to or published in any other scientific journal. All authors of this paper have read and approved the final submitted version and are aware that they are listed as an author on the paper. There are no financial or other interests with regard to the submitted manuscript that might be construed as a conflict of interest.

Data sharing statement: No additional data are available.

STROBE statement: The guidelines of the STROBE Statement have been adopted in this study.

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Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0

after CRS-HIPEC. The median age and body mass index of all patients were 59 years and 22.83 kg/m², respectively. Preoperative chemotherapy was administered in 55 patients (71%). Sixty-two patients (81%) had a history of at least one previous pelvic surgery. The median operation time and intraoperative hemorrhage volume were 630 min and 600 mL, respectively. Omentectomy was performed in 32 cases of primary ovarian cancer and 24 cases of recurrence. The median peritoneal cancer index was 16. The risk factors for delayed gastric emptying from the univariate analysis were body mass index < 23 kg/m² ($X^2 = 5.059$, $P = 0.025$), history of pelvic surgery ($X^2 = 4.498$, $P = 0.034$), history of chemotherapy ($X^2 = 4.334$, $P = 0.037$), operation time ≥ 7 h ($X^2 = 4.827$, $P = 0.047$), and intraoperative hemorrhage ≥ 800 mL ($X^2 = 7.112$, $P = 0.008$). Multivariable analysis revealed that age ≥ 70 years (HR = 7.127; 95%CI 1.122-45.264; $P = 0.037$) and intraoperative hemorrhage ≥ 800 mL (HR = 3.416; 95%CI 1.067-10.939; $P = 0.039$) were independently associated with postoperative delayed gastric emptying after CRS-HIPEC.

CONCLUSION

Postoperative gastrointestinal management, including prolonged nasogastric intubation, should be promoted for patients over 70 years or those with intraoperative bleeding exceeding 800 mL.

Key Words: Delayed gastric emptying; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Ovarian cancer; Complication; Nasogastric tube

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Core Tip: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are alternatives for ovarian cancer. Delayed gastric emptying (DGE), a common complication of this procedure, can cause discomfort and decrease quality of life postoperatively. However, little attention has been paid to this complication. Identifying patients at increased risk for DGE may aid patient selection as well as postoperative gastrointestinal management. A retrospective study was conducted, and risk factors for DGE were analyzed using univariate and multivariate analyses. We found that age ≥ 70 years and intraoperative hemorrhage ≥ 800 mL were independently associated with postoperative DGE after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Citation: Cui GX, Wang ZJ, Zhao J, Gong P, Zhao SH, Wang XX, Bai WP, Li Y. Risk factors for postoperative delayed gastric emptying in ovarian cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Clin Cases* 2021; 9(18): 4644-4653

URL: <https://www.wjgnet.com/2307-8960/full/v9/i18/4644.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i18.4644>

INTRODUCTION

Ovarian cancer, which has the highest mortality rate among gynecological malignancies in developed countries, is the seventh most common cancer in women globally, with 5-year survival rates below 45% [1,2]. Approximately 70% of cases are diagnosed at an advanced stage, and more than 60% of patients experience recurrence, though with a good initial response to treatment [3].

In recent years, cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) has emerged as an alternative treatment for ovarian cancer. Controversies still exist as to whether CRS-HIPEC can further improve the prognosis of ovarian cancer patients when compared with CRS alone. Some studies have shown promising results, and the morbidity and mortality rates of CRS-HIPEC are directly comparable to those of surgical oncology procedures of similar extent [4-8]. The procedure involves a considerable proportion of bowel resection and anastomosis. Much more attention has been given to organic lesions, such as intestinal

Grade B (Very good): 0
 Grade C (Good): C
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: December 19, 2020

Peer-review started: December 19, 2020

First decision: January 23, 2021

Revised: January 23, 2021

Accepted: March 17, 2021

Article in press: March 17, 2021

Published online: June 26, 2021

P-Reviewer: Cashin PH

S-Editor: Zhang L

L-Editor: Filipodia

P-Editor: Li JH



perforation, fistula and mechanical ileus, than to delayed gastric emptying (DGE), a kind of functional gastroparesis.

DGE, a common complication after abdominal surgery, can cause discomfort and decrease quality of life postoperatively. Characterized according to the definition of the International Study Group of Pancreatic Surgery, DGE can be classified into grades A, B, and C by its clinical impact[9]. Only grades B and C are regarded as clinically relevant[9,10]. Though not a life-threatening complication, DGE can increase the duration of postoperative hospitalization and hospital costs, decrease quality of life, and even affect long-term prognosis. However, few studies have focused on DGE in ovarian cancer patients after CRS-HIPEC.

The aim of this study was to identify the risk factors for DGE in patients with advanced and recurrent ovarian cancer treated with CRS-HIPEC. Identifying patients at increased risk for DGE may aid patient selection as well as postoperative gastrointestinal management.

MATERIALS AND METHODS

Patient selection

From March 2014 to April 2018, 77 patients with pathologically diagnosed advanced and recurrent ovarian cancer treated by CRS-HIPEC at the Department of Peritoneal Cancer Surgery and Gynecology, Beijing, China, were enrolled in this study. The major inclusion and exclusion criteria, as well as preoperative evaluations, have been previously reported[11] and were strictly implemented in this study to minimize bias. All patients provided written informed consent before enrollment, and the study was approved by the ethics committee and institutional review board.

CRS-HIPEC procedure

The extent of peritoneal spread was assessed after abdominal exploration using the peritoneal cancer index (PCI). Then maximal CRS was performed including primary tumor removal, complete resection of the tumor nodule with intestinal resection if necessary, and peritonectomy. The gastroepiploic artery was preserved during omentectomy to minimize the effect on gastric emptying, although there it has been reported that there is no association between preservation of the gastroepiploic artery during omentectomy and gastric emptying after CRS-HIPEC[12]. The completeness of cytoreduction was evaluated for each patient with a standardized cytoreduction scoring system[13]. HIPEC was then implemented using the open coliseum technique, the details of which have been described elsewhere, and all CRS-HIPES procedures were based on Sugarbaker's principles[14,15].

Definition of clinically relevant postoperative DGE

Clinically relevant postoperative DGE was defined as a nasogastric tube (NGT) left in place for ≥ 8 d or < 8 d but repeated emesis after removal of the NGT and/or need for reinsertion of the NGT or failure to tolerate unlimited oral intake by postoperative day 14[9,10].

Parameters observed in the study

The demographic data included age, body mass index (BMI), concomitant disease, preoperative chemotherapy, serum cancer antigen 125 (CA-125) level, and pleural effusion status. During CRS-HIPEC, we collected information about the operation time, PCI, intraoperative bleeding, number of organs removed, intestinal resection and anastomosis. The NGT intubation time and eating status were recorded after CRS-HIPEC.

Statistical analysis

The data were included in a prospective database established at the beginning of the surgery and were analyzed using SPSS software (version 18.0; SPSS incorporated, an IBM Company, Chicago, IL, United States). Data from 77 patients, without any missing data, are expressed as the median (range) and frequency. Univariate analyses were comparing patients who experienced DGE with patients who did not were performed using chi-square tests. A 95%CI ($P < 0.05$) was considered statistically significant. All of the statistically significant variables in the univariate analysis were entered into the multivariable logistic regression model to determine factors independently associated with DGE.

A statistical review of the study was performed by a biomedical statistician.

RESULTS

Demographic data and surgical characteristics

A total of 77 patients with pathologically confirmed ovarian cancer were enrolled in this study, with a median age of 59 years (range: 35-79 years). The median BMI of all patients was 22.83 kg/m² (range: 13.8-33.98). In total, 10% of the patients had diabetes mellitus, and 21% had high blood pressure. Preoperative chemotherapy was administered in 55 patients (71%), with an average number of 6 chemotherapy cycles per patient (range: 0 to 25 cycles). Cytoreductive surgery plus HIPEC was indicated in 32 patients (42%) with primary ovarian cancer and in the remaining 45 patients (58%) for recurrent disease. Sixty-two patients (81%) had a history of at least one previous pelvic surgery. The median serum CA-125 level was 277.2 U/mL (range: 7.2-10001.0 U/mL). The demographic data are shown in [Table 1](#).

[Table 2](#) summarizes the CRS-HIPEC characteristics. The median operation time and intraoperative hemorrhage volume were 630 min (range: 280-960) and 600 mL (range: 50-5000), respectively, with 69% of patients undergoing bowel resection. Omentectomy was performed in 32 cases of primary ovarian cancer and 24 cases of recurrence. The median PCI was 16 (range: 1-39), and 78% of patients underwent optimal cytoreductive surgery. The most commonly used chemotherapeutic agent was docetaxel, alone or in combination with carboplatin and mitomycin.

Univariate analysis of risk factors associated with DGE after CRS-HIPEC

The incidence rate of DGE was 36% (28/77). Univariate analysis found a BMI < 23 kg/m² ($P = 0.025$), no history of pelvic surgery ($P = 0.034$), fewer than 7 previous chemotherapy cycles ($P = 0.037$), operation time ≥ 7 h ($P = 0.047$) and intraoperative hemorrhage ≥ 800 mL ($P = 0.008$) to be associated with an increased rate of DGE ([Table 3](#)).

Patients who underwent gastrectomy, pancreatectomy, splenectomy, and left total diaphragmatic peritonectomy were divided into perigastric and gastric dissection groups. Perigastric and gastric dissection is known to be the greatest risk factor for DGE. However, it was not found to be related to DGE by univariate analysis ($P = 0.421$) in this study.

Multivariate analysis of risk factors associated with DGE after CRS-HIPEC

Age and all of the statistically significant variables in the univariate analysis, including BMI, history of pelvic surgery, number of previous chemotherapy cycles, operation time and intraoperative hemorrhage, were entered into the multivariable logistic regression model to determine factors independently associated with DGE.

We found age ≥ 70 years (odds ratio [OR] = 7.127, 95%CI: 1.122-45.264, $P = 0.037$) and intraoperative hemorrhage ≥ 800 mL (OR = 3.416, 95%CI: 1.067-10.939, $P = 0.039$) to be independent risk factors for DGE after CRS-HIPEC in advanced and recurrent ovarian cancer patients ([Table 4](#)).

DISCUSSION

Ovarian cancer, which generally presents at an advanced stage, is the most common cause of death due to a gynecological cancer[16]. After standard treatment, including cytoreductive surgery and systemic chemotherapy, the peritoneal surface is usually the primary site of disease recurrence, and the prognosis of these patients is poor when treated with conventional systemic chemotherapy. Thus, cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy has been developed, achieving longer recurrence-free survival and overall survival than surgery alone, and the side effect rate is acceptable[11].

The incidence of adverse events of CRS-HIPEC administered in ovarian cancer ranges from 15% to 66% and mainly includes anastomotic leakage, abdominal abscess, intestinal obstruction, pleural effusion, and hematological toxicity[11,17]. Delayed gastric emptying, a frequent intestinal adverse effect, is frequently overlooked and can affect the quality of life of patients, prolong the length of hospital stay, and even affect long-term prognosis. The aim of this study was to identify the risk factors for clinically relevant DGE in patients with advanced and recurrent ovarian cancer treated with

Table 1 Patients data (n = 77)

Characteristic	Value
Age (yr, median and range)	59 (35-75)
BMI (kg/m ² , median and range)	22.83 (13.8-33.98)
Concomitant disease, n (%)	
Diabetes mellitus	8 (10)
High blood pressure	16 (21)
History of chemotherapy (cycles, median and range)	6 (0-25)
Pelvic surgical history, n (%)	62 (81)
Serum CA-125 level (U/mL, median and range)	277.2 (7.2-10001.0)
Primary/recurrent ovarian cancer, n (%)	
Primary	32 (42)
Recurrent	45 (58)
FIGO stage for primary ovarian cancer (n)	
IIIB	7
IIIC	4
IVB	21
Histology, n (%)	
Serous	55 (71)
Others	22 (29)

BMI: Body mass index.

CRS-HIPEC.

The pathophysiology behind delayed gastric emptying has proven to be complicated, with multiple variables involved. In our analysis, we found that age ≥ 70 years and intraoperative hemorrhage ≥ 800 mL were independent risk factors for DGE after CRS-HIPEC in advanced and recurrent ovarian cancer patients. With increasing age, gastrointestinal function gradually weakens; thus, older people were more susceptible to DGE. The other risk factor associated with DGE was intraoperative hemorrhage. The specific mechanism of how blood loss affects DGE is not clear. We hypothesize that the blood redistributes with an increase in hemorrhage; hence, the gastric mucosa becomes ischemic, weakening gastrointestinal motility.

Perigastric and gastric dissection is known to be the greatest risk factors for DGE. However, it was not found to be related to DGE in our study ($P = 0.421$). The DGE rate in the perigastric and gastric dissection group was 46.2% (6/13), higher than that in the group without perigastric or gastric dissection (34.4%, 22/64). The possible reason for this may be that the sample size is too small. Perhaps there will be a significant difference between the two groups as the number of cases increases.

Delayed gastric emptying is a main complication after CRS-HIPEC with unknown origin in ovarian cancer. Extensive intestinal manipulation, intraperitoneal chemotherapy, and intraperitoneal hyperthermic perfusion during surgery are all plausible causes of this phenomenon. The definition of postsurgical delayed gastric emptying was uncertain and varied in different reports before an objective and generally applicable definition of DGE was developed by the International Study Group of Pancreatic Surgery[9]. Based on severity and clinical impact, DGE was classified into grades A, B, and C. Only grades B and C are regarded as clinically relevant and were studied in this study. Nausea caused by anesthesia, wound pain, stimulation from the nasogastric tube and so on are sometimes difficult to distinguish from nausea caused by DGE. However, the severity, duration and clinical impact of nausea caused by the above reasons usually cannot match the levels of DGE in grade A or B. Thus, these causes of nausea were not studied here.

Treatments for delayed gastric emptying in our ovarian cancer patients after CRS-HIPEC included symptomatic therapy and supplementation with electrolytes,

Table 2 Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy characteristics (n = 77)

Characteristic	Value
Operation time (minute, median and range)	630 (280-960)
Intraoperative hemorrhage (mL, median and range)	600 (50-5000)
Number of organs resected (median and range)	2 (0-9)
Resected organs, n (%)	
Ascending colon	18 (23)
Transverse colon	4 (5)
Descending colon	5 (6)
Sigmoid colon	19 (25)
Total colon	3 (4)
Stomach (partial)	3 (4)
Small intestine (partial)	13 (17)
Rectum	46 (60)
Liver (partial)	3 (4)
Spleen	7 (9)
Pancreas (partial)	1 (1)
Gallbladder	8 (10)
Omentectomy, n (%)	56 (73)
Urinary bladder, n (%)	2 (3)
Number of bowel resection, n (%)	53 (69)
PCI (median and range)	16 (1-39)
CCS, n (%)	
CC 0-1	60 (78)
CC 2-3	17 (22)
Chemotherapeutic agent, n (%)	
Docetaxel	4 (5)
Docetaxel + carboplatin	55 (71)
Mitomycin + docetaxel	4 (5)
Mitomycin + carboplatin	14 (19)

CC: Cytoreduction; CCS: Cytoreduction scoring; PCI: Peritoneal cancer index.

minerals, proteins, and calories to maintain water and electrolyte balance and reduce malnutrition. Common symptomatic medications were antiemetic drugs, such as ondansetron, vitamin B6, and promethazine. The specific dosage depended on the patient's age, weight and severity of DGE. Motility drugs were not used.

The limitations in the present study need to be addressed. First, this is a retrospective study with a relatively limited sample size, and an RCT study with large samples is needed to further confirm the risk factors for DGE and its effects on improved prognosis. Second, fundamental studies are needed to illustrate the potential mechanisms.

In conclusion, strengthened intestinal management, including prolonged nasogastric intubation, the use of gastrointestinal motility drugs and enteral nutrition, should be applied to patients aged ≥ 70 years or with intraoperative hemorrhage ≥ 800 mL when undergoing CRS-HIPEC.

Table 3 Univariate analysis of risk factors associated with delayed gastric emptying after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Variable	n	DGE		χ^2	P value
		Yes	No		
Age (yr)				2.697	0.101
≥ 70	9	6	3		
< 70	68	22	46		
BMI (kg/m ²)				5.059	0.025
≥ 23	35	8	27		
< 23	42	20	22		
Pelvic surgery history				4.498	0.034
Yes	62	19	43		
No	15	9	6		
Comorbidity (DM/HBP)				2.802	0.094
Yes	24	12	12		
No	53	16	37		
History of chemotherapy				4.334	0.037
≥ 7 cycles	34	8	26		
< 7 cycles	43	20	23		
CA-125 level				0.990	0.320
Normal (< 35 U/mL)	12	2	10		
Elevated (≥ 35 U/mL)	65	25	40		
Pleural effusion before surgery				0.359	0.549
Yes	19	8	11		
No	58	20	38		
PCI				1.967	0.161
≥ 10	52	22	30		
< 10	14	2	12		
Diaphragmatic invasion				0.717	0.397
Yes	23	10	13		
No	54	18	36		
Perigastric and gastric dissection				0.648	0.421
Yes	13	6	7		
No	64	22	42		
Operation time				4.827	0.047
≥ 7 h	65	27	38		
< 7 h	12	1	11		
Intraoperative hemorrhage				7.112	0.008
≥ 800 mL	29	16	13		
< 800 mL	48	12	36		
Anastomosis				3.634	0.057
Yes	53	23	30		
No	24	5	19		

Number of organs removed				2.495	0.114
≥ 4	27	13	14		
< 4	50	15	35		
Pleural effusion after surgery				3.667	0.056
Yes	44	20	24		
No	33	8	25		

DGE: Delayed gastric emptying; PCI: Peritoneal cancer index.

Table 4 Multivariate analysis of risk factors associated with delayed gastric emptying after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Variable	OR	95% Confidence interval		P value
		Lower	Upper	
Age (yr)				
≥ 70	7.127	1.122	45.264	0.037
< 70	1			
Intraoperative hemorrhage				
≥ 800 mL	3.416	1.067	10.939	0.039
< 800 mL	1			
BMI (kg/m ²)				
≥ 23	0.450	0.147	1.379	0.162
< 23	1			
Operation time				
≥ 7 h	3.206	0.329	31.226	0.316
< 7 h	1			
History of abdominal surgery				
Yes	0.787	0.175	3.538	0.755
No	1			
History of chemotherapy				
≥ 7 cycles	0.301	0.078	1.167	0.082
< 7 cycles	1			

BMI: Body mass index.

CONCLUSION

In conclusion, strengthened intestinal management, including prolonged nasogastric intubation, using gastrointestinal motility drugs and enteral nutrition, should be applied to patients aged ≥ 70 years or with intraoperative hemorrhage ≥ 800 mL when undergoing CRS-HIPEC.

ARTICLE HIGHLIGHTS

Research background

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) are alternatives for ovarian cancer. Delayed gastric emptying (DGE), a common complication of this procedure, can cause discomfort and decrease quality of life

postoperatively. However, little attention has been given to this complication.

Research motivation

Though not life-threatening, DGE can increase the duration of postoperative hospitalization, decrease quality of life, and even affect the long-term prognosis of patients after CRS-HIPEC. More research is needed to elucidate the pathophysiology, etiology and treatment of DGE.

Research objectives

The aim of this study was to identify the risk factors for DGE in patients with ovarian cancer treated with CRS-HIPEC. Identifying patients at increased risk for DGE may aid patient selection as well as postoperative gastrointestinal management.

Research methods

A retrospective study was conducted, and risk factors for DGE were analyzed using univariate and multivariate analyses.

Research results

Age ≥ 70 years and intraoperative hemorrhage ≥ 800 mL were independently associated with postoperative DGE after CRS-HIPEC. Perigastric and gastric dissection is known to be the greatest risk factor for DGE. However, it was not found to be related to DGE in our study. The possible reason may be that the sample size was too small.

Research conclusions

Postoperative gastrointestinal management, including prolonged nasogastric intubation, should be strengthened for patients over 70 years or with intraoperative bleeding exceeding 800 mL.

Research perspectives

Large-sample RCTs are needed to further identify the risk factors and management of DGE.

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