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RESEARCH ARTICLE

Predictors of major postoperative complications in cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy

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Abstract

Purpose Cytoreductive Surgery (CRS) ± Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is associated with a high incidence of postoperative morbidity. Our aim was to identify independent, potentially actionable perioperative predictors of major complications.

Methods We reviewed patients who underwent CRS ± HIPEC from June 2020 to January 2022 at a high-volume center. Postoperative complications were categorized using the Comprehensive Complication Index, with the upper quartile defining major complications. Multivariate logistic analysis identified predictive and protective factors.

Results Of 168 patients, 119 (70.8%) underwent HIPEC. Mean Comprehensive Complication Index was 12.6 (12.7) and upper quartile cut-off was 22.6. Medical complications were more frequent but less severe than surgical (63% vs 18%). Forty-six patients (27.4%) comprised the "major complications" group (mean CCI 30.1 vs 6.3). Multivariate logistic regression showed that heart disease (RR 1.9; 95% CI: 1.1 to 3.3), number of anastomoses (RR 2.4; 95% CI:1.3 to 4.6) and first 24-h fluid balance (RR 1.1; 95% CI: 1.1 to 1.2), were independently associated as risk factors for major complications, while opioid-free anesthesia (RR 0.6; 95% CI: 0.3 to 0.9) and high preoperative hemoglobin (RR 0.9; CI 95%: 0.9 to 0.9) were independent-protective factors.

Conclusion Preoperative heart diseases, number of anastomoses and first 24 h-fluid balance are independent risk factors for major postoperative complications, while high preoperative hemoglobin and opioid-free anesthesia are protective. Correction of anemia prior to surgery, avoiding positive fluid balance and incorporation of opioid-free anesthesia strategy are potential actionable measures to reduce postoperative morbidity.

Keywords Cytoreductive surgery · Comprehensive classification index · Predictor factors · Postoperative morbidity

Abbreviations

PC	Peritoneal carcinomatosis
CRS	Cytoreductive surgery
HIPEC	Hyperthermic intraperitoneal chemotherapy
OFA	Opioid-free anesthesia
CCI	Comprehensive complication index
TEA	Thoracic epidural analgesia
PCI	Peritoneal carcinomatosis index
OBA	Opioid-based anesthesia
FFP	Fresh frozen plasma
IV	Intravenous
ICU	Intensive care unit
ROC	Receiver operating characteristics
AUC	Area under the curve
CI	Confidence interval
RR	Risk ratio
OR	Odds ratio
IQR	Interquartile range
PONV	Postoperative nausea and vomiting
BMI	Body mass index
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
HTA	Hypertension
PMP	Pseudomyxoma peritonei
NET	Neuroendocrine tumor

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Introduction

Peritoneal carcinomatosis (PC), characterized by the presence of tumor implants on the parietal and visceral peritoneum, is a serious and difficult-to-treat manifestation of advanced disease in multiple gastrointestinal and gynecologic tumors and primary peritoneal neoplasms. Cytoreductive Surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) emerged as a therapeutic option for carefully selected patients with this condition [1] and gradually became supported by increasing amounts or evidence and more widely available. CRS is a highly complex surgical procedure where extensive peritoneal and visceral resections are performed which, coupled with the additional effect of HIPEC can result in significant tissue damage and alterations in homeostasis leading to the development of postoperative complications. Consequently, while improving the oncologic outcomes of PC, postoperative morbidity and mortality are still high for this surgery ranging from 22 to 66% [2] and 2 to 5%, respectively.

Strict patient selection, meticulous surgical technique and, as well as centralizing the procedure in specialized institutions, are factors that contribute to achieving the best clinical outcomes [3]. Risk factors are not limited to variables associated with the extent of tumbril involvement and consequent complexity of the surgery required for its complete removal and/or patient baseline characteristics and comorbidities. There could be potentially modifiable risk factors, such as perioperative fluid therapy management, transfusion policy, or opioid use, that could have a significant role in the incidence or type of complications [4, 5]. Liberal intraoperative fluid administration protocols have been associated with negative clinical effects in abdominal surgery. However, definitions of restrictive and liberal remain controversial in the literature [6, 7] and the true influence of fluid management on postoperative outcomes after CRS ± HIPEC remains controversial. Blood transfusions, even if not massive, have been associated with postoperative complications [8]. Transfusions are common in CRS, with up to 77% of patients requiring intraoperative allogenic packed red blood cell transfusion [9] and is therefore important to evaluate as a variable that may impact on postoperative morbidity. Finally opioid-free anesthesia (OFA) is an emerging anesthetic technique focused on avoiding the negative impact of intraoperative opioids on postoperative outcomes that has been scarcely studied in this complex surgery.

We aim to characterize perioperative care strategies in our highly-specialized, high-volume referral center for peritoneal surface malignancies, that incorporate the principles of goal-directed fluid management, strictly defined transfusion policies as well as opioid-sparing anesthesia and to examine their influence on the incidence of major postoperative complications classified by Comprehensive Complication Index (CCI).

Material and methods

Design and eligibility

The study is a retrospective-cohort analysis conceived to identify predictor factors of postoperative major complications after CRS ± HIPEC at a single, high-volume regional referral center. Our team performs at least 120 procedures per year and the majority of care processes including preoperative evaluation, intraoperative anesthetic and surgical management as well as postoperative pathways are protocolized. The study population included all patients undergoing CRS ± HIPEC from June 2020 to January 2022 after receiving IRB approval (Bellvitge University Hospital, protocol No. 008/22, March 10, 2022) and in accordance with the Declaration of Helsinki. Informed consent was waived given the retrospective nature of the study. The period was chosen based on when surgical activity in the unit normalized after the COVID-19 pandemic and before new postoperative protocols were introduced. Data was extracted from medical records and results are reported according to the STROBE checklist guidelines.

Considering that thoracic epidural anesthesia (TEA) is a gold standard analgesic technique for open abdominal major surgeries, patients in whom TEA was not performed due to medical contraindication, patient refusal or technical failure in placement of the catheter were excluded in order to standardize the sample. Currently, the OFA strategy is being evaluated as a variable that could improve outcomes. For this reason, the OFA strategy was included as a variable to be analyzed. Postoperative complications were classified according to the Clavien–Dindo Classification, a widely used system for grading the severity of complications arising from surgery according to the degree of invasiveness required for treatment [10]. We also used the Comprehensive Complication Index (CCI), a more recent modification of the Clavien–Dindo Classification that takes into account the number of complications, as well as their severity. The CCI is calculated by multiplying the grade of each complication by a weighting factor, and then summing the products [11]. This gives a single score that can be used to compare the overall complication burden of different surgical procedures or groups of patients. This scale has been validated for different abdominal surgeries [12], including CRS ± HIPEC [13]. CCI was calculated for each patient (https://www.cci-calculator.com/cciCalculator).

Preoperative period

A thorough and standardized preoperative evaluation was performed by the surgeon as well as the anesthesiologist.

Intraoperative period

Intraoperative anesthetic and surgical features were collected. Estimated blood loss were established-by weighing sponges and measuring the volume collected in suction bottles and drains. The peritoneal carcinomatosis index (PCI) was calculated intraoperatively to assess the extent of peritoneal disease, and is based on the number and size of peritoneal nodules, as well as the presence of ascites resulting in a numerical score ranging from 0 to 39 [14]. The extent of cytoreduction is classified according to the cytoreduction completeness score: CC-0, no residual disease; CC-1, minimal residual disease (up to 2.5 mm); CC-2, residual disease 2.5 mm to 2.5 cm; and CC-3, residual disease > 2.5 cm [14]. All anastomoses were performed before the HIPEC. Small-bowel and colo-colonic anastomoses were handsewn. Low colorectal anastomoses were performed with a circular stapler and reinforced with sero-muscular sutures, typically without a diverting ileostomy. HIPEC was performed with an open abdomen technique (Coliseum) with 1.25% glucose peritoneal dialysis solution as the carrier. Mitomycin C (30 mg/m2) or oxaliplatin (450 mg/m2) or irinotecan (360 mg/m2) was used for colon and appendiceal tumors, cisplatin (80 mg/m2) with doxorubicin (15 mg/m2) for gastric cancer and mesothelioma and cisplatin + doxorubicin or paclitaxel (60 mg/m2) for ovarian cancer. HIPEC was a priori planned as part of the surgical procedure in all cases of CRS except for primary cytoreduction of ovarian cancer, tumor histologies not susceptible to cytotoxic chemotherapy (such as neuroendocrine tumors, GIST etc.) or in cases of recurrent disease localized to only one abdominopelvic region in patients with colorectal or appendiceal cancer.

Two different anesthesia protocols previously reported by our group [5] were used according the personal preferences of the anesthesiologist: opioid-based anesthesia (OBA) or OFA protocol. Intraoperative blood products transfusion rate followed the Guidelines for Perioperative Care in CRS/HIPEC [15]. For fresh frozen plasma (FFP) administration, the decision was based on consensus between the anesthesiologist and attending surgeon. Generally, crystalloids were the main intravenous fluid used for maintenance during perioperative period. Fluid volume and vasopressors were adjusted to maintain an adequate tissue perfusion based on mean arterial pressure and urinary output. Colloids were employed in cases of excessive bleeding. Fluid balance was calculated as the difference between total volume of intravenous fluids and blood products administrated minus urine output, blood loss and insensible losses, estimated as 1 ml/kg/h during surgery [16].

All cases were planned with extubation in the operating room and overnight stay in the intensive care unit (ICU) prior to transfer to surgery ward.

Postoperative period

Postoperative variables outcomes and labs results were recorded (Table 2). First 24-h fluid balance comprised the period from the beginning of the surgery until 8 am the following day. Postoperative complications were recorded at 30 postoperative days. A complication was defined as any undesirable, unintended event as a direct result of the surgical intervention. Surgical complication was defined as an event directly related to the surgical procedure performed. Events involving organs or sites distant from the surgical field related to the patient's general medical condition were considered medical complications.

Statistical analysis

Descriptive statistics were presented as the mean and standard deviation for continuous variables, while categorical data were represented as numbers or frequencies. The CCI, used to identify worse outcomes, was presented both as a continuous and a dichotomous variable, using the upper quartile as the cut-off for defining major/severe complication, in accordance with established literature [17, 18]. We assessed data distribution using the Shapiro–Wilk test.

We compared the characteristics of patients categorized in the major complication cohort with those in the non-major complication cohort. For continuous variables, the Student *t* test was used, and for categorical variables, we used a Chi-square test or Fisher's exact test.

Multivariate logistic regression was used to assess the predictors associated with major complications, as baseline characteristics and perioperative variables. The best subset model was selected from all possible submodels; in this method every possible conceivable regression equation is fitted. Entry criterion was $p < 0.20$ in the bivariate analysis. To assess the overall model performance, we generated a receiver operating characteristic (ROC) curve based on these risk groups and calculated the area under the curve (AUC), comparing it with an AUC of 0.5. Criterions as the Akaike and Bayesian information criteria were used to compare the fit of the model. Hosmer–Lemeshow test was used to assess the goodness-of-fit of the final multivariate model. Split-sample model validation was performed.

Furthermore, multivariate logistic regression analysis was used to evaluate the variables associated with the most frequent medical and surgical complications. In bivariate analysis, results were reported as Odds ratio (OR) with 95%

confidence intervals (CI) for categorical variables and as mean difference with 95% CI for continuous variables. In multivariate regression analysis results were reported as OR and Risk Ratio (RR) with 95% CI. Imputation of missing values was not performed. The STATA statistical program (STATA v.17.0; StataCorp LLC, College).

Results

Population overview

During the period of the study, among 186 undergoing CRS ± HIPEC, 168 received TEA (60 (13) yrs.-old, 68.5% female) were included in the study.

Demographic and clinical data are shown in Table 1. The most prevalent primary tumor site was colorectal in 97 (57.7%) patients; followed by gynecological in 18 (10.7%) patients; pseudomyxoma peritonei in 31 (18.4%) patients; gastric in 11 (6.5%) patients and 11 (6.5%) patients presented other origins (urological, neuroendocrine tumor, mesothelioma, and liposarcoma). One hundred thirteen patients (67%) experienced at least one postoperative complication, with the mean CCI being 12.6 (12.7). The mean number of complications reported per patient was 1 (IQR 3), with 71 (42%) patients suffering 1 complication, 33 (20%) patients 2 complications, and 10 (6%) patients 3 complications. Following the Clavien–Dindo classification, of the 168(100%) patients, 60(35.7%) patients were graded as I, 43(25.6%) as II, 3(1.8%) as IIIa, 3(1.8%) as IIIb, 3(1.8%) as IVa and 1(0.6%) as IVb. Medical complications were more frequent than surgical complications (63 vs 18%, respectively) (Table 2). However, surgical complications, when occurring, were more severe. Specifically, a Clavien–Dindo score equal or greater than IIIa was more prevalent in surgical than in medical complications (23.3% vs 8.5%, respectively). As displayed in Table 2, the most frequent surgical complication was postoperative bleeding requiring transfusion of blood products in six cases and endoscopic treatment in 1 case. Lymphorrhagia, identified in six patients, was managed conservatively with abdominal drains in place. These drains were removed at a follow-up surgical visit 3 weeks postoperatively. Only two of the eight patients who developed pancreatic fistulas required cholangiography. Five patients developed superficial skin infections received bedside treatment. Four patients (2.4%) were diagnosed with anastomosis leakage and all of them required surgical reintervention. No in-hospital deaths were recorded in this cohort.

Results based on the occurrence *of major* postoperative complications

When measuring CCI, the upper quartile corresponded to 22.6; consequently, having a CCI score greater than 22.6 was chosen to define major complications. Forty-six patients (27.4%) suffered major complications (mean CCI 30.1) and

Table 1 Demographic and preoperative clinical data of 168 patients undergoing cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy and based on the occurrence of postoperative major complications (CCI ≥ 22.6). Data are expressed as mean (standard deviation) or number (%) and as mean difference with 95% CI for continuous variables and OR with 95% CI for categorical variables

		Total (n = 168)	Non-major complications (n = 122)	Major complications (n = 46)	p value	Coefficient (CI 95%)
Gender male		53 (31.5%)	41(33.6%)	12(26.1%)	0.350	0.7 (0.3 to 1.5)
Age (years)		60 (12.7)	60.6 (12.5)	60.3 (13.4)	0.902	-0.3 (-4.7 to 4.1)
BMI, Kg/m^2		25.7 (5.3)	25.6 (5.5)	26 (4.9)	0.685	0.4 (-1.4 to 2.2)
Smoking status		24 (14.3%)	17 (14%)	7 (6.6%)	0.848	1.1 (0.4 to 2.9)
ASA class	II	157 (94%)	116 (95.1%)	41 (89.1%)	0.175	0.4 (0.1 to 1.5)
	III	11 (6%)	6 (4.9%)	5 (10.9%)	0.175	2.4 (0.7 to 8.1)
Preoperative Hemoglobin, g/L		12.9 (1.6)	13.1 (1.6)	12.6 (1.6)	0.119	0.4 (-1 to 0.1)
Comorbidities						
Heart disease		14 (8.3%)	8 (6.6%)	6 (13.1%)	0.195	2.1 (0.7 to 6.5)
COPD		12 (7.1%)	7 (5.7%)	5 (10.9%)	0.313	2 (0.6 to 6.7)
CKD		19 (11.3%)	12 (9.8%)	7 (15.1%)	0.469	1.6 (0.6 to 4.5)
Stroke		3 (1.8%)	0	3 (6.5)	0.020*	*omitted*
HTA		47 (28%)	30 (24.6%)	17 (37%)	0.111	1.8 (0.9 to 3.7)
DM		20 (11.9%)	13 (10.7%)	7 (15.2%)	0.416	1.5 (0.6 to 4)
Previous chemotherapy		113 (67.3%)	86 (70.5%)	27 (58.7%)	0.146	0.0 (0.3 to 1.2)

BMI body mass index, *ASA* American society of anesthesiology classification of physical health, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *HTA* hypertension, *DM* diabetes mellitus

Table 2 Postoperative complications of 168 patients undergoing cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy and based on the occurrence of postoperative major complications (CCI ≥ 22.6). Data are expressed as mean (standard deviation) or number (%), and OR (95% CI)

	Total (*n* = 168)	Non-major complications (*n* = 122)	Major complications (*n* = 46)	*p* value	Coefficient (CI 95%)
Medical complications					
Postoperative nausea and vomiting	94 (56%)	55 (45.1%)	39 (84.8%)	0.000*	6.8 (2.8 to 16.4)
Cardiovascular (atrial fibrillation; heart failure)	8(4.8%)	3 (5.8%)	5 (10.9%)	0.036*	4.8 (1.1 to 21.1)
Paralytic ileus	16(9.5%)	2 (1.6%)	14 (30.4%)	0.000*	26 (5.7 to 121)
Acute kidney injury	12 (7.1%)	2 (1.6%)	10 (21.7%)	0.000*	16.7 (3.5 to 79.6)
Urinary tract infection	2(1.2%)	0	2 (4.3%)	0.074	*omitted*
Pulmonary embolism	1(0.6%)	0	1 (2.2%)	0.274	*omitted*
Sepsis	7(4.2%)	0	7 (15.2%)	0.000*	*omitted*
Respiratory (pneumonia caused by broncho aspiration)	1(0.6%)	1 (0.8%)	0	1	*omitted*
Others	3(1.8%)	0	3 (6.5%)	0.020*	*omitted*
Surgical complications					
Postoperative bleeding	10(6%)	2 (1.6%)	8 (17.4%)	0.001*	12.6 (2.6 to 62)
Anastomotic leakage	4(2.4%)	0	4 (8.7%)	0.005*	*omitted*
Lymphorrhagia	6(3.6%)	2 (1.6%)	4 (8.7%)	0.048*	5.7 (1.1 to 32)
Pancreatic fistula	8(4.8%)	1 (0.8%)	7 (15.2%)	0.001*	21.8 (2.6 to 182)
Superficial skin infection	5(3%)	2 (1.6%)	3 (6.5%)	0.127	4.2 (0.7 to 25.9)

ICU intensive care unit

formed the "major-complications" group whereas the 122 remaining ones were located in "absence of-major complications" group (mean CCI 6.3).

Demographic and preoperative clinical data for both groups are displayed in Table 1. The bivariate analysis did not show statistically significant differences in preoperative variables between groups except for the higher rate of previous stroke in major-complications group. Regarding to primary tumor site, the bivariate analysis also showed no statistically significant differences. Non-major complications compared to major complications group showed colorectal origin in 71(58.2%) vs 26(56.5%) patients ($p = 0.753$); gynecological in 13(10.7%) vs 5(10.9%) patients ($p = 0.968$); PMP in 20(16.4%) vs 11(23.9%) patients ($p = 0.541$); gastric in 10(8.2%) vs 1(2.2%) patients ($p = 0.120$); and others origins in 8(6.6%) vs 3(6.5%) patients ($p = 0.847$).

Patients who experienced major postoperative complications had lengthier surgeries than patients without major complications (399(163) *vs* 339(132) min, mean difference 60 min (95% CI, 12–108) min; $p = 0.015$, respectively), higher intraoperative blood transfusion rate (37% *vs* 16% patients, OR 2.1 (95% CI, 1.3–3.4); $p = 0.002$), and showed a tendency toward a higher median PCI (7(2–22) *vs* 5 (2–14); $p = 0.104$). Bowel resection was more common in the major complications group (33 (71.7%) *vs* 58 (47%) patients, respectively (OR 2.8 (95% CI, 1.3–5.8; $p = 0.008$), as well as, the number of anastomoses. Both bivariate and multivariate statistical analysis showed that the number of anastomoses is an independent risk predictor for the occurrence of major complications (0 vs 1: OR 2.7 (95% CI, 1.1 to 6.7); $p = 0.035$; 0 vs 2: OR 2.4 (95% CI, 1.3 to 4.6); $p = 0.006$; 0 vs 3 or more: OR 3 (95% CI, 1.1 to 7.9); $p = 0.033$). Moreover, the higher the number of anastomoses, the higher the risk of major complications (Table 3**)**. PCI was analyzed according to the number of anastomoses performed; when no bowel resection was required, median PCI (first and third quartiles) was 4 (2–7); when one anastomosis was required, PCI was 7 (2–15); in two anastomoses, PCI was 15 (3–28); and in 3 anastomosis or more, PCI was 31 (20–32). As for time of hyperthermic chemotherapy, this was also and no statistically significant differences were found regarding the appearance of major complications (7 (32%) vs 27 (28%); $p = 0.704$). In non-major complications group, the OFA strategy performed more frequently (64 vs 37%, OR 0.3 (95% CI: 0.2–0.7; $p = 0.002$)). Multivariate logistic regression showed that OFA strategy was a protective factor against the development of major postoperative complications (RR 0.6; 95% CI: 0.3 to 0.9; $p = 0.037$). First 24-h fluid balance was higher in the major complications group (4419 (3460) mL vs 3143 (1502) mL (95% CI: 217 to 2336; $p = 0.019$)). Likewise, the number of patients who received blood product transfusion (40 (23.8%) during the complete hospitalization period was higher in the major complications group (19 (41.3%) vs 21 (17.2%), OR 3.4 (95% CI: 1.6 to 7.2)); ($p = 0.001$). When transfusion rate was analyzed according to whether it was performed in the

Table 3 Intraoperative clinical data of 168 patients undergoing cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy and based on the occurrence of postoperative major complications (CCI ≥ 22.6). Data are expressed as mean (standard deviation) or number (%) and as mean difference with 95% CI for continuous variables and OR with 95% CI for categorical variables. PCI was expressed as median and first and third quartiles (Q1-Q3)

		Total ($n = 168$)	Non-major complications ($n = 122$)	Major complications ($n = 46$)	p value	Coefficient (CI 95%)
Intraoperative data						
OFA, n patients		95 (57%)	78 (64%)	17 (37%)	0.002*	0.3 (0.2 to 0.7)
Fluid therapy, ml/Kg/h		10.7 (3.3)	10.8 (3.5)	10.6 (2.5)	0.735	-0.2 (-1.3 to 0.9)
Blood loss, mL		369 (236)	405 (214)	356 (242)	0.223	50 (-31 to 130)
Urine output, ml/Kg/h		2.1 (1.2)	2.2 (1.3)	1.9 (1)	0.314	-0.2 (-0.6 to 0.2)
Fluid balance (mL)		472 (1384)	351 (1303)	793 (1549)	0.065	442 (-27 to 912)
Need of noradrenaline, n patients		43 (26%)	30 (25%)	13 (28%)	0.693	1.2 (0.6 to 2.6)
Blood-transfusion rate, n patients		36 (21.4%)	19 (16%)	17 (37%)	0.003*	3.2 (1.5 to 6.9)
Surgery data						
PCI		6 (2–15)	5 (2–14)	7 (2–22)	0.104	3 (0 to 7)
Time surgery (min)		356 (143)	339 (132)	399 (163)	0.015*	60 (12 to 108)
cytoreduction	CCO	151 (89.9)	111(91%)	40 (85%)	0.407	0.6 (0.2 to 2)
	CC1	17 (10.1%)	11 (9%)	6 (13%)	0.407	0.6 (0.5 to 5.4)
Bowel resection		91 (54.2%)	58 (47%)	33 (71.7%)	0.005*	2.8 (1.3 to 5.8)
Number of anastomoses						
0		*Reference*				
1		58 (34.5%)	38 (42.1%)	20 (15.9%)	0.021*	2.6 (1.2 to 5.8)
2		28 (16.7%)	18 (20.3%)	10 (7.7%)	0.043*	2.7 (1.1 to 7.3)
3 or more		5 (3%)	2 (3.6%)	3 (1.4%)	0.038*	7.4 (1.1 to 49)
HIPEC		119 (70.8%)	85 (60.7%)	34(73.9%)	0.590	0.8 (0.4 to 1.6)
30 min		22 (13.1%)	15 (68%)	7 (32%)	0.709	0.8 (0.3 to 2.2)
60 and 90 min		97 (57.7%)	70 (72%)	27 (28%)		
Drugs type						
Irinotecan		11 (10%)	8 (10.4%)	3 (9.1%)	0.369	
Oxiplatin		9 (8.2%)	4 (5.2%)	5 (15.2%)		
Cisplatin		2 (1.8%)	2 (2.6%)	0		
Cisplatin + doxorrubicin		12 (10.9%)	9 (11.7%)	3 (9.1%)		
Cisplatin + mytomicin		47 (42.7%)	31 (40.3%)	16 (48.5%)		
Mytomicin		29 (26.4%)	23 (29.9)	6 (18.2%)		
Postoperative outcomes						
Deferred extubation		2 (1.2%)	0	2 (4.3%)	0.074	*omitted*
24 h fluid balance, mL		3020 (1987)	3143 (1502)	4419 (3460)	0.019*	1276 (217 to 2336)
Need of noradrenaline, n patients		24	14 (11.5%)	10 (21.7%)	0.090	2.1 (0.9 to 5.2)
Hemoglobin at 24-postoperative hours, g/L		10.8 (6.1)	10.4 (1.4)	10 (1.2)	0.061	-0.4 (-0.9 to 0.02)
Blood-transfusion rate, n patients		40 (23.8%)	21 (17.2%)	19 (41.3%)	0.001*	3.4 (1.6 to 7.2)
In the first 24-h postoperatively		24	14 (11.5%)	11 (23.9%)	0.043*	2.4 (1 to 5.8)
After 24-h postoperatively		24	10 (8.2%)	14 (30.4%)	0.000*	4.9 (2 to 12.1)
CCI		12.6 (12.7)	6 (6.3)	30.1(7.6)	0.000	24 (21.8 to 26.3)
Start oral intake, days		4.9 (3)	4 (1.9)	7 (4.3)	0.000*	2.9 (1.6 to 4.2)
First flatus, days		4.1 (2.5)	3.8 (1.6)	5 (3.7)	0.011*	1.5 (0.4 to 2.6)
Start to ambulation, postoperative days		4 (1.7)	3.7 (1.2)	4.9 (2.5)	0.001*	1.3 (0.5 to 2.1)
ICU days of stay		1.7 (1.5)	1.4 (0.5)	2.4 (2.5)	0.009*	1 (0.3 to 1.8)
ICU -readmission		4	0	4 (8.7%)	0.005*	3.9 (3 to 5.1)
Hospital length of stay, days		10.2 (5)	8.8 (2.7)	13.8 (7.5)	0.000*	5 (2.7 to 7.3)

OFA opioid-free anesthesia, *PCI* peritoneal carcinomatosis index, *HIPEC* hyperthermic intraperitoneal chemotherapy, *CCI* comprehensive complication index, *ICU* intensive care unit first 24 postoperative hours or later, the major complications group showed higher transfusion requirements in both timeframes (Table 3). Table depicts the detailed incidence of postoperative complications in each group (Table 2).

After selection of the best predictive model from all possible submodels, the variables included in the selected model were heart disease, number of anastomoses, intraoperative and first 24-h fluid balance, OFA strategy, preoperative hemoglobin level, hemoglobin level on the first postoperative day, and gastric cancer primary. Multivariate logistic regression showed that heart disease, number of anastomoses, and first 24-h fluid balance, were independently associated as risk factors for major complications, while OFA and high preoperative hemoglobin levels were independent-protective factors. However, gastric cancer, intraoperative fluid balance and hemoglobin levels on postoperative day 1 were not independently associated with the occurrence of major complications (Fig. 1 Multivariable analysis of the association of perioperative variables with major postoperative complications among 168 patients undergoing Cytoreductive Surgery with or without Hyperthermic Intraperitoneal Chemotherapy. Data are expressed as Coefficient OR (95% CI) and RR (95% CI) and *p* value). The estimated model was very reliable because the prediction loss was 4.5%.

We also analyzed predictive factors for the most frequent medical (PONV) and surgical complication (postoperative bleeding). Multivariate regression for PONV showed that performing HIPEC is a risk factor with an OR 3.8 (95% CI: 1.7 to 8.8), whereas the use of OFA strategy (OR 0.3 (95% CI: 0.2 to 0.8) and male gender (OR 0.2 (95% CI: 0.1 to 0.4)) were protective factors (Table 4). We could not identify any independent predictors of postoperative bleeding, probably due to the overall low occurrence of this complication.

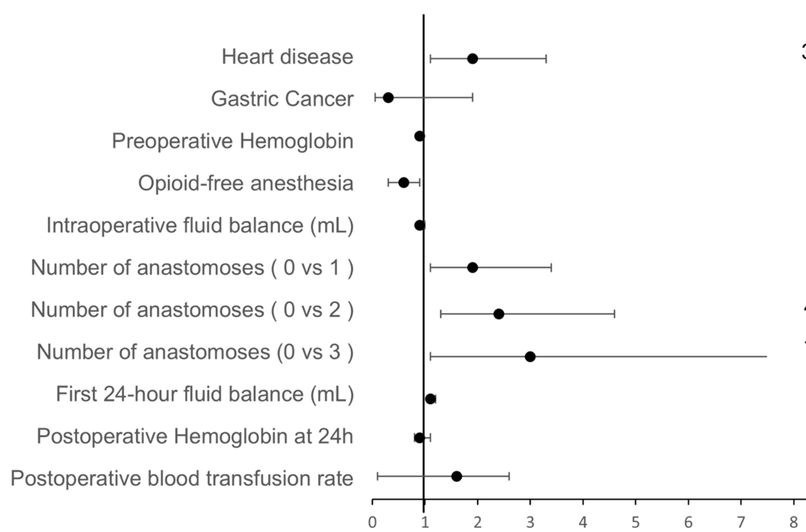
Table 4 Multivariate analysis of the association of perioperative variables with postoperative nausea and vomiting among 168 patients undergoing cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy. Data are expressed as Coefficient OR (95% CI) and RR (95% CI) and *p* value

Variables	OR (95% CI)	RR (95% CI)	*p* value
Gender (male)	0.2 (0.1 to 0.4)	0.5 (0.3 to 0.7)	0.000*
Opioid-free anesthesia	0.3 (0.2 to 0.8)	0.7 (0.5 to 0.9)	0.021*
Surgery time	0.9 (0.9 to 0.9)	1 (0.9 to 1)	0.152
Hyperthermic intraperitoneal chemotherapy	3.8 (1.7 to 8.8)	1.5 (1.1 to 2.1)	0.049*
Number of anastomoses			
0 vs 1	0.6 (0.3 to 1.4)	0.8 (0.6 to 1.1)	0.062
0 vs 2	0.6 (0.3 to 1.4)	0.7 (0.5 to 1.1)	0.124
First 24-h fluid balance (mL)	1.1 (1.1 to 1.1)	1 (0.9 to 1.1)	0.306

The occurrence of at least one major complication resulted in longer ICU and hospital stay, and slower functional recovery (Table 3).

Discussion

The findings of the present study showed that the overall incidence of postoperative complications in CRS ± HIPEC is still high (67%) even in a center with extensive experience. However, it is worth noting that only 27% of patients suffered major complications (i.e., CCI > 22.6) that result in longer ICU and hospital stays, as well as slower functional recovery. Multivariate logistic regression revealed that prior heart disease, number of anastomoses, and first



	OR (95% IC)	RR (95% IC)	P value
Heart disease	3.6 (1.1. to 14.2)	1.9 (1.1 to 3.3)	0.023*
Gastric Cancer	0.2 (0.1.8)	0.3 (0.05 to 1.9)	0.210
Preoperative Hemoglobin	0.8 (0.6 to 0.9)	0.9 (0.9 to 0.9)	0.008*
Opioid-free anesthesia	0.4 (0.2 to 0.9)	0.6 (0.3 to 0.9)	0.037*
Intraoperative fluid balance (mL)	0.9 (0.9 to 1.1)	0.9 (0.9 to 1.1)	0.086
Number of anastomoses (0 vs 1)	2.7 (1.1 to 6.7)	1.9 (1.1 to 3.4)	0.035*
Number of anastomoses (0 vs 2)	4.3 (1.4 to 13.4)	2.4 (1.3 to 4.6)	0.006*
Number of anastomoses (0 vs 3)	7.1 (0.7 to 72.3)	3 (1.1 to 7.9)	0.033*
First 24-hour fluid balance (mL)	1.1 (1.1 to 1.2)	1.1 (1.1 to 1.2)	0.047*
Postoperative Hemoglobin at 24h	0.9 (0.6 to 1.4)	0.8 (0.9 to 1.1)	0.691
Postoperative blood transfusion rate	2.3 (0.9 to 5.5)	1.6 (0.1 to 2.6)	0.077

Fig. 1 Forest plot of multivariate analysis of the association of perioperative variables with major postoperative complications

24-h fluid balance, were independently associated as risk factors for major complications, while high preoperative hemoglobin levels and OFA were protective factors.

Postoperative morbidity is a major healthcare concern that negatively impacts the cost of care, quality of life, and survival. In our cohort, postoperative morbidity lies in the upper limit of that reported in the literature [2], likely due to the fact that we reported as complication any deviation from the normal postoperative course including those that did not require active treatment. In fact, PONV was the most frequent medical complication reported and was usually solved with simple pharmacologic treatment. Interestingly, postoperative surgical complications were less frequent than medical complications although when occurred were more severe. The low incidence of postoperative bleeding (the most frequent surgical complication) (6%) contrasts with that previously reported by Carboni [19] were it was 22.9% with 6% of patients requiring reoperation. The differences in the cancer origin may explain that: while in our study was colorectal cancer in the study by Carboni et al. [19], it was ovarian, which required more frequent diaphragmatic surgery possibly associated with a higher risk of bleeding [20].

Identifying risk factors for postoperative complications is crucial for the development of targeted preventive interventions. The results of the present study demonstrate an association between two preoperative factors and the incidence of major postoperative complications. First, multivariate analysis showed that a high preoperative hemoglobin level was an independent-protective factor, RR 0.9 (95% CI: 0.9 to 0.9). According to previous studies in non-cardiac surgery, preoperative anemia was associated with adverse outcomes [21]. The most common causes of preoperative anemia in oncologic patients are blood loss from the tumor, renal dysfunction secondary to platinum-based chemotherapy and bone marrow dysfunction from chemotherapy [22]. Optimization of anemia in surgical patients leads to higher preoperative hemoglobin concentrations. Therefore, detection and optimization of preoperative anemia should be a priority during preoperative period. It is worth noting that normal or almost normal hemoglobin levels do not exclude iron deficiency that should be preoperatively treated as well. The use of erythropoietin and supplementation of folic acid or B12 vitamin may be considered in selected patients [15]. On the other hand, prior heart disease was also identified as predictor of postoperative complications. Large, prospective cohort studies have shown that chronic cardiac conditions provide a substrate for complications after surgery [23]. In the context of CRS ± HIPEC, a series of hemodynamic, homeostatic and proinflammatory changes happen that can aggravate stable coronary artery disease [24] and could be possible explanations for the association. Identifying patients with prior heart disease and ensuring maximal medical optimization as well as counseling them about potentially higher risk of postoperative complications is therefore recommended.

The association between postoperative complications and perioperative fluid balance is a complex issue that has been the subject of much research, both positive and negative fluid balance can be associated with an increased risk of complications [6, 25]. The methodological heterogeneity of the available studies makes it difficult to compare and draw robust conclusions. Moreover, the experience in CRS ± HIPEC is limited and has been mainly focused on intraoperative fluid therapy [6] without fully taking account the fluid losses and the resulting fluid balance. To our knowledge, no trials have evaluated the effects of the first 24-h fluid balance on surgical outcomes in CRS ± HIPEC surgery. Our findings are consistent with prior studies in colorectal surgery [25] where greater negative balance on the day of operation reduced postoperative complications. It has been hypothesized that a positive postoperative fluid balance can lead to increased fluid accumulation as part of the perioperative inflammatory response, which may compromise the microcirculation and tissue edema [25]. Some authors argue that the ideal perioperative fluid balance is one that is as close to neutral as possible. However, achieving this balance is difficult and requires extensive and close monitorization. The use of a hemodynamic goal-directed anesthetic protocol in CRS and HIPEC to individually adjust the fluid therapy has been strongly recommended [15].

Not surprisingly and according to previous studies in CRS ± HIPEC surgery [19, 26] we found that the greater the number of intestinal anastomoses performed, the greater the risk of postoperative complications. Several reasons may explain this. First, the risk of anastomotic leak increases with the number of anastomoses performed since each anastomosis represents a potential weak point in the bowel. Second, the more anastomoses that need to be performed, the longer and more aggressive the surgery will take and likely, this is associated with a greater extension of the disease [19], reflected in the PCI. In our study, the PCI increased from 4(2–7) in patients in whom no bowel resection was performed, to 31 (20–32) in those with 3 or more anastomoses. Finally, multiple anastomoses can reduce intestinal motility delaying the functional recovery.

Lastly from our evaluated factors, OFA strategy was associated as independent-protective factor on the incidence for major complications in both bivariate and multivariate analysis. We previously showed that OFA strategy decreases the occurrence of PONV [5]. The process of nausea and vomiting is coordinated by the vomiting center, which can be activated, among others, by the chemoreceptor trigger zone where opioid receptors are located. Therefore, avoiding or reducing opioids may reduce the occurrence of PONV. Moreover, the stimulatory actions of lidocaine itself on postoperative colonic motility may also help [27]. Another variable that was independently associated with PONV was the administration of HIPEC. It is plausible that the direct intraperitoneal administration of chemotherapeutic agents may result in gastrointestinal adverse effect such as PONV and/or dynamic ileus, even if literature in this regard is not robust because PONV is considered a common and mild secondary adverse effect, and therefore not always reported. Moreover, hyperthermia may also play a role since high temperature and humidity during surgery induces an increased systemic inflammatory response [28]. This temperature-mediated inflammatory state could activate, through several neuronal pathways, the nucleus tractus solitarius (NTS) and area postrema which is believed to be important sites for generating emesis [29].

The conclusions that can be drawn by our study are limited by its retrospective nature and single institution experience. The risk of bias is mitigated by the existence of predetermined clinical pathways for all aspects of patient management to reduce variability in care among different providers. The analysis of the different types of HIPEC administered is limited due to global changes in the most appropriate type of chemotherapy, as well as the optimal time of administration. Another point to note is that we established the third quartile of the CCI of our cohort as the cut-off point to establish the definition of major complications, in accordance with the literature. But perhaps, if clinical trials were conducted, the cut-off points could be optimized to obtain greater sensitivity and specificity.

Conclusion

Our results reinforce the need of exhaustive preoperative evaluation and optimization, particularly anemia, in patients undergoing CRS ± HIPEC. Perioperative management avoiding postoperative fluid overload and utilization of OFA could potentially help to reduce the incidence of severe complications. The greater the number of intestinal anastomoses performed, the closer monitorization for anastomotic leakage detection should be recommended. Hence, effective collaboration between anesthesiologists and surgeons should begin with a thorough preoperative evaluation, to identify potential risk factors for complications. This shared understanding allows for tailored anesthesia and surgical plans that minimize the risk of adverse events.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Bellvitge University Hospital approved this study (protocol No. 008/22, March 10, 2022).

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