Impact of preoperative carbohydrate loading on postoperative course and morbidity in debulking surgery for epithelial ovarian cancer

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Abstract. Despite the theoretical benefits, the favorable effect of preoperative carbohydrate loading on postoperative morbidity remains controversial. Most of the outcomes reported in the literature are derived from non-gynecologic surgery data, with only one study involving a limited number of patients specifically in gynecological oncology. The present study aimed to investigate the impact of carbohydrate loading, as a single element of enhanced recovery after surgery protocols, on postoperative course and morbidity in patients undergoing debulking surgery for epithelial ovarian cancer (EOC). The present study was a non-randomized, prospective cohort trial enrolling patients with EOC who underwent surgery between June 2018 and December 2021. An oral carbohydrate supplement with a dose of 50 g was given to patients 2-3 h before anesthesia. Data on postoperative course and morbidity were collected and compared with data of a historical cohort including consecutive patients who underwent surgery without a carbohydrate loading between January 2015 and June 2018. Analyses were performed on a total of 162 patients, including 72 patients in the carbohydrate loading group and 90 patients in the control group. Median length of hospital stay (11 days vs. 11 days; P=0.555), postoperative days 1-7 serum c-reactive protein levels (P=0.213), 30-day readmission (11.6% vs. 11.5%, P=0.985), 30-day relaparotomy (2.8% vs. 3.4%, P=0.809) and 30-day morbidity (48.6% vs. 46.7%; P=0.805) were comparable between the cohorts. No significant differences in grades of morbidities were identified between the cohorts (P=0.511). Multivariate analysis revealed that the sole independent risk factor for any postoperative morbidity was operative time. In conclusion, based on the results of the present study, postoperative course and morbidity seemed to be unaffected by carbohydrate loading in patients undergoing debulking surgery for EOC.

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Introduction

The stress response to the surgery is characterized by various inflammatory, hormonal and immune changes in the body. Primarily, the release of cortisol, catecholamines, glucagon, IL-1 and IL-6 leads to the insulin resistance and impaired immune functions (1). Prolonged preoperative fasting deteriorates these responses by causing detrimental catabolic effects including increased glycogenolysis, proteolysis and lipolysis and decreased insulin sensitivity with normal insulin levels (2). Several studies have reported that actual fasting time for patients undergoing elective surgery is usually longer than 12 h due to the delays in the operating theatre schedule; meaning that most patients are exposed to prolonged fasting and dehydration (3,4).

Given the concerns of regurgitation and pulmonary aspiration, fasting after midnight has traditionally been offered to all surgical patients. However, it has been shown that there were no differences in terms of gastric volume and acidity and pulmonary complications between the patients who were fasted overnight and those allowed to drink clear liquids up to 2 h before surgery (5). Following these results, a paradigm shift has occurred in the timing and administration of preoperative solids and liquids over the last decade. The major anesthesiology societies have started to recommend clear liquids up to 2 h and solids up to 6 h before anesthesia (6,7). Although these recommendations would prevent dehydration, they are still insufficient in minimizing perioperative catabolic stress response.

In recent years, there has been growing interest in preoperative use of carbohydrate-enriched drinks in order to ensure a metabolically fed-state and to overcome catabolic stress response. It has been shown that avoiding prolonged fasting and giving clear liquids containing sufficient carbohydrates before surgery induces an anabolic state, promoting tissue healing by decreasing insulin resistance and inflammatory mediators such as IL-6 (8). Currently, the consumption of at least 45 g of carbohydrate as a clear liquid 2-3 h preoperatively is considered as one of the key elements of enhanced recovery after surgery (ERAS) protocols (9).

Despite the theoretical benefits, however, the favorable effect of carbohydrate loading on postoperative morbidity has not been consistently demonstrated and remains controversial (10). Most of the outcomes reported in the literature were derived from non-gynecologic surgery data, with only one study involving a limited number of patients, specifically in gynecological oncology (11). The current study investigated the effect of preoperative carbohydrate loading as a single element of ERAS on postoperative course and morbidity in patients undergoing debulking surgery for epithelial ovarian cancer (EOC).

Materials and methods

Study design and endpoints. The present study was a non-randomized, prospective cohort trial enrolling consecutive patients with EOC who underwent debulking surgery, either primary or interval, at Antalya Training and Research Hospital between June 2018 and December 2021. Exclusion criteria were: Minimally invasive surgery, surgery for recurrent disease, hyperthermic intraperitoneal chemotherapy (HIPEC) and type 1 diabetes mellitus. The present study was approved by the Ethics Committee of the Antalya Training and Research Hospital (7 May, 2018; approval no. 021). Written informed consent was obtained from all participants.

Patients were fasted for solids from 02:00 a.m. the night before surgery, but were allowed to drink clear liquids until 06:00 a.m. on the day of surgery. An oral carbohydrate supplement (Nutricia Fantomalt®, Nutricia Turkiye), at a dose of 50 g diluted in 250 ml water, which contained 48 g carbohydrate and 192 kcal of energy was given to patients at 06:00 a.m. on the morning of surgery. The consumption time for the drink was 10 min. All patients underwent surgery as the first case of the day and operations were scheduled to start at 08:30 a.m.

Data regarding age, performance status, comorbidities, neoadjuvant chemotherapy, stage of the disease, tumor histotype, surgical resections, blood transfusion, operative time, need for intensive care unit (ICU), length of ICU stay, length of hospital stay, postoperative day 1 serum albumin level, postoperative day 1 to -7 serum c-reactive protein (CRP) levels, 30-day hospital readmission, 30-day relaparotomy, 30-day postoperative morbidities including deaths and the time interval between surgery and adjuvant therapy were collected following ethics committee approval.

Prospectively collected data of patients were compared with a historical cohort of consecutive patients who underwent debulking surgery for EOC at the same institution without a preoperative carbohydrate loading between January 2015 and June 2018.

Based on the results of previous studies (12,13) indicating a 50% reduction in postoperative morbidity with carbohydrate loading, it was calculated that a sample size of at least 68 patients per group was required to detect a 50% reduction in morbidity, with a two-sided 5% significance level and 80% power. It was anticipated that 90 patients with carbohydrate treatment would be recruited in this study based on a 1:1 ratio to the number of historical control group. However, 18 patients were excluded from the carbohydrate loading group: 7 had HIPEC, 8 had different primary tumor origin and 3 withdrew consent before surgery.

The primary endpoint of the present study was the effect of carbohydrate loading on postoperative course and morbidity and the secondary endpoint was determination of factors associated with postoperative morbidities. The postoperative morbidities were graded according to the Clavien-Dindo classification (14).

Perioperative management. Perioperative management strategies of patients, with the exception of fasting time and carbohydrate loading, were identical between the two cohorts. Patients in the historical cohort were subjected to conventional overnight fasting for solids and liquids. Although routinely implementing most of the ERAS elements in had been in the Antalya Training and Research Hospital since January 2015, there was not a strict policy in this regard.

A routine mechanical bowel preparation was not used in any patient. All patients received thromboembolism prophylaxis with a low-molecular weight heparin and wore anti-embolism stockings. An antimicrobial prophylaxis was initiated with 2 g of intravenous (IV) cefazolin within 60 min before skin incision and the dose was repeated every 3 h during the surgery. A vertical midline laparotomy was used in all patients. Perioperative fluid therapy was individualized according to invasive hemodynamic monitoring and urine output. The decision for ICU admission was at the discretion of the anesthesiologists. On postoperative day 1 the urinary catheter was removed and oral intake of clear liquids was allowed. The diet was advanced gradually as bowel functions returned. Drains were removed when the output decreased to <100 ml/24 h. Antibiotics were continued until drains were removed. Patients were discharged home if they were able to walk without assistance and tolerated regular diet.

Statistical analysis. Analyses were performed using SPSS version 20.0 (IBM Corp.). The differences between two cohorts were tested by independent samples T-test for parametric data and Mann-Whitney U-test for nonparametric data. Pearson Chi-Square test was used for comparison of categorical variables. Factors associated with postoperative morbidities were evaluated by both univariate and multivariate logistic regression analyses. Variables with a $P<0.05$ in univariate analyses were included into multivariate analyses. The effects of variables on morbidity were reported as adjusted odds ratios (OR) and 95% confidential intervals (CI). The predictive mean matching method was used in order to deal with missing values. Cut-off values of independent scale variables were calculated using receiver operating characteristic (ROC) analysis. An area under the curve value of >0.70 was considered satisfactory. For the ROC curve, the point with the largest sum of sensitivity and specificity was chosen as a threshold. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Preoperative characteristics and histopathological findings.

Variable	Preoperative carbohydrate loading		P-value
	Yes (n=72)	No (n=90)	
Age, years, median (range)	58 (22-80)	58 (36-82)	0.426[c]
ECOG performance status, n (%)			0.388[d]
0-1	57 (79.2)	66 (73.3)	
≥2	15 (20.8)	24 (26.7)	
Comorbidities, n (%)	24 (33.3)	40 (44.4)	0.151[d]
Cardiac comorbidity[a]	14 (19.4)	28 (31.1)	0.092[d]
Pulmonary comorbidity[b]	5 (6.9)	9 (10.0)	0.492[d]
Diabetes mellitus	9 (12.5)	15 (16.7)	0.458[d]
Neoadjuvant chemotherapy, n (%)	23 (31.9)	31 (34.4)	0.945[d]
3 cycles	9 (12.5)	12 (13.3)	
≥4 cycles	14 (19.4)	19 (21.1)	
FIGO stage, n (%)			0.803[d]
I	13 (18.1)	20 (22.2)	
II	7 (9.7)	9 (10.0)	
III	30 (41.7)	31 (34.4)	
IV	22 (30.6)	30 (33.3)	
Tumor histotype, n (%)			0.830[d]
High-grade serous	49 (68.1)	56 (62.2)	0.440[d]
Others			
Grade 2-3 endometrioid	2 (2.8)	2 (2.2)	
Carcinosarcoma	2 (2.8)	1 (1.1)	
Clear cell	6 (8.3)	5 (5.6)	
Low-grade serous	5 (6.9)	13 (14.4)	
Grade 1 endometrioid	4 (5.6)	6 (6.7)	
Mucinous	3 (4.2)	4 (4.4)	
Seromucinous	-	1 (1.1)	
Squamous cell carcinoma	1 (1.4)	1 (1.1)	
Wolffian adnexal tumor	-	1 (1.1)	

[a]Atherosclerotic disease, congestive heart failure, valvular disease, arrhythmia. [b]Asthma, chronic obstructive pulmonary disease, pulmonary thromboembolic disease. [c]Independent samples T test; [d]Pearson Chi-Square test. ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

Results

The final analyses were performed on a total of 162 patients, including 72 patients in the carbohydrate loading group and 90 patients in the control group. Study groups were comparable for preoperative characteristics and histopathological findings (Table I) In both groups, the majority of patients had International Federation of Gynecology and Obstetrics stage (15) III-IV disease (72.3% vs. 67.7%) and received primary debulking surgery (68.1% vs. 65.6%).

Intraoperative findings and surgical characteristics of study groups are summarized in Table II. There were no statistically significant differences between the groups in terms of ascites (36.1% vs. 38.9%), peritoneal carcinomatosis (61.1% vs. 57.8%), bowel resection (25.0% vs. 20.0%), peritonectomy (55.6% vs. 48.9%), splenectomy (12.5% vs. 12.2%), lymph node dissection (62.5% vs. 65.6%), rate of maximal cytoreduction (70.8% vs. 70.0%), median operative time (330 min vs. 330 min), blood transfusion (56.9% vs. 53.3%) and need for ICU (63.9% vs. 55.6%).

The comparison of postoperative course and morbidities between the study groups are presented in Table III. The median length of ICU stay (1 day vs. 1 day), length of hospital stay (11 days vs. 11 days), day 1 serum albumin levels (2.7 g/dl vs. 2.5 g/dl), day 1 to -7 serum CRP levels, 30-day readmission (11.6% vs. 11.5%), 30-day relaparotomy (2.8% vs. 3.4%) and the time interval between surgery and adjuvant therapy (35 days vs. 39 days) were comparable between the groups. At least one postoperative morbidity occurred in 48.6 and 46.7% of patients with and without carbohydrate loading, respectively (P=0.805). Wound infection was the most common morbidity in both groups (22.2% vs. 16.7%; P=0.372), followed by ileus (13.9% vs. 13.3%, P=0.918). No significant differences in grades of morbidities were identified between the groups (P=0.511).

Table II. Intraoperative findings and surgical characteristics.

	Preoperative carbohydrate loading		
Variable	Yes (n=72)	No (n=90)	P-value
Ascites, n (%)	26 (36.1)	35 (38.9)	0.717[a]
Large volume (seen on all quadrants)	13 (18.1)	21 (23.3)	0.412[a]
Omental cake, n (%)	26 (36.1)	34 (37.8)	0.827[a]
Peritoneal carcinomatosis, n (%)	44 (61.1)	52 (57.8)	0.668[a]
Diffuse, miliary	32 (44.4)	32 (35.6)	0.250[a]
Diaphragmatic disease, n (%)	22 (30.6)	22 (24.4)	0.385[a]
Small bowel serosal and/or mesentery involvement, (diffuse, miliary), n (%)	18 (25.0)	22 (24.4)	0.935[a]
Large bowel serosal and/or mesentery involvement, (diffuse, miliary), n (%)	19 (26.3)	21 (23.3)	0.654[a]
Spleen metastasis (any surface/hilar lesion), n (%)	7 (9.7)	12 (13.3)	0.478[a]
Liver metastasis (parenchymal lesion), n (%)	5 (6.9)	6 (6.7)	0.923[a]
Cytoreduction, n (%)			
Maximal (no visible residual disease)	51 (70.8)	63 (70.0)	0.908[a]
Optimal (residual tumor nodules <1 cm)	18 (25.0)	17 (18.9)	0.348[a]
Suboptimal (residual tumor nodules ≥1 cm)	3 (4.2)	10 (11.1)	0.106[a]
Bowel resection (large and/or small bowel), n (%)	18 (25.0)	18 (20.0)	0.447[a]
Large bowel	15 (20.8)	15 (16.7)	0.498[a]
Colorectal resection	12 (16.7)	13 (14.4)	
Right hemicolectomy	3 (4.2)	1 (1.1)	
Transverse colon resection	-	1 (1.1)	
Small bowel	4 (5.6)	4 (4.4)	0.746[a]
Peritonectomy (partial and/or total), n (%)	40 (55.6)	44 (48.9)	0.399[a]
Pelvic	39 (54.2)	42 (46.7)	0.343[a]
Paracolic	22 (30.6)	22 (24.4)	0.385[a]
Diaphragm	14 (19.4)	10 (11.1)	0.138[a]
Appendectomy, n (%)	27 (37.5)	33 (36.7)	0.913[a]
Splenectomy ± distal pancreatectomy, n (%)	9 (12.5)	11(12.2)	0.957[a]
Systematic pelvic-paraaortic LN dissection, n (%)	45 (62.5)	59 (65.6)	0.687[a]
Number of LNs removed, median (range)	55 (29-129)	60 (27-100)	0.757[b]
Operative time, min, median (range)	330 (240-610)	330 (195-530)	0.144[c]
Intraoperative blood transfusion, n (%)	41 (56.9)	48 (53.3)	0.646[a]
Need for intensive care unit, n (%)	46 (63.9)	50 (55.6)	0.283[a]

[a]Pearson Chi-Square test; [b]Independent samples T test; [c]Mann-Whitney U test. LN, lymph node.

A total of six deaths occurred postoperatively, with three (4.2%) in the carbohydrate loading group and three (3.3%) in the control group (P=0.780). One patient in the carbohydrate loading group and two patients in the control group succumbed due to unexplained sudden cardiac arrest occurring within the first 24 h after surgery. The other two mortalities in the carbohydrate loading group were due to a neglected small bowel perforation diagnosed 3 weeks after surgery and due to pulmonary thromboembolism on postoperative day 5, respectively. The third mortality in the control group was from a large bowel anastomotic leak on postoperative day 14.

In univariate analysis, four variables were significantly associated with any postoperative morbidity: Peritoneal carcinomatosis (P=0.035), operative time (P=0.001), ICU admission (P=0.042) and serum albumin level on postoperative day 1 (P=0.030). In multivariate analysis, however, only the 'operative time' remained as an independent factor associated with any postoperative morbidity after adjustment for other confounders (Table IV). Optimal cut-off value of operative time for predicting any morbidity was found as 292.5 min, with a sensitivity of 80% and specificity of 59% (Fig. 1A). Patients who had an operative time ≥292.5 min were 3.5 times more likely to experience any postoperative morbidity (OR: 3.531; 95% CI: 1.326-9402; P=0.012).

When the factors specifically associated with grade III-V morbidities were analyzed, ascites (P=0.005), peritoneal

Table III. Postoperative course and morbidities.

Variable	Preoperative carbohydrate loading		P-value
	Yes (n=72)	No (n=90)	
Length of ICU stay, days, median (range)	1 (1-69)	1 (1-14)	0.091[a]
Length of hospital stay, days, median (range)	11 (5-77)	11 (1-37)	0.555[a]
Day 1, serum albumin level, g/dl, median (range)	2.7 (1.0-3.4)	2.5 (0.8-3.9)	0.138[b]
Serum CRP level, mg/l, median (range)			
Day 1	63.0 (17.0-306)	106.5 (18.9-317)	0.213[a]
Day 2	214.0 (75.0-395)	224.0 (75.9-435)	0.675[b]
Day 3	235.5 (32.0-364)	210.0 (30.3-499)	0.980[b]
Day 4	154.5 (21.0-443)	145.5 (33.0-442)	0.709[b]
Day 5	95.0 (16.0-412)	98.0 (18.9-417)	0.608[a]
Day 6	53.0 (10.0-260)	57.3 (8.2-455)	0.989[a]
Day 7	57.0 (5.0-319)	82.3 (17.9-439)	0.529[a]
30-day hospital readmission, n (%)	8 (11.6)	10 (11.5)	0.985[c]
30-day relaparotomy, n (%)	2 (2.8)	3 (3.4)	0.809[c]
30-day postoperative morbidity, n (%)	35 (48.6)	42 (46.7)	0.805[c]
Eventration/evisceration	1 (1.4)	1 (1.1)	0.874[c]
Any infectious morbidity	21 (29.2)	21 (23.3)	0.400[c]
Wound infection	16 (22.2)	15 (16.7)	0.372[c]
Intra-abdominal infection/abscess	10 (13.9)	6 (6.7)	0.126[c]
Urinary infection	4 (5.6)	7 (7.8)	0.576[c]
Sepsis	3 (4.2)	1 (1.1)	0.213[c]
Gastrointestinal morbidity	11 (15.3)	14 (15.6)	0.961[c]
Ileus	10 (13.9)	12 (13.3)	0.918[c]
Anastomotic leakage	1 (1.4)	1 (1.1)	0.874[c]
Intestinal perforation	1 (1.4)	-	0.262[c]
Biliary leakage	-	1 (1.1)	0.370[c]
Pulmonary morbidity	11 (15.3)	8 (8.9)	0.209[c]
Pleural effusion	8 (11.1)	6 (6.7)	0.317[c]
Pneumo-mediastinum	1 (1.4)	-	0.262[c]
Pulmonary thromboembolism	3 (4.2)	1 (1.1)	0.213[c]
Pulmonary edema	1 (1.4)	5 (5.6)	0.163[c]
Transfusion-related acute lung injury	-	1 (1.1)	0.370[c]
Cardiac morbidity	2 (2.8)	5 (5.6)	0.388[c]
Unexplained sudden cardiac arrest	1 (1.4)	2 (2.2)	0.696[c]
Atrial fibrillation	1 (1.4)	3 (3.3)	0.428[c]
Others			
Chylous ascites	6 (8.3)	5 (5.6)	0.485[c]
Renal artery thrombosis	1 (1.4)	2 (2.2)	0.696[c]
Vesico-vaginal fistula	1 (1.4)	-	0.262[c]
Acute basilar artery occlusion	1 (1.4)	-	0.262[c]
Clavien-Dindo classification of morbidities, n (%)			0.511[c]
Grade 1	6 (8.3)	11 (12.2)	0.422[c]
Grade 2	10 (13.9)	17 (18.9)	0.396[c]
Grade 3	10 (13.9)	5 (5.6)	0.069[c]
Grade 4	6 (8.3)	6 (6.7)	0.687[c]
Grade 5 (mortality)	3 (4.2)	3 (3.3)	0.780[c]
Time interval between debulking surgery and adjuvant therapy, days, median (range)	35 (14-73)	39 (19-99)	0.451[b]

[a]Mann-Whitney U test; [b]Independent samples T test; [c]Pearson Chi-Square test. ICU, intensive care unit; CRP, c-reactive protein.

Table IV. Factors associated with any postoperative morbidity.

	Any morbidity					
	Unadjusted			Adjusted		
Variable	OR	95% CI	P-value	OR	95% CI	P-value
Preoperative carbohydrate loading (no vs. yes)	1.081	0.581-2.011	0.805	-	-	-
Age, years	0.996	0.969-1.023	0.761	-	-	-
ECOG performance status (0-1 vs. ≥2)	1.600	0.774-3.307	0.204	-	-	-
Diabetes mellitus (no vs. yes)	1.123	0.472-2.673	0.793	-	-	-
Neoadjuvant chemotherapy (no vs. yes)	0.928	0.482-1.787	0.824	-	-	-
Ascites, large volume (no vs. yes)	1.779	0.827-3.831	0.141	-	-	-
Peritoneal carcinomatosis, diffuse (no vs. yes)	1.987	1.049-3.765	**0.035**	-	-	0.826
Maximal cytoreduction (no vs. yes)	1.296	0.659-2.547	0.452	-	-	-
Large bowel resection (no vs. yes)	2.204	0.972-4.995	0.058	-	-	-
Total peritonectomy[a] (no vs. yes)	2.194	0.770-6.252	0.141	-	-	-
Diaphragm stripping (no vs. yes)	2.043	0.837-4.984	0.116	-	-	-
Splenectomy (no vs. yes)	1.119	0.439-2.855	0.813	-	-	-
Systematic pelvic-paraaortic LND (no vs. yes)	1.063	0.559-2.023	0.852	-	-	-
Operative time (≥ 292.5 min)[b]	5.750	2.745-12.043	**0.001**	3.531	1.326-9402	**0.012**
Intraoperative blood transfusion (no vs. yes)	1.776	0.949-3.326	0.073	-	-	-
Need for intensive care unit (no vs. yes)	1.938	1.023-3.673	**0.042**	-	-	0.676
Day 1, serum albumin level, g/dl	0.487	0.254-0.933	**0.030**	-	-	0.159
Day 1, serum CRP level, mg/l	1.005	0.999-1.011	0.076	-	-	-

[a]Pelvic, paracolic and diaphragm; [b]the most appropriate cut-off value determined by receiver operating characteristic analysis. Bold values denote statistical significance at the P<0.05 level. OR, Odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CRP, c-reactive protein; LND, lymph node dissection.

carcinomatosis (P=0.001), maximal cytoreduction (P=0.009), colon resection (P=0.001), total peritonectomy (P=0.031), diaphragmatic stripping (P=0.007), splenectomy (P=0.025), operative time (P=0.001), intraoperative blood transfusion (P=0.001), ICU admission (P=0.001), serum albumin level on postoperative day 1 (P=0.026) and serum CRP level on postoperative day 1 (P=0.005) were significant factors in univariate analysis; whereas splenectomy (P=0.049), operative time (P=0.021) and serum CRP level on postoperative day 1 (P=0.024) were found to be independent factors in multivariate analysis after adjustment for other confounders (Table V). Optimal cut-off values of operative time and day 1 serum CRP level for predicting grade III-V morbidities were 317 min (sensitivity: 78.8%, specificity: 67.8%) and 107.5 mg/l (sensitivity: 72.2%, specificity: 67.8%), respectively (Fig. 1B and C).

Discussion

The present study compared two cohorts of patients who underwent debulking surgery for EOC with or without preoperative carbohydrate loading. It revealed no significant differences between the cohorts in terms of postoperative course and morbidities. The length of ICU stay, length of hospital stay, day 1 serum albumin level, day 1-7 serum CRP levels, the rates of 30-day hospital readmission and 30-day relaparotomy, the rate and the severity of 30-day postoperative morbidities and the time interval between surgery and adjuvant therapy were comparable between the cohorts. The only independent risk factor for any morbidity after debulking surgery was operative time, while the independent risk factors specifically for grade III-V morbidities were operative time, splenectomy and day 1 serum CRP level.

The available literature regarding the effect of preoperative carbohydrate loading on postoperative morbidity is confusing and still a matter of debate. Earlier studies reported that postoperative symptoms, length of hospital stay and morbidities were significantly reduced with the use of oral carbohydrates as part of an ERAS protocol in patients undergoing colorectal resection (12,13). However, a large ERAS registry data of colorectal resections has shown that shorter hospital stay was related to carbohydrate loading, whereas reduced morbidities were only associated with the restrictive perioperative IV fluids (16). Similarly, a Cochrane review including all randomized controlled trials (RCT) of carbohydrate treatment in patients undergoing any elective surgery has demonstrated that carbohydrate loading was associated with earlier return of bowel functions and shorter length of hospital stay, but had no effect on morbidity (10). On the other hand, a more recent metaanalysis evaluating only abdominal surgeries has revealed that carbohydrate loading was associated with lower morbidity when compared with overnight fasting; but morbidity rates were similar between carbohydrate loading

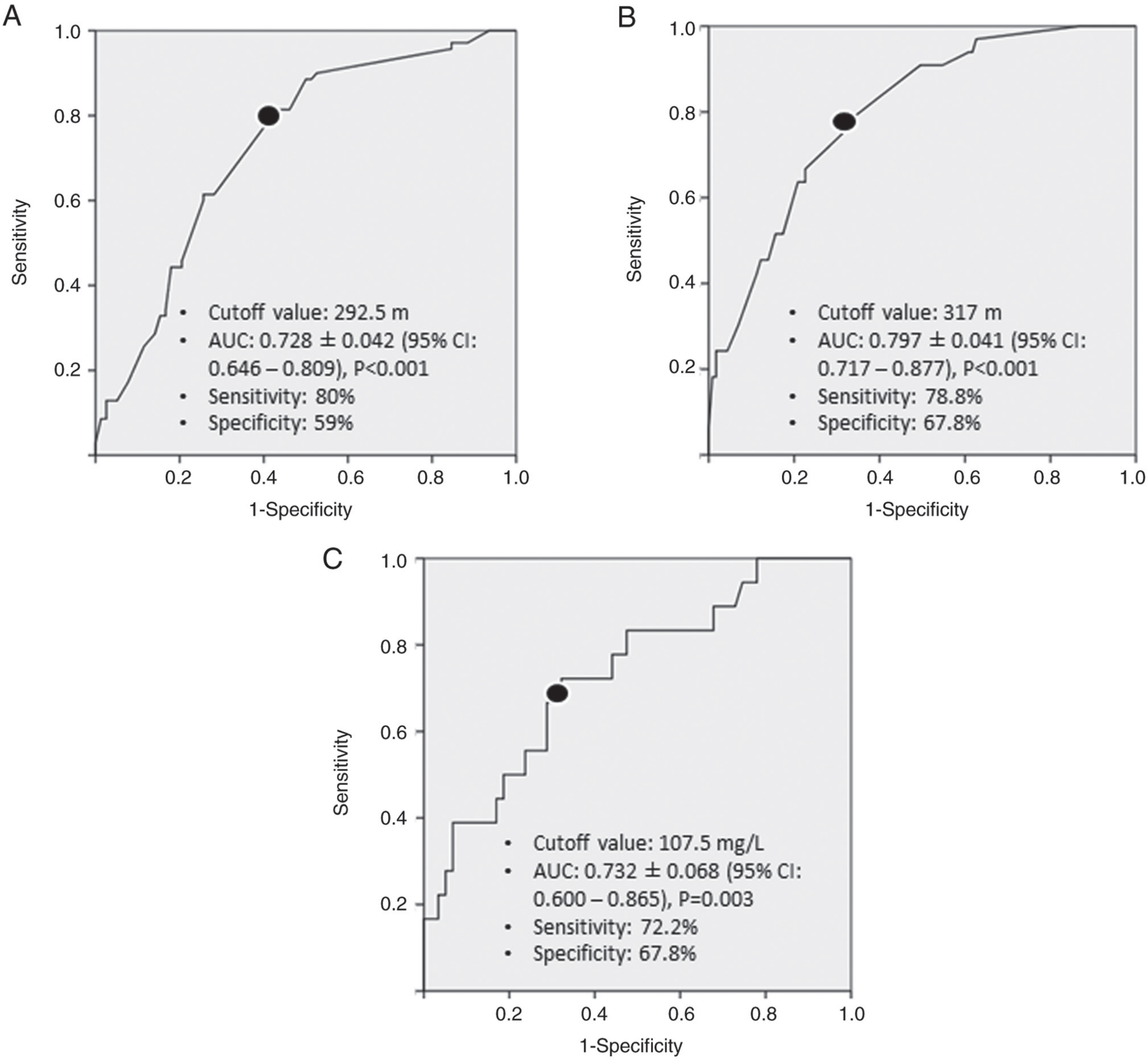

Figure 1. ROC analyses to calculate cut-off values of independent scale variables. (A) Optimal cut-off value for operative time in predicting any postoperative morbidity. (B) Optimal cut-off value for operative time in predicting grade III-V morbidity. (C) Optimal cut-off value for postoperative day 1 serum CRP level in predicting grade III-V morbidity. ROC, receiver operating characteristic; AUC, area under the ROC Curve; CRP, c-reactive protein.

and clean water administration (17). The main reason of the discrepancies between the results of the previous studies is the significant heterogeneity within the patient populations and surgical procedures.

Although there are various studies reporting ERAS outcomes in gynecological oncology (18), only one study has specifically investigated the impact of carbohydrate loading as a single element of ERAS on clinical outcomes. In a single-center RCT, Al-Hirmizy *et al* (11) randomized 75 patients with EOC to receive a carbohydrate-enriched drink (n=37) or placebo (n=38). The authors initially found that carbohydrate loading increased the length of hospital stay by one day compared with the placebo. Although not significant, morbidities were also found to be higher in the carbohydrate loading group compared with placebo. However, study groups were unbalanced in terms of type of surgery, with more patients in the placebo group undergoing interval debulking surgery. After adjusting factors that may affect length of hospital stay, the authors found no difference between the groups in regard to morbidities. The results of the present study are comparable to those of Al-Hirmizy *et al* (11). However, despite the lack of a randomized control group, the present study included a larger number of patients and more homogenous and consistent data with respect to baseline patient characteristics compared with Al-Hirmizy *et al* (11).

Debulking surgery for EOC is a highly complicated surgical proceedure involving multiple pelvic and upper abdominal resections performed concurrently. Postoperative morbidity rates have been reported to be as high as 67% (19). Similarly, in the current study, 77 of 162 patients (47.5%) developed at least one morbidity. It was also found that operative time was the only independent risk factor for any postoperative morbidity. The literature on morbidity after debulking surgery shows that these morbidities often have a multifactorial etiology that is not easy to prevent. Some of these factors include patient-related characteristics such as age, comorbidities, poor performance

Table V. Factors associated with grade III-V postoperative morbidities.

	Grade III-V morbidity					
	Unadjusted			Adjusted		
Variable	OR	95% CI	P-value	OR	95% CI	P-value
Preoperative carbohydrate loading (no vs. yes)	1.946	0.897-4.221	0.092	-	-	-
Age, years	1.018	0.984-1.053	0.310	-	-	-
ECOG performance status (0-1 vs. ≥2)	2.159	0.945-4.933	0.068	-	-	-
Diabetes mellitus (no vs. yes)	1.034	0.355-3.011	0.951	-	-	-
Neoadjuvant chemotherapy (no vs. yes)	1.184	0.532-2.632	0.679	-	-	-
Ascites, large volume (no vs. yes)	3.343	1.443-7.745	**0.005**	-	-	0.336
Peritoneal carcinomatosis, diffuse (no vs. yes)	7.212	2.990-17.392	**0.001**	-	-	0.945
Maximal cytoreduction (no vs. yes)	2.853	1.293-6.293	**0.009**	-	-	0.810
Large bowel resection (no vs. yes)	6.333	2.650-15.138	**0.001**	-	-	0.782
Total peritonectomy (no vs. yes)	3.204	1.116-9.201	**0.031**	-	-	0.830
Diaphragm stripping (no vs. yes)	3.571	1.414-9.023	**0.007**	-	-	0.913
Splenectomy (no vs. yes)	3.120	1.155-8.425	**0.025**	14.724	1.008-215.008	**0.049**
Systematic pelvic-paraaortic LND (no vs. yes)	0.513	0.236-1.114	0.092	-	-	-
Operative time (≥ 317 min)[a]	7.830	3.115-19.682	**0.001**	15.368	1.498-157.710	**0.021**
Intraoperative blood transfusion (no vs. yes)	4.863	1.881-12.570	**0.001**	-	-	0.690
Need for intensive care unit (no vs. yes)	9.545	2.773-32.854	**0.001**	-	-	0.304
Day 1, serum albumin level, g/dl	0.443	0.217-0.907	**0.026**	-	-	0.548
Day 1, serum CRP level (≥ 107.50 mg/l)[a]	5.337	1.660-17.163	**0.005**	7.795	1.311-46.340	**0.024**

[a]Most appropriate cut-off value determined by receiver operating characteristic analysis. Bold values denote statistical significance at the P<0.05 level. OR, Odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CRP, c-reactive protein; LND, lymph node dissection.

status, ascites and high tumor burden, while others are surgery- and center-related characteristics such as extensive resections, prolonged operative time, poor surgical care and low surgical volume (19-21). This multifactorial etiology may underlie the inability to demonstrate the theoretical benefit of carbohydrate loading on postoperative course and morbidity. In addition, the fact that the present study did not have data on the genetic profiles of its patients may have led to misinterpretation of the impact of carbohydrate loading on postoperative course and morbidity. Although the literature data on this subject are conflicting, some studies have shown that tumor burden, invasion patterns, resectability rates and postoperative complications may differ between EOC patients with and without germline breast cancer gene (BRCA) mutation. Petrillo *et al* (22) investigated the association between BRCA mutation status and disease presentation in a large series of patients with advanced high-grade serous EOC, including 107 patients with BRCA1/2 mutation and 166 patients without BRCA mutation. The authors reported that EOC patients with a BRCA mutation had a significantly higher incidence of peritoneal spread without an ovarian mass (25.2% vs. 13.9%), bulky lymph nodes (30.8% vs. 17.5%) and increased tumor burden (42.1% vs. 27.1%) than those without a BRCA mutation. They concluded that more complex surgical procedures may be required to achieve complete resection in BRCA-mutant patients compared with non-mutant patients, which may lead to longer operation times and more severe postoperative complications. Kotsopoulos *et al* (23) examined the clinicopathological characteristics of 1,421 patients with EOC, of whom 177 had BRCA1/2 mutation. The authors reported a significantly lower complete resection rate (19% vs. 39%) in patients with a BRCA mutation compared with non-mutant patients. By contrast, in a more recent study involving a total of 612 patients with EOC, of whom 134 had a BRCA1/2 mutation, Ataseven *et al* (24) found no effect of BRCA status on disease burden, surgical complexity, complete resection rates (BRCA mutant: 74.4%; BRCA wild-type: 69.0%; P=0.274) and postoperative grade III-V complication rates (BRCA mutant: 12.0%; BRCA wild-type: 19.1%; P=0.082).

In the current study, operative time, splenectomy and postoperative day 1 serum CRP level were independent risk factors for grade III-V morbidities specifically. The optimal cut-off value for day 1 serum CRP was found to be 107.5 mg/l, with a sensitivity of 72.2% and specificity of 67.8%. CRP is an acute-phase protein that is elevated in the presence of an inflammatory process. Postoperatively, serum CRP levels increase in response to surgical stress, peaking within 48-72 h and then decrease (25). A number of studies have shown that CRP levels remain elevated in complicated postoperative conditions (25-28). Schutz *et al* (26) studied the CRP kinetics between postoperative day 1 and day-30 after orthopedic surgery. The authors reported that serum CRP levels were significantly higher in patients with a postoperative complication than in patients without a complication, with a cut-off value of 105 mg/l on the first postoperative day. However, the authors noted that the sensitivity and specificity of just one CRP value above the threshold for predicting postoperative complications was only 48%. Nam *et al* (27) estimated the first five postoperative day serum CRP cut-off values for predicting early postoperative complications including pneumonia, wound infection, intra-abdominal infection and anastomotic leakage after surgery for colorectal cancer to be 65, 108, 114, 66 and 57 mg/l, respectively. In a meta-analysis of 23 studies with more than 6,600 patients, Yeung *et al* (28) investigated the association between anastomotic leakage and serum CRP levels following colorectal surgery. The authors reported that anastomotic leakage was associated with higher CRP levels on each postoperative day compared with no leakage after colorectal surgery. A cut-off value of 110 mg/l on postoperative day 1 was found to have a sensitivity of 60% and specificity of 73% in predicting anastomotic leakage. Our cut-off value for day 1 CRP level is almost similar to the findings of Yeung *et al* (28). However, it should be noted that due to the different definitions of complications used in the literature and differences in surgical procedures, it may not always be appropriate to determine and recommend a cut-off value for CRP as a predictor of postoperative complications.

The main limitation of the current study was its retrospective design of control group, which may lead to a possible selection bias. Another limitation is the difficulty of analyzing postoperative course and morbidities in the historical control group in a detailed and reliable manner. Lastly, the single-center nature of the study is a barrier against generalizability of its findings. However, despite the limitations, the present study is the second (11) to examine the exclusive role of carbohydrate loading as a single element of ERAS in a controversial issue, which makes it valuable.

In conclusion, preoperative carbohydrate loading may have some benefits, especially in gastrointestinal surgeries where carbohydrate homeostasis is essential. However, based on the results of the current study, postoperative course and morbidity seems to be unaffected by carbohydrate loading in patients undergoing debulking surgery for EOC. More high-quality evidence is needed to recommend the routine use of carbohydrate loading in patients with EOC.

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Availability of data and materials

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

Authors' contributions

TT, IU and SD designed the whole study and agreed to be accountable for all aspects of it. AK, MuG, AA, NY, MCK, NA, SK and MeG contributed to the acquisition and curation of data. TT, SK and MeG analyzed and interpreted the data. TT and AA drafted the manuscript. IU and SD critically revised the manuscript. TT and IU confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Antalya Training and Research Hospital (7 May, 2018; approval no. 021). Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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