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ORIGINAL ARTICLE

The impact of personalized nutritional support on postoperative outcome within the enhanced recovery after surgery (ERAS) program for liver resections: results from the NutriCatt protocol

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Abstract

Background Malnutrition in liver surgery is correlated with higher postoperative complications and longer length of hospital stay (LOHS), the same items that ERAS programs try to optimize. However, to date, standardized dietary protocols have not been defined within ERAS programs. Aim of this study was to evaluate the impact on LOHS and postoperative complications, of a personalized nutritional protocol (NutriCatt) with diet and oral branched-chain amino acid (BCAA) supplementation, adopted within the ERAS program.

Methods 1960 consecutive liver resections were performed from January 2000 to September 2018. Exclusion criteria: perihilar cholangiocarcinoma, simultaneous colorectal and liver resections. Four groups for analysis: resections before 2009 (1st period); from 2009 to 2016 (2nd period, including laparoscopic resections); between 2016 and September 2017 (ERAS); after September 2017 (ERAS + NutriCatt).

Results LOHS declined ($p < 0.0001$), from a median of 10 days (1st period) to 8, 7 and 6 in 2nd period, ERAS and ERAS + NutriCatt groups, respectively. At multivariable analysis for risk of LOHS > 8 days, the 2nd period, ERAS and ERAS + NutriCatt groups showed a protective effect. These results were confirmed for both minor and major resections. LOHS was significantly lower in ERAS + Nutricatt group than in ERAS group, without increasing risk of postoperative complications, although the rate of laparoscopic resections was similar in these two groups and complexity of liver resections was significantly higher in the last period.

Conclusions Adoption of a personalized nutritional protocol with BCAA supplementation within the ERAS program for liver resections was a safe and effective approach that may impact on reducing the LOHS.

Keywords ERAS · Minimally invasive liver resections · Malnutrition · Nutritional support · NutriCatt protocol · Personalized therapy · Oral branched-chain amino acid supplementation

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Introduction

The Enhanced Recovery After Surgery (ERAS) program was first introduced by Kehlet et al. for colorectal surgery in 1997 [1, 2]. The ERAS program is a multimodal pathway that combines several aspects regarding the perioperative care to minimize the pain and stress during and after surgery and to accelerate and improve the postoperative recovery. This clinical pathway aims to decrease the postoperative complications with consequent reduction of the length of hospital stay (LOHS). The ERAS programs focus on minimal use of opioid analgesia, as well as early mobilization and early oral feeding. ERAS was initially applied to patients undergoing colorectal surgery [3, 4]. However, indications have rapidly extended to other surgeries like pancreatic [5–7], gastric [8], or esophageal [9] surgery and to cardiovascular [10], orthopedic [11], and gynecological [12] specialties. During recent years, several studies showed that the ERAS program in liver surgery was feasible, safe, and effective [13–18]. Recent meta-analyses confirmed that the postoperative recovery time and LOHS following liver resections were significantly better in the ERAS group than in the control group [19–21]. However, several protocols reported in the literature indicate a wide variability. With the intent to standardize the ERAS items in liver surgery, recommendations have been published by the ERAS Society in 2016 [22].

It has been estimated that 17–46% of surgical patients are identified as malnourished at admission [23, 24]. Malnutrition adversely affects every organ system, and it is correlated with higher postoperative complications including mortality and morbidity, more extended hospitalization and a higher risk of readmission [25, 26], that represent the most critical end-points of the ERAS programs. For these reasons, perioperative nutrition represents a fundamental aspect in the management of patients undergoing major surgery, and dietetic items have been included in many ERAS programs.

The importance of nutritional status is particularly relevant in the group of patients undergoing liver surgery. Underlying liver disease, together with malnutrition, may affect liver regeneration after liver resection with a consequent higher risk of postoperative liver failure [27]. For these reasons, routine nutritional screening should be mandatory for all patients before liver surgery because recognizing nutritional problems at admission could help to optimize patient treatment [22, 23]. However, nutritional evaluation is not routinely performed in clinical practice, and different assessment tools are often used with a consequent different reported prevalence of malnutrition. Moreover, the ERAS Society guidelines for liver resection recommend 5–7 days of oral supplements before surgery in patients at risk of malnutrition, but to date, no dietary protocols have been defined for the preadmission period and the postoperative course [22]. Type and dosage of preoperative enteral nutrition are still controversial and have not been well defined [22].

This study aimed to evaluate the impact on LOHS and postoperative complications of a standardized and personalized nutritional protocol adopted within the ERAS program for liver resections.

Materials and methods

Study population

All consecutive liver resections performed in our Unit from January 2000 to September 2018 were retrospectively analyzed. Data were extracted from a prospectively collected database established in our Unit in January 1987 for all consecutive admissions related to possible liver resection.

Exclusion criteria were as follows: (a) liver resection for perihilar cholangiocarcinoma with biliary resection and reconstruction, and (b) simultaneous colorectal and liver resection.

The program for minimally invasive liver surgery (MILS) started in our Unit in 2009, and the ERAS program was introduced in 2016. From September 2017 a standardized and personalized nutritional protocol (the NutriCatt protocol), approved by the Ethics Committee of the Catholic University of the Sacred Heart (Prot. n. 33896/16; ID: 1326), was added to the ERAS program.

Liver resections were divided into 4 groups according to the time of surgery: liver surgery before 2009 (Group A: 1st period, including all open resections); liver surgery from 2009 to 2016 (Group B: 2nd period, including open liver resections and MILS); liver surgery between 2016 and September 2017 (Group C: ERAS program) and liver surgery after September 2017 (Group D: ERAS + Nutricatt protocol).

Nutritional evaluation

A nutritional evaluation before, during, and after hospital admission was conducted. Details on the protocol have been previously described [28]. Nutritional risk was assessed according to the Nutritional Risk Screening-2002 (NRS-2002), endorsed by the European Society for Clinical Nutrition and Metabolism (ESPEN) [29].

Specialized dietitians collected anthropometrical data and performed bioelectrical impedance analysis (BIA). Bodyweight was measured using a professional balance beam scale with height rod (Seca 700 Physician's Balance, Seca®) in subjects having no footwear for each visit. Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). Body circumferences were obtained at preadmission, using a plastic fiber tape (Seca 201 Girth Measuring Tape, Seca®), according to accepted standards [30] and reported in centimeters (cm). BIA was performed in each visit with the same instrument (BodyStat© 4000, BodyStat LTD), with patients lying down supine on the bed, arms not touching the torso and legs not touching at the thigh, according to accepted standards [31]. Resistance (Res), Reactance (Xc), and Phase Angle (PhA) at 50 kHz were measured. PhA was obtained *R* and Xc, according to the following formula: PhA = arctan (Xc/*R*) × (180/).

Fat mass (FM) and fat-free mass (FFM) were derived, according to Company equations.

Bodyweight and BIA were performed in three distinct phases: on preadmission, admission and discharge.

Nutritional protocol (NutriCatt protocol)

Nutricatt protocol consists of a nutritional pre-habilitation protocol of several phases, from preadmission (3 weeks before admission) to discharge. At preadmission, a personalized diet is provided to the patients together with oral branched-chain amino acid (BCAA) supplementation 14 days before liver surgery. The personalized diet, in line with international guidelines on nutrition in cancer patients [28], is divided into 5 daily meals (breakfast, lunch, dinner and two snacks) and provides about 25–35 kcal/kg/day, depending on body mass index and nutritional targets for each patient; a protein amount of 1.5 g/kg/day and a lipid amount of 30% of energy requirements. Carbohydrates represent 45–55% of total kcal. An adequate fiber intake (25–30 g/day, both soluble and insoluble) is prescribed. BCAA tablets contain 500 mg of BCAAs (L-leucine 250 mg, L-isoleucine 125 mg, L-valine 125 mg). Two tablets are given three times a day.

During hospitalization, pre-operative fasting (from midnight) is avoided; maltodextrins and clear liquids were allowed until 2 h to intervention according to the ERAS program. At discharge, patients receive a personalized home diet with oral BCAA supplementation for 1 month. Patients are also evaluated 1 month after surgery for diet counseling.

Surgical procedure

Liver resections were defined according to the International Hepato-Pancreato-Biliary Association (IHPBA) terminology [32]. Resections of three or more segments were classified as major hepatectomies. Multiple resections included patients undergoing ≥ three parenchymal sparing liver resections for liver metastases. The surgical technique used in our unit for liver resection has been described previously [33–35]. Briefly, parenchymal transection was performed by the Cavitron ultrasonic surgical aspirator (CUSA 200; Valleylab, Boulder, CO) and wet bipolar forceps; hemostasis and biliostasis were obtained with absorbable clips (Absolok AP200 and AP300, Ethicon, Johnson & Johnson Medical Devices Companies); or with 3/0–4/0 absorbable stitches and unabsorbable ones on hepatic veins branches. Intermittent hepatic pedicle clamping was not routinely started at the beginning of liver resection but was used only when bleeding was hindering a clear view of the operative field. In the case of MILS, the patient was placed in supine position or middle left lateral position according to the tumor location, with the surgeon between the legs [36]. Five trocars were usually inserted [36]. Liver resection was carried out by the 80-degree articulating vessel sealer (Aesculap Caiman; B. Braun, Tuttlingen, Germany) and by CUSA.

Outcome evaluation

Primary end-point was LOHS. Secondary end-point was postoperative complications. Complications were scored according to the Clavien grading system [37]. Severe post-resection complications were classified as grade ≥ 3. Postoperative mortality was defined as 90-day mortality.

Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQR). Categorical variables were expressed in numbers and percentages. Kruskal–Wallis test was used for comparing continuous variables in the four investigated groups. Chi-squared test was used for comparing categorical variables.

A one-way analysis of variance (ANOVA) was used to identify significant differences between anthropometric and BIA-derived values among the three periods of observation.

In the absence of a clear and internationally recognized definition of "long LOHS", we calculated it according to its median value on the entire population. The decision to adopt this method for identifying the threshold value was realized in accordance with previously published statistical reports [38].

Logistic regression analyses for the risk of long post-resection LOHS and post-resection severe complications were constructed. LOHS was defined long when exceeding the median value of 8 days. A preliminary univariable model was created. All the variables showing a $P < 0.2$ were used for constructing the multivariable model. Beta-coefficients, standard error, odds ratio (OR), and 95% confidence intervals (95% CI) were reported.

A separate sub-analysis focused only on patients undergoing minor or major resections was also performed: multivariable logistic regression analyses were similarly used.

Another sub-analysis was realized in order to further investigate the potential beneficial effect of the ERAS + Nutricatt protocol respect to the ERAS approach alone. To compensate for the nonrandomized design of this retrospective study, a Propensity Score Matching (PSM) was computed [39]. The primary goal of the PSM was to achieve causal inference of an intervention (in this case, the ERAS + Nutricatt protocol or not). In other terms, the PSM analysis generated a weighted sample, in which the distribution of confounding variables or prognostically important covariates was similar between treated and untreated subjects. The score was created using a multivariate logistic regression model considering ERAS + Nutricatt protocol (no versus yes) as the dependent variable. We constructed the model using five possible clinical relevant confounders as covariates: HCC, metastases, MILS, major hepatectomy, and multiple resections. All the covariates were available at the time of surgery, with the intent to avoid the risk of a possible immortal time bias in covariate selection. PSM was performed using a "nearest neighbor matching" algorithm to match to each ERAS + Nutricatt group patient a control group patient having the closest propensity score. A caliper of few than 0.20 times the standard deviation of the scores was used [40]. Each pair was used once. Unpaired patients were discarded from the analysis. A final 1:1 match was generated. Therefore, logistic regression analyses for the risk of long postoperative LOHS and of postoperative severe complications were constructed in this post-PSM population.

In all the analyses, a $P < 0.05$ was considered statistically significant. Analyses and plots were carried out with SPSS 23.0 Software (SPSS Inc., Chicago, IL, USA).

Results

Between January 2000 and September 2018, a total of 2222 liver resections were performed at our Unit. Two hundred sixty-two liver resections did not fulfill the inclusion criteria (resections for perihilar cholangiocarcinoma and those performed simultaneously with colorectal resection) and were excluded.

The selected population of 1960 liver resections was classified into four groups: Group A, 1st period, $n = 550$; Group B, 2nd period, $n = 1036$; Group C, ERAS program, $n = 261$; and Group D, ERAS + Nutricatt protocol, $n = 113$.

Demographic characteristics observed in the entire population are reported in Table 1. In the whole population, the rate of major postoperative complications (grade ≥ 3) was 8.1% (159 liver resections) and the 90-day postoperative mortality rate was 0.8% (15 liver resections).

At preadmission, 99 patients were evaluated by the NRS-2002 and 8.1% (8 patients) were considered at risk of

Table 1 Demographic characteristics of the four groups

Variables	Period				*p* value
	2000–2008 1st period, open resections ($n = 550$)	2009–2015 2nd period, open + MILS ($n = 1036$)	2016–2017 ERAS ($n = 261$)	2017–2018 ERAS + NutriCatt ($n = 113$)	
	Median (IQR) or *n* (%)				
Indication for resection					< 0.0001
Metastatic disease	243 (44.2)	634 (61.2)	163 (62.5)	83 (73.5	
HCC	103 (18.7)	158 (15.3)	36 (13.8)	18 (15.9)	
Cholangiocellular carcinoma	40 (7.3)	59 (5.7)	6 (2.3)	6 (5.3)	
Gallbladder cancer	41 (7.5)	38 (3.7)	8 (3.1)	0 (–)	
Benign disease	58 (10.6)	71 (6.9)	19 (7.2)	2 (1.8)	
Intra-hepatic stones	28 (5.1)	43 (4.2)	21 (8.0)	3 (2.7)	
Other	37 (6.7)	33 (3.2)	8 (3.1)	1 (0.9)	
MILS	0 (–)	111 (10.7)	74 (28.4)	33 (29.2)	<0.0001
Major hepatic resection	211 (38.4)	264 (25.5)	62 (23.8)	16 (14.2)	<0.0001
Multiple resections	33 (6.0)	190 (18.3)	44 (16.9)	43 (38.1)	<0.0001
Severe postoperative complications (Grade ≥ 3)	54 (9.8)	78 (7.5)	20 (7.7)	7 (6.2)	0.4
LOHS (days)	10 (8–13)	8 (6–10)	7 (5–10)	6 (5–8)	< 0.0001
Postoperative mortality	6 (1.1)	8 (0.8)	1 (0.4)	0 (–)	0.5

MILS minimally invasive liver surgery, *ERAS* Enhanced Recovery After Surgery, *LOHS* length of hospital stay, *IQR* interquartile ranges, *HCC* hepatocellular carcinoma

Table 2 Patients' nutritional characteristics in the ERAS + NutriCatt period

	Preadmission	Admission	Discharge	*p*
Height (cm)	165.78.75			–
Weight (kg)	75.6±15.6	–	75.3±16.1	0.90
NRS-2002 ≥ 3	8 (7.9%)	–	–	–
Wrist (cm)	17.3±1.5	–	–	–
MUAC (cm)	30.4±3.9	–	–	–
Waist (cm)	94.9±13.6	–	–	–
Hip (cm)	101.5±9.9	–	–	–
Res	497±96	484±89	499±90	0.56
Xc	47±9	44±11	45±11	0.15
Phase Angle	5.52±0.97	5.23±0.98	5.18±0.93	0.051

malnutrition. Bodyweight and BIA parameters remained stable from the admission to discharge (Table 2).

A changing trend was observed during the study period in the four groups in terms of indications for surgery. Indeed, rate of resection for benign disease significantly decreased from Group A (10.6%) to Group D (1.8%), while the percentage of resections for metastases increased from the 1st period (Group A) (44.2%) to the ERAS + NutriCatt Group (Group D) (73.5%) ($p < 0.0001$). Laparoscopic approach steadily increased across the periods ($p < 0.0001$): the first minimally-invasive resections were reported in the 2nd period (2009–2015) when laparoscopic resections accounted 10% of procedures, and in the ERAS + NutriCatt Group the total number of MILS cases merged 30% of all the resections. Similarly, a progressive increase in the number of multiple parenchymal sparing resections was observed: from 6% in the 1st period Group to 38.1% in the ERAS + NutriCatt Group ($p < 0.0001$). On the opposite, the number of major resections declined across the periods: 38.4% in the 1st period Group, while in the ERAS + NutriCatt Group this rate reduced to only 14.2% ($p < 0.0001$).

LOHS declined accordingly ($p < 0.0001$), passing from a median of ten days in the 1st period Group to 8, 7 and 6 days in the 2nd period, ERAS, and ERAS + NutriCatt Groups, respectively. The decline in the LOHS is clearly shown in Fig. 1, in which an inverse linear correlation is reported between the LOHS and the year when the patient underwent liver resection ($p < 0.0001$).

Postoperative severe complications rates (grade ≥ 3) were not significantly different in the four groups ($p = 0.4$), although a reduction in the percentages was seen from the 1st period Group (9.8%) to the ERAS + NutriCatt Group (6.2%). Similarly, no differences were observed regarding the rate of 90-day postoperative mortality ($p = 0.5$). In addition, in this case, although not statistically significant, a decline in the percentages was seen from the 1st period

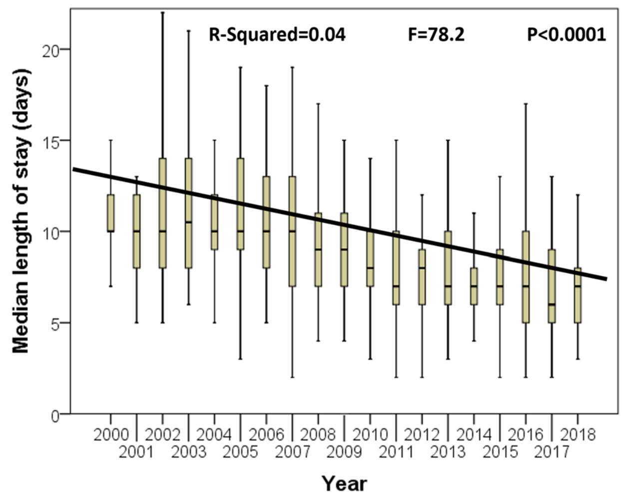

Fig. 1 Modification of the median LOHS duration observed in the entire population during the study period

(1.1%) to the ERAS + NutriCatt Group where the postoperative mortality was nil.

Predictors of LOHS > 8 days

At multivariable logistic regression for the risk of LOHS > 8 days, all the groups B, C, and D, after the 1st period management (2000–2008) showed a protective effect (Table 3). Specifically, the period 2009–2015 (Group B) had an OR 0.30 (95% CI 0.24–0.39; $p < 0.0001$), with a reduced risk for a longer LOHS of 70% respect to the 1st period management. Similarly, Group C (ERAS program) had an OR 0.33 (95% CI 0.23–0.47; $p < 0.0001$), with a 67% reduced risk. Lastly, Group D (ERAS + Nutricatt protocol) had an OR 0.23 (95% CI 0.14–0.38; $p < 0.0001$), showing the best reduction of the risk (77%) among the different periods.

Major hepatic resections, HCC as an indication for resection and multiple resections were independent risk factors for a longer LOHS after resection. On the contrary, the minimally invasive approach and metastases as an indication for resection were protectors for the risk of long LOHS.

Predictors of LOHS > 8 days after minor or major resection

A sub-analysis investigating the risk factors for a long LOHS was separately performed according to the type of liver resections: minor or major resection (Table 4). In both the sub-analyses, similar results were observed. In minor resection cases, 2nd period, ERAS and ERAS + NutriCatt periods were independent protective factors respect to the 1st period management ($p < 0.0001$).

Table 3 Multivariable logistic regression analysis for the identification of the risk factors associated with a LOHS overpassing the median period of 8 days

Variables	Beta-coefficient	SE	OR	95%CI lower	upper	*p* value
Study period of time						
2000–2008 (1st period)	Ref.	–	1.00	–	–	–
2009–2015 (2nd period)	− 1.19	0.12	0.30	0.24	0.39	< 0.0001
2016–2017 (ERAS)	− 1.11	0.18	0.33	0.23	0.47	< 0.000
2017–2018 (ERAS + NutriCatt)	− 0.47	0.26	0.23	0.14	0.38	< 0.0001
HCC	0.60	0.17	1.82	1.32	2.53	< 0.0001
MILS	− 1.72	0.25	0.18	0.11	0.30	< 0.0001
Major hepatic resections	1.38	0.12	3.98	3.14	5.04	< 0.0001
Multiple resections	0.49	0.15	1.63	1.20	2.20	0.002
Metastases	− 0.35	0.13	0.71	0.55	0.91	0.006

Hosmer–Lemeshow test *p* value: 0.4; − 2Log likelihood: 2233.2

SE standard error, *OR* odds ratio, *CI* confidence intervals, *MILS* minimally invasive liver surgery, *ERAS* Enhanced Recovery After Surgery, *HCC* hepatocellular carcinoma

Table 4 Multivariable logistic regression analysis for the identification of the risk factors associated with a length of stay overpassing the median period of 8 days

Variables	Beta-coefficient	SE	OR	95%CI lower	upper	*p* value
Minor resections						
Study period of time						
2000–2008 (1st period)	Ref.	–	1.00	–	–	–
2009–2015 (2nd period)	− 1.24	0.15	0.29	0.22	0.38	< 0.0001
2016–2017 (ERAS)	− 1.12	0.22	0.33	0.21	0.50	< 0.0001
2017–2018 (ERAS + NutriCatt)	− 1.42	0.30	0.24	0.14	0.43	< 0.0001
MILS	− 1.75	0.29	0.17	0.10	0.31	<0.0001
HCC	0.56	0.19	1.75	1.20	2.55	0.004
Multiple resections	0.46	0.16	1.58	1.16	2.15	0.004
Metastases	− 0.30	0.16	0.74	0.54	1.02	0.06
Major resections						
Study period of time						
2000–2008 (1st period)	Ref.	–	1.00	–	–	–
2009–2015 (2nd period)	− 1.08	0.22	0.34	0.22	0.53	< 0.0001
2016–2017 (ERAS)	− 1.09	0.33	0.34	0.18	0.65	0.001
2017–2018 (ERAS + NutriCatt)	− 1.69	0.56	0.19	0.06	0.55	0.003
MILS	− 1.48	0.54	0.23	0.08	0.66	0.007
HCC	0.94	0.40	2.57	1.17	5.63	0.02
Metastases	− 0.41	0.21	0.67	0.44	1.01	0.05

Subclasses of type of liver resections (minor or major resection)

MinOR Hosmer–Lemeshow test *p* value: 0.8; − 2Log likelihood: 1595.3

MajOR Hosmer–Lemeshow test *p* value: 1.0; − 2Log likelihood: 629.2

SE, standard error, *OR* odds ratio, *CI* confidence intervals, *MILS* minimally invasive liver surgery, *ERAS* Enhanced Recovery After Surgery, *HCC* hepatocellular carcinoma

In major resections, the protective effect observed in the 2nd period, ERAS and ERAS + NutriCatt periods respect to the 1st period management was even superior.

Differences of LOHS in the four Groups according to the type of liver resection performed are shown in Fig. 2. In both the cases of minor and major resections, an inverse linear regression was observed between the investigated Groups and their corresponding median LOHS, with significantly shorter hospital stays reported in the most recent periods.

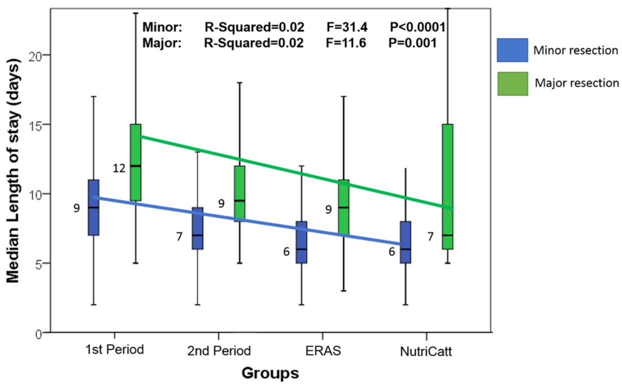

Fig. 2 Modification of the median LOHS duration observed in the sub-groups of patients undergoing major vs. minor resections

Predictors of severe postoperative complications (Grade ≥ 3)

Major liver resections and multiple resections were independent risk factors for severe postoperative complications. On the opposite, metastases as an indication for resection and MILS were independent protective variables. The period of resection failed to be statistically significant (Table 5).

Two separate sub-analyses according to the type of liver resections (minor and major resections) were performed. In case of minor resections, multiple resections were the unique independent risk factor for severe complications and metastases as an indication for resection were protective factors.

In the major resection cases, the only independent risk factor identified was HCC as an indication for resection (Table 5).

Predictors of LOHS > 8 days: post-Propensity Score Match population

After a PSM was performed matching in a 1:1 fashion the groups C (ERAS) and D (ERAS + Nutricatt), two sub-groups of 113 vs. 113 cases were selected. Therefore, a sub-analysis investigating the risk factors for a long LOHS was performed (Table 6). After balancing the two groups for potential confounders, a protective, although minimal, the effect was reported comparing group C with D, with OR 0.91 (95% CI 0.86–0.97; $p = 0.002$). Also MILS showed a protective effect, with an OR 0.06 (95% CI 0.007–0.47; $p = 0.008$), while all the other factors failed to be statistically significant.

On Table 7 the PSM groups were also used to evaluate risk factors for severe postoperative complications. Only multiple resections resulted as an independent risk factor for severe postoperative complications in the sub-population of PSM patients. All the other tested variables, namely the period of surgery, MILS, HCC, multiple resections, metastases, and major resection failed to be significant.

Table 5 Multivariable logistic regression analysis for the identification of the risk factors associated with severe postoperative complications (grade ≥ 3 according to Dindo-Clavien Classification)

Variables	Beta-coefficient	SE	OR	95% CI lower	upper	*p* value
Overall liver resections[a]						
Metastases	− 0.63	0.18	0.53	0.38	0.76	< 0.0001
Major resections	0.97	0.19	2.64	1.84	3.80	< 0.0001
MILS	− 2.18	0.72	0.11	0.03	0.46	0.002
Multiple resections	0.64	0.27	1.90	1.13	3.19	0.02
Minor resections[b]						
MILS	− 1.94	0.72	0.14	0.04	0.59	0.007
Metastases	− 0.63	0.26	0.53	0.32	0.88	0.01
Multiple resections	0.64	0.28	1.91	1.10	3.29	0.02
Major resections[c]						
HCC	0.80	0.31	2.21	1.21	4.07	< 0.0001

Overall liver resections and subclasses of minor and major resections. Backward Wald method adopted

Entire = Hosmer–Lemeshow test *p* value: 1.0; − 2Log likelihood: 1037.9

MinOR Hosmer–Lemeshow test *p* value: 1.0; − 2Log likelihood: 603.3

MajOR Hosmer–Lemeshow test *p* value: 1.0; − 2Log likelihood: 440.4

SE standard error, *OR* odds ratio; *CI* confidence intervals, *MILS* minimally invasive liver surgery, *HCC* hepatocellular carcinoma

*Variables initially introduced in the model: Period of surgery, MILS, HCC, multiple resections, metastases, and major resection

**Variables initially introduced in the model: Period of surgery, MILS, HCC, multiple resections, and metastases

***Variables initially introduced in the model: Period of surgery, MILS, HCC, and metastases

Table 6 Multivariable logistic regression analysis for the identification of the risk factors associated with a LOHS overpassing the median period of 8 days: post-PSM population

Variables	Beta-coefficient	SE	OR	95% CI lower	upper	*p* value
Study period of time	Ref.	–	1.00	–	–	–
2016–2017 (ERAS)	− 0.09	0.03	0.91	0.86	0.97	0.002
2017–2018 (ERAS + NutriCatt)						
HCC	0.80	0.50	2.22	0.83	5.95	0.11
MILS	− 2.90	1.09	0.06	0.007	0.47	0.008
Major hepatic resections	0.84	0.69	2.31	0.60	8.97	0.23
Multiple resections	0.20	0.57	1.23	0.40	3.76	0.72
Metastases	− 0.13	0.40	0.88	0.40	1.93	0.75

Hosmer–Lemeshow test *p* value: 0.5; − 2Log likelihood: 248.9

SE standard error, *OR* odds ratio, *CI* confidence intervals, *MILS* minimally invasive liver surgery,0 *ERAS* enhanced recovery after surgery, *HCC* hepatocellular carcinoma

Table 7 Multivariable logistic regression analysis (Backward Wald method) for the identification of the risk factors associated with severe post-operative complications (grade ≥ 3 according to Dindo-Clavien Classification): post-PSM population

Variables	Beta-coefficient	SE	OR	95%CI lower	upper	*P* value
Multiple resections	2.52	0.70	12.42	3.15	49.00	< 0.0001

Variables initially introduced in the model: Period of surgery, MILS, HCC, multiple resections, metastases, and major resection

Hosmer–Lemeshow test *p* value: 0.33; − 2Log likelihood: 73.0

SE standard error, *OR* odds ratio, *CI* confidence intervals

Discussion

Our study showed that the adoption of a standardized and personalized nutritional protocol within the ERAS program for liver resections may be related to the reduction of the LOHS without any increase in postoperative morbidity and mortality.

The ERAS program was first introduced in colorectal surgery in 1997 [1, 2], and then was extended to several surgical specialties [5–12]. The two principal aims of this clinical pathway are the reduction of postoperative complications and LOHS, with a consequent reduction in healthcare costs. Several studies demonstrated that the ERAS program was feasible and effective also in liver surgery, where postoperative morbidity was lower, and LOHS was shorter if compared to series not using ERAS [13–21].

It has been demonstrated that malnutrition in surgical patients is strictly correlated with significantly higher postoperative complications and with significantly longer hospitalization [25, 26, 41, 42], the same factors that the ERAS program has tried to optimize. This aspect is particularly more evident in the field of liver surgery because the nutritional status is one of the preoperative factors, including age, body mass index, previous chemotherapy, and comorbidities such as diabetes or chronic liver disease, that can affect the degree of liver regeneration [43]. Malnutrition is correlated with a higher risk of postoperative liver failure and may show a negative impact on postoperative complications and LOHS in patients undergoing liver resection [27]. For these reasons, both the ERAS program and the peri-operative nutrition therapy should represent two synergistic approaches of the same surgical care plan.

Preoperative identification of malnutrition and nutrition therapy before surgery are two essential steps in patients undergoing liver resection. In 2016 the ERAS Society published the first recommendations to standardize the items in liver surgery [22]. Concerning the issue of malnourished patients, these guidelines recommended 5–7 days of oral supplements before surgery in patients at risk of malnutrition [22]. However, to date, the generic term of oral supplements, described in the ERAS programs, has not been clearly defined and standardized dietary protocols have not been specifically analysed.

In our study, we evaluated the impact of a personalized nutritional support on postoperative outcome in patients undergoing liver resection within the ERAS program. In the so-called "NutriCatt program", a specialized unit of Clinical Nutrition and Dietetics assessed the nutritional risk in patients undergoing liver surgery, collected all anthropometrical data, and performed the BIA analysis. This assessment was performed in all patients several times, from pre-admission to discharge and also one month after discharge. In this way, the patient received a standardized and personalized diet that was modified according to the frequent nutritional evaluation during the perioperative period.

By analysing our surgical series from 2000 to 2018, indications for resection changed significantly during the years, and in particular, the rate of resected metastatic disease increased dramatically from 44.2 to 73.5% ($p < 0.0001$). As a consequence of this changing trend of surgical indications, the rate of multiple parenchymal-sparing liver resections, considered as the treatment of choice for liver metastases, significantly increased from 6.0 to 38.1% ($p < 0.0001$) and the rate of major resections significantly decreased from 38.4 to 14.2% ($p < 0.0001$). According to the IHPBA terminology [32], multiple parenchymal-sparing liver resections are classified as minor resections. However, they are often complex liver resections [44], that usually require a longer duration of surgery than major resections [45], and are associated with a higher risk of postoperative complications than that observed after a single minor resection. Indeed, in our multivariable logistic regression analysis for the identification of the risk factors associated with severe postoperative complications (grade ≥ 3 according to Dindo-Clavien Classification), both multiple resections and major resections were independent predictors of severe morbidity in the whole series. By analysing our surgical series, we can see that indications for resection of malignant disease significantly increased over the years and the overall complexity of liver resections increased. However, in this surgical scenario, rates of severe postoperative complications and postoperative mortality remained stable during the study period and the LOHS significantly decreased from a median of 10 days to 6 days ($p < 0.0001$).

At the multivariable logistic regression analysis, hepatocellular carcinoma as an indication for resection, major resections, and multiple resections were identified as independent risk factors for a longer LOHS. Interestingly, resections performed during the 2nd period (including MILS), during ERAS program and ERAS + NutriCatt program showed a protective effect with a significantly reduced risk of longer LOHS.

The MILS program started in 2009 in our Unit [36]. The advantages of MILS are those of all laparoscopic procedures [46, 47]. They include the reduction of the abdominal wall damage with a decreased postoperative pain, shorter hospital stay and an earlier return to previous activity with significant improvements in quality of life after surgery [46, 47]. The minimally invasive approach has changed the perioperative management of patients undergoing liver resection and it represents one of the first fast-track approaches to such patients. In our study, the minimally invasive procedure was an independent protective variable for severe postoperative complications (OR 0.11; $p = 0.002$). The impact of MILS in reducing the LOHS was evident in our series (Fig. 1). Indeed, the median LOHS significantly decreased during the years from 10 days in the 1st period Group to 6 days in the last period, together with a significant increase of the rate of laparoscopic liver resections (from 10.7 to 29.2%).

The ERAS program started in our Unit in 2016, and after September 2017 it was implemented by a standardized and personalized nutritional protocol (the NutriCatt protocol) defined by the Clinical Nutrition and Dietetics Unit of our Hospital, for each patient undergoing liver resection. In this way, our fast-track protocol, initially adopted only for patients undergoing MILS, was extended to all patients undergoing liver resections and, in particular, also to patients undergoing conventional open approach. By analysing the results in Fig. 1, it is interesting to note that, although the rates of MILS were similar in 2016 (ERAS period: 28.4%) and 2017 (ERAS + NutriCatt period: 29.2%), the LOHS continued to significantly reduce during these two periods of time, to 7 and 6 days, respectively. Indeed, both the ERAS program and the ERAS + NutriCatt program showed a protective effect in reducing the LOHS.

An original aspect of our program (NutriCatt Protocol) was a personalized diet and the supplementation with BCAA. According to the NRS-2002, almost 8% of the ERAS-NutriCatt evaluated patients was considered at risk of malnutrition. The relative low percentage is probably due to a careful preoperative selection of surgical patients. It should be highlighted that such patients were at risk of malnutrition and not malnourished patients. For these reasons, the Nutricatt protocol was not changed and patients underwent regular nutritional evaluation during hospitalization. Of note, all patients maintained weight and body composition stable from the admission to discharge, despite a major abdominal surgery (Table 2).

Regarding BCAA supplementation, in the rat model of hepatectomy, BCAAs have been reported to stimulate hepatocyte growth factor production and to promote hepatocyte regeneration [48]. In clinical trials, perioperative BCAA treatment in patients with liver cirrhosis undergoing hepatectomy for HCC, showed a quicker improvement of liver function during the early postoperative period, with a consequent impact in reducing the LOHS [49]. Most of the published studies demonstrated that BCAA supplementation improved functional liver regeneration and function with the prevention of ascites in patients undergoing liver resection. However, all these studies focused on very small series of cirrhotic patients undergoing resection for HCC [50, 51].

Our study analysed the impact of a personalized diet with BCAA supplementation in 113 patients undergoing liver surgery with different indications. In this group of patients, our analysis showed that a standardized evaluation of surgical patients' nutritional status and a personalized perioperative nutritional support may contribute to improve the outcome of patients within the ERAS approach. Indeed, the overall rate of complex procedures associated with a significantly higher risk of major complications (major resections + multiple resections) was significantly higher in the ERAS + NutriCatt group than in the ERAS group (52.3% vs. 40.7%, respectively; $p = 0.038$). However, rates of postoperative morbidity and mortality were not significantly different between the two groups and the LOHS in patients with nutritional support was significantly lower than that observed in the ERAS group (6 days vs. 7 days, respectively). The protective effect of the NutriCatt program was confirmed in both minor and major liver resections. In other words, the ERAS + NutriCatt protocol was equally safe and effective as the ERAS protocol. However, the reduction of LOHS was obtained in the NutriCatt group, where the complexity of liver surgery was significantly higher than that of the previous periods, without increasing the rates of postoperative morbidity and mortality.

Some limitations of the present study could be advanced. This is a retrospective study over a long period of time and the degree of complexity of minor liver resections performed in the past was not available. Multiple parenchymal sparing liver resections were defined according to the number of minor resections in the same patient. This could be a bias but the showed increasing trend of this type of operation, together with a decreasing trend of major resections, may demonstrate that this type of classification has worked in our analysis, as in other papers focusing on parenchymal sparing resections [52, 53].

Conclusions

In conclusions, despite the limitations of a retrospective study, our analysis showed that the adoption of a standardized and personalized nutritional protocol with BCAA supplementation within the ERAS program for liver resections was a safe and effective approach that may represent a possible further tool for reducing the LOHS.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Ethical approval This is a retrospective study which has been conducted in accordance with the ethical standards as laid in the 1964 Helsinki Declaration.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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