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ORIGINAL SCIENTIFIC REPORT

A Novel Approach to Major Surgery: Tracking Its Pathophysiologic Footprints

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Abstract

Background To study the 'metabolic profile' of different surgical procedures and correlate it with pertinent surgical details and postoperative complications.

Methods We conducted a prospective pilot study of 70 patients, ten for each of the seven following groups: (1) laparoscopic cholecystectomy, (2) incisional hernia repair, (3) laparoscopic and (4) open colon surgery, (5) upper gastrointestinal, (6) hepatic, and (7) pancreatic resections. Biochemical assessment included white blood cell count (WBC), C-reactive protein (CRP), glucose, triglycerides (TG), albumin (Alb), and pre-albumin (Pre-Alb), from the day before surgery until 5 days thereafter. Biological markers were compared for major versus minor surgery groups, which were defined on a clinical basis. Univariable analysis was used to identify risk factors for postoperative complications and $p < 0.05$ was the significance threshold.

Results Common findings in all surgery groups were the acute inflammatory response (↑: WBC, CRP, ↓: TG, Alb, pre-Alb). Using cut-off values of 240 min operative (OR) time and 300 ml estimated blood loss (EBL), laparoscopic cholecystectomy, incisional hernia repair, and laparoscopic colectomy could be distinguished from open colectomy, upper gastrointestinal, liver, and pancreas resections. In a biochemical level, increased CRP and reduced postoperative Alb levels were highly discriminative of all types of 'major surgery.' Significant risk factors for postoperative complications were age, male gender, malignancy, longer OR time, higher blood loss, high CRP, and low Alb levels.

Conclusions Biochemically, CRP and Alb levels can help quantify the magnitude of the surgical trauma, which is correlated with adverse outcomes.

Introduction

Modern surgery is apt to be characterized by its different impressive technical progresses that have been achieved during recent decades. In the meantime, important developments on the methodological plane have also taken place, e.g., validated and widely used classification systems for complications, screening tools for malnutrition, and standardized scores for staging different diseases [1, 2]. It is therefore striking that such a widely used term as "major surgery" has not yet been clearly defined. In a recent attempt, 'major' has been considered a surgical procedure that is extensive, involves removal of whole or parts of

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organs and/or is life threatening [3], or even a procedure associated with $a > 1$ % mortality [4].

Finally, all turns around patient's care in surgery; hence it may be most meaningful to define major surgery from a patient's perspective, describing its pathophysiological reactions after the surgical trauma. Surgical interventions cause inevitably a postoperative metabolic stress response [5, 6] These inflammatory and metabolic changes are part of the patient's reaction and may be used to more precisely describe the magnitude of the surgical intervention, the 'aggressiveness' and the associated morbidity [3, 7, 8]. In this perspective, recent improvements in perioperative care, such as perioperative nutrition and multimodal enhanced recovery pathways have proven to attenuate the overshooting stress response and thus to improve clinical outcomes [7–9]. The magnitude of a surgical intervention (major vs. minor) is therefore likely to depend not only on the type of procedure (classical definition), but also on the surgical access (minimal invasive), technical expertise (OR time, blood loss), and on perioperative care. Lastly, individual patients will react differently to defined surgical interventions. This being said, it is appealing to assess the common final pathway, namely the metabolic response to surgical trauma.

The aims of the study were therefore to (I) assess the metabolic and inflammatory profile of different surgical procedures and to correlate these «metabolic profiles» with pertinent surgical details and (II) to identify risk factors for postoperative complications.

Materials and methods

From December 2011 to July 2012, 70 consecutive patients who fulfilled the inclusion criteria were enrolled in this prospective, observational study. The study was approved by the local ethic committee (protocol number #273/11) and conducted according to the principles of the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all patients at least 24 h before their inclusion to the study.

Patients and surgical procedures

Male and female patients between 18 and 75 years who were scheduled for elective surgery for benign or malignant disease were eligible for the study; there was no restriction regarding the ASA physical status. Exclusion criteria included emergency surgery, pre-existing severe organ failure, such as renal failure (creatinin clearance <20 ml/min), liver cirrhosis Child B and C, heart failure (NHYA class IV), severe COPD), immunosuppressive treatment, pregnancy, and no signed informed consent.

Surgical interventions were limited to seven different procedures (Table 1): laparoscopic cholecystectomy, open (extraperitoneal) incisional hernia repair, laparoscopic colectomy, open colectomy, upper gastrointestinal (GI) tract resections (i.e., gastrectomy, esophagectomy), major liver resections (>3 segments), and pancreas resections (duodenopancreatectomy, pancreas tail resections). Ten consecutive patients in each group were included. All interventions were performed under general anesthesia, and epidural analgesia was used in selected patient group (i.e., open colectomy, incisional hernia repair, upper GI resection, and pancreas, and liver resections). The catheter was inserted at the upper thoracic level (T4–T5); and as anesthetic solution we used a combination of bupivacaine (0.0625–1.125 %), adrenalin (0.1 mg/ml), and fentanyl (2 μg/ml). Epidural analgesia was started intraoperatively and used until postoperative day 4 or 5, when it was substituted by oral analgesics. Patients undergoing open and laparoscopic colectomy were the first ones included in an enhanced recovery pathway at the time and received carbohydrate drinks until 2 h preoperatively, while the other patient groups were kept nil-per-month 6 h preoperatively. Carbohydrate load consisted of a glucose/maltodextrin solution, in a concentration of 25 g/200 ml. Patients

Table 1 Types of surgical interventions and its characteristics used for different definitions of what is "major surgery"

Type of intervention	Open surgical access	Organ resection	Peritoneal trauma	Clinical perception
Laparoscopic cholecystectomy				
Incisional hernia repair*	X			
Laparoscopic colectomy		X		
Open colectomy	X	X	X	
Upper GI resections	X	X	X	X
Liver resections	X	X	X	X
Pancreatic resections	X	X	X	X

* Extraperitoneal

received 800 ml in the evening before and 400 ml 2 h before the intervention.

The different surgical procedures were labeled as "minor" or "major" surgery by use of different widely used criteria (Table 1): (I) surgical access: open versus minimal invasive, (II) organ resection, (III) peritoneal trauma (opening of the abdominal cavity), and (IV) clinical perception of the surgeon (upper GI, liver, pancreas).

Dataset and outcome measurements

Data were entered prospectively in a priori designed computerized database. Relevant demographic and clinical information were recorded for each patient (Table 2). Nutritional status was assessed at hospital admission using the risk score (NRS) calculated preoperatively by the team of clinical nutrition or the investigating authors [1] and the percentage of preoperative BW loss in the last 3–6 months, whereby >10 % was considered clinically significant [10, 11].

Furthermore, pertinent information on the surgical intervention and perioperative care which might influence stress response was recorded (Table 2) and postoperative complications were classified according to a validated five-scale system [2].

Blood samples were taken once daily at 7 a.m. from the day before surgery (postoperative day-1, POD-1) until POD 5. Measurements on POD 0 were performed 4–6 h after surgery. The following parameters were analyzed in each sample: white blood cell count (WBC), C-reactive protein (CRP), glucose, triglycerides (TG), serum albumin (Alb), and pre-albumin (pre-Alb). All blood samples were taken in a fasting state, after parenteral or enteral feeding had been stopped for 4 and 6 h, respectively.

Statistics

Fisher's exact test was used for the comparison of categorical variables. Student's *t* test and Mann–Whitney *U* test were employed to compare normal and non-normal continuous variables, respectively. Biological markers were compared for major versus minor surgery groups (Table 1) in order to overcome multiple group comparisons between the seven procedure groups. Adjustment for confounding factors was performed using multiple logistic regression models and univariable risk factors with a $p \leq 0.1$ entered the model. All tests were two-tailed. A *p* value of less than 0.05 was considered significant.

Data analysis was performed with the Statistical Package for Social Sciences (SPSS 21.0, Inc., Chicago, IL) and Prism 5.2 (GraphPad® Software Inc, 2236 Avenida de la Playa La Jolla, CA 92037 USA).

Table 2 Overview over potential patient-related confounders of the postsurgical metabolic stress response

	N (%)	Median (range)
Age (years)		64.5 (27–86)
Gender: male/female (%)	48/22 (69/31)	
BMI (kg/m^2)		25 (17–37)
ASA physical status (%)		
I–II	52 (74)	
III	18 (26)	
Active smoking (%)	21 (30)	
Alcohol consumption (%)	27 (39)	
Weight loss ≥10 % (%)	8 (11)	
Nutritional ris k score ≥3 (%)	36 (51)	
Diabetes (%)	14 (20)	
Type I/II	1/13 (1/19)	
Insulin treatment	5 (7)	
Patients under statin therapy (%)	25 (36)	
Preoperative HDL (mmol/l)		1.3 (0.1–3.5)
Preoperative Psyst (mmHg)		133 (92–182)
Abdominal perimeter (cm)		95 (65–173)
Malignant disease (%)	23 (33)	
Enhanced recovery program (ERAS®) (%)	19 (27)	
Epidural analgesia (%)	47 (67)	

Demographic data of the study group, taken into account as potential confounders for the postoperative metabolic response

BMI body mass index, *ASA* American Society of Anesthesiologists, *Psyst* systolic pressure, *HDL* high density lipoproteins, *ERAS®* enhanced recovery after surgery

Results

Patient characteristics (Table 2)

According to the study protocol, 70 consecutive eligible patients were recruited. Their median age was 64.5 years (range 27–86 years); most of them ($n = 52$, 74 %) were assessed as ASA physical status I and II. The median BMI was 25 kg/m^2 (range 17–37 kg/m^2). All patients were able to eat preoperatively, but eight patients (11 %) experienced a significant weight loss (≥10 % of baseline body weight) with three patients belonging to the upper GI resection group (33 %). Thirty-six patients (51 %) were assessed as at increased nutritional risk with a NRS score ≥3. However, the latter should be considered with precaution as 'major' interventions are considered to represent a high nutritional risk using the NRS, irrespective of the individual patients' nutritional status. Fourteen (20 %) patients were diabetic, from whom five patients (7 %) required insulin treatment. No patient suffered from exocrine or endocrine pancreatic insufficiency. In all, 23 (33 %) were found to be at high risk for metabolic syndrome, whereby the highest percentage was observed in the pancreatic resection group (50 %).

Surgical details

Mean OR time and blood loss differed considerably between groups, ranging from 65 ± 21 to 337 ± 92 min and from 0 up to 550 ± 428 ml, respectively (Fig. 1a, b). Using cut-off values of $\geq$240 min OR time and $\geq$300 ml EBL, laparoscopic cholecystectomy, incisional hernia repair, and laparoscopic colectomy could be distinguished from open colectomy, upper GI, liver, and pancreas resections. These latter groups were also characterized by a large opening of the peritoneal cavity (Table 1). Of note, ERAS pathways were implemented in 2011 in our department, starting with open and laparoscopic colon resections. In the present study, 19 out of 20 colon resections were included in ERAS protocols; the remaining patient underwent an extensive adhesiolysis and a low rectal resection with a protective ileostomy.

Clinical outcome

No patient had a complication after cholecystectomy, while in all other patient groups several patients developed at least one complication: six patients after incisional hernia repair, four patients after laparoscopic colectomy, eight patients after open colectomy, seven patients after upper GI resections, seven patients after liver and nine patients after pancreas resections.

Total number of complications and its related severity are shown in Fig. 2. The peritoneal trauma group had more overall and major complications compared to cholecystectomy, incisional hernia repair, and laparoscopic colectomy. The latter group achieved oral intake within 24 h after surgery and left hospital within 1 week. This was exceptional for patients in the peritoneal trauma group (Fig. 3a, b). All patients were allowed to drink and eat at POD 0, bar patients after esophageal resection and total gastrectomy (only drinking). These patients received early enteral feeding until POD 4 when oral feeding was started. A paralytic ileus was observed in three patients in the open colectomy group. Patients who underwent pancreatic resections showed the most prolonged time to resumption of oral feeding with a median of 4 days (range 2–12 days) which was related to a prolonged gastroparesis as a typical complication of pancreas surgery.

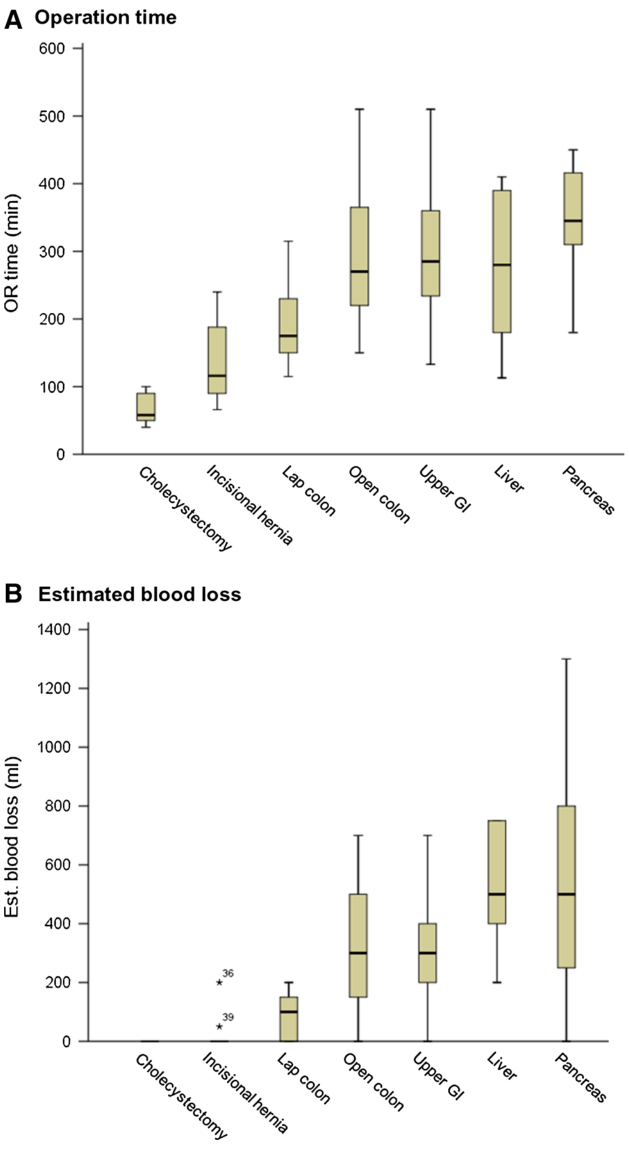


Fig. 1 Operation time and estimated blood loss by surgery group. **a** Operation time for the seven groups. The four 'major surgery groups' stand out with operative times >240 min. **b** Laparoscopic cholecystectomy and incisional hernia reported negligible blood loss and again major surgery stands out with a median EBL >300 ml

Metabolic response (Fig. 4a–f)

Leucocyte counts showed a sharp increase in all groups with peaks at 18 h after surgery. Serum CRP levels revealed a similar increase; however, peaks were reached at POD2-3. Serum glucose levels immediately increased after the surgical trauma at POD 0 in all groups, but its further postoperative course revealed a large variability. Triglyceride levels declined massively at POD0, and showed a rapid but incomplete normalization that started

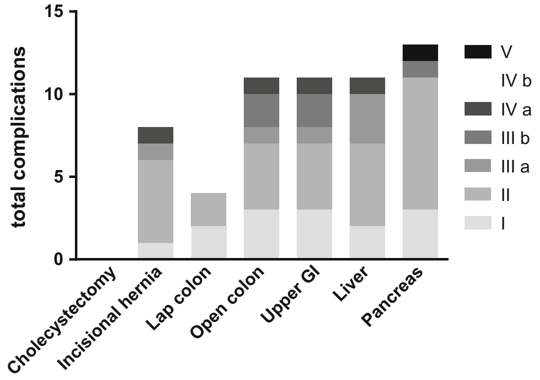


Fig. 2 Complications by surgery group. Total complications per group graded by severity according to Dindo et al. [2]. Increasing gray tones indicate more severe complications (>grade IIIA); only one case of mortality was observed (*in black*), in the pancreatic resection group

on POD1. Alb showed a sharp decline already 6 h after surgery that was similar to serum triglycerides. Postoperatively, Alb continued to decrease for several days. Bar one exception (laparoscopic cholecystectomy), pre-Alb steadily decreased during the whole postoperative course without showing any normalization.

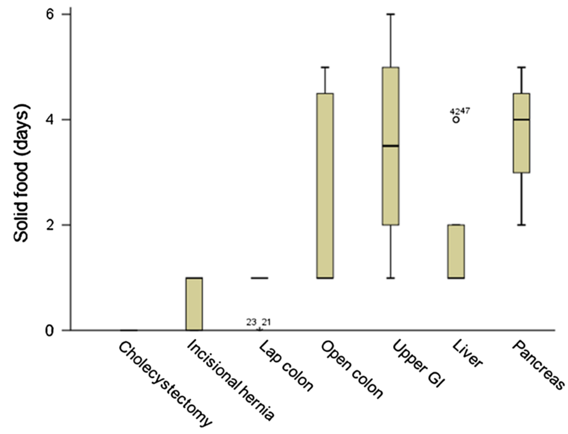
In order to take into consideration the different baseline values and kinetics of the parameters, we analyzed the maximal variations (Δmax or Δmin) for leucocytes, CRP, triglycerides, Alb, and pre-Alb (Table 3). CRP, Alb, and triglycerides were discriminative for open versus minimal invasive approaches (surgical access). CRP and Alb were significantly different for the groups defined by peritoneal trauma and clinical perception (upper GI, liver, pancreas), while only Alb was different comparing operations with organ resection versus laparoscopic cholecystectomy and incisional hernia repair.

Leucocytes, triglycerides, and pre-Alb had little or no obvious discriminative value to distinguish putative major from minor surgeries. To the contrary, CRP and Alb appeared to represent the magnitude of surgical trauma in a quantitative manner. With the exception of liver surgery, Fig. 5 shows the same step-wise increase for maximal CRP values as it was shown for OR time, EBL, complications, oral intake, and hospital stay (Figs. 1, 2, 3).

The role of the opening of the abdominal cavity

Laparoscopic cholecystectomy, incisional hernia, and laparoscopic colectomy share as common feature that the integrity of the abdominal cavity is preserved. These three patient groups had a shorter operative time, less blood loss, a better clinical outcome (complications, oral intake, hospital stay), as well as an attenuated metabolic response

A Oral intake



B Hospital stay

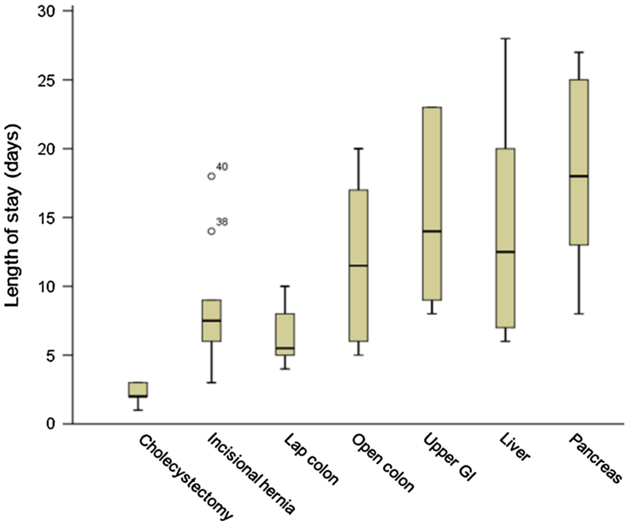


Fig. 3 Oral intake and hospital stay by surgery group. **a** Time to resumption of oral intake was significantly longer among pancreatic resections and upper GI resections. Open colectomy patients were also longer to resume oral diet despite their inclusion in ERAS pathways, due to paralytic ileus. **b** Length of postoperative hospital length of stay (days) was also higher among the same three aforementioned groups

(CRP Δmax and Alb Δmin) compared to patients who underwent open colectomy, upper gastrointestinal, liver, and pancreas resections (Table 4).

Risk factors for postoperative complications

Univariable analysis was performed to evaluate the relationship of various demographic, surgical, and biological factors on the incidence of postoperative complications. As a result, increased age, male gender, prolonged operative time, and higher EBL were significantly correlated, as well as organ resection and high CRP and low Alb values (Table 5). On multivariable analysis, none of these factors

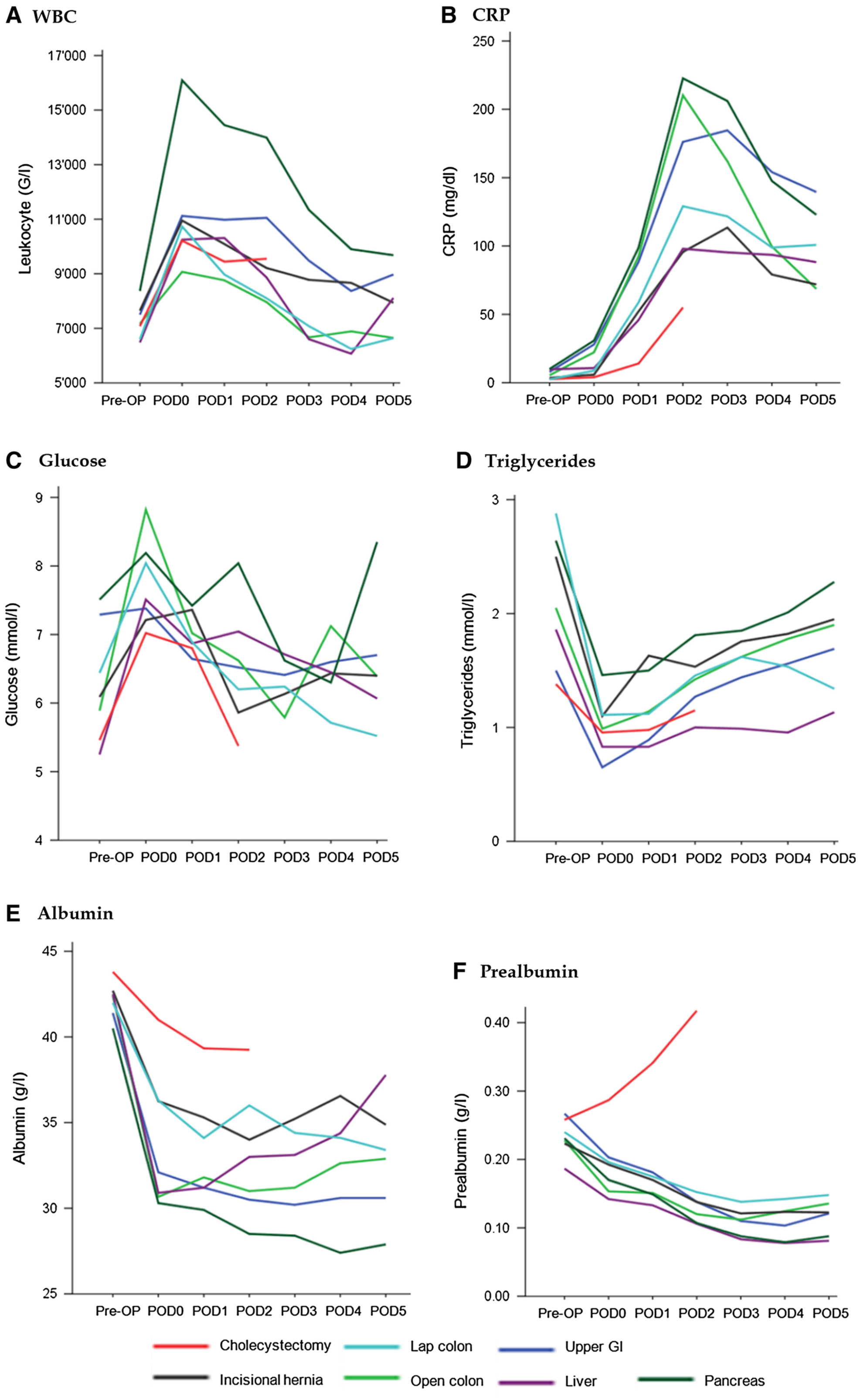


Fig. 4 Postoperative biochemical and metabolic response. Illustration of the postoperative variation (mean values) of each biochemical parameter, for the seven chosen study groups. The color codes given below depict correlate each curve with one of the seven study groups. *WBC* white blood cell count, *CRP* C-reactive protein, *pre-OP* preoperative, *POD* postoperative day

Table 3 Major versus minor surgery: discriminative potential of biological parameters

Grouping by	Surgical access	Organ resection	Peritoneal trauma	Clinical perception
Biological markers				
Leukocytes, Δmax (G/l)	449 ± 827	1458 ± 919	372 ± 852	708 ± 863
p	0.590	0.112	0.664	0.416
CRP max (mg/dl)	77 ± 21	37 ± 23	68 ± 23	68 ± 25
p	0.001	0.102	0.004	0.027
Triglycerides, Δmin (mmol/l)	0.869 ± 0.214	0.172 ± 0.277	0.274 ± 0.313	0.229 ± 0.362
p	<0.001	0.537	0.386	0.533
Albumin, Δmin (g/l)	4.866 ± 1.241	3.756 ± 1.317	5.490 ± 1.168	4.867 ± 1.231
p	<0.001	0.006	<0.001	<0.001
Pre-albumin, Δmin (g/l)	0.022 ± 0.011	0.031 ± 0.017	0.030 ± 0.016	0.030 ± 0.021
p	0.051	0.072	0.068	0.175

Displayed as mean ± SD

Δmin and Δmax represent the maximal postoperative amplitudes compared with preoperative baseline values

CRP C-reactive protein

Bold typing indicates statistical significance with a $p < 0.05$

The seven types of surgery were grouped according to four clinically driven definitions according to Table 1. Then, biochemical markers were compared between major and minor procedures according to the respective definition. This table summarizes the mean differences

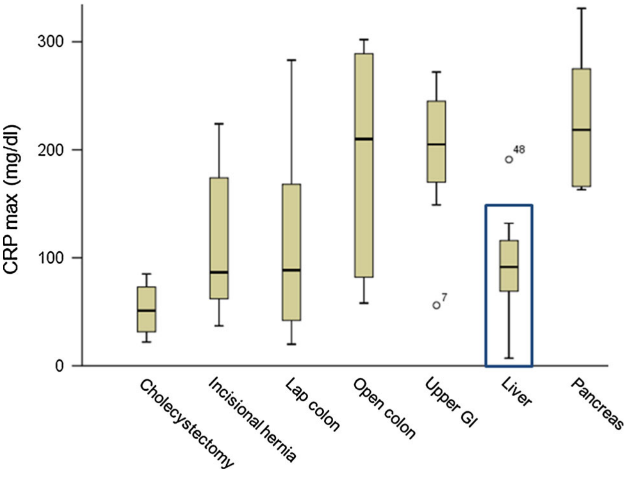


Fig. 5 C-reactive protein and extent of surgery. Of interest was the postoperative course of CRP protein, which was significantly higher for the three ‘major’ surgery groups: pancreatic resections, upper GI, and open colon resections. Liver surgery did not follow this pattern with a postoperative CRP profile more alike the ‘minor’ intervention groups. *CRP* C-reactive protein

proved to be independently correlated with overall or major complications.

Discussion

The present study aimed to identify different characteristics to better describe the term major surgery. To this end, early postoperative metabolic changes were assessed and correlated to a variety of clinical findings. A prolonged operative time (≥240 min), an increased blood loss (≥300 ml), serum CRP, serum albumin, and postoperative complication rates are key factors defining major surgical interventions. In addition, surgical interventions requiring a large opening of the abdominal cavity for organ resections must also be considered as major surgery.

The lack of a generally accepted definition of major surgery should be nowadays considered as a relevant shortcoming impairing surgical research, even though several attempts have been made during recent decades and an informal common sense on it use seems to exist [3, 12].

First of all, the type of intervention seems to determine the magnitude of surgery, i.e., whether organs are resected or malignant disease is present. Moreover, pathophysiologic aspects, such as metabolic and inflammatory reactions, and insulin resistance are gaining increasing importance and might be valuable parameters to identify major interventions. [6, 13–16].

Metabolic response to surgery

A considerable amount of research elucidated the stress response after trauma and surgery, which appears to develop as follows: after the post-traumatic sympathetic system activation, hypothalamic centers and then pituitary gland are stimulated, to launch a complex cascade of endocrine and immunological response resulting in profound changes in protein, fat, carbohydrate, and water-electrolyte metabolism [13, 17]. IL-6 with its pro-inflammatory activity seems to be

Table 4 Major surgery defined by peritoneal trauma/major opening of the peritoneal cavity

	Preservation of the abdominal cavity cholecystectomy, incisional hernia, lap. colectomy	Opening of the abdominal cavity open colon, upper GI, liver, and pancreas resection	P
Operation time (min)	130 ± 74	306 ± 108	<0.001
Estimated blood loss (ml)	34 ± 66	581 ± 827	<0.001
Number of patients with complications	10/30	31/40	<0.001
Resumption of oral diet (days)	0 (1)	3.5 (3)	0.001
Hospital stay (days)	5 (5)	12.5 (9)	<0.001
CRP Δmax	110 ± 90	178 ± 85	0.004
Albumin Δmin	5.1 ± 3.9	10.6 ± 5.6	<0.001

Mean ± SD or median (interquartile range) as appropriate

Δmin and Δmax represent the maximal postoperative amplitudes compared with preoperative baseline values

IQR interquartile range

Table 5 Clinical, surgical, and metabolic risk factors for postoperative complications (univariable analysis)

Demographics	*p*	Metabolic parameters	*p*
Age	0.047	Leucocyte delta max	0.579
Male gender	0.043	CRP Δmax	0.001
BMI	1.000	TG delta min	0.184
NRS	0.056	Albumin Δmin	0.005
Active alcohol abuse	1.000	Pre-albumin delta min	0.142
Active smoking	0.795		
>10 % weight loss	0.226	Operative characteristics	
Insulin-dependent diabetes	0.395	OR time	0.000
Arterial hypertension	0.580	EBL	0.024
Malignant disease	0.038	Organ resection	0.003

BMI body mass index, *NRS* nutritional risk score, *CRP* C-reactive protein, *Alb* albumin, *pre-Alb* pre-albumin, *TG* triglycerides, *OR* operative room, *EBL* estimated blood loss

Δmin and Δmax represent the maximal postoperative amplitudes compared with preoperative baseline values

Bold typing indicates statistical significance with a $p < 0.05$

of paramount importance to the magnitude of surgical stress response [14, 18–20]. Recent studies suggest a correlation between IL-6 levels and insulin resistance [21–23]. Insulin resistance is a well-known reaction after trauma and surgery, which results in a hypercatabolic state, with increased protein breakdown, lipolysis, and free fatty acid (FFA) oxidation [5, 6, 24].

In our study, postoperative metabolic profiles correspond well with the above-described pattern of surgical stress response.

Serum albumin is a negative acute phase protein with a half-life of 20 days, and pre-Alb is its precursor molecule during hepatic synthesis, with a half-life of 2–4 days; the latter is used as a more sensitive marker of malnutrition. Hepatic Alb production is abruptly reduced during acute phase response and replaced by the production of acute phase proteins (CRP, fibrinogen, macroglobulin) [13]. Moreover, in the immediate postoperative phase, basal energy expenditure increases 5–60 %; and up to 20 % of body proteins are consumed during the first 3 postoperative weeks (most of it within the first 10 days) to favor glyconeogenesis [17]. There is good evidence in the literature that glutamine plays an important role in the protein breakdown process as it serves during the acute phase as a premium fuel for enterocytes and immune system cells [25, 26]. This is the pathophysiological cornerstone in preoperative immunonutrition that aims to prevent visceral and skeletal muscle protein breakdown [3, 7].

C-reactive protein is produced in the liver in response to systemic inflammation or trauma, induced by IL-6, and has opsonizing properties, binding to the surface of dead or dying cells to trigger their destruction via the complement [27]. Serum CPR levels are routinely used to monitor postoperative systemic inflammatory response [28], and seem to be closely related to the extent of surgical trauma [29, 30]. In our study, CRP was found consistently elevated in the immediate postoperative phase, in particular for the ‘major surgical trauma’ subgroups 4–7. Of note, CRP synthesis can be significantly decreased in patients with hepatic insufficiency or after hepatic resection [31].

Lipid metabolism in the immediate postoperative phase is characterized by IL-6-stimulated lipolysis, which is accentuated in the insulin resistance context and results in TG breakdown to FFA and glycerol [13, 32]. As fat is a major fuel for traumatized patients, during the acute posttraumatic phase there seem to be increased plasmatic FFA levels and turnover rates [33]. In our results, we observed a decrease in serum TG levels in the immediate postoperative phase. Thörne et al. [34] have recently demonstrated using the hypertriglyceridemic clamp that postoperative plasma elimination of FFA is up to 2.6 times higher than in the preoperative state. As it has previously been suggested, IL-6 has a strong hypolipidemic effect, with a mean decrease in postoperative cholesterol levels of 9 %, and TG by 31 % [35]. TG levels rapidly decrease even after isolated IL-6 infusion, as clearing of VLDL-TG outweighs their hepatic production [20, 33, 36]. On the contrary, hypertriglyceridemia has been often described as a marker of inflammation in a septic or chronic context, and has been constantly associated to a compromised immune and cardio-respiratory function, and thus worse outcomes [37–40]. In our study, the limited follow-up time of 5 days was selected to depict the metabolic changes due to the intervention itself and to limit the contribution of postoperative complications to the metabolic stress response studied. It can be speculated that a longer follow-up time could allow the apparition of hypertriglyceridemia in case of persistent inflammation.

From a surgical point of view, we differentiated ‘major’ trauma operations, represented by open colectomy, pancreatic, liver, and upper GI resections, from ‘minor trauma’ interventions, such as laparoscopic cholecystectomy, laparoscopic colectomy, and incisional hernia repair; the latter is systematically performed without entering the peritoneal cavity in our institution. Open colectomy has been considered as ‘major,’ even though it can often be relatively atraumatic in lean patients. This is because in our institution most colonic resections were performed by laparoscopy, so laparotomy is reserved for more complicated and extensive resections.

Our results confirm a significant metabolic reaction for the ‘major surgery’ group, with CRP and Alb changes being most representative. There are data in the literature to support our findings. Jansson et al. [30] measured the intraperitoneal cytokine levels after elective surgery, to find that peritoneal values of TNF-alpha and IL-6 are over 100-fold increased compared to systemic ones, suggesting that the extent of peritoneal damage is a major source of the postoperative inflammatory response. This could explain why the incisional hernia repair, an often long-lasting and traumatic operation in the extraperitoneal space, did not present a ‘major’ surgery metabolic profile. The role of laparoscopy in the postoperative stress response has also been studied, and it seems that attenuated inflammatory reaction is due not only to the minimal invasive peritoneal incisions and tissue manipulation, but also to the ‘protective’ role of intraperitoneal carbon dioxide, which seems to inhibit peritoneal TNF-alpha and IL-1 production [18, 29, 41–43].

When analyzing the risk factors associated with postoperative complications, we came across some of the same parameters that demarcate major surgery: operative time and estimated blood loss (EBL) from a surgical point of view and CRP and Alb changes from a metabolic point of view.

This is one of the first studies that associate clinical and metabolic appreciations of major surgery with postoperative outcomes. Han et al. [44] recently studied the differences in surgical stress response and postoperative outcomes between conventional and single-port cholecystectomy. No significant differences were found, given the similar operative characteristics between the two study groups. As we chose to study a wider variety of interventions, we were able to discern a stronger metabolic response for major interventions, which were also correlated with more postoperative complications. This in accordance with Thorell et al. [6] who showed a significant correlation between insulin resistance as marker for post-surgical stress and four different surgical procedures of different magnitude. In this pioneer study the authors were able to demonstrate that insulin resistance was directly correlated to the ‘invasiveness’ of the surgical technique, and this had an impact on the postoperative metabolic derangement and the patients’ length of hospital stay.

One of our study’s major limitations is the small sample size, associated with a considerable heterogeneity of the different surgical groups. As no published data were found on the same subject, a power calculation did not seem reasonable and we decided to run a pilot study, using ten patients per group as a ‘rule of thumb.’ In addition, the parameters chosen to depict the postoperative metabolic profile are far from exhaustive; for example, different cytokines and hormones are known to be affected in the postoperative phase. However, aim of our study was to find commonly used biochemical markers that can be easily reproduced in everyday practice; insulin resistance markers and cytokines are time consuming and expensive parameters that are of little practical use. Also, our study population had some inherent bias, despite the homogeneity in each one of the seven groups studied. At the time of the study, only a small proportion of patients (open and laparoscopic colon resections) was included in ERAS pathways, as liver and pancreatic resections were included only after 2012. Thus, preoperative carbohydrate loading was only administered to these patients, attenuating their metabolic stress response. Epidural analgesia was also administered selectively in open colon, pancreatic, liver, and esophageal resections and this also has been described as an attenuating factor of the postoperative stress response.

In conclusion, magnitude of surgery depends on a complex interplay of demographic and surgical parameters. It is accurately reflected by the metabolic stress response and closely related to clinical outcomes. The immediate serum Alb decrease merits to be explored further as measure for surgical stress and predictor for adverse outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest

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