Laparoscopic cholecystectomy: evaluation of liver function tests

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AIM: *The changes in liver function tests (LFTs) after laparoscopic cholecystectomy (LC) have been described in the literature. The aims of this study are to value the increases of the LFTs and its clinical appearance after LC. Furthermore we studied the correlation of the changes of LFTs with the operative time and the role of elevated BMI.*
MATERIAL OF STUDY: *In the period October 2012 – May 2013, 81 patients undergone to elective LC were analyzed by examining bilirubin, AST, ALT, ALP, GGT at the admission, 1 and 3 days after surgery. Correlations of the length of intervention and BMI with changes of LFTs are evaluated. During surgery, the intrabdominal pressure has been 12 mmHg in all patients. The Student t test, PCC (Pearson's correlation coefficient) OR (odds ratio) were performed to determine statistical significance.*
RESULTS: *The level of (serum) AST, ALT increased significantly during 24-48 hours after LC (p < 0,0001). The increase of (total and direct) bilirubin has not the statistical significance. On the contrary ALP, GGT was significantly decreased (p < 0,001). Three days after surgery LFTs returned to normal level in the patients with previous normal level of tests. The length of intervention doesn't show correlations with changes of LFTs (PCC 0.2). the BMI >28 led increased risk of changes of LFTs (OR 2.44).*
CONCLUSIONS: *The changes of LFTs are transient and clinically silent in patients with a normal liver function. Nevertheless must be evaluated preoperative BMI and liver dysfunction.*

KEY WORDS: Laparoscopic cholecystectomy, Liver function tests

Introduction and Aim

Laparoscopic cholecystectomy (LC) is the gold standard treatment of symptomatic gallstones. Despite its numerous advantages (shorter hospital stay, limited postoperative pain, better cosmetic results [1,2]) this procedure may impair, in many patients, the liver function tests (LFTs). The observation of postoperative changes in the level of LFTs after open cholecystectomy (OC) has been reported in the literature [3,4]. The changes in LFTs after LC were first studied by Halevy [5] in 1994, who demonstrated an increase of up to 70% with no adverse clinical outcome. Since then, many studies have been conducted to evaluate these changes and to understand their cause. Changes in postoperative LFTs reflect hemodynamic disturbance in hepatic and abdominal viscera blood flow and anesthetic hepatotoxicity. The aims of this study are to value the increases of the LFTs and its clinical appearance after LC. On the other hand we have studied the correlation of the changes of LFTs with the operative time and the role of elevated BMI.

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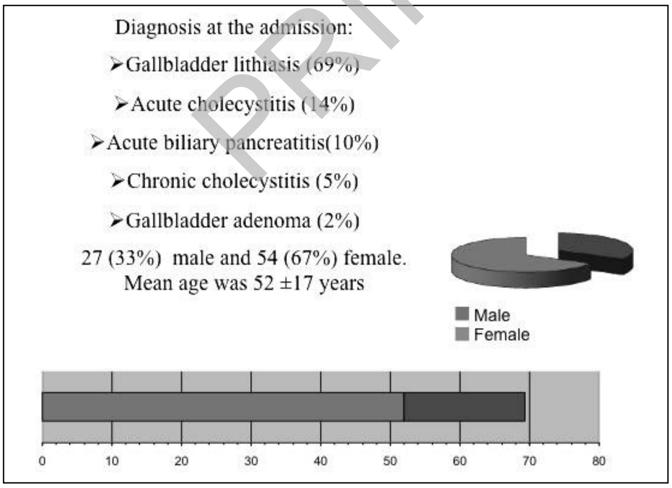
Patients and Methods

We studied 84 patients underwent LC in the period from October 2012 to May 2013. The exclusion criteria were the conversion to OC (3/84), liver cirrhosis, and patients with ASA grade III or more. Local ethics commitee approval was obtained.
Eighty-one patients were included in the study: 27 (33%) were male and 54 (67%) were female; mean age was 52 ± 17 years. The admission diagnosis were: gallbladder lithiasis (69%), acute cholecystitis (14%), acute biliary pancreatitis (10%), chronic cholecystitis (5%), gallbladder adenoma (2%) (Table I). Within this group (81 patients) were included 69 patients (86%) with normal preoperative LFTs, but there were also 12 patients (14%) with mildly raised LFTs due to simple hepatic steatotis [6].
LC was performed under general anesthesia, with a standardized anesthetic procedure. The same class of anesthetic agents were used for all patients, but their dosages were individually titrated. All the patients were intubated nasograstically. Laparoscopic operations were performed by the same surgical team, using four trocars, with patients in reverse Trendelemburg's position.
Pneumoperitoneum is created, according to Hasson's technique, insufflating the abdomen with CO_2 to a maximum pressure of 12 mmHg. Dissection of the gallbladder from the liver was performer with the use of monopolar diathermy to avoid hepatic enzyme alterations of iatrogenic origin. No patients had intraoperative manipulations of the biliary tract such as intraoperative cholangiography.
Intraoperative arterial blood pressure, oxygen saturation and pulse rates of patients was closely monitored. No haemodynamic alterations were noted during LC.
Postoperatively, all patients were given the same intravenous glucose infusions and electrolytes for the first 24 hours. Short-term antibiotic therapy in simple gallbladder lithiasis, further antibiotics for two days (ceftazidime) in acute cholecystitis and acute biliary pancreatitis. It was given diclophenac sodium for postoperative pain control. Subhepatic abdominal drain was used in all cases and removed after 24 hours.
LFTs evaluated were: bilirubin, total (BT) and direct (BD), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transpeptidase (GGT), alkaline phosphatase (ALP). The controls have been made before, 24 hours and 3 days after surgery.
Biochemical analyses for these tests were done using the same analyzer. The accepted normal values for LFTs were: BT 0,2-1,2 mg/dl, BD 0,2-0,3 mg/dl, AST 2-40 iU/l, ALT 2-40 iU/l, GGT 7-42 iU/l, ALP 38-126 iU/l.

TABLE I - *81 LC – Admission diagnosis. Demographic data.*



Statistical analyses

– The mean and the standard deviation of the collection data were collected.
– The student t test is performed to value the statistical significance of the changes of LFTs; a p value less than 0,001 was considered statistically significant.
– Pearson's correlation coefficient (PCC) is used to evaluate the correlation between changes of LFTs and operative time. Odds ratio performer to demonstrate if a BMI > 28 can be a risk factor for a postoperative increase of LFTs.

Results

The first outcomes concern the general morbidity and mortality (Table II): there are no data considerable.
The following data show, the percentage of patients, in which we obtained an alteration of each LFTs, between before and at 24 hours after surgery. First of all into the entire cohort of 81 patients there are the correlations of the results between pre and postoperative (24 hours) evaluation. The statistical study of the changes of LFTs after 24 hours show that the increase of total and direct bilirubin is not statistical significant; on the contrary the increase of AST and ALT is significant ($p<0,001$); the decrease of ALP and GGT is significant ($p<0,001$).

TABLE II - *81 LC: Overall morbidity.*

	81 Patients
Surgery Time (Minutes)	85
Hospital Stay (Days)	3.2
Operative Site Infections	1 (1.2%)
Pulmonary Infections	2 (2.4%)
Bile Leackege By Cystic Duct	-
Injury Of Biliary Duct	-
Late Incisional Hernia On Umbelical Port-Site	2 (2.4%)
Mortality	-

Table III - *81 LC. statistical analysis (T student test) of the changes in LFTs 24 h after LC.*

	MEDIA	STANDARD DEVIATION	DIFFERENCE	VARIATION
BIL TOT PRE	0,86	± 0,36	0,24	+ 28,35%
BIL TOT POST	1,11	± 0,65		
BIL DIR PRE	0,18	± 0,10	0,03	+ 18,98%
BIL DIR POST	0,21	± 0,13		
GOT / AST PRE	25,59	± 14,89	16,11	+ 62,95%
GOT / AST POST	41,70	± 34,40		
GPT / ALT PRE	34,74	± 31,15	15,73	+ 45,27%
GPT / ALT POST	50,47	± 42,07		
ALP PRE	73,58	± 29,90	-11,37	- 15,45%
ALP POST	62,21	± 25,99		
GGT PRE	60,80	± 63,02	-4,86	- 8,00%
GGT POST	55,94	± 57,91		

In the table III the details of the statistical study by t Student test (p<0,001) about the changes of LFTs 24 hours after LC. We have also evaluated how great were the changes of LFTs (Table IV).

On the whole the size of the changes of LFTs in the immediate postoperative period was remarkable.

In particular the increase of 100% or more of the transaminase regards more of 50% of the patients. We have also evaluated the changes of LFTs 24 hours after LC based on the operative time.

Our conclusion was that operative time doesn't show correlations with changes of LFTs (Pearson correlation coefficient r=0,2) (Table V). On the other hands we have studied the changes of LFTs 24 hours after LC based on BMI. In the patients with BMI <28 the average increases of LFTs were 12,71% and the median increases were 10,63%. On the contrary in the patients with BMI >28 the average increases of LFTs were 26,71% and the median increases were 25,40%.

In conclusion the BMI > 28 led increased risk of changes of LTFs. In these patients in fact the Odds ratio (OR) was 2,44. The relative risk (RR) was 1.26 (Table VI). Very interesting is the control of the changes of LFTs 3 days after LC. Our results show that in 69 patients (previous normal LFTs) (86%) the LFTs returned to normal level. At this delayed control (3 days after LC), 12 patients (14%) (previous LFTs alterations due to simple hepatic steatosis) show the persistent alterations of LFTs

Table IV - *81 LC. The size of the changes in LFTs 24 h after LC.*

	DECREASES	INCREASES <50%	INCREASES BETWEEN 50%-100%	INCREASES > 100%	INCREASES >200%
Bil. Tot	17 (20,99%)	37 (45,68%)	12 (14,81%)	14 (17,28%)	2 (2,47%)
Bil. Dir.	22 (27,16%)	14 (17,28%)	14 (17,28%)	26 (32,10%)	2 (2,47%)
AST	16 (19,75%)	20 (24,69%)	21 (25,93%)	11 (13,58%)	12 (14,81%)
ALT	22 (27,16%)	18 (22,22%)	12 (14,81%)	18 (22,22%)	10 (12,35%)
ALP	63 (77,78%)	16 (19,75%)	0 (0,00%)	2 (2,47%)	0 (0,00%)
GammaGT	53 (65,43%)	16 (19,75%)	3 (3,70%)	4 (4,94%)	5 (6,17%)

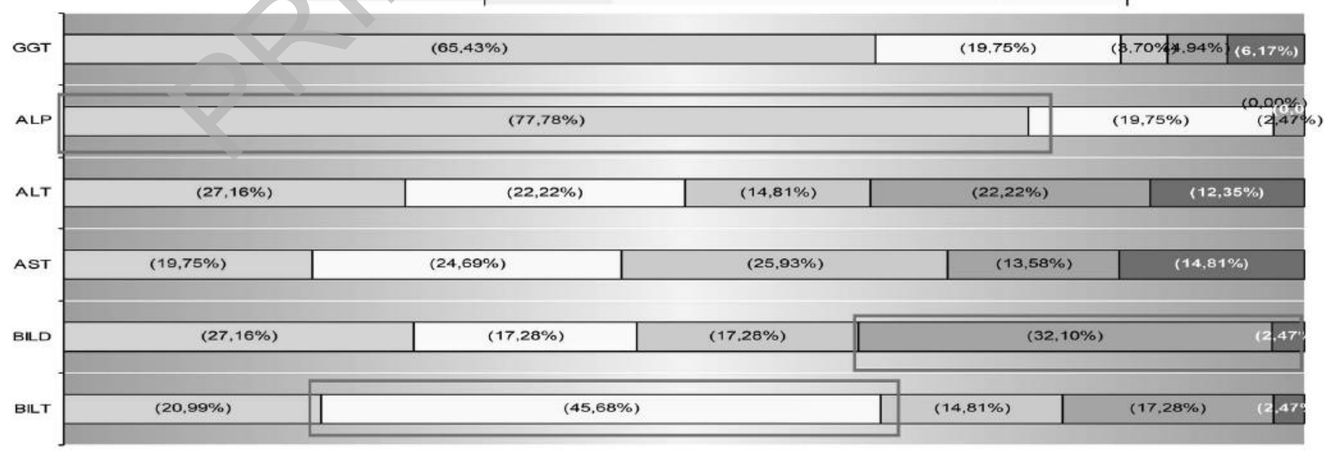


TABLE V - *81 LC. Changes in LFTs 24 h after LC based on operative time (PCC r=0,2).*

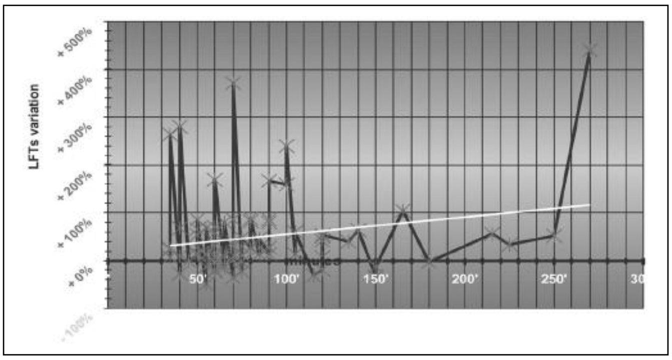
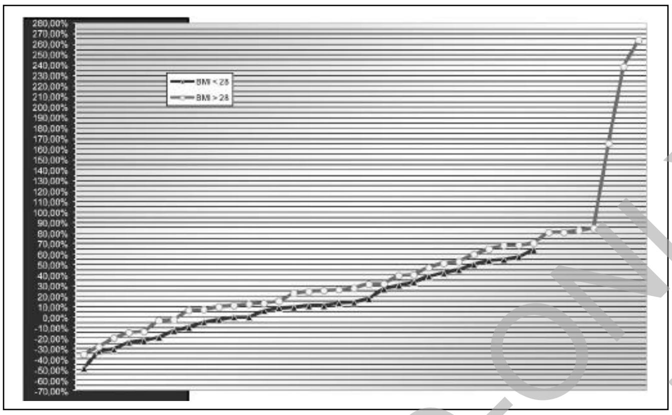


TABLE VI - 81 LC. Changes in LFTs 24 h after LC based on BMI: OR 2.44 – RR 1.26.



without further increase. These 12 patients before LC had increased BT, BD (5 patients) and transaminases (7 patients); one or more tests were altered in many patients (Table VII). In the table VIII the detailed persistent postoperative increases for each liver test in these 12 patients have been reported. In many patients one or more tests were altered. A deep evaluation of a clinical and instrumental study of these patients shows another clinical feature: 8 patients with elevated BMI (> 28). Moreover 2 of these patients had at the admission acute cholecystitis. At the postoperative control in these 12 patients there were not the changes in the clinical conditions or further signs of hepatic disease.

Discussion

In an attempt to evaluate and to study the effects during LC of increased intrabdominal pressure and reduced splancnic and hepatic blood flow many studies were conducted to detect and to study the changes in LFTs. The most sensitive function tests among the liver test to detect organ damage are the transaminases enzymes.

TABLE VII - *Alterations of LFTs in 12 patients (14%) before LC.*

Total direct bilirubin	5 patients
ALT	4 patients
AST	3 patients
ALP	1 patient
GGT	5 patients

TABLE VIII - *Persistent alterations of LFTs in 12 patients (14%) 3 days after LC.*

Total bilirubin	7 patients (8.6%)
Direct bilirubin	4 patients (4.9%)
ALT	8 patients (9.8%)
AST	7 patients (8.6%)
ALP	3 patients (3.7%)
GGT	6 patients (7.4%)

Alanine transaminase (ALT) rises dramatically in acute liver damage. Aspartate transaminase (AST) is associated with liver parenchymal cells and it rises in acute liver damage. Transaminases are enzymes located in the hepatocytes and are markers of hepatocellular diseases. Injury to cellular membrane allows these enzymes to leave the liver cells, with quick increases in serum after liver damage. AST is also present in red blood cells, cardiac and skeletal muscle and is less specific to the liver dysfunction[7]. Alkaline phosphates (ALP) is an enzyme in cell's lining the bile ducts; it rises with bile duct distruction. Bilirubin is a product of heme created from the blood by taking the bilirubin into hepatocytes, becomes conjugated and is secreted into the bile [8]. Gamma-glutamyltransferase (GGT) is another enzyme that occurs in liver cells. This is very sensitive and can raise by alcohol abuse or drugs. This has a low specificity. Elevated serum GGT activity can be found in diseases of the liver, biliary system, pancreas, etc.

The changes of LFTs after LC require some explanations: first, whether the changes are constant or only one exception; also to determine what is the explication of the phenomenon and finally what is the clinical significance of these changes. Although the postoperative changes in LFTs has been described in the past [3,4] after OC, clinical implications have not been considered. After worldwide employment of LC these observations have been studied and proposed as clinical problem.

The changes in LFTs after LC are a rule and are connected with laparoscopic approach. There are a lot of confirmations by the literature [9-16]. Nevertheless, in the literature there are conflicting data on this issue. Bickel et Al.[17], in contrary to previously published data, had validated, based in their experiences and evaluations, that the induction of CO_2 pneumoperitoneum does not cause increased LFTs. The increase of the intrabdominal pressure during CO_2 pneumoperitoneum for surgical procedures such as LC does not affect significantly hepatic metabolism. Moreover LFTs are not a sensitive parameters to reflect minor hepatic damage due to ischemia/reperfusion during pneumoperitoneum. It is also possible to presume that routine examination of LFT has no predictive value. Following these considerations has been also proposed that the increase of LFTs after LC may be not associated with any deleterious effect and, in absence of clinical indications the preoperative evaluation of liver function is unnecessary [10]. These communications are not confirmed in the literature.

There are also the comparative studies between laparoscopic and open surgery regarding effect of the intervention on the LFTs [9]. The surgical procedures that can cause disorder in the liver function tests, there are in both procedures: open and laparoscopic. Organ manipulation, traction, compression, retraction on the liver during open cholecystectomy; high pressure pneumoperitoneum but minor surgical trauma during the intervention with laparoscopic approach. The comparison of postoperative changes of LFTs between laparoscopic and open cholecystectomy has shown a increase statistically significant in the patients undergone to laparoscopic approach. ALT had doubled in the first 48 hours from the preoperative mean in 58,2% in LC patients versus only 6.3% in the OC group [14]. This study confirms these results. In our experience the increases of the transaminases after LC were more than 50% in majority of the patients. In the cohort of Hasukic [12] a higher number of patients had increased values of ALT and AST in LC group compared to OC group: the difference was statistically significant.

An isolated elevation of only one test result should raise suspicion that a source other than liver is the cause. Therefore it seems to be more opportune to use a series of liver tests to gain high specificity especially to give the changes to liver damage during surgical procedures. The connection of changes in LFTs with laparoscopic approach has had some confirmations by the literature [9,18]. We can try to explain this event.

There are two conditions that can cause the alterations of LFTs: the increased intraperitoneal pressure and the use of CO_2 to induce pneunoperitoneum.

Pneumoperitoneum induces hepatic hypoperfusion. The normal portal blood pressure arise 8 mmHg, but the intrabdominal pressure employed in laparoscopy can arise 15 mmHg (high pressure pneumoperitoneum). The increased intrabdominal pressure could reduce portal flow and cause alteration in liver function. Hepatic arterial buffer response [19] is the unique autoregolatory mechanism of hepatic perfusion.

Pneumoperitoneum causes a reduction of portal venous inflow, marked decrease in total liver perfusion, inadequate oxygen supply with the consequence of hepatocellular injury. This phenomenon is not compensate by hepatic arterial blood flow [20]. This hepatocellular ischemic injury, due to increased abdominal pressure, can explain the elevation of AST and ALT, liver tests that were more changed. Also the anesthesia procedures/drugs employed can induce hepatic hypoperfusion. Moreover CO_2 employed to induce the pneumoperitoneum has the vasoconstrictive effect can reduce visceral blood flow [21]. Finally we have to consider the role of the entity of intrabdominal pressures. The intrabdominal pressures of 15-20 mmHg reduces blood flow to the viscera but overall the portal venous flow. There is a connection between the intrabdominal pressure and reduction of portal venous flow: more pression causes more reduction of blood flow. A selective setting of intrabdominal pressure during laparoscopic surgery is advisable. In our experience the intrabdominal pressure is fixed to 12 mmHg in all patients but this choice should be strictly considered in patients with compromised liver function.

The clinical significance of the changes of LFTs after LC can be another point of discussion. The changes of the liver tests after LC are transient with the swift return to normal level within few days in the patients with normal liver functions. In our experience in 86% of the patients (69/81) the LFTs returned to normal level at the control 3 days after surgery. All these patients had normal LFTs at the admission and BMI <28. Moreover they have not shown any clinical manifestation. Therefore these changes are clinically silent in patients with a normal liver function [14].

The time of intervention could be considered as relevant factor to cause the increase of LFTs. In this regard our study surely shows that the operative time (range between 45' and 270') doesn't have correlation with changes of LFTs (PCC r = 0,2). On the contrary the BMI can be a risk factor for the postoperative changes of LFTs. In our experience the patients with BMI > 28 have had major increases of liver tests compared to patients with BMI < 28 (OR = 2.44 – RR = 1.26). These results can be explicated by the major intrabdominal pressure (>12 mmHg) necessary to obtain and maintain the CO_2 pneumoperitoneum because the weight of the abdominal wall in obese patients.

The last point of discussion is about the changes of LFTs post LC in the patients with previous altered liver tests due to hepatic steatosis and with BMI > 28. In our experience 12 patients (14%) had, at the admission in the hospital, altered liver tests (table VI). In these patients we diagnosed hepatic steatosis and elevated (>28) BMI. The control at 3 days after LC has shown persistent alterations of LFTs, but no patient had changes of the clinical condition or further signs of hepatic disease. Therefore in the patients with previous liver dysfunction the changes of LFTs can be persistent, with a slow return to the values prior to surgery, but without changes of clinical conditions: in fact laparoscopic approach is the best choice also for cirrhotic patients. In these patients a low pressure pneumoperitoneum should be preferred.

Conclusions

In conclusion the routinely control of the liver tests prior to the LC must be considered strictly necessary for the detection of hepatobiliary diseases that can be present also without or with mild clinical expression: hepatic dysfunctions, cirrhosis, biliary stones, inflammatory or neoplastic strictures, ecc. In summary it should be present another hepatobiliary disease besides gallbladder lithiasis. Usually in the patients with preoperative normal liver functions, the changes of LFTs are transient and clinically silent. In the patients with simple hepatic steatosis, BMI > 28 and altered preoperative raised LFTs, the postoperative changes are more evident but however without changes of clinical conditions. In these patients it is advisable to use lower pneumoperitoneum pressures (no more than 12 mmHg).

Riassunto

Le modificazioni dei test di funzionalità epatica (LFTs) dopo colecistectomia laparoscopica (LC) sono state descritte in letteratura. Gli obiettivi di questo studio sono: verificare e valutare quantitativamente gli incrementi dei test di funzionalità epatica dopo LC; studiare la correlazione delle variazioni dei tests con il tempo operatorio e il ruolo del BMI elevato. Nel periodo ottobre 2012 - maggio 2013, 81 pazienti sottoposti a LC elettiva sono stati analizzati esaminando bilirubina, AST, ALT, ALT, G-GT al ricovero, uno e tre giorni dopo l'intervento chirurgico. Con l'intervento chirurgico laparoscopico, la pressione intra-addominale è stata 12 mmHg in tutti i pazienti. Il test t di Student, PCC (r di Pearson), OR (odd ratio) sono stati utilizzati per determinare la significatività statistica di tutte le variazioni dei tests. I livelli sierici di AST e ALT sono aumentati significativamente 24 ore dopo LC ($p < 0{,}0001$). L'aumento della bilirubina (totale e diretta) non ha significatività statistica. Al contrario ALP e G-GT sono diminuiti significativamente ($p < 0{,}001$). Tre giorni dopo l'intervento i tests di funzionalità epatica sono tornati al livello normale nell'86% dei pazienti. Al contrario 12 pazienti (14%),8 dei quali con BMI >28, al controllo 3 giorni dopo la colecistectomia, con LFTs alterati prima dell'intervento per semplice steatosi epatica, mostravano persistenti alterazioni dei tests senza modificazioni delle condizioni cliniche o ulteriori segni di malattia epatica. La durata dell'intervento non ha mostrato correlazione con i cambiamenti dei tests di funzionalità epatica (PCC 0.2). Mentre il BMI> 28 ha comportato un aumento del rischio di alterazione dei test di funzionalità epatica (OR 2.44). In conclusione i cambiamenti dei tests di funzionalità epatica sono transitori e clinicamente silenti nei pazienti con funzionalità epatica normale. Tuttavia è opportuna la valutazione preoperatoria del BMI e delle disfunzioni epatiche anche di modesta entità.

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