

Change in Liver Function Tests After Liver Mobilization for Gynecologic Cancers; Does Metastasectomy Affect the Course?

Jinekolojik Kanserlerde Karaciğer Mobilizasyonu Sonrası Karaciğer Fonksiyon Testlerindeki Değişim; Metastazektomi Seyri Etkiler mi?

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ABSTRACT

Aim: Evaluate the fluctuation of aminotransferase levels after liver mobilization for gynecologic cancers and determine the effect of liver metastasectomy on this change.

Materials and Methods: We retrospectively evaluate the patients who underwent liver mobilization for gynecologic cancers from 09/2019 to 10/2022. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin serum levels were monitored.

Results: 69 patients were enrolled in the study. Liver function tests (LFTs) immediately tended to increase following surgery. ALT levels peaked at the postoperative 6 th hour (median: 119.5 U/L; range: 13-762) and AST peaked in the 2 nd hour after the surgery (median: 204 U/L; range: 11-717). Both ALT and AST tended to normalize on the 6 th postoperative day (24/28 U/L). Liver tumor resection was performed on 26 patients. Liver metastasectomy caused high both AST and ALT levels ($p=0.013$ and $p=0.022$, respectively) on the 2 nd postoperative day. This effect continued especially in ALT from the 2 nd day to the 10 th postoperative day. Subsequently, both groups became similar. Liver metastasectomy caused higher AST and ALT on the 2 nd postoperative day compared with the non-metastasectomy group.

Conclusion: Both liver mobilization and liver metastasectomy procedures are associated with a transient increase in LFTs. Although liver mobilization in itself causes high LFTs in the immediate postoperative period, this effect is more significant in liver metastasectomy. High LFTs returned to normal values within 2 weeks in both two groups. Fluid replacement and avoidance of hepatotoxic drugs can prevent the aggravation of the clinical course.

Keywords: Liver mobilization, liver metastasectomy, liver function tests, ovarian cancer

ÖZ

Amaç: Jinekolojik kanserler nedeniyle yapılan karaciğer mobilizasyonu sonrası aminotransferaz düzeylerindeki dalgalanmaları değerlendirmek ve karaciğer metastazektomisinin bu değişim üzerindeki etkisini belirlemek.

Gereç ve Yöntemler: 09/2019 ile 10/2022 tarihleri arasında jinekolojik kanserler nedeniyle karaciğer mobilizasyonu uygulanan hastalar retrospektif olarak değerlendirildi. Alanin aminotransferaz (ALT), aspartat aminotransferaz (AST) ve bilirubin serum düzeyleri ölçüldü.

Bulgular: Çalışmaya 69 hasta dahil edildi. Karaciğer fonksiyon testleri (KCFT) ameliyat sonrasında hemen yükselme eğilimindeydi. ALT düzeyleri ameliyat sonrası 6. saatte (medyan: 119.5 U/L; aralık: 13-762) ve AST düzeyleri 2. saatte en yüksek seviyeye ulaştı (medyan: 204 U/L; aralık: 11-717). ALT ve AST düzeyleri postoperatif 6. günde normale dönme eğilimindeydi (24/28 U/L). 26 hastaya karaciğerden metastazektomi yapıldı. Karaciğer metastazektomisi, postoperatif 2. günde hem AST hem de ALT düzeylerinde yüksekliğe neden oldu (sırasıyla $p=0.013$ ve $p=0.022$). Bu etki özellikle ALT düzeyinde postoperatif 2. günden 10. güne kadar devam etti. Takip eden süreçte her iki grup benzer hale geldi. Karaciğer metastazektomisi, metastazektomi uygulanmayan grupla karşılaştırıldığında postoperatif 2. günde daha yüksek AST ve ALT düzeylerine yol açtı.

Sonuç: Karaciğer mobilizasyonu ve karaciğer metastazektomisi işlemleri geçici KCFT artışı ile ilişkilidir. Karaciğer mobilizasyonu tek başına erken postoperatif dönemde KCFT yüksekliğine yol açsa da, bu etki metastazektomi yapılan hastalarda daha belirgindir. Her iki grupta da KCFT değerleri 2 hafta içinde normale dönmektedir. Sıvı replasmanı ve hepatotoksik ilaçlardan kaçınılması, klinik seyrin kötüleşmesini önleyebilir.

Anahtar Kelimeler: Karaciğer mobilizasyonu, karaciğer metastazektomi, karaciğer fonksiyon testleri, over kanseri

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INTRODUCTION

Liver mobilization, which is used in right upper quadrant surgeries, liver metastasectomy, diaphragm stripping, and full-thickness resection provides adequate exposure for surgical resection. Diaphragm metastases, especially to the right diaphragm because of the anticlockwise direction of peritoneal fluid flow, are common in epithelial ovarian cancer (EOC) [1]. Eisenkop et al. suggested that up to 40% of patients with EOC present with bulky metastatic disease to the diaphragm and resectability of the tumor can be one of the major obstacles to achieving optimal cytoreductive surgery (CRS) with <1 cm visible tumor after surgery [2]. Previous reports showed that resection of these implants improved the survival of patients with advanced ovarian cancer [3].

In this procedure, freeing the ligaments and peritoneal attachment of the liver may cause a transient increase in liver function tests (LFTs). Liver cell damage markers (liver fatty acid-binding protein, arginase-1, glutathione-s-transferase-a and cell-free circulating albumin mRNA) increase significantly during mobilization of the liver [4, 5]. However, relevant clinical results are not defined clearly in studies. Although elevated enzyme levels may be asymptomatic, progression to liver failure is also observed. In relevant studies, high levels of LFTs tend to normalize in 1 week. Patient-dependent factors may further worsen the clinical course [6, 7].

Our study's primary endpoint was to define the fluctuation of aminotransferase levels in liver mobilization. The secondary endpoint was to determine the effect of liver metastasectomy on this change.

MATERIALS AND METHODS

Sixty-nine patients who underwent liver mobilization during CRS for gynecologic cancer at our institution from September 2019 to October 2022 were enrolled in the study. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy and systematic lymphadenectomy were performed as standard surgical procedures. In addition, extensive surgical procedures requiring liver mobilization including unilateral/bilateral diaphragm stripping, diaphragm full-thickness resection, cardiophrenic lymph node dissection, tumor resection at the porta hepatis, liver parenchyma, or capsular metastasectomy were performed to achieve non-residue tumors at the end of CRS. To mobilize the liver, the ligamentum teres was divided. The anterior right coronary ligament was dissected by protecting the inferior vena cava and distal right hepatic vein. Then, the right hepatic lobe was mobilized medially. All surgical procedures were performed by gynecologic

oncologists. The study was approved by the Non-Interventional Clinical Research Institutional Review Board. Informed consent was received from all patients before surgery to use their medical data in medical research.

All patients were followed up in the postoperative intensive care unit and administered antibiotic therapy, paracetamol, and non-steroid anti-inflammatory drugs for pain palliation as routine clinical practice. Complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, and indirect bilirubin serum levels were monitored at the postoperative 2nd and 6th hours and daily thereafter from the first postoperative day to discharge. Normal reference ranges were used as <35 U/L AST, and <50 ALT U/L. Preoperative blood tests were performed at least 1 week before the surgery.

The demographic characteristics of the patients were retrospectively retrieved from the electronic medical record system and the patients' files. Surgical notes were used to determine whether liver tumor resection was performed.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 25.0 software package (IBM SPSS Inc, Chicago, IL, USA). Descriptive statistics are expressed as median (min-max) for continuous variables and number/percentage for categorical variables. The ANOVA Table Test was used for continuous parameters. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of the study group was 58.3±10.67 (range; 27-79) years. Of all 69 patients, 54 (78.2%) had ovarian cancer, 14 (20.2%) had endometrium cancer, and one (1.4 %) had extragenital malignancy. Forty-seven patients underwent primary CRS, 18 patients underwent interval CRS, and four patients underwent secondary CRS. Forty-seven patients had co-morbidities. Clinicopathologic features are detailed in Table 1.

Preoperative ALT values were above the upper reference limit (median: 21.5 U/L; range: 8-89) in 10.6% of total patients, and AST values were normal (median: 19 U/L; range: 2-47) in the entire study group. LFTs immediately tended to increase following surgery. Both ALT and AST serum levels tended to normalize on the 6th postoperative day (24/28 U/L). On the 6th postoperative day, only 26.1% of patients had ALT and 18.8% of patients had AST values above the upper reference limit. Serum levels AST increased in 95.5% of the patients in the 2nd hour after the surgery and this

Table 1. Clinical features

Clinical Features		Mean $\pm$ SD	Median (Range)
Age		58.3 $\pm$ 10.67	59 (27-79)
Size of liver tumor metastasectomy (cm)		2.6 $\pm$ 2.27	2 (1-12)
		n	%
Liver tumor metastasectomy	Not performed	43	62.3
	Performed	26	37.7
Co-morbidities	Absent	22	31.9
	Present	47	68.1
Primary site	Ovary	54	78.3
	Endometrium	14	20.3
	Extra-genital	1	1.4
Surgical procedure	Primary cytoreduction	47	68.1
	Interval cytoreduction after NACT	18	26.1
	Secondary cytoreduction	4	5.8

SD: Standard Deviation

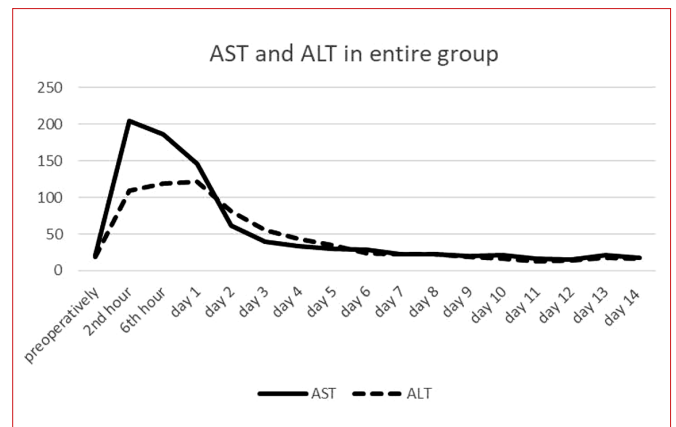
NACT: Neoadjuvant chemotherapy

Table 2. The values for postoperative LFTs in entire cohort

Time Mean $\pm$ SD		AST (U/L)			ALT (U/L)		
		Median (Range)	Above the reference value (%) ¹	Mean $\pm$ SD	Median (Range)	Above the reference value (%) ²	Mean $\pm$ SD
Preoperatively		24.6 $\pm$ 12.33	21.5 (8-89)	10.6	20.6 $\pm$ 9.25	19 (2-47)	0
Postoperatively	2 nd hour	232 $\pm$ 165.27	204 (11-717)	95.5	156.1 $\pm$ 140.39	109 (6-702))	85.1
	6 th hour	240 $\pm$ 212.42	186.5 (24-1261)	96.4	177.6 $\pm$ 163.51	119.5 (13-762)	89.3
	Day 1	227.1 $\pm$ 338.33	146 (19-2562)	94	162.1 $\pm$ 167.59	122 (10-1031)	80.6
	Day 2	243.6 $\pm$ 695.85	61 (12-4007)	100	202.4 $\pm$ 527.76	81 (8-3234)	60
	Day 3	246.9 $\pm$ 1242.62	40 (8-3210)	60.7	137.8 $\pm$ 392.23	56 (8-3234)	54.1
	Day 4	219.1 $\pm$ 1248.36	33 (4-9615)	47.8	124.8 $\pm$ 394.36	43 (4-2859)	30.4
	Day 5	44.1 $\pm$ 50.30	30 (5-283)	42.1	62.1 $\pm$ 100.34	35 (7-590)	35.1
	Day 6	35 $\pm$ 23.51	28 (10-114)	26.1	49.6 $\pm$ 67.48	24 (2-349)	18.8
	Day 7	26.9 $\pm$ 18.47	22 (7-90)	8.7	45.2 $\pm$ 57.81	22 (7-252)	10.1
	Day 8	25.7 $\pm$ 14.59	22.5 (9-65)	8.7	35.5 $\pm$ 39.74	22 (4-174)	8.7
	Day 9	25.1 $\pm$ 13.69	20.5 (10-58)	7.2	35 $\pm$ 37.42	19 (5-125)	7.2
	Day 10	23.2 $\pm$ 12.69	21 (9-48)	2.9	30.1 $\pm$ 33.22	16 (6-104)	4.3
	Day 11	20.3 $\pm$ 10.94	16 (8-53))	1.4	20.9 $\pm$ 19.03	13 (5-64)	2.9
	Day 12	18.5 $\pm$ 9.21	15 (9-40)	1.4	14 $\pm$ 5.53	14 (7-23)	0
	Day 13	21.3 $\pm$ 11.00	21 (5-48)	1.4	21.6 $\pm$ 20.87	17 (4-81)	1.4
	Day 14	19.7 $\pm$ 10.78	17 (5-44)	1.4	15.7 $\pm$ 9.72	16 (4-35)	0

¹: The reference limit of AST <35 U/L²: The reference limit of ALT <50 U/L

rate increased to 100% on the 2nd postoperative day. AST levels peaked in the 2nd hour after the surgery (median: 204 U/L; range: 11-717) and decreased gradually by the following period. AST levels normalized 98.6% of all patients on the 11th postoperative day. Similar to AST, ALT values rose in 85.1% of the study group in the 2nd hour after the surgery. ALT levels peaked at the postoperative 6th hour (median: 119.5 U/L; range: 13-762) and gradually decreased in the following days. The highest value of ALT (median: 122 U/L; range: 10-1031) on the postoperative 1st day tended to decrease from the 2nd postoperative day and regressed to the normal level in all patients on the 12th day. The transient increase was observed in only 1.4% of the total study group on the 14th postoperative day;

**Figure 1.** The fluctuation of ALT and AST after liver mobilization

ALT values normalized in all patients (Table 2) (Figure 1). Multiorgan failure was observed in only one patient. We performed Morrison's pouch stripping, bilateral diaphragm stripping, and liver parenchyma metastasectomy in addition to standard staging surgery. The tumor removed from the liver in this patient was 1x0.3x0.3 cm. Maximal cytoreduction was achieved (no visible tumor after surgery) in this case. Although the first two postoperative days the laboratory tests are normal; the LFTs began to rise (creatinine: 1.11 mg/dL, ALT: 3234 U/L, AST: 3210 U/L, total bilirubin: 2.7 mg/dL, direct bilirubin: 1.8 mg/dL, INR: 5.5) on the 3rd postoperative day. Hepatotoxic drugs were avoided and adequate fluid replacement was administered. The

patient was followed in the intensive care unit. Multiorgan failure developed on the postoperative 3rd day and the patient died on the postoperative 4th day. Bilirubin values were normal in the total study group except for this patient.

Liver tumor resection was performed on 26 patients. The median tumor size was 2 (range 1-12) cm. It was statistically significant that liver metastasectomy caused high both AST and ALT levels ($p=0.013$ and $p=0.022$, respectively) on the 2nd postoperative day. This effect continued especially in ALT from the 2nd day to the 10th postoperative day. Subsequently, both groups became similar (Table 3) (Figure 2 and Figure 3).

Tablo 3. The values for postoperative LFTs in liver metastasectomy group

Time		Enzyme	Tumor Resection Group		Non Tumor Resection Group		P value
			Mean±SD	Median (Range)	Mean±SD	Median (Range)	
Preoperatively		AST	25.6±14.84	21.5 (8-89)	23.1±6.93	21.5 (13-39))	0.430
		ALT	21.3±6.58	20 (2-47)	19.5±8.78	18 (6-40)	0.434
Postoperatively	2 nd hour	AST	224±165.84	186 (19-717)	244.7±166.83	212 (11-661)	0.620
		ALT	139.6±107.40	107 (13-423)	182.1±180.10	115 (6-702)	0.230
	6 th hour	AST	229.6±236.37	173 (24-1261)	254±179.54	212.5 (42-752))	0.674
		ALT	173.3±164.29	109 (13-762)	183.3±165.82	131.5 (16-694)	0.824
	Day 1	AST	177±169.16	135 (19-882)	306.2±495.77	153 (27-2562)	0.129
		ALT	136.4±107.88	113 (10-477)	202.6±229.65	131 (13-1031)	0.116
	Day 2	AST	75.9±66.86	56 (12-396)	512±1077.97	87 (13-4007)	0.013
		ALT	85±64.95	74 (9-275))	390.3±822.26	95 (8-3234)	0.022
	Day 3	AST	42.5±26.60	38.5 (8-160)	636.2±2094.81	48 (10-9615)	0.076
		ALT	58.9±41.97	45 (8-173)	288.2±649.54	73 (12-2859)	0.029
	Day 4	AST	40.9±44.01	27 (4-257)	498.1±1993.0	42 (10-9615)	0.042
		ALT	41.8±30.08	36 (4-149)	254.7±616.18	56 (6-2859)	0.172
	Day 5	AST	41.5±45.52	29.5 (5-257)	48.5±58.54	32 (8-283)	0.619
		ALT	41.1±29.47	33 (7-133)	98±156.57	40 (9-590)	0.037
	Day 6	AST	35.3±26.06	28 (10-114)	34.4±18.68	28 (18-78)	0.897
		ALT	35.6±28.86	24 (2-116)	75.1±103.64	24 (9-349)	0.051
	Day 7	AST	25.4±20.34	25 (7-90)	28.7±16.48	19.5 (14-58)	0.622
		ALT	27.1±25.19	18 (7-110)	67.1±77.38	32 (7-252)	0.054
	Day 8	AST	23.5±12.161	23 (9-53)	28.62±17.35	22 (11-65)	0.353
		ALT	22.9±18.65	15.5 (4-71)	53±53.71	28 (10-174)	0.035
	Day 9	AST	21.5±11.43	18 (10-42)	30.2±15.64	25 (11-58)	0.144
		ALT	19.9±21.94	15 (5-88)	55±45.24	28 (6-125)	0.029
	Day 10	AST	19.1±10.38	17 (10-39)	27.8±14.44	24.5 (9-48)	0.234
		ALT	13.9±6.74	15 (6-23)	49±42.38	43 (7-104)	0.052
	Day 11	AST	18±7.31	16 (8-29)	23.7±15.04	17 (14-53)	0.344

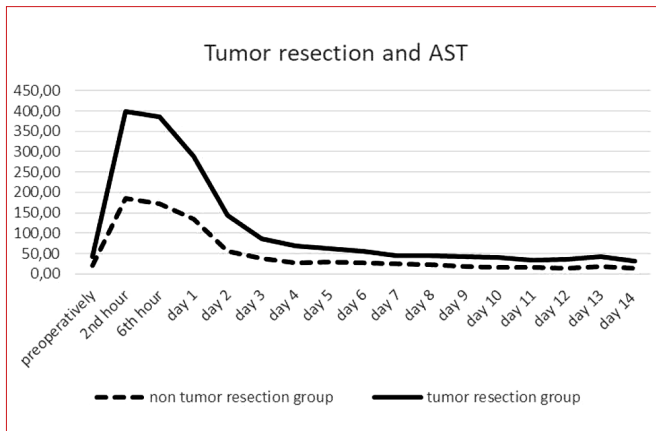


Figure 2. The fluctuation of AST in liver tumor metastasectomy and non-metastasectomy group

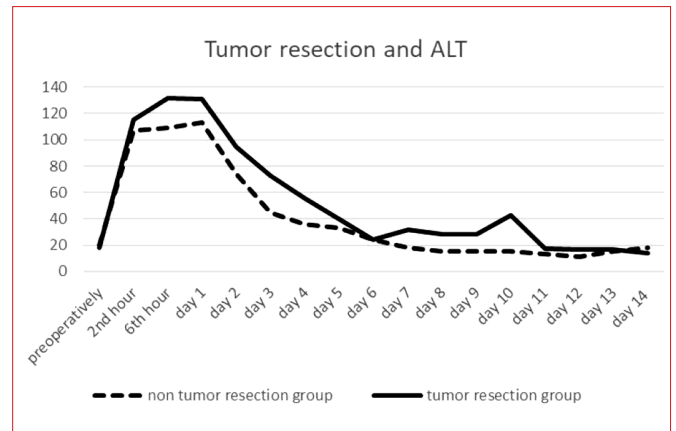


Figure 3. The fluctuation of ALT in liver tumor metastasectomy and non-metastasectomy group

DISCUSSION

Risk factors and etiologies have been suggested for postoperative liver injury after right upper quadrant surgery with liver mobilization and liver metastasectomy. Clamping of the portal triad (inflow occlusion), also called the Pringle Maneuver, which is used to decrease blood loss, can cause hepatocellular apoptosis, necrosis, and eventually liver dysfunction with the ischemia/reperfusion mechanism [8]. According to Matzinger's Danger Model, injured cells and their intracellular necrotic products, which could potentially be a danger signal, activate antigen-presenting cells and this cascade leads to a systemic inflammatory response [9]. Liver injury can be observed as a clinical manifestation of the systemic inflammatory response [10].

Studies showed that mobilization of the liver in itself causes hepatocellular injury [9, 11]. Besides mobilization, surgical techniques, duration and type of anesthetic agents, chemotherapy history, and biliary surgery may lead to postoperative liver function impairment [11-13]. Different surgical techniques may be preferred to avoid extensive mobilization of the liver. Laparoscopic liver resection or choosing liver resection using the anterior approach compared with conventional surgery with extensive mobilization may protect against hepatocellular damage or hepatic inflammation [14, 15].

In our study, we noted an increase in LFTs following liver mobilization. The AST serum levels were high in all patients on the 2nd day. ALT levels peaked at the postoperative 6th hour and gradually decreased in the following days. These high levels of both transferases spontaneously normalized at 11-12 postoperative days, in keeping with the only study that evaluated the postoperative trends in hepatic function following extensive right upper quadrant surgery [6]. In that study, Nasser et al.

evaluated 132 patients with advanced epithelial ovarian cancer. All patients underwent right upper quadrant surgery. ALT appeared to be the most fluctuant LFT, which peaked on the postoperative 1st day and returned to normal 5 days postoperatively. The bilirubin levels did not reflect similar fluctuation. Naik et al. showed ALT and AST levels 10-12 times above the reference limit in all three arms of liver transplantation patients (acute cellular rejection in adults; pediatrics and non-acute cellular rejection in adults). Increased transaminases reached normal levels within a week in uncomplicated cases [16].

In our data, liver metastasectomy caused more high both AST and ALT levels on the 2nd postoperative day compared with the non-metastasectomy group. Whereas ALT increased more significantly, both ALT and AST became similar and normalized in the following days. High levels persisted in only one patient. The patient was discharged on the 14th day of hospitalization because they had no clinical symptoms relevant to liver functions. LFTs normalized in the outpatient follow-up. Multiorgan failure developed in only one patient who had diabetes and mitral valve replacement in her medical history. Liver tumor metastasectomy was performed in addition to standard surgery. Sufficient fluid replacement was administered, we avoided hepatotoxic drugs, and the patient was followed in the intensive care unit. Clinical worsening and death were attributed to high-risk comorbid diseases rather than extensive surgery. In a study by Nasser et al., only one patient died within 5 days of surgery. The development of liver failure in this case was attributed to the neuroendocrine component and cytokines released from the neuroendocrine tumor, rather than excessive mobilization. This patient did not respond to the fluid resuscitation and avoidance of hepatotoxic medication, which was suggested to prevent liver failure. As known, there is no consensus on the adequate minimal volume of the liver to avoid

liver failure after resection. The volume range from 10% to 40% is adequate [17]. However, hepatic failure can also be observed in adequate liver volume [18]. In our study, insufficient residual liver volume was not observed.

This study has limitations. The number of metastatic lesions in the liver and the total volume of the tumors were not assessed in our retrospectively designed study. However, in our study, we compared fluctuations of LFTs in the groups that underwent liver mobilization without metastasectomy and liver metastasectomy. Laboratory parameters were followed daily during the immediate postoperative period until discharge. To our knowledge, no study has compared the serum levels of LFTs in these two groups in gynecologic oncology.

In conclusion, both liver mobilization and liver metastasectomy procedures are associated with a transient increase in LFTs. Although liver mobilization in itself causes high LFT values in the immediate postoperative period, this effect is more significant in liver metastasectomy. High serum levels of LFTs returned to normal values within 2 weeks in both two groups. Studies have not demonstrated the clinical significance of this increase and its role in predicting liver failure. Adequate fluid replacement and avoidance of hepatotoxic drugs can prevent the aggravation of the clinical course.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol has been approved by the research institute's committee on human research.

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