Extracellular Histones H3 as a Prognostic Blood Marker for Delayed Liver Function Recovery After Donor Hepatectomy

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ABSTRACT

Background. Early prediction of liver dysfunction after liver resection remains a challenge. We hypothesized that extracellular histone concentrations are a promising new biomarker for the detection of liver injury after donor hepatectomy.

Methods. This prospective study considered 93 living donors who underwent hepatectomy. Blood samples of donors were collected on postoperative day 1, and histone levels in the plasma samples of the patients were measured with total histone H3 sandwich ELISA kits. Among 86 right lobe donors, 23 (26.7%) were deemed to have a delayed liver function recovery according to the International Study Group of Liver Surgery's definition of posthepatectomy liver failure, whereas 63 (73.3%) were considered to have an adequate liver function recovery.

Results. The area under the receiver operating characteristic (ROC) curve for circulating histones in predicting persistent liver dysfunction was 0.618 ± 0.06 (95% confidence interval [CI], 0.501-0.735; P = .091). The cutoff point value obtained from the analysis of ROC curves was 0.895, with a sensitivity of 95.7% and a specificity of 32.9%, respectively, for examining a delayed liver function recovery (P = .015). The Fisher analysis significantly verified these results empirical influence function % 7.90 (95% CI, 3.91-11.90; P = .006). The univariate analysis determined that postoperative histones were identified as an independent risk factor of delayed liver function recovery (odds ratio, 10.8; 95% CI, 1.4-84.9; P = .024).

Conclusions. The circulating histone negatively correlates with liver dysfunctions after donor hepatectomy and had the best value in predicting liver dysfunction within 24 hours after liver resection.

In the field of biomarker discovery, extracellular histones have emerged as sensitive, specific, and stable markers for cell stress and injury. Histones bind and package nuclear DNA into nucleosomes, which can be released into the bloodstream on cell activation or damage [1,2]. Graft-derived cell-free DNA, which is released into the bloodstream by necrotic and apoptotic cells, is a promising noninvasive organ integrity biomarker [3].

Several clinical studies indicate that circulating cell-free histones serve as potential blood markers, and investigations are focused mainly on sepsis, trauma, and malignancy [4,5,6,7]. One study has recently investigated the release of histones concerning cellular injury resulting from liver cirrhosis, and cumulative extracellular histones expression has been considered a parameter of liver function in nontransplanted cirrhotic research livers. Median plasma histone levels were 5- or 6-fold higher in patients with acute liver failure than in patients with chronic liver disease or healthy controls, respectively [8].

Several conventional liver function tests (LFTs) are routinely used to assess the remnant liver to maintain synthetic, excretory, and detoxifying functions. Considering the lack of a standardized definition of liver failure after liver resection, the

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0041-1345/20
https://doi.org/10.1016/j.transproceed.2021.07.023

International Study Group of Liver Surgery recently proposed to define posthepatectomy liver dysfunction, characterized by an increased international normalized ratio (INR) and hyperbilirubinemia on or after postoperative day 5, together with a grading system of severity [9].

Therefore, new, noninvasive biomarkers are needed that can be used to monitor liver dysfunction to rapidly and reliably detect liver failure. We hypothesized that the quantitative measurement of extracellular histone concentration is a promising new biomarker for the detection of liver injury after donor hepatectomy.

The current study aimed to assess whether histones in the peripheral blood correlated with, and are predictive for, delayed liver function recovery, as measured by classic markers.

We analyzed risk factors for postoperative delayed liver function recovery and evaluated the extracellular histones concentration in peripheral blood as a biomarker of liver dysfunction in donors after right hepatectomy.

MATERIALS AND METHODS

Study Design

This study focused on the 93 patients who underwent donor hepatectomy. Traditional LFTs were performed, and plasma extracellular histone concentration was monitored in all donors at the transplant center as part of a prospective, observational, cohort trial.

All living donors who underwent the right hepatectomy preserving the middle hepatic vein at the Liver Transplantation Institute of Malatya, Turkey, between November 2018 and October 2019 were considered for this prospective study, and the institutional review board approved the study. Donor demographic characteristics and operative outcomes were reviewed from a prospectively maintained database and were analyzed retrospectively.

We defined delayed liver function recovery as a marker for liver condition according to the definition of posthepatectomy liver failure by the International Study Group of Liver Surgery, which is characterized by an increased international normalized ratio and hyperbilirubinemia on or after postoperative day 5 [9].

To assess the outcomes, the donors were divided into 2 groups: the adequate group, including 63 (73.3%) patients with adequate liver function recovery; and the delayed group, including 23 (26.7%) patients with increased international normalized ratio and hyperbilirubinemia on or after postoperative day 5.

Histones levels were assessed as a first outcome, and the standard LFTs were assessed as secondary outcomes, and these dates were compared retrospectively between the adequate and delayed liver function recovery groups. To assess the outcomes of living donors with a different remnant liver volume (RLV), body mass index (BMI), and the extracellular histones H3 level were then compared.

Blood samples were obtained on the first day after transplantation in donors, and plasma samples were prepared from whole blood following immediate centrifugation for 4 minutes at 2000 *g* at room temperature and stored at −80°C until further histone H3 analyses.

Plasma Analyses

Total histone H3 levels in the plasma samples of patients were measured with PathScan Total Histone H3 sandwich ELISA kit (Cell Signaling Technology, Danvers, Mass, United States) according to the manufacturer's instructions. Briefly, plasma samples were obtained from the patients' blood samples, and lysates were prepared with the protocol for suspension cells. A 100 μl undiluted lysate sample was placed into the microwell coated with Histone H3 rabbit mAb and incubated at 37°C for 2 hours. The wells were washed with 1 × wash buffer after the wells' contents were discharged. In the following steps, detection antibody, horseradish peroxidase-linked secondary antibody, and tetramethylbenzidine substrate were added to microwells with the application of washing and incubation procedures. Finally, the stop solution was added, and then the plates were read at 450 nm. All ELISA procedures were carried out in DS2 automated ELISA processing devices (Dynex Technologies Inc, Chantilly, Va, United States). Absorbance values were obtained, and total histone H3 levels were calculated with the controls consisting of the known lysate concentrations according to the kit instructions. Cell Signaling Technology recommended this kit for research use only and not for use in diagnostic procedures.

Postoperative laboratory variables included the conventional LFTs, albumin, INR, lactate dehydrogenase (LDH), c-reactive protein (CRP), procalcitonin (PCT), and ammonium, which were measured using routine biochemical methods. The baseline and laboratory values from postoperative days 1, 3, 5, and 7 were measured at the transplant center performing the donation. Therefore, our study illustrates the greatest changes, which typically occurred within 7 days of the operation.

Baseline Demographic Characteristics

All patients were healthy with no underlying primary diseases. The mean donor age of the 93 living donors was 29.3 years (range, 18 to 48 years). There were no differences between the groups concerning age or sex.

Most grafts (86 cases, 92.5%) were taken from the right lobe for adult recipients. There were 7 (7.5%) cases of left lobe resection. BMIs of 50 (58%) of the donors were within normal range (16-24 kg/m^2), and BMIs in 36 (42%) donors were higher than 24 kg/m^2 (range, 24-31 kg/m^2). Among 86 right lobe patients, the 40 (46.5%) donors' RLV was more than 32% of origin liver volume and 46 (53.5%) patients' RLV was less than 32% of origin liver volume.

The demographic characteristics of the donors at the time of evaluation are detailed in Table 1. Of the 86 right lobe donors, 23 (26.7%) were deemed to have a delayed liver function recovery, whereas 63 (73.3%) were considered to have an adequate liver function recovery. Univariate dates (donor age, sex, BMI, graft type, RLV, operative time, liver functional tests, and inflammatory markers) and histones H3 levels were analyzed to identify risk factors for delayed liver functional recovery after donor hepatectomy.

There were no significant differences between the 2 groups in terms of operative parameters, including the hospital stay, sex, and the actual RLV.

In the delayed liver function recovery groups, patients with BMIs of more than 24 kg/m^2 were significantly higher than the adequate group ($P = .035$). However, differences in RLV size in both groups were not significant ($P > .8$) (Table 1).

Statistical Analysis

Continuous dates were reported as medians with standard deviations (SD) and were compared by Mann-Whitney *U* test (2 groups). Categorical data were compared using Fisher and Snedecor exact tests. Spearman rank correlation was used for correlation analysis. Receiver operating characteristic (ROC) curves were constructed for predictive variables, and the area under the curve (AUC) was calculated with 95% confidence intervals (CI). Optimal cutoff values for sensitivity and specificity for each parameter were derived from the ROC curves. All tests

Table 1. Baseline Characteristics of Donors in Groups

	Adequate Liver Function Recovery		Delayed Liver Function Recovery		*P* Value
	n = 63	%	n = 23	%	
BMI normal	42	66.7	8	34.8	.035*
BMI >24 kg/m^2	21	33.3	15	65.2	
RLV <32%	34	54.0	12	52.2	.883
RLV ≥32%	29	46,0	11	47.8	
Men	34	54.0	14	60.9	.685
Women	29	46.0	9	39.1	

BMI, body mass index; RLV, remnant volume.
* *P* <.05.

were 2-tailed, and statistical significance was set at $P < .05$. The analyses were performed using SPSS version 22.0 (IBM Inc, Armonk, NY, United States).

RESULTS

Postoperative Laboratory Variables Between Histones H3 and LFTs in Groups

Levels of circulating histones in the adequate and delayed liver function recovery group patients are shown in Fig 1A. Postoperative extracellular histones H3 levels were significantly less in the delayed liver functional recovery group (mean 0.776 ± 0.018; 95% CI, 0.771-0.862) than in the adequate recovery group (mean 0.846 ± 0.019; 95% CI, 0.808-0.884; $P = .046$).

The AUC value for the potential predictor of persistent liver dysfunction is illustrated in Fig 1B. The cutoff point value obtained from the analysis of ROC curves for the lowest histones counts was 0.895 with a sensitivity of 95.7% ± 4.3 and a specificity of 32.9% ± 5.6 for examining the possible relationship between a delayed liver function recovery. χ^2 *P* value for sensitivity was .015.

Low levels of circulating histones the first day after donation had a stronger predictive value. The area under the ROC curve for circulating histones in predicting persistent liver dysfunction was 0.618 ± 0.06 (95% CI, 0.501-0.735; $P = .091$); these dates mean that histones were at least as accurate as biochemical markers. The Fisher-Snedecor analysis significantly verified these results empirical influence function % 7.90 (95% CI, 3.91-11.90; $P = .006$).

Baseline laboratory characteristics and clinical outcomes for each group are illustrated in Fig 2 and Tables 2 and 3.

The alanine transaminase (ALT) level reached its median peak of 302.6 U/L the first day after the operation in the adequate group, reached 328.7 U/L in the delayed group ($P = .558$), and decreased to 87.7 U/L vs 82.5 U/L on day 7 after the operation ($P = .752$).

The postoperative median peak serum AST levels in both groups were observed on the first day in the adequate and delayed liver recovery groups: 237 U/L and 279.3 U/L, respectively ($P = .242$). The AST levels decreased to 52.3 vs 54.1

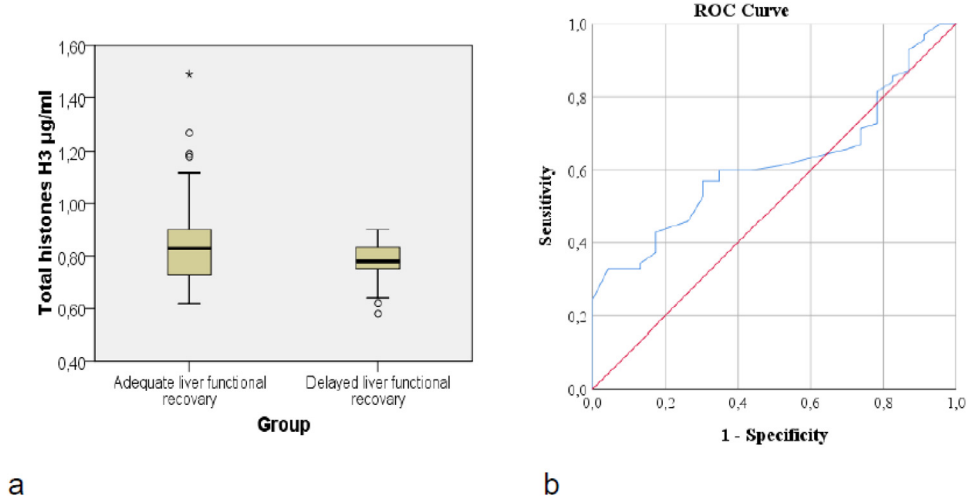

Fig 1. (A) Comparison of circulating histones levels between groups, **P* < .05 vs each other group (Mann-Whitney *U* test). **(B)** Area under the receiver operating characteristic (ROC) curves for prediction of delayed liver functional recovery (sensitivity of 95.7% ± 4.3%; $P = .015$).

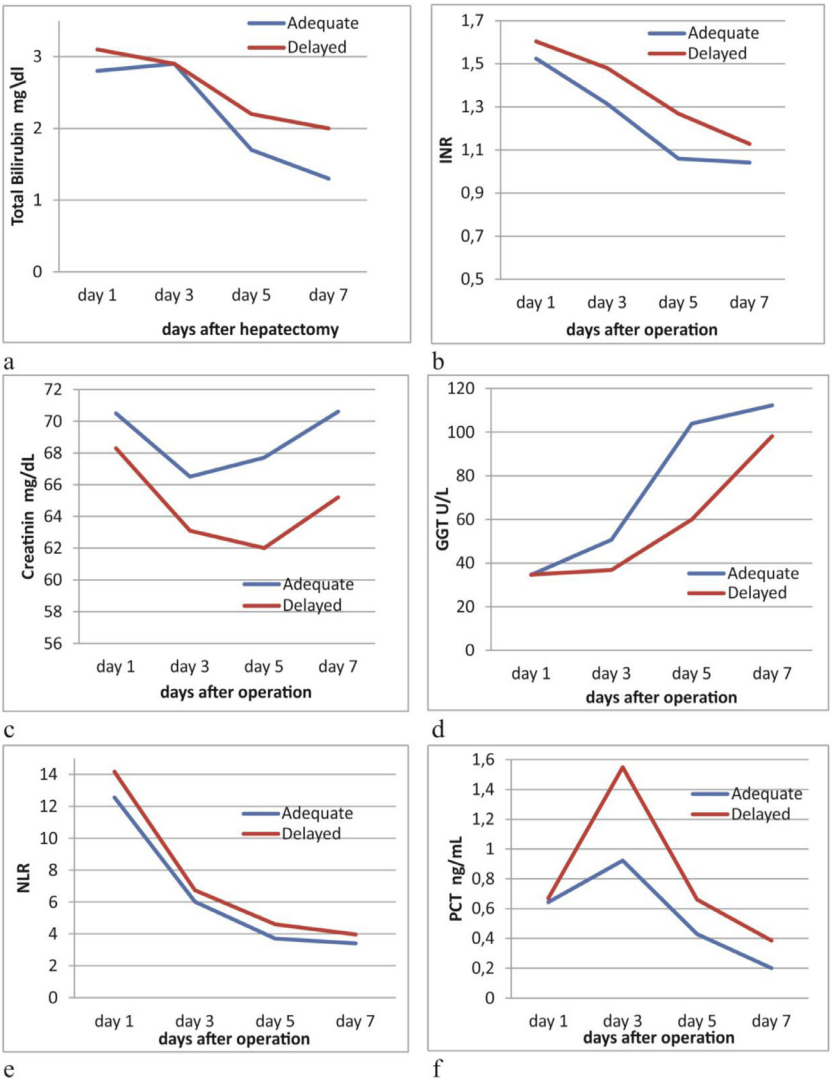

Fig 2. (A) Mean total bilirubin levels in both groups (*P < .05 on days 5 and 7). **(B)** Mean INR levels between groups (*P < .05 on days 5 and 7). **(C)** Mean creatinine values between groups (*P < .05 on days 5 and 7). **(D)** Mean GGT levels between groups (* P < .05 on day 5). **(E)** Mean NLR values between groups (*P < .05 on day 5). **(F)** Mean PCT levels between groups (*P < .05 on day 7). GGT, gamma-glutamyl transferase; INR, international normalized ratio; NLR, neutrophil-lymphocyte ratio; PCT, procalcitonin.

(P = .825) 7 days later. ALT and AST levels did not differ between the 2 groups (Tables 2 and 3).

The median peak serum total bilirubin level for all donors reached a maximum on a postoperative day 1 (2.8 vs 3.2 mg/dL; P = .215) and returned to baseline levels on postoperative day 7 in the adequate recovery group when compared with the delayed group (1.3 vs 2.0 mg/dL). These differences at 1 week were significant (P = .022) (Fig 2A).

The liver enzyme elevation and hyperbilirubinemia in the immediate postoperative period declined smoothly over a week in all donors. No donors developed postoperative liver failure.

The alkaline phosphatase levels in the adequate and delayed recovery groups were 71.4 U/L vs 73.9 U/L on the first day and were elevated to 109.2 U/L vs 107.1 U/L, respectively, on day 7 (P = .862).

The gamma-glutamyl transpeptidase (GGT) levels did not differ between the groups on the first postoperative day (34.6 vs 34.7) (P = .825) but significantly increased in a delayed group on a postoperative day 5 (103.0 vs 60.0) (P = .005) (Tables 2 and 3, Fig 2D). We also observed the significant differences in creatinine values between groups 5 (P = .006) and 7 days after resection (P = .013) (Fig 2C).

The peak serum INR level was observed on the first postoperative day and did not differ between the 2 groups (1.52 vs 1.60; P = .53) and decreased to 1.06 in the adequate group vs 1.27 on delayed liver function recovery group on day 5 after an operation. Significant differences between these factors were observed at the 5 and 7 day follow-up time points (P < .05) (Table 3, Fig 2B).

The mean albumin levels did not differ between the adequate and delayed liver functional recovery groups. The P values were greater than .05 at 1, 3, 5, and 7 days after donation for these parameters.

In all donors, the mean serum ammonium level reached its median peak on day 3 after the resection and was higher in the

Table 2. LFTs Characteristics of Donors on Postoperative Day 1

	Adequate Liver Function Recovery		Delayed Liver Function Recovery		*P* Value
	n	95% CI	n	95% CI	
Histones H3	63	0.808-0.884	23	0.771-0.862	.046*
ALT	63	263.8-341.4	23	222.8-434.7	.661
AST	63	212.7-261.4	23	178.3-380.4	.242
ALP	63	95.3-77.5	23	62.2-85.7	.683
GGT	63	30.9-47.7	23	24.4-38.3	.215
Bilirubin Total	63	2.53-3.10	23	2.72-3.56	.560
LDH	63	404.6-456.0	23	369.5-546.4	.411
Ammonium	63	87.8-109.4	23	90.1-132.0 91.2-112.2	.246
Albumin	63	31.8-33.4	23	31.6-34.4	.540
INR	63	1.39-1.66	23	1.41-1.80	.530

ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CI, confidence interval; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; LFT, liver function tests; INR, international normalized ratio.

* $P < .05$.

delayed recovery group over time ($P = .112$). But these differences were not significant and normalized within 1 week in both groups.

The postresection laboratory values of LDH reached their peak of 430.3 on the first day in the adequate group and 457.9 in the delayed group ($P = .411$). These dates returned to normal limits in both groups on day 5 (265.2 and 277.7; $P = .494$).

In our study, there was no difference in postoperative platelet count between patients with and without delayed liver functionary recovery group. The platelet count decreased from the baseline in the first 1 to 3 postoperative days ($P = .162$) and returned to baseline levels on postoperative day 5 ($P = .334$). But preoperative platelet counts were not associated with delayed liver function recovery. Because our analysis did not report values after day 7, we may have missed an immediate but transient postoperative increase in the platelet count.

Significant systemic inflammation was also pronounced in patients with delayed recovery in liver function, which is associated with low histone levels. We also observed changes in the white blood count (WBC). The average WBC of the donors on the first day was 16.7 × 109/L in the adequate group and 19.0 × 109/L in the delayed group ($P = .069$). These levels decreased to 8.5 × 109/L and 9.2 × 109/L 1 week after donation ($P = .205$) (Table 4).

The inflammatory biomarker CRP levels did not differ between the 2 groups in the postoperative period. The median serum CRP levels in the adequate and delayed liver recovery groups were observed on the first day at 14.7 g/dL and 7.1 g/dL, respectively ($P = .418$). These levels increased to 22.1 g/dL vs 30.3 g/dL ($P = .134$) 5 days later (Table 4).

The neutrophil-lymphocyte ratio (NLR) as an indicator of systemic inflammation did not differ between the groups at 1 and 3 days after donation. But these parameters decreased on day 5 and were significantly higher in the delayed liver functional recovery group (4.6 vs 3.7; $P = .037$) (Fig 2E).

The mean PCT values were significantly increased on day 7 in patients in the delayed liver functionary recovery group (3.9 ng/mL vs 2.0 ng/mL; $P = .014$) (Fig 2F).

The only significant difference in outcomes concerned the peak serum total bilirubin, GGT, and INR levels, which were higher in the delayed recovery group vs the adequate group, but creatinine values were significantly lower in the delayed group.

In this clinical study, we assessed the relationship between decreased histone H3 levels and LFTs. The univariate analysis determined that postoperative histone level identified was an independent risk factor of delayed liver function recovery (odds ratio [OR], 10.8; 95% CI, 1.4-84.9; $P = .024$).

Table 3. LFTs Characteristics of Donors on Postoperative Day 7

	Adequate Liver Function Recovery		Delayed Liver Function Recovery		*P* Value
	n	95% CI	n	95% CI	
ALT	63	68.8-106.6	23	61.2-103.8	.752
AST	63	42.7-61.9	23	43.9-64.4	.825
ALP	63	97.5-120.8	23	83.9-130,4	.131
GGT	63	84.9-121.2	23	47.8-72.1	.005*
Bilirubin Total	63	1.2-1.4	23	1.1-2.8	.022*
LDH	63	245.5-284.8	23	247.7-307.9	.494
Ammonium	63	80.8-90.8	23	75.9-95.4	.968
Albumin	63	31.4-33.3	23	30.5-33.5	.715
INR	63	1.009-1.007	23	1.05-1.2	.018*

ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase; LFT, liver function tests.

* $P < .05$.

Table 4. The Systemic Inflammation Markers of Donors on Postoperative Days 1 and 7

	Days	Adequate Liver Function Recovery		Delayed Liver Function Recovery		*P* Value
		n	95% CI	n	95% CI	
CRP	I	63	3.2-26.2	23	2.1-12.1	.418
	VII		10.9-17.2		11.1-30.3	.084
PCT	I	63	0.30-0.99	23	0.00-1.47	.941
	VII		0.17-0.23		0.15-0.62	.014*
L	I	63	15.5.7-17.7	23	15.9-22.0	.069
	VII		7.8-8.9		7.7-10.6	.205
N/L Ratio	I	63	11.2-14.0	23	11.0-17.3	.271
	VII		3.3-4.1		3.6-5.6	.037*
PLT	I	63	196.0-227.6	23	192.4-263.0	.330
	VII		232-272		199-279	.525

CI, confidence interval; CRP, c-reactive protein; L, leukocytes; N/L, neutrophil-lymphocyte ratio; PCT, procalcitonin; PLT, platelets.
* $P < .05$.

A significant negative association was found between circulating histone levels and a mean value of INR on day 3 ($r = -0.442$, $P = 0.035$) and serum Albumin levels on day 5 ($r = -0.520$, $P = 0.011$) after an operation in delayed liver function recovery group.

The peak level of serum total bilirubin was significantly higher in the delayed group than in the adequate group. Patients with low histone levels had prolonged liver dysfunction, as indicated by a significantly increased INR almost until postoperative day 7. Furthermore, serum GGT was significantly increased in the delayed group on postoperative day 7. These data also suggest that postoperative histones H3 levels are associated with liver dysfunction immediately after donor hepatectomy.

Histones did not predict or correlate with infection or sepsis markers but correlated with leukocyte counts ($r = 0.484$, $P = 0.019$) on the first day after donation in the delayed group. The degree of the correlations between histone levels and WBCs was not stronger over time.

Histone levels showed significant correlation with total bilirubin ($r = 0.339$, $P = .009$), LDH ($r = 0.307$, $P = .018$), and ALT (r = 0.259, $P = 0.047$) levels on day 3 after resection, and WBCs at 1 week ($r = 0.275$, $P = 0.035$), as calculated by Spearman correlation analysis in the adequate group. But NLR ($r = -0.269$, $P = 0.040$) and INR ($r = -0.331$, $P = 0.010$) values correlated negatively with extracellular histones levels on 1 and 7 days.

To assess the outcomes of liver resection volume the donors were divided into 2 groups: the group with a RLV of <32%, and the group with an RLV of ≥32%. The 2 groups were then compared. We investigated the correlation between RLV and histone counts in both groups. The correlations at 1 week ($P = .883$) were not significant. We also compared histone levels in right and left lobe donors, and differences were not significant ($P = .57$).

Univariate analysis revealed that 5 variables (BMI index, total bilirubin, GGT levels, postoperative serum INR, and histones H3 levels of <0.895), were found to be independent risk factors for delayed liver function recovery.

DISCUSSION

We described an important role of circulating histones in the context of liver dysfunction in donors after hepatectomy. According to the literature, this is the first study to report the value of circulating histones H3 in donors.

A key finding is that the presence of circulating histones negatively and strongly correlates with liver dysfunctions after hepatectomy, thus indicating that circulating histones may serve as a novel biomarker with prognostic implications for donors. Circulating histones levels <0.895 had the best AUC value, with a sensitivity of 95.7% ± 4.3 ($P = .015$) in predicting liver dysfunction within 24 hours after liver resection.

Our results are the first to show depression, as well as a prognostic significance, of circulating H3 in donors after hepatectomy. However, the implications of this phenomenon have been documented only recently, and this discrepancy may be due to the time point of blood collection or a fundamental difference in the liver parenchyma.

Our further analysis showed a clear correlation between histone levels and some inflammation markers or LFTs in donors. For example, histone levels were associated with WBCs, negatively correlated with serum albumin and INRs, but weakly correlated with ALT and ammonium levels.

The laboratory values AST, ALT, and LDH were increased on day 1 postresection, presumably from ischemia, reperfusion damage, but rapidly declined in patients within 7 days. But alkaline phosphatase and GGT levels reached their peak at 1 week of the operation in both groups.

The only significant difference in outcomes concerned the peak serum total bilirubin level, INR, and GGT levels, which were higher in the delayed group vs the adequate group.

We made a correlation analysis of histone levels and inflammatory markers in donors and observed that plasma histone levels were significantly associated with WBCs ($r = 0.275$, $P = .035$), but negatively associated with NLR ($r = -0.269$, $P = .040$), all of which are important markers of systemic inflammation. Although, we observed a weak association between circulating histones and CRP and PCT values in all donors.

In recent years, several studies have demonstrated that extracellular histones play an important role in cell stress and injury. Xu et al showed that circulating histones are key mediators of cell damage and organ dysfunction during sepsis [1].

A study by Thålin et al [6] was the first to show an elevation, as well as a prognostic significance, of circulating H3Cit in patients with cancer. These findings also support previous data on the prognostic significance of high plasma levels of interleukin 8 and interleukin 6 in patients with cancer [6].

Huang et al [10] studied the role of circulating histones in sterile inflammatory liver injury and showed that endogenous histones serve as a crucial link between initial tissue damage and activation of inflammation [10].

Takahashi et al [11] reported that the postoperative lowest platelet percentage of ≤60% was identified as an independent risk factor of delayed liver function recovery (OR, 6.85; $P <$ .01). This study focused on platelets as a promoter of liver regeneration. Accordingly, a decrease in platelet counts was identified as a delay in postoperative liver function recovery. In our study, the preoperative platelet counts were not associated with delayed liver function recovery [11]. van Smaalen et al [12] have demonstrated previously that extracellular histone concentrations were significantly higher in perfusates of kidneys with post-transplant graft dysfunction and were an independent risk factor for delayed graft function (OR, 2.152; 95% CI, 1.199-3.863) but not for primary nonfunction (OR, 1.342; 95% CI, 0.900-2.002) [12].

This hypothesis is supported by Wen et al [8], showing that cumulative extracellular histones expression has been considered a parameter of liver function in nontransplanted cirrhotic research livers. Median plasma histone levels were 5- or 6-fold higher in patients with acute liver failure than in patients with chronic liver disease. There was a slight elevation of histone levels in patients with chronic liver disease in contrast to healthy controls, but the difference was not significant [8].

Therefore, it is essential to find the earliest possible indicator of liver dysfunctions after hepatectomy to establish effective interventions for promoting liver regeneration and avoiding liver failure.

Based on these results, we hypothesized that the quantitative measurement of extracellular histone concentration is a promising new biomarker for the detection of liver injury after donor hepatectomy. Collectively, our results suggested that circulating histones were closely related to systemic inflammation after donor hepatectomy, which might adversely affect liver dysfunction.

Also, the significant association between low-circulating histones and high concentrations of inflammatory markers suggests that the presence of systemic inflammation and concomitant liver dysfunction in donors may be mainly attributed to fewer quantities of histones in the circulation of patients.

Our study has some limitations. First, this study involved a small number of patients. However, our study reports (usually daily) values during the immediate postoperative period. This analysis did not report values after day 7, so we may have missed an important postoperative change after discharging of donors.

CONCLUSIONS

In this study, the determination of extracellular histones H3 in plasma by ELISA allowed for earlier and more sensitive discrimination of liver dysfunction in donors compared with conventional LFTs. Collectively, these findings demonstrate that circulating histones are critical mediators of systemic inflammation and cellular damage after right donor hemihepatectomy, which may be potentially translatable for clinical use to predict delayed liver function recovery.

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