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The Ratio of Plasma Neutrophil Gelatinase-Associated Lipocalin Predicts Acute Kidney Injury in Patients Undergoing Liver Transplantation

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ABSTRACT

Background. Postoperative acute kidney injury (AKI) is associated with high morbidity and mortality after liver transplantation (OLT). Previous studies have shown the value of plasma neutrophil gelatinase-associated lipocalin (NGAL) taken 2 hours after reperfusion of the liver graft as an early marker predicting AKI. The study was performed to determine whether plasma NGAL concentrations obtained as early as 1 hour after reperfusion was predictive of AKI and whether the NGAL ratio was an early predictor for AKI in the first 48 hours after OLT.

Methods. Twenty-six liver transplant recipients donated plasma samples for NGAL determinations at induction (T1), at graft reperfusion (T3) as well as after 1 (T4) and hours 2 (T5), and at the end of the surgery (T7). AKI was defined at 48 hours after liver transplantation according to the acute kidney injury network criteria. Predictive ability was assessed using areas under the curve of receiver operator characteristic analyses.

Results. The area under the curve of the receiver operator characteristics curve of (plasma NGAL concentration at T4)/(plasma NGAL concentration at T1) to predict AKI was 0.717 at T5, 0.765 at T7, 0.714 at T8 (24 hours post-OLT), and 0.781 at T9 (48 hours post-OLT).

Conclusion. The plasma NGAL concentrations taken 1 hour after reperfusion of the liver graft seem to be predictive of AKI; the NGAL changing ratio may be an early predictor for AKI in the first 48 hours after OLT.

ACUTE kidney injury (AKI) is an independent risk factor of poor prognosis after liver transplantation (OLT) prevention of this complication may improve the survival rate.[1] The incidence of AKI has been reported to range between 17% and 95% according to various criteria.[2–5] AKI, which may increase the risk of chronic renal failure, which requires renal replacement therapy (RRT), leading to an high postoperative mortality.[6–9] In addition, AKI among patients undergoing OLT influences mortality even after 5 years, which is most likely due to the greater incidence of chronic kidney disease and cardiovascular event.[10–13] The etiology of AKI after OLT is multifactorial:

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0041-1345/12/$–see front matter
doi:10.1016/j.transproceed.2012.01.068

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Pretransplant AKI, serum albumin, surgery duration, intraoperative blood transfusion, treatment duration with dopamine, liver graft dysfunction, bacterial infection, early postoperative ischemia, and immunosuppressant toxicity.[6, 7, 14]

The definition of AKI is not uniform in the current literature. An elevated serum creatinine value is usually considered to be an indicator of AKI. However, creatinine is a delayed, unreliable indicator of AKI for a variety of reasons.[15, 16] Current, promising, novel biomarkers for AKI include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, liver-type fatty acid binding protein, and interleukin-18.[17] NGAL has been identified to be among the most upregulated genes in the kidney early after acute injury in animal models.[18] NGAL expression has been studied in various clinical settings, such as cardiopulmonary bypass, renal transplantation, chronic kidney disease, and contrast-induced nephropathy. Elevated NGAL plasma or urine concentrations, may be related to renal disorders.[19]

Previous studies concerning NGAL in OLT have shown intraoperative NGAL concentrations to be strongly associated with postoperative AKI.[20] A combination of postoperative plasma NGAL and APACHE II score predict AKI with an high sensitivity and specificity after OLT.[21] The intraoperative NGAL concentrations obtained 2 hours after reperfusion of the liver graft and the absolute NGAL value have been chosen to predict postoperative AKI in OLT. The current study was performed to determine whether the plasma NGAL concentration at 1 hour after liver graft perfusion was predictive of AKI, and whether the NGAL ratio was an alternative early marker for postoperative AKI among OLT.

MATERIALS AND METHODS

Study Population

Twenty-six adult enrolled patients all underwent OLT using the piggyback technique. Exclusion criteria were end-stage renal disease (glomerular filtration rate estimated by Modification of Diet in Renal Disease equation of <15 mL/min), age <18 years, and inability to complete the informed consent. This prospective, clinical study was approved by our institutional Review Board; valid, written, informed consents were obtained from each patient prior to undergoing the operation.

Study Design

Blood samples containing sodium heparin as the anticoagulant were obtained for the measurements of sCr and NGAL. The blood samples were obtained at anesthesia induction (T1), 1 hour after the surgical incision (T2), the time of reperfusion (T3) as well as 1 (T4), 2 (T5), 4 hours (T6), and the end of the surgery (T7). In addition samples were obtained at 24 (T8), and 48 hours after liver transplantation (T9). The samples were immediately placed in ice water at 4°C. Plasma separated by immediate centrifugation (3500 rpm/10 minutes) as the supernate was stored at −80°C until the analysis within one week.

Clinical Outcomes

The primary outcome was AKI, which was modified according to the criteria of the Acute Kidney Injury Network (AKIN).[9] AKI was defined as an increase in Serum creatinine of ≥0.3 mg/dL or ≥150% from baseline within 48 hours of OLT. Secondary outcomes included lengths of intensive care and hospital stays after OLT, the necessity of RRT, and mortality.

Measurement of Creatinine and NGAL

Serum creatinine samples were analyzed at our central laboratory. The plasma levels of NGAL were analyzed via are enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn) according to the manufacturer's instructions.

Statistical Analysis

Categorical variables were expressed as number (%), and continuous variables as mean values and standard deviations. Categorical variables were analyzed using the Fisher exact test, whereas continuous variables, using the Mann–Whitney U test. Logistic regression was used to evaluate the relationship between AKI and plasma NGAL or plasma NGAL ratio at each time. The ability of a biomarker to predict an outcome was assessed using the area under the curve generated by receiver operator characteristic analysis. The area under the receiver operating curve (AUROC) was calculated to assess the ability of the continuous variable to distinguish the categorical state. Statistical analysis was performed using SPSS statistical software version 17.0 (Chicago, Ill). $P < .05$ was considered significant.

RESULTS

Clinical Characteristics of Recipients

The demographic features of the 26 patients undergoing OLT who were enrolled into this study are shown in Table 1.

Outcomes and Plasma NGAL

Thirteen patients (50%) developed AKI within 48 hours after OLT. Their average intensive care stay was 14.6 ±

Table 1. Demographic Data

	Non-AKI	AKI	All	P
Patient number	13 (50%)	13 (50%)	126 (100%)	
Age (y)	56.8 ± 8.0	56.1 ± 8.1	56.5 ± 7.9	.797
Male	10 (77%)	10 (77%)	20 (77%)	1
Height (cm)	166.9 ± 10.8	160.6 ± 8.9	163.8 ± 10.2	.091
Weight (kg)	69.2 ± 13.8	60.7 ± 8.5	65.0 ± 12.1	.048
BMI (kg/m^2)	24.9 ± 5.7	23.6 ± 3.3	24.3 ± 4.6	.701
MELD score	16.0 ± 10.1	17.2 ± 7.8	16.6 ± 8.9	.520
Disease				
Hepatitis B	11 (85%)	6 (46%)	17 (65%)	.097
Hepatitis C	2 (15%)	6 (46%)	8 (31%)	.202
HCC	11 (85%)	8 (62%)	19 (73%)	.378
Liver cirrhosis	13 (100%)	10 (77%)	23 (88%)	.220
Diabetes	5 (38%)	1 (8%)	6 (23%)	.160
Hypertension	4 (31%)	1 (8%)	5 (19%)	.322
Alcoholism	3 (23%)	3 (23%)	6 (23%)	1

Abbreviations: AKI, acute kidney injury; BMI, body mass index; MELD, Model for End-Stage Liver Disease; HCC, hepatocellular carcinoma.

Note. Data are given as mean values ± standard deviation or number (%); AKI was defined as increase in serum creatinine of ≥0.3 mg/dL or increase to ≥150% from baseline within 48 hours of liver transplantation.

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