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Isolated increase in serum alkaline phosphatase after liver transplantation: Risk factors and outcomes analysis

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ABSTRACT

Background: Isolated increase in serum alkaline phosphatase (IISAlp) is frequently observed in liver transplant recipients visiting outpatient clinics. However, whether the increase is associated with risk factors or poor survival is unknown.

Methods: We retrospectively reviewed the medical records of liver transplant recipients who were followed up during 1999–2009 and had IISAlp 1 month after liver transplantation, which was sustained for at least 6 months. Clinical parameters, survival, and risk factors were analyzed and compared between recipients who survived longer than 6 months after transplantation.

Results: Among 307 liver transplant recipients, 44 had IISAlp. Compared with the control group, the patients with IISAlp were more frequently of the pediatric population, recipients of female donor or living-related partial liver grafts, and found to have biliary-related pretransplant disorders, lower body weight, and shorter warm ischemic time ($P < 0.01$). One patient with IISAlp died of acute myeloid leukemia during the follow-up period. The mean time to observation of IISAlp after liver transplantation was 6.3 ± 0.8 months. The mean follow-up duration was 5.5 ± 0.2 years. Stepwise multivariate analysis showed that being a pediatric or living-related liver transplant recipient was an independent risk factor for IISAlp, with adjusted hazard ratios (95% confidence interval) of 5.41 (2.59–11.28) and 3.0 (0.98–9.27), respectively.

Conclusions: Therefore, being a pediatric or living-related liver transplant recipient was an independent risk factor for IISAlp. However, IISAlp was not associated with poor survival after liver transplantation. Hence, patients who have undergone liver transplantation do not require frequent routine examination of serum alkaline phosphatase levels.

1. Introduction

Alkaline phosphatase (Alp) is an ectoenzyme present in many tissues, including those of the liver, bone, intestine, kidney, placenta, and leukocytes. More than 95% of serum Alp activity is derived from hepatocytes and osteoblasts.[1] Alp plays an active role in downregulating the secretory activities of the intrahepatic biliary epithelium, including decreasing bile flow and biliary bicarbonate excretion.[2] Moreover, it is involved in endotoxin detoxification and can reduce organ injuries (i.e., in the lungs, liver, and kidneys) in conditions such as ischemic-reperfusion damage or septic shock.[3–5] Growing children, pregnant women, people consuming a high-fat diet, and healthy individuals who have the blood group O or B and secrete the H-blood group substance in the postprandial period have been found to have abnormally high Alp levels.[6,7] Patients with hepatic, bone, pulmonary, renal, intestinal, and hematopoietic diseases or malignancies may present with nonspecific elevation of serum Alp levels. Hence, in these patients, diagnoses are often inferred from symptoms, abnormal examination results, or other existing abnormalities in laboratory test results and are not based solely on the elevation of serum Alp levels.

Abbreviations: Alp, alkaline phosphatase; IISAlp, isolated increase in serum Alp; CMV, cytomegalovirus; ANOVA, analysis of variance; aHRs, adjusted hazard ratios; 95% CI, 95% confidence interval; PTCD, percutaneous transhepatic cholangio drainage; NFAT, nuclear factor activated T-cells; RANKL, receptor activator of NF-κB ligand; AML, acute myeloid leukemia.

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Liver transplantation has become the standard treatment strategy for end-stage liver disease. After surgery, liver transplant recipients visiting outpatient clinics are frequently observed to have isolated increase in serum Alp (IISAlp), without other abnormal laboratory test results. In the studies performed by Arikan et al.,[8] O'Riordan et al.,[9] and Egawa et al.,[10] isolated transient hyperphosphatasemia (<6 months) occurred in 2.8%–4.3% of pediatric liver transplant recipients. Although transient IISAlp was found to be benign in some studies,[8,11] it may signal the onset of hepatic dysfunction due to cytomegalovirus infection, organ rejection, or biliary tract complications.[9,12] Thus, whether IISAlp is associated with risk factors or poor survival in the long term is not known. The aim of this study was to identify risk factors and analyze outcomes of liver transplant recipients with IISAlp during outpatient follow-up.

2. Materials and methods

The present study was conducted in accordance with the Helsinki Declaration of 1975. We retrospectively reviewed the medical records of liver recipients who were followed up at the National Taiwan University Hospital between January 1999 and December 2009, had IISAlp at 1 month after liver transplantation, and for whom IISAlp was sustained for at least 6 months. Serum Alp activity was routinely monitored using a colorimetric method (Hitachi 747; according to the assay conditions recommended by the International Federation of Clinical Chemistry: 37 °C as incubation temperature and *p*-nitrophenyl phosphate as substrate) at the time of serum liver enzyme measurement (normal range used in our hospital laboratory service: 60–220 IU/L). IISAlp was defined as serum levels higher than 220 IU/L, without other abnormal liver function test results. Specifically, the aspartate and alanine aminotransferase levels and bilirubin levels of the study subjects were within twice the normal range and lower than 1.5 U/L, respectively. After liver transplantation surgery, the patients were followed up at least once every 2 months after discharge from the hospital. A complete liver panel was performed at every follow-up visit. The clinical parameters of the recipients (age, sex, body weight, pretransplant diagnosis, and immunosuppressant use) and donors (age, sex, donor source [living or deceased], Alp level, and warm and cold ischemic times) were compared with those of the other recipients who survived longer than 6 months after the operation during the same period. Patient death was considered as the primary outcome of interest, followed by episodes of biopsy-proven transplant rejection, biliary complications, renal failure, malignancies, and bone diseases. The patients were followed up until December 2011. Data have been presented as mean ± standard deviation values. The Student *t* test, analysis of variance, chi-square test, or Fisher exact test was used, as appropriate, for the intergroup comparison of variables. Logistic regression models were used to adjust for potential confounding factors in the multivariate analysis. The adjusted hazard ratios and associated 95% confidence intervals (CIs) were based on the results of the logistic regression analysis with backward selection, taking *P* values of <0.05 and >0.1 as inclusion and exclusion criteria, respectively, for variable selection. A 2-sided $P < 0.05$ was considered statistically significant.

3. Results

Among the 307 liver transplant recipients, 44 (14.5%) had IISAlp. For the remaining 263 patients, 46 patients who survived less than 6 months were excluded and the remaining 217 liver transplant recipients who did not have IISAlp were assigned to the control group (Fig. 1). Compared with the control group, the patients with IISAlp were more frequently observed to be of the pediatric population, be recipients of female donor or living-related partial grafts, and have biliary-related pretransplant disorders (biliary atresia, progressive familial intrahepatic cholestasis, Alagille syndrome, primary biliary cirrhosis, and primary sclerosing cholangitis), lower body weight, and shorter warm ischemic time ($P < 0.01$, Table 1). The mean time to observation of the IISAlp after liver transplantation was 6.3 ± 0.8 months. The mean IISAlps, stratified according to age, are shown in Fig. 2. The IISAlps in the patients aged 1–5 years were significantly different from those of the adult patients ($P = 0.016$). Among the patients with IISAlp, 33 (75%) received tacrolimus and 11 (25%) received cyclosporine as the primary immunosuppressant. Among the patients who did not have IISAlp, 155 (71.4%) received tacrolimus and 62 (28.6%) received cyclosporine as the primary immunosuppressant (Table 2). However, the use of immunosuppressants was not significantly associated with the occurrence of IISAlp ($P = 0.63$). The mean follow-up time was 5.5 ± 0.2 years.

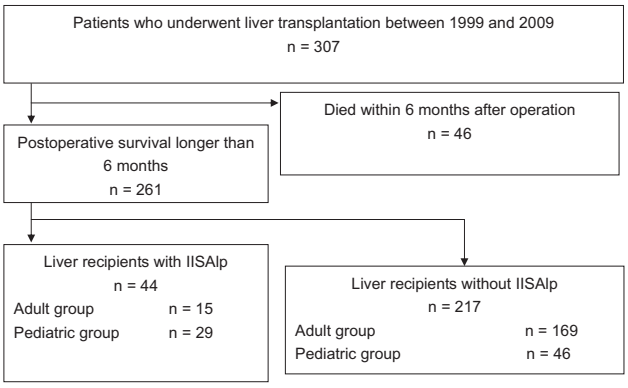

Fig. 1. Patient selection process and inclusion/exclusion criteria. IISAlp: isolated increase in serum alkaline phosphatase.

The adult group had a higher percentage of patients with elevated gamma-glutamyl transpeptidase levels than the pediatric group ($P = 0.028$; Table 3). None of the adult patients with IISAlp and normal gamma-glutamyl transpeptidase level had an adverse outcome. One pediatric patient died of acute myeloid leukemia diagnosed 16 months after IISAlp occurred during the follow-up period. Three patients had chronic biliary stenosis and underwent percutaneous transhepatic cholangio drainage, 2 had transplant rejections, 1 had chronic renal failure requiring hemodialysis, and 1 had recurrence of cholangiocarcinoma. No bone disease was documented.

In the univariate analysis, belonging to the pediatric group, having a low body weight, having a biliary-related disease, and having had a living donor were significant risk factors of IISAlp, with hazard ratios (95% CI) of 7.19 (3.56–14.52), 0.96 (0.95–0.98),

Table 1
Clinical features of liver transplant recipients with and without IISAlp.

IISAlp	With	Without	*P* value
n	44	217	
Total follow-up period, mean ± SD, month	66.6 ± 13.5	85.2 ± 42.9	
Age, years, *n* (%)			<0.01
0–1	10 (22.7)	14 (6.5)	
1–5	16 (36.4)	21 (9.7)	
5–18	3 (6.8)	11 (5.1)	
>18	15 (34.1)	169 (77.9)	
Male, *n* (%)	23 (52.3)	130 (59.9)	0.085
Body weight, mean ± SD, kg	26.9 ± 24.3	51.2 ± 23.5	<0.01
Underlying diagnosis			
Biliary related,[a] *n* (%)	26 (59.1)	66 (30.4)	<0.01
Two bile ducts anastomosed, *n* (%)	3 (6.8)	6 (2.8)	0.37
Donor clinical parameters			
Age, mean ± SD, years	34.5 ± 9.0	31.8 ± 10.3	0.11
Male, *n* (%)	14 (31.8)	122 (56.2)	<0.01
Living donor, *n* (%)	40 (90.9)	138 (63.6)	<0.01
Alkaline phosphatase level, mean ± SD, U/L	132.4 ± 86.3	135.1 ± 76.5	0.36
Warm ischemic time, mean ± SD, min	42.2 ± 12.1	51.8 ± 19.8	<0.01
Cold ischemic time, mean ± SD, min	148.2 ± 132.3	143.7 ± 133.5	0.89

IISAlp: isolated increase in serum alkaline phosphatase; SD: standard deviation.
[a] Biliary-related diagnosis: biliary atresia, progressive familial intrahepatic cholestasis, Alagille syndrome, primary biliary cirrhosis, and primary sclerosing cholangitis.