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Correlation between gamma-glutamyl transpeptidase activity and outcomes after Kasai portoenterostomy for biliary atresia

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ABSTRACT

Background/purpose: The role of serum gamma-glutamyl transpeptidase (GGT) levels in predicting clinical outcomes after Kasai portoenterostomy (KPE) is unknown. This study analyzed whether postoperative GGT along with the aspartate aminotransferase-to-platelet ratio index (APRi) predicted prognosis of biliary atresia (BA).
Methods: Data were retrospectively reviewed for 169 BA patients categorized into jaundice-free (JF) (total bilirubin <2.0 mg/dL ≤6 months post-KPE) and persistent jaundice (PJ) groups (total bilirubin ≥2.0 mg/dL ≤6 months post-KPE). Serum biochemical markers, including GGT levels, were measured monthly after KPE, and mean GGT levels and APRi were compared between groups. Factors predicting native liver survival (NLS) were determined using a Cox regression analysis.
Results: GGT concentrations >550 IU/L at month 5 (hazard ratio: 1.74, $P < 0.05$), an APRi >0.605 at month 4 (hazard ratio: 3.78, $P = 0.001$), and being jaundice-free at 6 months (hazard ratio: 5.49, $P < 0.001$) were independent risk factors for decreased NLS.
Conclusions: Serum GGT concentrations >550 IU/L at month 5 and an APRi >0.605 at month 4 post-KPE were associated with significantly lower NLS rates. Among JF patients, those with GGT concentrations >550 IU/L at month 5 and APRi >0.605 at month 4 showed poorer outcomes.
Type of study: Retrospective comparative study
Level of evidence: Level III.

Biliary atresia (BA) is a progressive neonatal obliterative cholangiopathy of the intrahepatic and extrahepatic bile ducts, often leading to hepatic fibrosis and end-stage liver disease. Although early diagnosis and timely performance of Kasai portoenterostomy (KPE) can restore bile flow and improve native liver survival (NLS), more than half of children with BA are placed on the waiting list for liver transplantation (LT) during their lifetimes [1,2].

Among various prognostic factors for liver failure after KPE, clearance of jaundice is considered the most important, along with the patient's age at the time of KPE, severity of cirrhosis, experience of the surgeon, occurrence of postoperative cholangitis, duct diameter at the porta hepatis, and hepatic hilum morphology. With respect to laboratory values, the aspartate aminotransferase-to-platelet ratio index (APRi) has been used to assess hepatic fibrosis in patients with BA and has been suggested as a predictive parameter of NLS [3,4].

Gamma-glutamyl transpeptidase (GGT) is an epithelial enzyme that catalyzes extracellular glutathione and its conjugate [5]. Traditionally, an elevated serum GGT level has been utilized to indicate cholestatic, alcoholic, and fatty liver diseases. An elevated serum GGT level has also been reported to have high accuracy for differentiating cases of suspected BA from other cases of neonatal cholestasis [6,7]. However, GGT activity is not necessarily considered a routine laboratory test because it is believed to have little prognostic value in patients with BA. In contrast to its diagnostic value, the prognostic role and longitudinal trends of serum GGT levels after KPE have thus far been unexamined.

The first aim of this study was to report the trends for GGT after KPE. The second aim was to analyze the value of using the postoperative serum GGT level along with the above-mentioned APRi as predictive factors for the prognosis of patients with BA.

1. Material and methods

1.1. Patients

One hundred and eighty-two patients with BA underwent KPE between January 2004 and July 2015 at the Severance Children's Hospital,

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRi, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BA, biliary atresia; CI, confidence interval; DB, direct bilirubin; GGT, gamma-glutamyl transpeptidase; JF, jaundice-free; KPE, Kasai portoenterostomy; LT, liver transplantation; NLS, native liver survival; PJ, persistent jaundice; ROC, receiver operating characteristic; TB, total bilirubin.

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Seoul, Korea. From among the initial 182 cases, 13 patients were excluded for the following reasons: (1) 10 patients who had undergone redo KPE at our institution for showing a poor early response to initial KPE performed at other hospitals; (2) 1 patient who died of traumatic brain injury; and (3) 2 patients with a native liver who underwent follow-up for less than 1 year. We performed a retrospective chart review of the remaining 169 cases of BA. During the study period, all patient characteristics and radiologic and laboratory data were entered into a computerized database and reviewed after approval by the Institutional Review Board/Ethics Committee of Severance Hospital. The need for informed consent was waived owing to the study's retrospective nature (approval number: 4-2016-0858).

All KPE procedures were performed by a single surgeon, using the extended portoenterostomy technique. Postoperative care included the use of antibiotics for 1 month, ursodeoxycholic acid, and nutritional and vitamin supplementation for all patients undergoing KPE. The onset time and duration of steroid therapy depended on the patient's jaundice-free (JF) status. Our steroid protocol consists of parenteral methylprednisolone (gradual tapering of the following doses: 10, 8, 6, 5, 4, 3, and 2 mg/kg/d every 24 h) followed by 8 to 12 weeks of oral prednisone (2 mg/kg/d).

1.2. Data collection

Baseline data included sex, date of birth, age at KPE, whether early cholangitis occurred after KPE, time to becoming JF, whether LT was performed, date of LT, date of last follow-up, and final outcome. Data regarding serum levels of platelets, total bilirubin (TB), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and GGT were collected. Each variable was reviewed before and then monthly after KPE until 6 months postoperatively. The APRi was calculated as the serum AST level (IU/L)/upper normal limit (50 IU/L) × 100/platelet count (10^3/μL). Early cholangitis was defined as fever (>38.0 °C) accompanied by elevated serum TB, leukocytosis with left shift, and normal to acholic stools within 6 months after KPE. The study population was categorized into the JF group (serum total bilirubin <2.0 mg within 6 months after KPE) and the persistent jaundice (PJ) group (serum total bilirubin ≥2.0 mg within 6 months after KPE). The changing trends in GGT and APRi in each group within 6 months postoperatively were compared.

1.3. Statistical analysis

Continuous data are expressed as means with standard deviations, and categorical variables are presented as proportions and analyzed using the chi-squared test. Survival was calculated on the basis of the interval from birth to the patient's death or loss of their native liver. NLS rates were estimated using the Kaplan–Meier method. The log-rank method was used to test the equality of survival distributions among the groups. Potential prognostic factors affecting NLS were determined using univariate and multivariate analyses; variables found to be significant in the univariate analysis were tested by a multivariate analysis using the Cox proportional hazards model. A receiver operating characteristic (ROC) curve analysis was performed to clarify the cutoff value of GGT and APRi each month pre- and postoperatively. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM-SPSS, Inc., Chicago, IL, USA) and R language version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a p value of <0.05.

2. Results

2.1. Baseline characteristics

Fig. 1 summarizes the treatment and outcomes of the included BA patients. Of the 169 patients included in the analysis, 125 (74.0%) became JF, but jaundice remained in 44 patients (26.0%). Eighteen patients in the JF group finally progressed to an unfavorable condition requiring LT, and 3 patients died without LT, while 104 patients remained JF. Accordingly, 13 out of 169 enrolled patients died (7.7%), 41 patients survived after LT (24.3%), and 115 (68.0%) patients survived with their native livers within a median follow-up period of 62 months (interquartile range, 29–94 months).

The baseline characteristics and preoperative data of the enrolled patients are presented in Table 1 according to the clearance of jaundice at 6 months after KPE. Compared with patients in the PJ group, patients in the JF group were younger at KPE (59.4 vs. 75.7 days, p = 0.003) and had lower TB (7.72 vs. 9.53 mg/dL, p = 0.008) and lower ALP (528.1 vs. 638.0 IU/L, p = 0.037) levels. The male/female ratio; presence of early cholangitis; preoperative albumin, AST, ALT, APRi and GGT levels; and maximum duct diameter at the porta hepatis were not significantly different between the two groups.

2.2. Chronological changes in postoperative GGT levels and APRi in the JF and PJ groups

Serum GGT levels for the JF and PJ groups were obtained over a period of 6 months after KPE (Fig. 2A). Mean serum GGT levels increased, with no significant differences between the JF and PJ groups during the first month. Patients in the JF group showed significantly lower mean GGT values beginning in month 2 and continuing to month 6. Serum GGT activity in the JF group peaked in the first month and decreased thereafter, while GGT activity in the PJ group peaked in the second month, with a higher level than that in the JF group, and decreased beginning in the third month.

Using serum AST and platelet count, the monthly mean APRi for the JF and PJ groups was calculated over a period of 6 months after KPE (Fig. 2B). In the PJ group, the APRi was significantly higher at all postoperative time points (P < 0.05) than that in the JF group, while the preoperative APRi was not statistically different between groups (P = 0.076). In the PJ group, the mean APRi was lowest, at 1.04, in the first month and gradually increased after that time. APRi did not show a typical rising and falling pattern, in contrast to the pattern for GGT.

2.3. ROC curve for determining the cutoff GGT and APRi values associated with clinical outcomes

We established GGT and APRi cutoff values at each time point in patients with BA that were predictive of achieving 5-year NLS. The optimal pair of sensitivity and specificity was indicated by the point at which the ROC value was closest to the upper left corner of the curve. Four time points of GGT measurements and APRi (months 3–6) that were significantly different between the two groups, based on the Student t-test analysis, were selected for the ROC analysis to determine their association with outcomes at each time point (Table 2). The greatest area under the receiver operating characteristic curve (AUROC) of the selected GGT measurement at month 5 for achieving 5-year NLS was 0.737. The ideal cutoff value of GGT determined by the ROC analysis was set at 550 IU/L at month 5. The greatest AUROC for APRi for 5-year NLS was 0.801 at month 4. The ideal cutoff value of APRi determined by the ROC analysis was set at 0.605 at month 4.

2.4. Factors associated with clinical outcomes

The impacts of the cutoff value of GGT and APRi, along with several known prognostic factors, were evaluated using Cox regression analyses over the follow-up period (Table 3). The prognostic performance of GGT >550 IU/L at month 5 (hazard ratio: 1.74; 95% CI: 1.40–2.87; P = 0.026), APRi >0.605 at month 4 (hazard ratio: 3.78; 95% CI: 1.73–8.30; P = 0.001), and TB <2.0 mg/dL by 6 months (hazard ratio: 4.64, 95% CI: 2.43–8.87, P < 0.001) was significant for NLS based on the results of the multivariate analysis.