SHORT REPORT

Prediction of asialoglycoprotein receptors by correlated liver function parameters before hepatectomy

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Abstract

Flow cytometric analysis of asialoglycoprotein receptor (ASGPR) levels on the surface of hepatocytes, which were obtained from the liver specimens of patients that received hepatectomy, were used as predictors of liver dysfunction after major hepatectomy for primary hepatocellular carcinoma (HCC) in Chinese patients, based on our previous study which confirmed the value of ASGPR levels on the surface of hepatocytes in evaluating the liver reserve function. The current study was planned to establish a conversion formula for the value of ASGPR with correlated liver function parameters. It was conducted from January 1, 2014, to June 30, 2015, at Beijing DiTan Hospital, Beijing, China, and comprised 55 patients having undergone major hepatectomy. The outcomes of hepatectomy were compared with ASGPR levels and preoperative liver function parameters. A multiple linear regression model was used to identify the converted ASGPR value. The calculated ASGPR level was derived as: 80.695 + 0.002 × cholinesterases (CHE) (IU/L) - 0.620 × indocyanine green retention rate at 15 min (ICGR15)(%) - 0.655 × total bilirubin (TB) (umol/L). Receiver-operator characteristic curve analysis showed that the sensitivity and specificity of the ASGPR value ≤68.18% were 100% and 77.3% respectively for predicting liver dysfunction after hepatectomy. The converted ASGPR value may be reliable index for hepatic functional reserve in patients undergoing hepatectomy.

Keywords: Asialoglycoprotein receptor, ASGPR, Hepatocellular carcinoma, Liver failure, Hepatectomy.

Introduction

Flow cytometric analysis of asialoglycoprotein receptor (ASGPR) levels on the surface of hepatocytes, which were obtained from the liver specimens of patients that received hepatectomy, were used as predictors of liver dysfunction after major hepatectomy for primary hepatocellular carcinoma (HCC) in Chinese patients, based on our previous study.[1] In order to assess ASPGR as a non-invasive preoperative diagnostic test, we examined the correlation between ASGPR levels and conventional hepatic functional parameters. Based on this analysis, we sought to establish a conversion formula for ASGPR as correlated with hepatic function parameters to assess hepatic functional reserve and the risks of hepatectomy.

Methods and Results

The study was conducted from January 1, 2014, to June 30, 2015, at Beijing DiTan Hospital, Beijing, China, and comprised 55 patients with HCC and cirrhosis who had undergone major hepatectomy. The European Association for the Study of the Liver guidelines[2] were used to diagnose all patients with HCC before treatment. All patients in the study were classified as Child-Pugh[3] A

Table-1: Demographic and clinical characteristics of patients.

Characteristic	Value
Age (years)	47 (39-54)
Male/Fmale	37/18
Surgical duration (min)	130(130-140)
Blood loss (mL)	500 (500-600)
The hepatic hilum blocking time (min)	16 (12-18)
MELD score	5 (4-6)
ALT (IU/L)	47.6 (35.5-57.0)
AST (IU/L)	60.5 (43.6-76.4)
TB (umol/L)	16.6 (12.1-18.4)
CHE (IU/L)	6530 (5132-7642)
ALB (g/L)	38.7 (37.2-40.5)
PTA (%)	76.4 (68.9-81.5)
INR	1.33 (1.25-1.45)
PLT ($\times 10^9$/L)	82 (76-93)
ICGR15 (%)	21.3 (14.8-24.3)
ASGPR (%)	72.2 (68.6-74.6)

Note: The data are shown as median (interquartile range) or n .
MELD: Model for End-Stage Liver Disease
ALT: Alanine aminotransferase
AST: Aspartate aminotransferse
TB: Total bilirubin.
CHE: Cholinesterases
ALB: Serum albumin
PTA: Prothrombin activity
INR: International normalised ratio
PLT: Blood platelet count
ICGR15: Indocyanine green retention rate at 15 min
ASGPR: Asialoglycoprotein receptor.

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Table-2: The covariates included in the model by multiple linear regression.

Independent variables	Coefficient	Std. Error	r	t	P
(Constant)	80.6951				
CHE	0.002013	0.0005588	0.4503	3.602	0.0007
ICGR15	-0.6198	0.1123	-0.6116	-5.521	<0.0001
TB	-0.6545	0.1545	-0.5101	-4.235	0.0001

CHE, cholinesterases. ICGR15, indocyanine green retention rate at 15 min. TB, total bilirubin.

regarding liver function before surgery. If the residual liver volume with optimal blood outflow and inflow and if biliary drainage was expected to be sufficient, technical feasibility was established. After the patient received general anaesthesia, surgical resection was performed using a bilateral subcostal incision. The preferred surgical method for liver resection was anatomic resection in the form of segmentectomy, as described by Hasegawa et al.[4] Hyperbilirubinaemia or a serum total bilirubin (TB) level over 5.0 mg/dl and persistent ascites or pleural effusion was the basis for defining postoperative hepatic dysfunction.[5]

Measuring aspartate aminotransferse (AST), alanine aminotransferase (ALT), TB, serum albumin (ALB), cholinesterases (CHE), prothrombin activity (PTA), international normalised ratio (INR), blood platelet count (PLT) and model for end-stage liver disease (MELD) score were standard procedures before surgery. The ICGR15 was measured by a photopiece applied to the fingertip (DDG-3300K; Nihon Kohden Corp., Tokyo, Japan) without blood sampling.[6] Measurement of hepatocyte ASGPR was carried out according to our previous research methods.[1]

SPSS version 21 was used for statistical analyses. A Fisher's exact test was used to compare dichotomous variables. Correlations between the ASGPR value and conventional hepatic functional parameters were examined by calculating Pearson's correlation coefficient. The multiple linear regression formula was calculated using the correlated parameters. Receiver-operator characteristic (ROC) curve analysis was performed for the converted ASGPR value. Cut-off value points were determined with area under the curve (AUC) and the corresponding sensitivity and specificity values. A Z test was used to compare the AUC-converted and actual ASGPR values. Two-tailed significance tests were employed. Statistical significance was assessed as $p<0.05$.

Of the 55 patients in the study, 37(67%) were males (Table-1) No patient was lost during the 3-month follow-up period. Postoperative hepatic dysfunction occurred in 11(20%) patients.

Significant correlations were observed between ASGPR and CHE ($r = 0.826$, $p< 0.01$); ASGPR and ICGR15 ($r = -0.818$, $p< 0.01$); ASGPR and PLT ($r = 0.805$, $p< 0.01$); ASGPR and INR ($r = 0.763$, $p< 0.01$); ASGPR and PTA ($r = 0.699$, $p< 0.01$); ASGPR and TB ($r = -0.692$, $p< 0.01$); ASGPR and ALT ($r = -0.461$, $p< 0.01$) and ASGPR and AST ($r = -0.366$, $p< 0.01$). A multiple linear regression model was used to identify the ASGPR value. The covariates included in the model were CHE, ICGR15 and TB (Table-2), and the following formula was obtained: Converted ASGPR (%) = 80.695 + 0.002 × CHE(IU/L) - 0.620 × ICGR15(%) - 0.655 × TB (umol/L). The area under the ASGPR and converted ASGPR value-dependent ROC curves was 0.860 (95% confidence interval [CI]: 0.739 to 0.938) and 0.932 (95% CI: 0.591 to 0.839), respectively, and there was no statistically significant differences ($z = 1.345$, $p= 0.178$).

The cut-off value of converted ASGPR to predict postoperative hepatic dysfunction was 68.18% according to ROC analysis. The sensitivity and specificity were 100% and 77.3%. The positive and negative predictive values were 52.4% and 100% respectively. We divided patients into two groups according to this standard. A total of 21(39%) patients had a converted ASGPR $\leq$ 68.18%, 11 (52.38%) of whom had postoperative liver dysfunction. In contrast, among 34(61%) patients with a converted ASGPR >68.18%, no one had postoperative liver dysfunction ($p<0.01$).

Conclusion

In this study, we hypothesised that a converted ASGPR level could be calculated based on other hepatic functional parameters. In order to facilitate clinical testing, we chose the parameters of conventional liver function tests, ICGR15, and MELD scores as indices of preoperative liver function. We examined the correlations among the preoperative liver function parameters and ASGPR level. Subsequently, ICGR15, serum CHE level, and serum TB level were selected as candidates for the estimation equation.

From our analysis, a multiple linear regression model was derived: Converted ASGPR (%) = 80.695 + 0.002 × CHE(IU/L) - 0.620 × ICGR15(%) - 0.655 × TB(umol/L). The

measurement of the blood ICGR15 could reveal the metabolic function of the liver.[7] Elevated plasma concentrations of bilirubin are specific markers for serious liver injury and, therefore, liver function loss.[8] Changes in serum CHE activity have been observed in chronic hepatitis and cirrhosis.[9] Thus, the three parameters used for the conversion formula could comprehensively reflect main functions of the liver.

ROC curve results suggested that converted ASGPR was similar to actual ASGPR in predicting postoperative liver dysfunction. There was a higher rate of liver dysfunction when the converted value was ≤68.18%%. In order to further test the diagnostic accuracy of the converted ASGPR value, we assumed that the incidence of postoperative hepatic dysfunction was the overall disease prevalence for hepatectomy patients, and the positive and negative predictive values of the converted ASGPR were calculated. At a cut-off of 68.18%, converted ASGPR has a high negative predictive value, which can increase confidence in postoperative liver function when planning surgery, but a modest positive predictive value limits its use for exclusion of the risk of postoperative liver failure. This is a reminder that other appropriate indicators should be employed to remedy the defects of the conversion model in our future research.

Our study had a small sample from a single centre which prevents its scope from generalising its results.

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