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RESEARCH ARTICLE

Glutathione S-transferase O2 gene rs157077 polymorphism predicts response to transarterial chemoembolization in hepatocellular carcinoma

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Abstract Some genetic alterations of glutathione *S*-transferase omega 2 (GSTO2) have been reported to increase the risk of many malignancies, including hepatocellular carcinoma (HCC); however, their prognostic capability remained unresolved in HCC patients treated with transarterial chemoembolization (TACE). To fill this gap, we genotyped three well-defined polymorphisms in *GSTO2* to assess whether they can predict overall survival among 228 HCC patients under TACE treatment. The median follow-up time and survival time were 22.0 months (range 3.0–60.0) and 19.2 months, respectively. Only one of three polymorphisms examined, rs157077, was significantly associated with overall survival of TACE-treated HCC (P=0.003), and its mutant allele conferred a higher risk of death than its wild homozygotes (hazard ratio 1.58, 95 % confidence interval 1.17–2.14). Moreover, carriers of this mutant allele had higher tissue GSTO2 expression, reinforcing the prognostic capability of *GSTO2* rs157077 for HCC, especially in combination with age and tumor–node–metastasis (TNM) stage. Taken together, we for the first time provided evidence supporting the prognostic role of *GSTO2* in the progression of TACE-treated HCC.

Keywords Glutathione *S*-transferase omega · Hepatocellular carcinoma · Prognosis · Transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, especially in China, and it largely remains incurable [1]. As estimated, only 10–37 % of HCC patients with advanced tumor or poor hepatic functional reserve are suitable for surgery [2], and it is a high priority to adopt nonsurgical local therapy in routine clinical practice to improve survival and palliation of HCC patients [3]. Transarterial chemoembolization (TACE), as a minimally invasive treatment, has been recommended as a first-line palliative therapy for nonsurgical cases with large or multifocal lesions and no vascular invasion of distant metastasis [4]. However, the prognosis for HCC patients treated with TACE varied greatly according to host characteristics [5, 6] and disease status [7]. Traditional clinicopathological features such as tumor stage, histological grade, and concentration of serum alpha-fetoprotein (AFP) seem to insufficiently predict clinical outcomes in HCC patients. Therefore, there is an urgent need to develop novel discriminatory biomarkers for HCC patients with different clinical outcomes. The recent decade has witnessed extraordinary advances in investigating imaging and serological markers to predict survival and response to TACE treatment [8–11]. However, very few studies so far

have explored the prognostic capability of potential genetic markers.

Glutathione *S*-transferases (GSTs) are a family of phase II isoenzymes that detoxify toxicant [12], and its dysfunction has been documented to be closely related with chemotherapeutic response [13–15]. Glutathione *S*-transferase omega 2 (GSTO2) belongs to the omega class of GSTs, and its detoxifying property is partially genetically determined [16]. Several lines of supportive evidence indicated that genetic alterations in *GSTO2* were associated with significant risks of many digestive cancers, such as hepatocellular carcinoma, gastric cancer, and colorectal cancer [17, 18]. However, evidence for the prognostic capability of genetic alterations in *GSTO2* for cancer is sparse. To address this issue, in this study, we explored three polymorphisms in *GSTO2* and assessed the associations of these polymorphisms with overall survival in a cohort of 228 Chinese HCC patients under TACE therapy.

Materials and methods

Study participants

All study participants were consecutively recruited at the Department of Hepatobiliary Surgery and Department of Cardiology and Periphery Vascular Medicine, the First Affiliated Hospital of Xi'an Jiaotong University in Xi'an, China, and they were newly diagnosed and histopathologically confirmed HCC patients. All study patients received TACE treatment and had no previous history of other cancers or cancer-related treatments. Participants received other treatments (such as chemotherapy, interventional therapy, or biological target therapy) after surgical operation was excluded for further analysis. Ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University approved this study. Written informed consent was obtained from each participant before enrollment.

Demographic and clinical data

For each participant, demographic data included age at diagnosis, gender, hepatitis B surface antigen (HBsAg) status, liver cirrhosis, Child–Pugh score, serum AFP level, and tumor–node–metastasis (TNM) stage (I, II, or III) and were recorded. Venous blood was stored in Vacutainer tubes at 4 °C. Genomic DNA was extracted from peripheral blood leukocytes using E.Z.N.A. Blood DNA Midi Kit (Omega Bio-Tek, Norcross, GA, USA), according to the manufacturer's instructions. All participants were followed up postoperatively at 3-month intervals in the 1st year, 6-month intervals in the 2nd year, and annually thereafter. The survival time was defined as the period from the date of first treatment to the date of death or last follow-up.

Polymorphism selection and genotyping

Three examined polymorphisms (rs156699, rs157077, and rs7085725) within *GSTO2* were selected from NIEHS, a set of web-based single nucleotide polymorphism (SNP) selection toll (National Institute of Environmental Health Sciences, http://snpinfo.niehs.nih.gov/snpinfo/snptag.htm). They were common polymorphisms with a minor allele frequency ≥0.05 in a population of Chinese Han in Beijing (CHB) and a design score cutoff ≥0.6. Genotyping was performed using the Sequenom MassARRAY iPLEX genotyping system (Sequenom Inc., San Diego, CA, USA). Data management and analyses were performed using Sequenom Typer 4.0 software.

Table 1 Univariate and multivariate analysis of factors associated with HCC overall survival

Variable	Outcome, *n* (%)		AHR (95 % CI)	*P* value[a]
	Dead	Alive		
Age (years)				*<0.001*
≤55	88 (75.9)	28 (24.1)	1 (reference)	
>55	108 (96.4)	4 (3.6)	1.48 (1.01–2.18)	
Gender				0.121
Male	162 (85.3)	28 (14.7)	1 (reference)	
Female	34 (89.5)	4 (10.5)	1.34 (0.93–1.95)	
HBsAg status				0.519
Negative	47 (85.5)	8 (14.5)	1 (reference)	
Positive	149 (86.1)	24 (13.9)	1.12 (0.80–1.56)	
Cirrhosis				0.828
Absent	27 (75.0)	9 (25.0)	1 (reference)	
Present	169 (88.0)	23 (12.0)	0.96 (0.63–1.44)	
Child–Pugh score				0.123
A	131 (86.2)	21 (13.8)	1 (reference)	
B	65 (85.5)	11 (14.5)	1.10 (0.83–1.46)	
AFP level (ng/mL)				0.526
<200	114 (87.0)	17 (13.0)	1 (reference)	
≥200	82 (84.5)	15 (15.5)	1.00 (0.68–1.46)	
Tumor size (cm)				0.182
<5	89 (89.0)	11 (11.0)	1 (reference)	
≥5	107 (83.6)	21 (16.4)	1.22 (0.91–1.62)	
TNM stage				*<0.001*
I+II	73 (70.9)	30 (29.1)	1 (reference)	
III	123 (98.4)	2 (1.6)	1.38 (1.13–1.67)	

[a] *P* value was derived from multivariate analysis using Cox proportional hazard regression model. Adjusted hazard ratio was adjusted by age and TNM stage. Significant *P* values are shown in italics

AHR adjusted hazard ratio, *95 % CI* 95 % confidence interval

Table 2 Associations between polymorphisms of the three polymorphisms within *GSTO2* and overall survival in HCC patients

SNPs	Genotype	Outcome, *n* (%)		AHR (95 % CI)	*P* value[a]
		Dead	Alive		
rs156699	TT	123 (83.7)	24 (16.3)	1 (reference)	
	TC+CC	73 (90.1)	8 (9.9)	1.05 (0.78–1.41)	0.732
rs157077	AA	63 (77.8)	18 (22.2)	1 (reference)	
	AG+GG	133 (90.5)	14 (9.5)	*1.58 (1.17–2.14)*	*0.003*
rs7085725	TT	148 (85.5)	25 (14.5)	1 (reference)	
	TC+CC	48 (87.3)	7 (12.7)	0.79 (0.57–1.10)	0.156

[a] *P* value was derived from multivariate analysis using Cox proportional hazard regression model. Adjusted hazard ratio was adjusted by age and TNM stage. Significant values are shown in italics

AHR adjusted hazard ratio, *95 % CI* 95 % confidence interval

Statistical analysis

All statistical analyses were performed using the SPSS software version 21.0 statistical package for Microsoft Windows (SPSS, Chicago, IL, USA). Study power was computed using the Power and Sample Size Calculation (PS) software version 3.0.7. Each genotype of examined polymorphisms was examined in a logistic regression model. Risk estimates are expressed as hazard ratios (HRs) and its 95 % confidence interval [95 % confidence interval (CI)] as estimated from multivariate Cox proportional hazard model. Multivariate analysis was adjusted by age and TNM stage. Kaplan–Meier curves and log-rank tests were used to assess the overall survival associated with different genotypes. All statistical tests

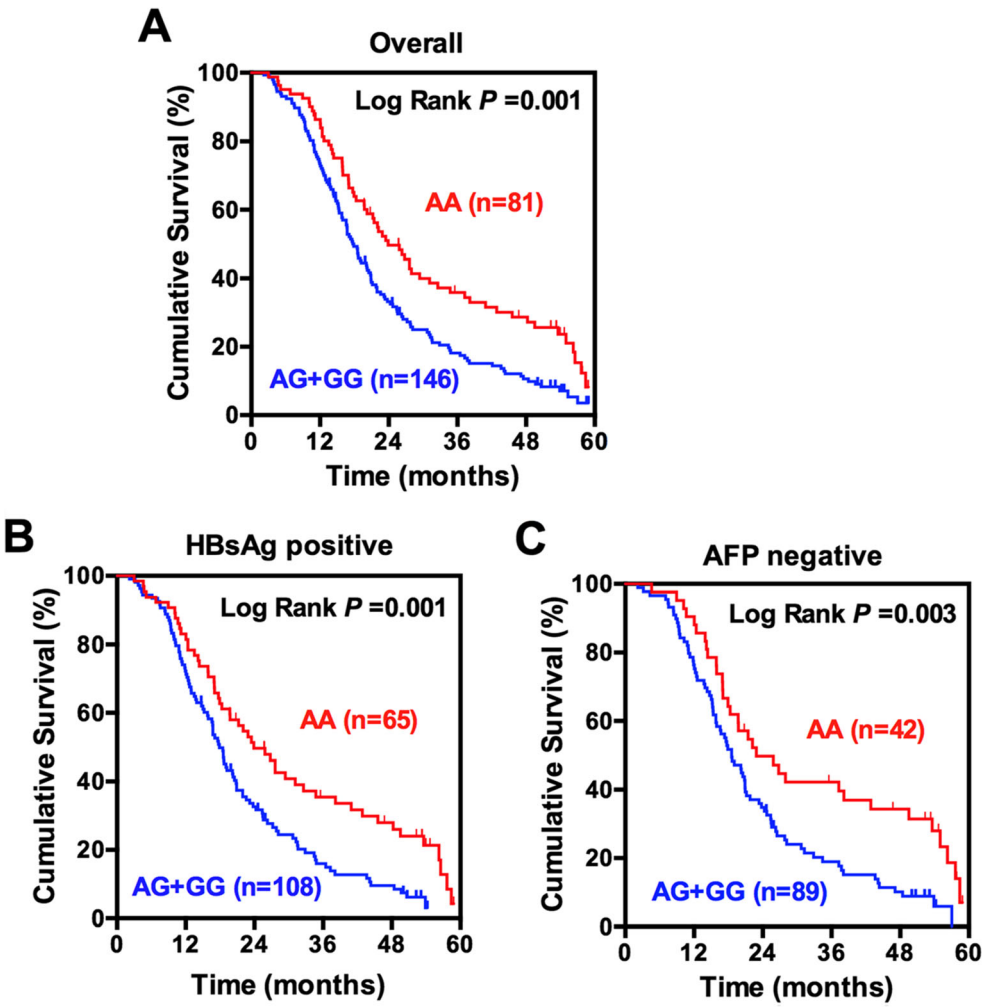

Fig. 1 Kaplan–Meier curves for HCC patients carrying the rs157077 mutant allele. **a** In all patients. **b** In HBV-positive patients. **c** in AFP-negative (<200 ng/mL) patients

were two-sided, and $P<0.05$ was accepted as statistically significant.

Results

Clinical characteristics of study participants

Clinical characteristics of all 228 HCC patients treated with TACE are shown in Table 1. For all the patients, the median age at the time of HCC diagnosis was 55 years (range 21–87). The majority of patients were males (83.3 %) and complicated by HBsAg positive (75.9 %) and liver cirrhosis (84.2 %) status, 66.7 % of patients were classified as Child A, and 56.1 % of patients presented with tumor size ≥5 cm. More than half of the patients (57.5 %) had low serum AFP level (<200 ng/mL). The percentages of patients with TNM stages I, II, and III were 18.4, 14.9, and 66.7 %, respectively. At the end of follow-up, 14.0 % ($n=32$) of patients were dead, and the median survival time was 19.2 months. Furthermore, Cox regression analyses showed poorer overall survival in patients with older age [adjusted HR (95 % CI)=1.48 (1.01–2.18); $P<0.001$] and advanced TNM stage [adjusted HR (95 % CI)=1.38 (1.13–1.67); $P<0.001$].

Association of rs157077 with overall survival

The influences of the three examined polymorphisms in *GSTO2* were assessed on overall survival of HCC patients treated with TACE (Table 2). Under the dominant model, rs157077 was significantly associated with the overall survival. Patients carrying the mutant allele of rs157077 had a significantly increased risk of death [adjusted HR (95 % CI)= 1.58 (1.17–2.14)], compared with those homozygous for the wild type ($P=0.003$). Kaplan–Meier analysis showed a significantly shorter median survival time in rs157077 mutant allele carriers than those homozygous for the wild type (17.0 vs. 21.2 months; log rank $P=0.001$) (Fig. 1a).

The effect of rs157077 on the overall survival in HCC patients was further stratified by demographic and clinicopathological characteristics. As shown in Table 3, the significant increased death risk conferred by rs157077 was observed in younger patients [HR (95 % CI)=1.71 (1.05–2.81); $P=0.033$], HBsAg-positive patients [HR (95 % CI)=1.65 (1.16–2.35), $P=0.006$], and AFP-negative patients [HR (95 % CI)=1.72 (1.12–2.65); $P=0.014$]. Log-rank test further indicated significant shorter OS time of mutant allele carriers in those patients with abovementioned factors (Fig. 1b, c).

Association of rs157077 with GSTO2 expression

The expression quantitative trait locus (eQTL) analysis was conducted to explore whether rs157077 have functional relevance using Genevar software. Genevar analysis showed that the mutant allele (G) was consistently correlated with higher expression of *GSTO2* in adipose and skin tissues obtained from healthy female twins (Fig. 2).

Survival tree analysis

A survival tree analysis was performed to explore the potential prognostic capability of rs157077. The top splitting factor was TNM stage, followed by age and rs157077, resulting in a four-terminal node tree (Fig. 3a). The median survival time was 15.8 months for terminal node 1 (HCC patients with TNM stage III) and 18.7 months for terminal node 2 (patients with TNM stage I+II and age >55 years). In those HCC patients with younger age (≤55 years), TNM stage I+II and carrying the rs157077 homozygous wild type had a better clinical

Table 3 Stratified analyses on the association between rs157077 genotypes and overall survival of HCC patients

Variable	Dead/alive		AHR (95 % CI)	*P* value[a]
	AA	AG+GG		
Age (years)				
≤55	25/17	63/11	*1.71 (1.05–2.81)*	*0.033*
>55	38/1	70/3	1.04 (0.70–1.55)	0.859
Gender				
Male	56/18	106/10	1.36 (0.98–1.90)	0.067
Female	7/0	27/4	0.74 (0.26–2.07)	0.559
HBsAg status				
Negative	40/15	87/9	1.60 (0.82–3.12)	0.167
Positive	23/3	46/5	*1.65 (1.16–2.35)*	*0.006*
Cirrhosis				
Absent	12/4	35/4	1.56 (0.58–4.15)	0.375
Present	51/14	98/10	1.26 (0.90–1.75)	0.174
Child–Pugh score				
A	6/4	21/5	1.29 (0.88–1.88)	0.186
B	57/14	112/9	1.54 (0.89–2.66)	0.119
AFP level (ng/mL)				
<200	42/11	89/10	*1.72 (1.12–2.65)*	*0.014*
≥200	20/8	13/1	1.07 (0.66–1.72)	0.790
Tumor size (cm)				
<5	33/9	81/8	1.51 (0.94–2.45)	0.090
≥5	30/9	52/6	1.28 (0.85–1.94)	0.244
TNM stage				
I+II	25/7	64/4	1.28 (0.80–2.05)	0.313
III	38/11	69/10	1.27 (0.83–1.92)	0.270

[a] *P* value was derived from multivariate analysis using Cox proportional hazard regression model. Adjusted hazard ratio was adjusted by age and TNM stage. Significant values are shown in italics

AHR adjusted hazard ratio, *95 % CI* 95 % confidence interval

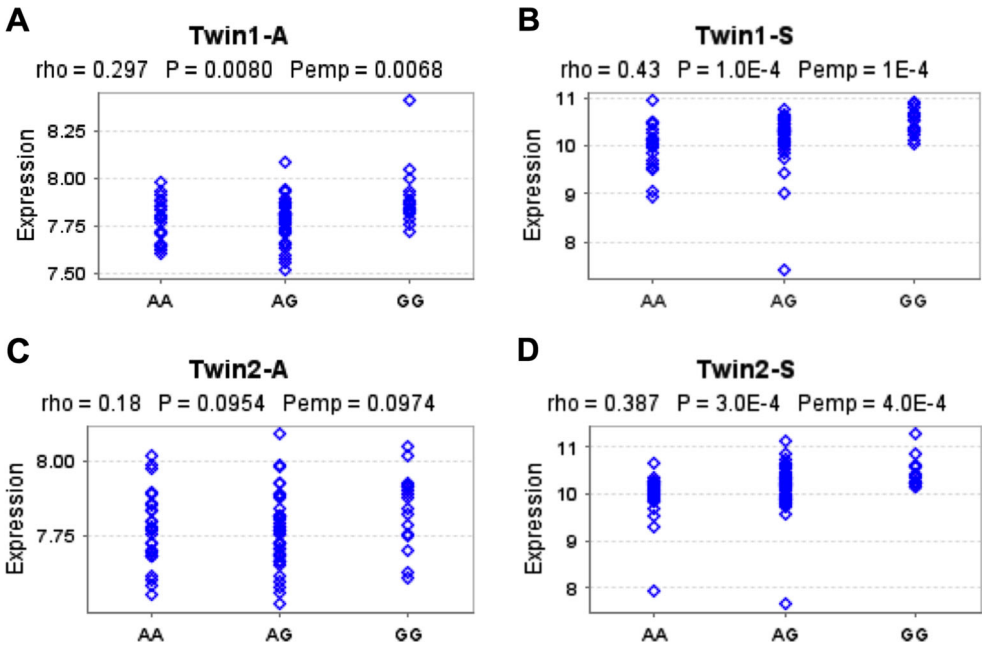

Fig. 2 Association between the rs157077 genotype and the *GSTO2* expression in tissues from healthy female twins based on an eQTL analysis in the Genevar database of SNP–gene associations. **a**, **c** Adipose tissue. **b**, **d** Skin tissue; *rho* correlation value, *Pemp* non-parametric permutation *P* value for 10,000 reiterations

outcome with a median survival time of 45.6 months, when compared with those mutant allele carriers ($P<0.001$; Fig. 3b).

Discussion

In the present study, we evaluated the prognostic capability of the three polymorphisms within *GSTO2* among 228 TACE-treated HCC patients. We found that only rs157077 was significantly associated with the overall survival of HCC patients. To the best of our knowledge, this is the first study to investigate the prognostic value of *GST* genetic alterations for the TACE-treated HCC.

TACE is a widely used therapy in clinical practice for mid-stage HCC, and its anti-tumoral effect is mainly achieved through the occlusion-related hypoxia and chemotherapy-induced cytotoxicity, implicating in the induction of oxidative damage and cell death after DNA damage. As an important oxygen free radical-scavenging enzyme, GSTO2 protects normal hepatocytes against oxidative damage induced by chemical toxicant [19, 20]. Considering that GSTO2 activity is under genetic control [16], it is therefore reasonable to assume that *GSTO2* genetic alterations might affect cancer risk and prognosis. Indeed, previous case–control studies have demonstrated that some *GSTO2* polymorphisms were associated with an increased risk of cancer [18, 21–24], possibly by modulating *GSTO2* gene expression level [25]. However, the genetic effect of *GSTO2* on cancer prognosis is still largely unknown. In the present study, we, for the first time, identified a common polymorphism, rs157077, in *GSTO2* as a primary factor to predict the clinical outcome of HCC patients either in

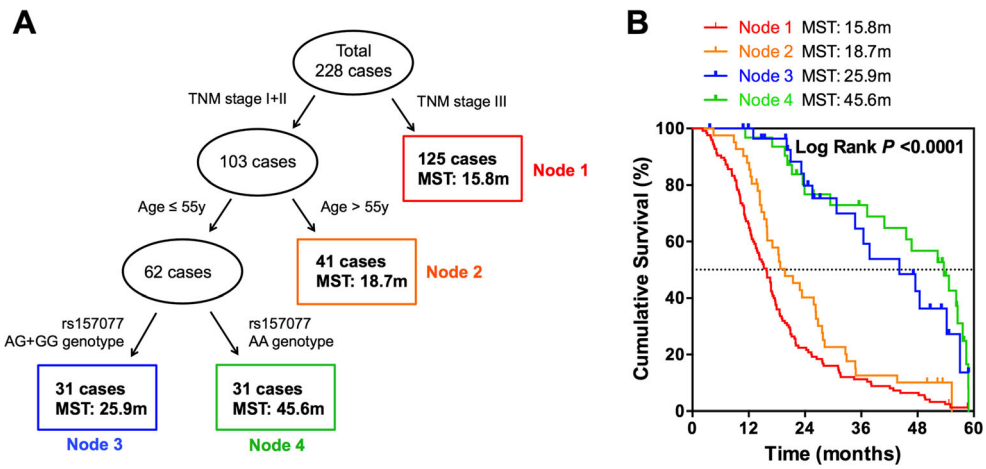

Fig. 3 Classification and regression tree analysis of rs157077. **a** Survival tree analysis of rs157077 with HCC overall survival. The *number under each node* represents a median survival time. **b** Overall survival according to different risk groups identified by survival tree analysis

overall or in stratified analysis. The potential contribution of rs157077 to overall survival was also consolidated by survival tree analysis. When combining rs157077 with age and TNM stage, two important prognosis factors, our risk prediction model exhibited strong prognostic capability for TACE-treated HCC patients.

To date, little is known about the functional role of *GSTO2* in carcinogenesis. It has been observed that the *GSTO1* gene, which was a paralog gene and exhibited very similar biological function to *GSTO2*, was over-expressed in chemo- and radio-resistant cancer cells [26, 27] and was involved in cancer cell invasion and metastasis [28]. On the basis of these observations, *GSTO2* is believed to play an important role in cancer progression and alteration of *GSTO2* which determine cancer patients' survival. In the present study, we found that the mutant allele of rs157077 in *GSTO2* was significantly correlated with *GSTO2* expression in tissues, the finding serving as a potential explanation that rs157077 mutant allele carriers had shorter survival time after TACE treatment, compared with the wild homozygotes, which might be due to their higher *GSTO2* expression.

Another important finding of our study was that *GSTO2* rs157077 was identified to be significantly associated with overall survival in AFP-negative patients. AFP, the only universally recognized tumor marker for HCC [29], served as a marker for prognosticating response to TACE therapy for a long time. However, estimates of the prognostic value of serum AFP level between studies differed widely [30, 31]. Considering that approximately 70 % of TACE-treated HCC patients are AFP negative [32], new prognostic biomarkers are needed to improve treatment efficacy. Our findings supported the use of rs157077 as an ancillary method to predict TACE response in AFP-negative HCC patients.

Several possible limitations should be acknowledged for this study. First, the moderate sample size might limit the validity of some stratified analyses. Second, only three polymorphisms within *GSTO2* were examined. It is highly encouraged to incorporate other polymorphisms, especially the low-penetrance polymorphisms in *GSTO2* and other relevant genes. Third, the fact that our study participants were of northwestern Han Chinese descent limited the generalizability of our findings, calling for further evaluation to determine whether these findings can be generalized to other ethnic groups.

In conclusion, this study provided the first epidemiological evidence in favor of a role of rs157077 in the prognostic prediction of a Chinese population of HCC patients under TACE therapy. If validated, this genetic polymorphism may potentially be developed as a simple non-invasive predictive biomarker.

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Conflicts of interest None

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