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Review Article

Prognostic value of serum gamma-glutamyltransferase in patients with hepatocellular carcinoma: a meta-analysis

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Abstract: Inconsistent findings have emerged concerning the prognostic value of serum gamma-glutamyltransferase (GGT) in patients with hepatocellular carcinoma (HCC). The current meta-analysis aimed to evaluate the prognostic value of serum GGT in HCC patients. Eligible studies were identified through a search of PubMed, Web of Science, and Embase databases, from inception to May 2018. Only studies reporting the association of elevated serum GGT levels with overall survival (OS) and recurrence-free survival (RFS) in HCC patients were included. Hazard ratios (HR) and 95% confidence intervals (CI) were pooled for high versus low serum GGT levels as effective measures. Twelve studies, with 2,621 HCC patients, were identified and analyzed. The present meta-analysis showed that HCC patients with elevated serum GGT levels were significantly associated with poor OS (HR 2.05; 95% CI, 1.78-2.37) and RFS (HR 1.60; 95% CI 1.39-1.85). Subgroup analysis yielded similar prognostic values for OS in different cut-off values of serum GGT, sample sizes, and treatment method groups. Results suggest that elevated serum GGT levels are independent predicators of poor survival and disease recurrence in HCC patients, especially for Chinese patients.

Keywords: Hepatocellular carcinoma, prognosis, overall survival, recurrence-free survival, meta-analysis

Introduction

Liver cancer is the sixth most frequent malignant tumor and the third leading cause of cancer-related mortality [1]. Approximately 90% of all primary liver cancers are hepatocellular carcinoma (HCC) [2, 3]. Despite dramatic improvements in treatment and surveillance schedules, prognosis of HCC patients remains poor due to a lack of precise markers of tumor recurrence and distant metastasis [4]. Five-year survival rates of HCC patients are around 5% to 6% [5]. These patients should receive more active treatment. Development of new prognostic biomarkers is very important for improvement of outcomes in HCC patients. However, current clinical uses of prognostic biomarkers for HCC are imperfect [6]. Therefore, there are unmet needs in the identification of additional prognostic biomarkers, particularly circulating biomarkers for prognosis and recurrence of HCC.

Gamma-glutamyltransferase (GGT) is a membrane-bound enzyme involved in glutathione metabolism [7]. Serum GGT has been recognized as a well-known biological biomarker of hepatic dysfunction, alcohol consumption, acute/chronic liver disease, and oxidative stress [8]. A growing number of studies have reported that HCC patients with elevated serum GGT levels are associated with poor overall survival (OS) and/or early recurrence [9]. However, inconsistent findings have emerged concerning the value of GGT in predicting OS in HCC [10-12]. Furthermore, reported risk estimates have varied across studies, due to different demo-

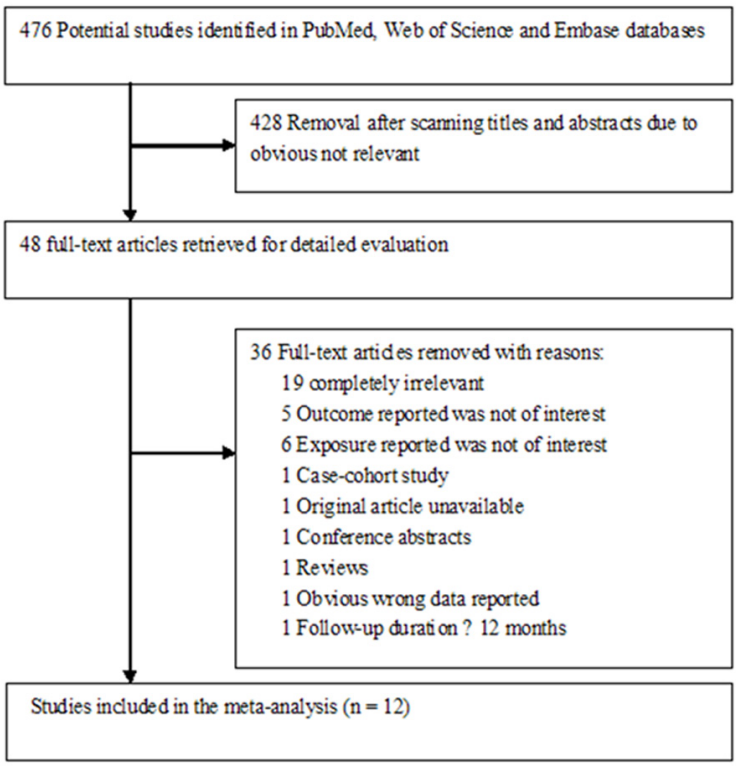

Figure 1. Flowchart of the study selection process.

graphic features, clinicopathologic characteristics, follow-up durations, or cutoff values of GGT.

To the best of our knowledge, there are no previous reviews and meta-analyses assessing the relationship of serum GGT levels and prognosis of HCC. Thus, the current study attempted to evaluate the prognostic value of elevated serum GGT for OS and recurrence-free survival (RFS) in patients with HCC through meta-analysis.

Materials and methods

Literature search

The present meta-analysis was conducted in accordance with guidelines of the Meta-Analysis of Observational Studies in Epidemiology [13]. Two independent authors conducted a comprehensive literature search using PubMed, Embase, and Web of Science, up to May 2018. The literature search was based on combinations of the following keywords: "gamma-glutamyltransferase" OR "γ-Glutamyltransferase" AND "liver cancer" OR "liver neoplasm" OR "hepatic cancer" AND "prognosis" OR "prognostic" OR "survival" OR "mortality" OR "death" OR "recurrence". In addition, researchers manually retrieved reference lists of relevant articles.

Study selection

Eligible studies included this meta-analysis met the following inclusion criteria: 1) Enrolled patients with HCC; 2) Measurement of serum GGT level before and after treatment of HCC; 3) Evaluation of OS and RFS based on GGT cutoff values; and 4) Reported multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI) for OS or RFS. OS was defined as the interval between medical treatment and the death date or last follow-up. RFS was calculated from the date of treatment and recurrence. Exclusion criteria included: 1) Conference abstracts and case-control or case-cohort designs; 2) Follow-up durations of less than 1 year; 3) Reported unadjusted risk estimates; and 4) Reported risk estimates based on continuous GGT levels.

Data extraction and quality assessment

Two authors, independently, extracted data from the selected articles using a standardized form. The following items were extracted: first author's name, year of publication, origin of study, study design, type of HCC, sample size, percentage of men, mean/median age of patients, treatment type, GGT cutoff value, duration of follow-up, and adjustment variables. The methodological quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, with a maximum score of 9 stars [14]. Studies achieving a total of 6 stars or more were deemed as high quality studies. Any disagreements regarding data extraction and quality assessment were resolved by validation with a third author.

Data synthesis and analyses

Reported multivariable adjusted HRs and corresponding 95% CIs were used to pool the prog-

Table 1. Characteristics of individual studies in the meta-analysis

Author/year	Region	Design	Patients	Sample size (% men)	Mean/median age (years)	Treatment type	GGT cutoff	Follow up	Outcome measures/ HR (95%CI)	Adjustment for covariates	Overall NOS
Ju et al. 2009 [17]	China	Retrospective	Hepatitis B virus-related HCC	290 (NR)	NR	SR	60 U/L	26.8 months	OS: 2.09 (1.39-3.17)	Multivariate analysis	6
Zhang et al. 2011 [18]	China	Retrospective	Intermediate HCC	277 (87.7)	54 (1285)	TACE	50 U/L	18.7 months	OS: 1.74 (1.15-2.64)	Multivariate analysis	6
Guiu et al. 2012 [19]	France	Retrospective	HCC	88 (80.7)	68.2 ± 10	TACE	165 U/L	12.4 months	OS: 3.05 (1.12-8.30)	Multivariate analysis	5
Zhao et al. 2012 [20]	China	Retrospective	Multinodular HCC	162 (82.7)	50.2 (2776)	SR	64 U/L	38.3 months	OS: 3.79 (1.48-9.96)	Multivariate analysis	5
Nishikawa et al. 2013 [11]	Japan	Retrospective	Naïve HBV related HCC	74 (66.2)	62 (3284)	AT	50 U/L	3.4 years	RFS: 2.94 (1.31-6.60)	Multivariate analysis	5
Chen et al. 2014 [21]	China	Retrospective	Intermediate HCC	154 (53.9)	55 (23-71)	TACE, RT	85 U/L	60 months	OS: 2.32 (1.13-3.64)	Multivariate analysis	7
Xu et al. 2014 [22]	China	Retrospective	HCC	139 (80.8)	53.5 (2480)	SR	115 U/L	2.91 years	OS: 1.67 (1.05-2.67)	Multivariate analysis	6
Ma et al. 2014 [23]	China	Retrospective	HCC	254 (77.2)	NR	RFA	75 U/L	27 months	OS: 1.95 (1.05-3.64); RFS: 1.64 (1.13-2.38)	Multivariate analysis	6
Song et al. 2015 [24]	Japan	Retrospective	Single primary HCC	384 (79.4)	65 (1985)	SR	100 U/L (OS); 50 U/L (RFS)	57.5 months	OS: 1.77 (1.09-2.90); RFS: 1.37 (1.03-1.82)	Multivariate analysis	7
Wu et al. 2016 [25]	China	Retrospective	HBV-related HCC	469 (84)	48 (1781)	SR	81.5 U/L	42 months	OS: 2.38 (1.60-3.52); RFS: 1.68 (1.29-2.20)	Multivariate analysis	7
Fu et al. 2016 [26]	China	Retrospective	HCC	308 (88.6)	51 (21-79)	SR	88 U/L	29 months	OS: 2.04 (1.51-2.77); RFS: 1.62 (1.22-2.14)	Multivariate analysis	7
Chang et al. 2016 [27]	China	Retrospective	Hepatitis C virus-related HCC	110 (67.2)	67.6 (24-83)	TACE	50 U/L	20 months	OS: 2.26 (1.20-4.28)	Multivariate analysis	6

Abbreviation: HCC, hepatocellular carcinoma; GGT, γ-glutamyl transferase; RFA, radiofrequency ablation; LT, liver transplantation; TACE, transcatheter arterial chemoembolization; SR, surgical resection; RT, radiotherapy; AT, antiviral therapy; OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; NR, not reported; NOS, Newcastle-Ottawa scale.

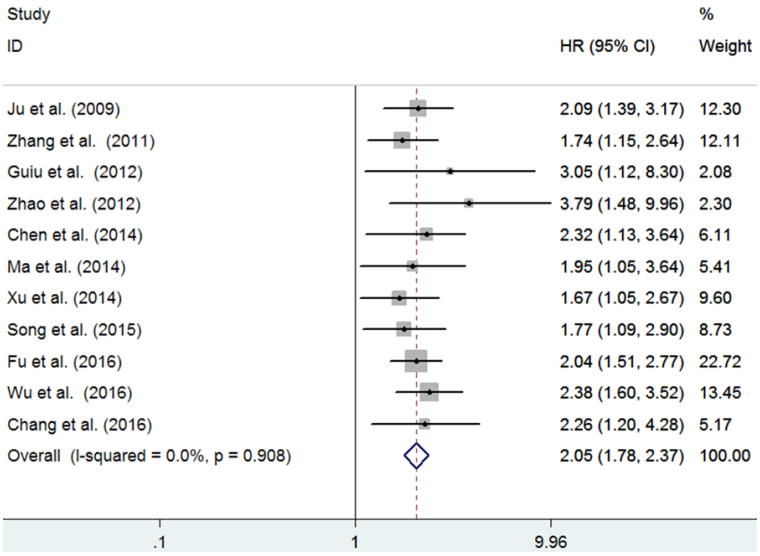

Figure 2. Forest plots showing HR and 95% CI of overall survival for high versus low serum gamma-glutamyltransferase in a fixed-effects model.

nostic value of GGT for HCC patients. Heterogeneity of risk estimates across studies were tested using the Cochrane Q statistic (p<0.10 indicates statistically significant heterogeneity) and the I^2 statistic (≥50% suggests statistically significant heterogeneity). A random-effects model was applied to pool the effects estimate in the presence of heterogeneity. Otherwise, a fixed-effects model was selected. To evaluate publication bias, both Begg's rank correlation test [15] and Egger's linear regression test [16] were conducted, with p<0.10 indicating statistical significance. Sensitivity analysis was conducted by excluding one study at a time. Subgroup analyses were performed by sample sizes, treatment methods, follow-up durations, GGT cutoff values, and NOS scores. All statistical analyses were performed with STATA 12.0 (STATA Corp LP, College Station, TX, USA).

Results

Search results and study characteristics

Briefly, a total of 476 potentially relevant articles were identified using abovementioned search strategies. After scanning titles and abstracts, 428 articles were removed. Subsequently, the remaining 48 articles were retrieved for detailed evaluation of the full texts. Finally, a total of 12 articles [11, 17-27] were included in the meta-analysis. **Figure 1** provides a flowchart of the study selection process.

Baseline characteristics of included trials are presented in **Table 1**. All included studies were retrospectively designed. Included studies were published from 2009 to 2016 and conducted in China [17, 18, 20-23, 25-27], Japan [11, 24], and France [19]. Sample sizes of included studies varied from 74 to 469. Six studies [17, 20, 22, 24-26] enrolled patients with surgical resections, three studies [18, 19, 27] included patients with transcatheter arterial chemoembolization (TACE), one study [21] enrolled patients with both TACE and radiotherapy, and one study [23] enrolled patients with radiofrequency ablation. Eight studies [17, 18, 21-27], achieving 6 to 7 NOS stars, were judged as high quality.

Impact of serum GGT on survival in HCC patients

Eleven studies [17-27] reported data on serum GGT and OS in HCC patients. As shown in **Figure 2**, pooled results show that elevated serum GGT was associated with poorer OS (HR 2.05; 95% CI 1.78-2.37), in a fixed-effects model, when compared with low serum GGT. There was no heterogeneity across studies (I^2=0%; p= 0.908). Sensitivity analyses indicated few changes in the pooled summary measures when any one study was removed. Begg's test (p=0.244) and Egger's test (p=0.479) did not indicate evidence of publication bias. **Table 2** summarizes results of subgroup analyses based on treatment methods, sample sizes, GGT cut-off values, follow-up durations, and NOS scores.

Impact of serum GGT on relapse in HCC patients

Five studies [11, 23-26] provided results of serum GGT and RFS in HCC patients. As shown in **Figure 3**, combined data reveals that elevated serum GGT was associated with RFS (HR 1.60; 95% CI 1.39-1.85), in a fixed-effects

Table 2. Subgroup analyses on overall survival

Subgroup	No. of studies	Pooled hazard ratio	95% confidence interval	Heterogeneity between studies
Sample sizes				
≥200	5	2.18	1.63-2.90	p=0.552; I^2=0.0%
<200	6	2.01	1.70-2.38	p=0.915; I^2=0.0%
Region				
China	2	2.06	1.77-2.40	p=0.877; I^2=0.0%
Others	9	1.97	1.27-3.05	p=0.339; I^2=0.0%
Treatment type				
TACE	3	1.98	1.43-2.75	p=0.535; I^2=0.0%
SR	6	2.06	1.73-2.45	p=0.663; I^2=0.0%
GGT cutoff value				
≥80 U/L	5	2.06	1.71-2.47	p=0.789; I^2=0.0%
<80 U/L	6	2.04	1.61-2.59	p=0.678; I^2=0.0%
Follow-up duration				
≥3 years	4	2.25	1.74-2.93	p=0.540; I^2=0.0%
<3 years	7	1.97	1.66-2.34	p=0.932; I^2=0.0%
NOS				
≥6 stars	9	2.01	1.73-2.32	p=0.964; I^2=0.0%
<6 stars	2	3.42	1.71-6.82	p=0.758; I^2=0.0%

Abbreviations: GGT, γ-glutamyl transferase; TACE, transcatheter arterial chemoembolization; SR, surgical resection; NOS, Newcastle-Ottawa Scale.

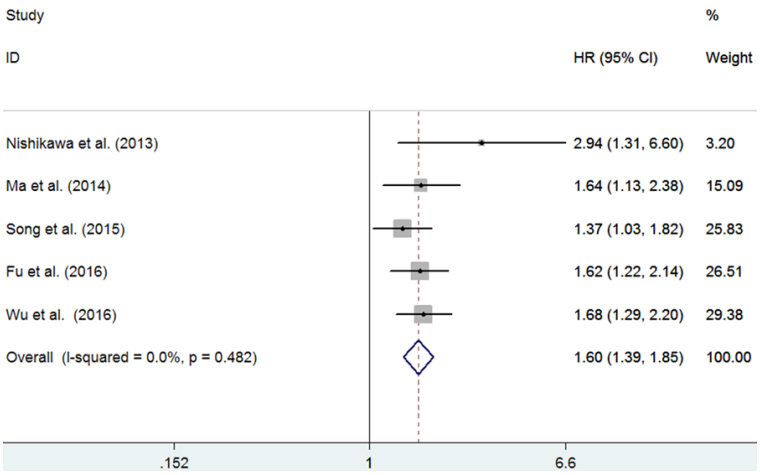

Figure 3. Forest plots showing HR and 95% CI of recurrence-free survival for high versus low serum gamma-glutamyltransferase in a fixed-effects model.

model, with no heterogeneity across studies (I^2=0%; p=0.485). Sensitivity analyses showed that the pooled risk estimate did not significantly change when removing any one included study. No significant publication bias was observed, according to Begg's (p=0.806) and Egger's tests (p=0.131).

Discussion

Present results were obtained by analyzing data on 2,621 HCC patients in 12 retrospective studies. The principal findings of this meta-analysis suggest that elevated serum GGT is independently associated with poor OS and RFS in HCC patients. HCC patients with elevated serum GGT levels significantly increased by 105% and 60% regarding risk of death and disease recurrence, compared to patients with low GGT levels. Sensitivity analysis, removing an individual study each time, confirmed the stability of pooling results.

Subgroup analyses revealed that elevated serum GGT was significantly associated with poor OS in HCC treated by surgical resections or TACE. Increased serum GGT levels causing risk of overall mortality was similar in patients that underwent hepatic resections or TACE. A close association between elevated serum GGT levels and OS was found in the subgroup with follow-up times of more than 3 years. However, no significant differences were observed in different sample sizes or GGT cutoff value subgroups. Results of subgroup analyses further confirmed that HCC patients with elevated

serum GGT levels had poorer survival. In a case-cohort study of 5,555 middle-aged Taiwanese men, elevated serum GGT (>51 U/L) was independently associated with HCC-specific mortality [28]. Furthermore, serum GGT levels were a useful tool when continuous variables were used [29-31]. In addition to OS, the present meta-analysis indicates that elevated serum GGT is an independent predictor of RFS. HCC patients with high levels of GGT had a greater risk of early recurrence. Analysis of serum GGT levels by continuous variables also supported the significant prognostic significance on relapse.

GGT is routinely tested as a traditional liver function marker. A well-designed meta-analysis showed that elevated serum GGT was independently associated with an increased risk of cardiovascular, cancer-related, and all-cause mortality in the general population [32]. Serum GGT elevation can be observed in patients with hepatitis, liver cirrhosis, or primary or secondary liver cancer. Abnormal GGT expression has been found in several human tumors [33]. Elevated serum GGT levels also act as independent prognostic indicators of poor prognosis in patients with esophageal squamous cell carcinoma [34], nonmetastatic renal cell carcinoma [35], metastatic breast cancer [36], ovarian cancer [37], and endometrial cancer [38].

The prognostic mechanisms of GGT in HCC, however, have not been fully elucidated. One possible explanation is that oxidative stress may mediate the roles of GGT in tumorigenesis [39]. Elevated serum GGT levels have been correlated with microvascular invasion of HCC. Therefore, circulating GGT levels may be associated with HCC progression. Tumor recurrence and hyperplasia adversely affect liver function. Moreover, GGT may be linked to the degree of malignancy of HCC.

The current meta-analysis had several limitations. First, all included studies were retrospectively designed in a single-center conduction. This may have increased potential selection bias and recall bias. Second, cutoff values of GGT elevation were not unified and varied from 50 to 165 U/L across included studies. Different cutoff values of GGT across studies might be correlated to assay methods or sampling time. A definitive GGT cutoff value based on future well-designed studies is highly recommended. Third, this study failed to perform subgroup analysis according to the clinicopathologic data of selected patients, particularly for etiological factors of HCC. Fourth, most included studies were from China, a predominantly HBV endemic area. Thus, application of current results in other regions should be interpreted with caution.

Fifth, detailed results on the association of GGT with OS were not provided in the original studies with negative findings [11]. Thus, pooling HR may have overestimated the actual risk estimate.

In conclusion, the current meta-analysis provides evidence that elevated serum GGT is an independent predicator of poor survival and disease recurrence in HCC patients. Future well-designed studies are necessary to investigate the underlying mechanisms of GGT elevation on poor prognosis of HCC. More importantly, the prognosis of HCC patients is dependent on both tumor and liver factors. Thus, a combination of GGT with other factors may be a practical way to improve prognosis.

Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.
[2] Forner A, Llovet JM and Bruix J. Hepatocellular carcinoma. Lancet 2012; 379: 1245-1255.
[3] Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M and Gores G. Hepatocellular carcinoma. Nat Rev Dis Primers 2016; 2: 16018.
[4] Maluccio M and Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. CA Cancer J Clin 2012; 62: 394-399.
[5] Buonaguro L, Petrizzo A, Tagliamonte M, Tornesello ML and Buonaguro FM. Challenges in cancer vaccine development for hepatocellular carcinoma. J Hepatol 2013; 59: 897-903.

[6] Huang J and Zeng Y. Current clinical uses of the biomarkers for hepatocellular carcinoma. Drug Discov Ther 2014; 8: 98-99.
[7] Orlowski M and Meister A. The Gamma-glutamyl cycle: a possible transport system for amino acids. Proc Natl Acad Sci U S A 1970; 67: 1248-1255.
[8] Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001; 38: 263-355.
[9] Wang Z, Song P, Xia J, Inagaki Y, Tang W and Kokudo N. Can Gamma-glutamyl transferase levels contribute to a better prognosis for patients with hepatocellular carcinoma? Drug Discov Ther 2014; 8: 134-138.
[10] Lise M, Bacchetti S, Da Pian P, Nitti D, Pilati PL and Pigato P. Prognostic factors affecting long term outcome after liver resection for hepatocellular carcinoma: results in a series of 100 Italian patients. Cancer 1998; 82: 1028-1036.
[11] Nishikawa H, Nishijima N, Arimoto A, Inuzuka T, Kita R, Kimura T and Osaki Y. Prognostic factors in patients with hepatitis B virus-related hepatocellular carcinoma undergoing nucleoside analog antiviral therapy. Oncol Lett 2013; 6: 1213-1218.
[12] Yan X, Fu X, Deng M, Chen J, He J, Shi J and Qiu Y. Infiltrative hepatocellular carcinoma: assessment of factors associated with outcomes in patients undergoing hepatectomy. Medicine (Baltimore) 2016; 95: e3589.
[13] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of observational studies in epidemiology (MOOSE) group. JAMA 2000; 283: 2008-2012.
[14] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P. The newcastle-ottawa scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (assessed October 15, 2018).
[15] Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.
[16] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[17] Ju MJ, Qiu SJ, Fan J, Zhou J, Gao Q, Cai MY, Li YW and Tang ZY. Preoperative serum Gamma-glutamyl transferase to alanine aminotransferase ratio is a convenient prognostic marker for child-pugh a hepatocellular carcinoma after operation. J Gastroenterol 2009; 44: 635-642.
[18] Zhang JB, Chen Y, Zhang B, Xie X, Zhang L, Ge N, Ren Z and Ye SL. Prognostic significance of serum Gamma-glutamyl transferase in patients with intermediate hepatocellular carcinoma treated with transcatheter arterial chemoembolization. Eur J Gastroenterol Hepatol 2011; 23: 787-793.
[19] Guiu B, Deschamps F, Boulin M, Boige V, Malka D, Ducreux M, Hillon P and de Baere T. Serum gamma-glutamyl-transferase independently predicts outcome after transarterial chemoembolization of hepatocellular carcinoma: external validation. Cardiovasc Intervent Radiol 2012; 35: 1102-1108.
[20] Zhao WC, Zhang HB, Yang N, Fu Y, Qian W, Chen BD, Fan LF and Yang GS. Preoperative predictors of short-term survival after hepatectomy for multinodular hepatocellular carcinoma. World J Gastroenterol 2012; 18: 3272-3281.
[21] Chen D, Wang R, Meng X, Yan H, Jiang S, Feng R, Zhu K, Xu X, Dou X and Jin L. Prognostic value of serum Gamma-glutamyl transferase in unresectable hepatocellular carcinoma patients treated with transcatheter arterial chemoembolization combined with conformal radiotherapy. Oncol Lett 2014; 8: 2298-2304.
[22] Xu XS, Wan Y, Song SD, Chen W, Miao RC, Zhou YY, Zhang LQ, Qu K, Liu SN, Zhang YL, Dong YF and Liu C. Model based on Gamma-glutamyltransferase and alkaline phosphatase for hepatocellular carcinoma prognosis. World J Gastroenterol 2014; 20: 10944-10952.
[23] Ma H, Zhang L, Tang B, Wang Y, Chen R, Zhang B, Chen Y, Ge N, Wang Y, Gan Y, Ye S and Ren Z. Gamma-glutamyltranspeptidase is a prognostic marker of survival and recurrence in radiofrequency-ablation treatment of hepatocellular carcinoma. Ann Surg Oncol 2014; 21: 3084-3089.
[24] Song P, Inagaki Y, Wang Z, Hasegawa K, Sakamoto Y, Arita J, Tang W and Kokudo N. High levels of Gamma-glutamyl transferase and indocyanine green retention rate at 15 min as preoperative predictors of tumor recurrence in patients with hepatocellular carcinoma. Medicine (Baltimore) 2015; 94: e810.
[25] Wu SJ, Lin YX, Ye H, Xiong XZ, Li FY and Cheng NS. Prognostic value of alkaline phosphatase, gamma-glutamyl transpeptidase and lactate dehydrogenase in hepatocellular carcinoma patients treated with liver resection. Int J Surg 2016; 36: 143-151.
[26] Fu S, Guo Z, Li S, Kuang M, Hu W, Hua Y, He X and Peng B. Prognostic value of preoperative serum gamma-glutamyltranspeptidase in patients with hepatocellular carcinoma after hepatectomy. Tumour Biol 2016; 37: 3433-3440.
[27] Chang ZF, Liu FY, Duan F, Wang ZJ, Yan JY and Wang MQ. Prognostic significance of serum

gamma-glutamyl transferase before transcatheter arterial chemoembolization in patients with hepatitis C virus-related hepatocellular carcinoma. Zhonghua Zhong Liu Za Zhi 2016; 38: 202-205.

[28] Hernaez R, Yeh HC, Lazo M, Chung HM, Hamilton JP, Koteish A, Potter JJ, Brancati FL and Clark JM. Elevated ALT and GGT predict all-cause mortality and hepatocellular carcinoma in taiwanese male: a case-cohort study. Hepatol Int 2013; 7: 1040-1049.

[29] Faber W, Sharafi S, Stockmann M, Denecke T, Sinn B, Puhl G, Bahra M, Malinowski MB, Neuhaus P and Seehofer D. Long-term results of liver resection for hepatocellular carcinoma in noncirrhotic liver. Surgery 2013; 153: 510-517.

[30] Yang Z, Ye P, Xu Q, Lu Y, Tang B, Wang Q, Chen S and Chen X. Elevation of serum GGT and LDH levels, together with higher BCLC staging are associated with poor overall survival from hepatocellular carcinoma: a retrospective analysis. Discov Med 2015; 19: 409-418.

[31] Liu H, Zhang A, Qian N, Gao L, Xu L, Zhang W, Jiang K, Cai S, Huang Z and Dong J. Postoperative transarterial chemoembolization benefits patients with high gamma-glutamyl transferase levels after curative hepatectomy for hepatocellular carcinoma: a survival stratification analysis. Tohoku J Exp Med 2012; 227: 269-280.

[32] Long Y, Zeng F, Shi J, Tian H and Chen T. Gamma-glutamyltransferase predicts increased risk of mortality: a systematic review and meta-analysis of prospective observational studies. Free Radic Res 2014; 48: 716-728.

[33] Hanigan MH, Frierson HF Jr, Swanson PE and De Young BR. Altered expression of gamma-glutamyl transpeptidase in human tumors. Hum Pathol 1999; 30: 300-305.

[34] Yang F, Zhang S, Yang H, Luo K, Wen J, Hu Y, Hu R, Huang Q, Chen J and Fu J. Prognostic significance of Gamma-glutamyltransferase in patients with resectable esophageal squamous cell carcinoma. Dis Esophagus 2015; 28: 496-504.

[35] Luo C, Xu B, Fan Y, Yu W, Zhang Q and Jin J. Preoperative Gamma-glutamyltransferase is associated with cancer-specific survival and recurrence-free survival of nonmetastatic renal cell carcinoma with venous tumor thrombus. Biomed Res Int 2017; 2017: 3142926.

[36] Staudigl C, Concin N, Grimm C, Pfeiler G, Nehoda R, Singer CF and Polterauer S. Prognostic relevance of pretherapeutic gamma-glutamyltransferase in patients with primary metastatic breast cancer. PLoS One 2015; 10: e0125317.

[37] Grimm C, Hofstetter G, Aust S, Mutz-Dehbalaie I, Bruch M, Heinze G, Rahhal-Schupp J, Reinthaller A, Concin N and Polterauer S. Association of gamma-glutamyltransferase with severity of disease at diagnosis and prognosis of ovarian cancer. Br J Cancer 2013; 109: 610-614.

[38] Seebacher V, Polterauer S, Grimm C, Rahhal J, Hofstetter G, Bauer EM, Husslein H, Leipold H, Marth C, Reinthaller A and Concin N. Prognostic significance of gamma-glutamyltransferase in patients with endometrial cancer: a multicentre trial. Br J Cancer 2012; 106: 1551-1555.

[39] Hanigan MH. Gamma-glutamyl transpeptidase: redox regulation and drug resistance. Adv Cancer Res 2014; 122: 103-141.