Commentary

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Can gamma-glutamyl transferase levels contribute to a better prognosis for patients with hepatocellular carcinoma?

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Summary **Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Hepatic resection has long been considered a main treatment option for HCC, but the high rate of recurrence after hepatic resection remains a problem that impacts the prognosis and survival of patients with HCC. Thus, clarifying the factors for survival and risk factors for tumor recurrence after hepatic resection is crucial. Imaging studies are currently emphasized before selecting a treatment and predicting the prognosis for patients with HCC. Recently, laboratory testing of des-gamma-carboxyprothrombin (DCP), alpha-fetoprotein (AFP), indocyanine green 15 min after administration (ICG-R15), and γ-glutamyl transpeptidase (γ-GTP) has garnered attention as a way to select treatment and predict the prognosis of patients with HCC. γ-GTP in particular has critical clinical significance as an indicator of prognosis. This indicator helps to predict prognosis and it helps with the selection of further treatment, as was revealed by studies based on different subgroups of patients published in the past 5 years. The reason for the association between γ-GTP and early recurrence and poor survival is being investigated. Preoperative laboratory results (DCP, AFP, ICG-R15, and γ-GTP) may warrant attention and need to be fully evaluated before selecting a treatment and predicting prognosis in order to improve the prognosis for patients with HCC.**

Keywords: Hepatocellular carcinoma (HCC), laboratory results, γ-glutamyl transpeptidase (γ-GTP), prognosis, recurrence

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer deaths worldwide, accounting for 80-90% of all cases of liver cancer with an estimated global incidence of 782,000 new cases and nearly 746,000 deaths in 2012 (*1*).

Hepatic resection has long been considered a main treatment option for HCC. Improved diagnostic procedures, surgical techniques, and perioperative management have contributed to better outcomes of hepatic resection, even in patients with more advanced, resectable HCC (*2*). However, the high rate of recurrence after hepatic resection remains a problem that impacts the prognosis and survival of patients with HCC, as indicated by a cumulative recurrence rate of 50-60% at 3 years and a cumulative recurrence rate of 60-80% at 5 years (*3-7*). Thus, clarifying the factors for survival and risk factors for tumor recurrence after hepatic resection is crucial. This could help with the selection of an optimal treatment, help with monitoring to reduce the rate of recurrence, and also improve the quality of care for patients with HCC.

As shown in Table 1, imaging studies, pathology, and laboratory results have identified some indices as prognostic factors for patients with HCC (*8-11*). Tumor size, tumor number, and microvascular invasion (MVI) indicated in imaging studies are regarded as factors for survival and risk factors for tumor recurrence, and imaging studies have been emphasized before selecting a treatment and predicting the prognosis for patients with HCC. As some studies have indicated, however,

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a tumor may recur in about 60.0% of patients with a single tumor smaller than 2.0 cm (*12*). Thus, more approaches to predict prognostic factors are urgently needed in addition to imaging studies. Pathology cannot confirm pathologic changes prior to surgery. In contrast, laboratory testing of des-gamma-carboxyprothrombin (DCP), alpha-fetoprotein (AFP), indocyanine green 15 min after administration (ICG-R15), and γ-glutamyl transpeptidase (γ-GTP) can be performed preoperatively. Thus, these indices warrant further attention as a way to select a treatment and predict prognosis for patients with HCC.

Patients with positive laboratory results for DCP, AFP, ICG-R15, and γ-GTP have a higher risk of recurrence and worse survival (*13-15*). These patients should receive more active treatment including anatomical hepatic resection, liver transplantation, preoperative and postoperative transcatheter arterial chemoembolization (TACE), and closer follow up. Laboratory results for DCP and AFP are related to malignancy features such as vascular invasion and metastasis. ICG-R15 is thought to be related to liver function (*13,16*). Most recently, γ-GTP has been identified as an independent prognostic risk for patients with HCC (*14,17*).

Table 1. Factors related to prognosis for patients with HCC

Examinations	Indicator
Laboratory results	DCP AFP ICG-R15 γ-GTP
Imaging studies	Tumor size Tumor number Vascular invasion
Pathology	Tumor differentiation Microvascular invasion Intrahepatic metastasis

DCP: des-γ-carboxy-prothrombin, AFP: alpha-fetoprotein, ICG-R15: indocyanine green 15 min after administration, γ-GTP: γ-glutamyl transpeptidase.

γ-GTP is a nearly ubiquitous epithelial enzyme that initiates the degradation of extracellular glutathione and its conjugates, and γ-GTP is correlated with biotransformation, nucleic acid metabolism, and tumorigenesis (*10*). γ-GTP was investigated and utilized as a liver function test or liver enzyme in the 1960s and 1970s (*18*). An increase in γ-GTP can be detected in patients with hepatitis, liver cirrhosis, or primary or secondary liver cancer (*19,20*). γ-GTP was used as a diagnostic tumor marker for liver disease with a high sensitivity of 83-100% but a low specificity of 32% (*21*). Thus, for a long time γ-GTP was not considered to be a useful tumor marker for the detection of liver disease. However, γ-GTP has critical clinical significance as an indicator of prognosis. This indicator helps to predict prognosis and it helps to select further treatment, as was revealed by studies based on different subgroups of patients published in the past 5 years (*10,22-29*).

As shown in Table 2, patients with high levels of γ-GTP had a greater risk of early recurrence and shorter

Table 2. Investigation of γ-GTP as a prognostic factor based on different subgroups of patients with HCC

Authors (Year)	Patients with HCC	Treatment	Results	*Ref.*
Ju *et al*. (2009)	219 patients with HBV-related HCC (2002-2006)	hepatic resection	Preoperative γ-GTP was independently associated with survival	(*22*)
Liu *et al*. (2012)	428 HCC cases	hepatic resection	Long-term outcomes for patients with γ-GTP > 80 U/L were poor	(*23*)
Zhao *et al*. (2012)	162 patients with multi-nodular HCC and Child-Pugh class A liver function	hepatic resection	γ-GTP > 64 U/L was a significant predictive factor for 1-year survival	(*24*)
Zhao *et al*. (2013)	266 patients with multi-nodular HCC	hepatic resection	γ-GTP > 130 U/L was a preoperative predictor for microvascular invasion	(*25*)
Faber *et al*. (2013)	148 patients with HCC and no liver cirrhosis or extrahepatic metastases	hepatic resection	γ-GTP > 50 U/L could be a poor prognostic factor for cumulative survival	(*26*)
Carr *et al*. (2010)	413 patients with biopsy-proven unresectable HCC and low AFP levels	–	γ-GTP ≥ 110 U/L was one of the most significant factors for survival	(*27*)
Zhang *et al*. (2011)	277 patients with intermediate HCC	TACE	γ-GTP > 50 U/L was an independent prognostic factor for overall survival	(*10*)
Guiu *et al*. (2011)	88 patients with HCC	TACE	γ-GTP ≥ 165 U/L as an independent predictor associated with OS	(*28*)
Nishikawa *et al*. (2013)	74 patients with HBV-related HCC	entecavir	γ-GTP ≥ 50 U/L was significant predictive factor linked to recurrence-free survival	(*29*)

TACE: transcatheter arterial chemoembolization.

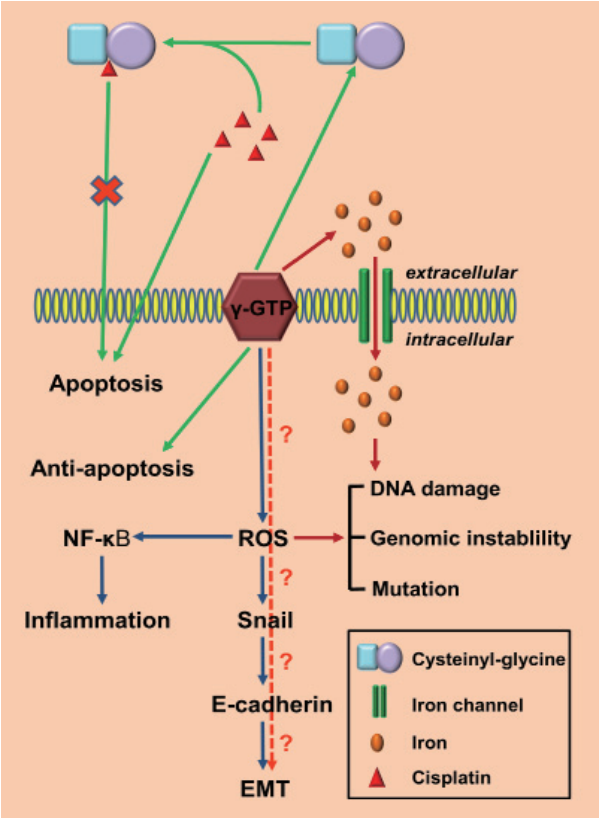

Figure 1. The molecular mechanism of γ-GTP in cancer cells. γ-GTP can promote chemotherapy resistance by increasing cysteinyl-glycine, which complexes with cisplatin. Ion channels are overactivated by γ-GTP to induce damage at the genetic level. Moreover, γ-GTP plays a role in countering apoptosis in lymphoma cells. In addition, ROS is elevated by γ-GTP and subsequently leads to damage at the genetic level, inflammation, invasion, and metastasis.

overall survival, including patients with HBV-related HCC, those with HCC and low AFP levels, those with non-cirrhotic HCC, multi-nodular HCC, and those who underwent TACE. Curative hepatic resection and a close follow-up are suggested for these patients. The combination of γ-GTP and other prognostic factors, such as tumor size, tumor number, microvascular invasion, or laboratory results for AFP and DCP, warrants further attention when selecting a treatment and predicting the prognosis for patients with HCC.

The reason why γ-GTP is significantly associated with early recurrence and poor survival has yet to be clearly indicated. There are two possible reasons: *i*) γ-GTP may be associated with worse liver function *via* induction of DNA instability and subsequent oncogenesis; *ii*) γ-GTP may be associated with the degree of malignancy of HCC, such as vascular invasion, tumor metastasis, or worse tumor differentiation.

A growing number of studies have described mechanisms of γ-GTP over the last two decades. One study suggested that γ-GTP promoted DNA damage, genomic instability, and genetic mutation by increasing the uptake of iron (*30*), and the role of iron in carcinogenesis was reviewed by Weinberg (*31*). This mechanism is thought to lead to the death of normal liver cells or the loss of normal liver function. The pro-oxidant role of γ-GTP has been reported and the subsequent production of reactive oxygen species (ROS) may promote certain intra- and extracellular molecular signals (*32*). Recently, ROS were reported to promote epithelial-to-mesenchymal transition *via* the Snail-E-cadherin pathway (*33*) and to induce inflammation and invasion *via* the NF-κB pathway (*34,35*). A study of U937 lymphoma cells found that γ-GTP may play a role in anti-apoptotic signaling (*36*). A study has confirmed that cysteinyl-glycine, which is catalyzed by γ-GTP, is able to form complexes with cisplatin and that such adducts are not readily transported through the cell membrane (*37*). These mechanisms are thought to account for the progression of HCC. Although the molecular-biological significance of γ-GTP to worse liver function and the progression of HCC is suggested (Figure 1), this significance should be clarified in further studies.

In conclusion, preoperative laboratory results (DCP, AFP, ICG-R15, and γ-GTP) should be fully evaluated before selecting a treatment and predicting prognosis in order to improve the prognosis for patients with HCC. Recent studies have identified γ-GTP as an independent prognostic factor for patients with HCC, and further studies of the reason for the association between γ-GTP and early recurrence and poor survival are urgently needed.

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