

r-GT, a promising marker for HCC development after SVR in hepatitis C patients?

Liver cancer is the sixth most common cancer (749,000 new cases) and the third leading cause of cancer-related deaths (692,000 cases) worldwide and accounts for 7% of all deaths. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global concern.¹

Approximately 80% of HCC cases are associated with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections.² In North America, Europe and Japan, infection with HCV is the main risk factor for HCC, together with alcohol abuse.^{2,3} Infection with HCV increases the risk for HCC, with a 15-20 fold increased incidence compared with HCV-negative subjects in cross-sectional and case-control studies.²

Current randomized controlled studies and meta-analysis indicate that the risk for HCC development is reduced 57% to 75% in patients with HCV who achieve a sustained virological response (SVR) with antiviral treatment such as interferon.^{1,2,4} However, even after the achievement of a SVR with antiviral treatment, some patients still develop HCC. An older age, higher α fetoprotein (AFP) levels, lower platelet counts and a high fibrotic stage before antiviral treatment were reported to be independent risk factors for HCC development in patients after SVR.⁵ However, the risk factors for HCC development after SVR in non-cirrhotic patients remain unclear.

Recently, in the Journal of Hepatology (in press), Huang et al. reported their investigation of potential non-invasive markers for HCC development after SVR in hepatitis C patients.⁶ First, the authors explored the incidence of HCC development in 642 hepatitis C patients who achieved a SVR after interferon-based therapy. Thirty-three of the 642 (5.1%) patients developed HCC, with cumulative incidence rates 0.5%, 2.7% and 5.8% after one, three and five years of follow-up, respectively. Second, the authors evaluated the predictive factors for HCC development. The Cox regression analysis revealed that the predictive factors for HCC were liver cirrhosis (HR 4.98, $P < 0.001$), age (HR 1.06, $P = 0.005$) and the baseline gamma-glutamyl transferase (r-GT) levels (HR 1.008, $P < 0.001$). Subsequently, the authors performed a subclass analysis. While the cumulative incidence of HCC did not differ significantly between cirrhotic patients with and without high baseline r-GT levels ($P = 0.53$), it was significantly higher in non-cirrhotic patients with higher r-GT levels compared with those with lower r-GT levels ($P < 0.001$). The Cox regression analysis revealed that high baseline r-GT levels remain the strongest factor independently associated with HCC development in non-cirrhotic patients after SVR (HR 6.44, $P = 0.001$), even after the liver fibrotic stage was taken into consideration. The authors concluded that higher r-GT levels are a potential non-invasive marker for HCC development after SVR in non-cirrhotic patients.

r-GT is a heterodimeric glycoprotein that catalyzes the transpeptidation and hydrolysis of an α -glutamyl group from glutathione and other α -glutamyl compounds.⁷⁻⁹ It is present predominantly in the liver. Elevated r-GT levels usually indicate the presence of underlying liver disease, such as cholestatic liver disease, alcoholic liver disease, non-alcoholic fatty liver disease and drug-induced liver damage.

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Akiyoshi Kinoshita, Hirokazu Nishino

Division of Gastroenterology and Hepatology, The Jikei University Daisan Hospital, Japan

Correspondence: Akiyoshi Kinoshita, Division of Gastroenterology and Hepatology, The Jikei University Daisan Hospital, 4-1-1, Izumihon-cho, Komae-shi, Tokyo, 201-8601, Japan, Tel 03-3480-1151, Fax 03-3480-6688, Email aki.kino@jikei.ac.jp

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In addition to liver disease, the r-GT level has been shown to correlate with the risk of mortality from all causes and the incidence and mortality of cardiovascular disease, diabetes and cancer.¹⁰⁻¹³ It is not fully understood why an elevated r-GT level is associated with increased morbidity and mortality under so many diverse conditions. However, an experimental study has demonstrated that active r-GT is present in atherosclerotic plaques and may play a role in the development of reactive oxygen species.^{10,11} The relationship between r-GT and oxidative stress may contribute to the increased morbidity and mortality in patients with elevated r-GT levels. With regard to HCC, elevated r-GT levels have previously been demonstrated to be associated with an increased risk for HCC development.¹⁴

The study by Huang et al. is the first to show that elevated r-GT levels are associated with HCC development after the achievement of a SVR in non-cirrhotic patients, irrespective of the liver fibrotic stage. These findings would help clinicians to identify non-cirrhotic patients after SVR who potentially remain at high risk for the development of HCC.

Acknowledgement

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Conflicts of Interest

There is no conflict of interest.

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