Branched-chain amino acids to tyrosine ratio value as a potential prognostic factor for hepatocellular carcinoma

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Abstract

The prognosis of hepatocellular carcinoma (HCC) depends on tumor extension as well as hepatic function. Hepatic functional reserve is recognized as a factor affecting survival in the treatment of HCC; the Child-Pugh classification system is the most extensively used method for assessing hepatic functional reserve in patients with chronic liver disease, using serum albumin level to achieve accurate assessment of the status of protein metabolism. However, insufficient attention has been given to the status of amino acid (AA) metabolism in chronic liver disease and HCC. Fischer’s ratio is the molar ratio of branched-chain AAs (BCAAs: leucine, valine, isoleucine) to aromatic AAs (phenylalanine, tyrosine) and is important for assessing liver metabolism, hepatic functional reserve and the severity of liver dysfunction. Although this ratio is difficult to determine in clinical situations, BCAAs/tyrosine molar concentration ratio (BTR) has been proposed as a simpler substitute. BTR correlates with various liver function examinations, including markers of hepatic fibrosis, hepatic blood flow and hepatocyte function, and can thus be considered as reflecting the degree of hepatic impairment. This manuscript examines the literature to clarify whether BTR can serve as a prognostic factor for treatment of HCC.
matically with the identification of high-risk populations and the advancement of diagnostic imaging and treatment. However, recurrence of HCC is frequent in the early post-treatment period even in patients who have undergone radical hepatectomy or radical local treatment including percutaneous treatment, because HCC arises from chronic liver disease. The recurrence rate after treatment of HCC is higher than that of cancer in other organs.

Therefore, despite initial remission of HCC after surgical and interventional treatments, limits are seen on the prolongation of survival. In other words, the therapeutic options available to deal with recurrence determine survival of patients, because risk of recurrence is high even if radical therapy is undertaken.

Treatment tactics may be selected depending on the tumor stage and severity of underlying liver disease.

The reasons for poor survival are that intrahepatic distant recurrence is common and, even more importantly, decompensation occurs due to a decrease in hepatic functional reserve that accompanies progression of chronic liver disease. Therefore, death due to liver failure represents a major problem. In other words, hepatic functional reserve is recognized as a factor affecting survival. However, sufficient research into the effects of the reserve liver function has not been carried out.

### BRANCHED-CHAIN AMINO ACIDS TO TYROSINE RATIO AS STATUS OF AMINO ACID METABOLISM

When treating HCC, the Child-Pugh classification system is the most extensively used method worldwide for assessing the hepatic function in patients with chronic liver disease, and represents an important assessment factor. The Child-Pugh classification has been widely used to evaluate hepatic functional reserve in cirrhotic patients, and has a good correlation with prognosis\(^\text{[3]}\), but cannot be used to predict survival in patients with HCC.

In the Child-Pugh classification, the serum albumin level is used to achieve accurate assessment of the status of protein metabolism. However, to date, no attention has been given to the status of amino acid (AA) metabolism in chronic liver disease and HCC.

Amino acid abnormalities are reportedly common even in patients who have liver cirrhosis but no hepatic encephalopathy and in patients with chronic hepatitis\(^\text{[4]}\). The amino acid molar ratio called Fischer’s ratio [branched chain amino acids (BCAAs): leucine, valine, isoleucine]/[aromatic amino acids (AAs): phenylalanine, tyrosine] is important for assessing liver metabolism, hepatic functional reserve and the severity of liver dysfunction\(^\text{[5]}\). Protein malnutrition is a result of amino acid imbalance. Accordingly, to accurately assess the status of protein metabolism in HCC patients with a background of chronic liver disease, determining not only the serum albumin level but also the status of amino acid metabolism is essential.

Proteins contained in biological cells are broken down into amino acids, while at the same time proteins are newly synthesized from free amino acids. Metabolic turnover is achieved when the breakdown and synthetic processes are in balance. The liver is the main organ involved in protein and amino acid metabolism. Hypoalbuminemia and fluctuations in plasma free-amino acid concentrations are usually seen in patients with chronic liver disease. Serum albumin is a protein that is synthesized and secreted by hepatocytes, and is used as an index of hepatic synthetic capacity for protein. This parameter is particularly important for evaluating the severity and prognosis of cirrhosis.

Fluctuations in plasma free-amino acid concentrations are particularly observed in cirrhosis. These changes include marked decreases in BCAAs and increases in AAs, methionine, and other amino acids. The molar concentration ratio of BCAAs/AAs (Fischer’s ratio) and the BCAAs/tyrosine molar concentration ratio (BTR) decreases with increasing severity of hepatic damage. The Fischer’s ratio has long been used for analysis of plasma free-amino acid concentrations, while BTR represents a simplified version of Fischer’s ratio\(^\text{[6]}\). Azuma et al.\(^\text{[7]}\) proposed the BTR as a substitute for Fischer’s ratio as an index of hepatic damage, and later reported that BTR reflected the progression of chronic liver disease.

Fluctuations in plasma free-amino acid concentrations are also seen in compensatory cirrhosis. For that reason, amino acid metabolic abnormalities in the liver become more severe as the state of chronic liver disease worsens.

On the other hand, assessing hepatic functional reserve from the perspective of amino acid metabolism can prove useful in different ways compared with investigations of the degree of hepatic fibrosis, hepatic blood flow and hepatocyte function. BTR correlates with each of the various liver function examinations, including fibrosis markers, which indicate the degree of hepatic fibrosis; indocyanine green retention rate 15 min (ICG R15), which primarily indicates hepatic blood flow; and asialo-scintigraphy, which reflects hepatocyte function. BTR also reportedly shows significant correlations with albumin value and cholinesterase (Ch-E) levels\(^\text{[5]}\). As a result, BTR can be thought to reflect the degree of hepatic impairment.

BTR offers a significant indicator of reserve liver function. However, to date, no reports have clarified the potential of BTR as a prognostic factor at the time of treating HCC.

### RELATIONSHIP BETWEEN BTR AND TREATMENT OF HCC

The significance of amino acid analysis for assessing hepatic functional reserve has not been elucidated in patients with HCC.

In the case of poor nutritional status, BTR decreases in advance of decreases in serum albumin level. For
that reason, early identification of patients at risk of hypoalbuminemia is possible; specifically, determination of BTR enables prediction of changes in the serum albumin level\[^{[6-12]}\], in turn allowing prediction of the need for administration of BCAAs. Moreover, because of the existence of that time-lag, monitoring of BTR separately from albumin is necessary when considering prognostic factors for HCC. A large-scale clinical study has demonstrated the usefulness of administering oral BCAA preparations to patients showing decreased BTR\[^{[9]}\]. In other words, there is a strong possibility that determining BTR provides a prognostic factor for HCC.

In this paper, I have undertaken a review of the published literature with regard to whether BTR can serve as a prognostic factor for HCC.

A small number of experimental and clinical studies have examined BTR in terms of amino acid fluctuations following hepatectomy\[^{[10-12]}\]. In experimental models, BTR is correlated with the extent of hepatectomy, with the post-operative interval time and with the liver weight when animals are sacrificed. In clinical studies, BTR has been determined on the immediate post-operative day and every day during the first post-operative week\[^{[10-12]}\]. In addition, BTR reportedly decreased following hepatectomy, but then recovered on post-operative day 3 with administration of a BCAA-rich amino acid transfa

CONCLUSION

Nutritional management plays an important role in the treatment of HCC, particularly in patients with chronic liver disease. With the objective of improving protein metabolism in patients with cirrhosis, supplemental therapy using oral BCAA preparations is administered to patients with decreased BTR. We can hope that this approach will be found to improve the prognosis of HCC, and that BTR will be thought to be useful as an indicator of such improvement. In the future, it will be necessary to carry out a large-scale prospective study designed to elucidate these points.

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S- Editor Tian L  L- Editor Logan S  E- Editor Li JY