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Review:

Advances in predicting the prognosis of hepatocellular carcinoma recipients after liver transplantation*

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Abstract: Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors worldwide. Liver transplantation (LT) is known as a curative and therapeutic modality. However, the survival rates of recipients after LT are still not good enough because of tumor recurrence. To improve the survival rates of recipients after LT, identifying predictive factors for prognosis after LT and establishing a model assessing prognosis are very important to HCC patients. There has recently been a lot of clinical and basic research on recurrence and prognosis after LT. Progress has been made, especially in selection criteria for LT recipients and risk factors for predicting prognosis after LT. Hangzhou criteria, in line with China's high current incidence rate of primary liver, are first proposed by Chinese scholars of LT, and are accepted world-wide, and make an important contribution to the development of LT.

Key words: Hepatocellular carcinoma; Liver transplantation; Recurrence; Risk factor; Prognosis
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1 Introduction

Primary liver cancer is one of the most frequent malignant tumors in the world, and is also a global disease with a high mortality rate. The incidence rate of primary liver cancer in China is up to 8/100000, ranking first in the world. Primary liver cancer can be divided into three types according to the pathology: hepatocellular carcinoma (HCC), cholangiocarcinoma, and mixed type. Of liver cancers, HCC accounts for about 80%. Approximately 686 thousand of the world's patients are diagnosed as HCC each year (WHO, 2016). In Asia, about 300 million people are infected with hepatitis B. The infection rate of hepatitis B virus (HBV) is as high as the incidence of 55% in the world, and the corresponding incidence of hepatitis B related to HCC is also high. The actual surgical resection rate of most HCC patients with cirrhosis is often not ideal, or even less than 30%, while the postoperative early recurrence rate can be as high as 59% (Li et al., 2016). With the continuous improvement of liver transplantation (LT) surgical technique and postoperative management, more and more attention is being paid to the treatment of HCC.

LT is an effective therapy for the treatment of primary liver cancer, especially when the cancer cannot be removed by surgery (McHugh et al., 2010). The advantage of LT for HCC is not only completely removing the HCC tumor during the transplantation, but also removing liver cirrhosis tissue. LT can be a radical treatment for HCC, while retaining normal liver function (Patel et al., 2015). The 5-year survival rate of HCC patients after LT was reported to be

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63%–80% (Silva et al., 2013; Agopian et al., 2015; Yao et al., 2015), while the 5-year survival rate of HCC patients after radical resection was only 25%–50% (Kumaran, 2014; Akoad and Pomfret, 2015; Guo et al., 2015; Hirokawa et al., 2015). LT can significantly improve survival rate and can treat cirrhosis and HCC. However, the main factors affecting the prognosis of HCC after LT are always controversial. The recurrence of HCC after LT significantly reduces the survival rate of recipients. At present, there is still a lack of a sensitive and specific evaluation tool for predicting the prognosis of HCC after LT. It is very important to improve the prognosis of LT recipients by screening new types of prognostic factors of HCC and establishing an early warning mechanism of the prognosis after LT.

2 Various types of liver transplantation standards proposed

In order to reduce the recurrence rates and improve long-term survival rates of patients with liver cancer after LT, the selection criteria of recipients are controlled. The tumor size, number, and vascular invasion are risk factors of HCC recurrence. Depending on risk factors, Milan criteria, Up-to-seven criteria, Hangzhou criteria, UCSF (University of California at San Francisco) criteria and univariate and multivariate analyses are the ones most commonly used for the prognosis of LT patients as selection criteria.

2.1 Milan criteria

The Milan criteria are the first proposed LT selection criteria for liver cancer recipients, summed up and promoted by Mazzaferro et al. (1996). Milan criteria are the most widely used criteria for patient selection (a single tumor up to 5 cm or up to 3 tumors with none larger than 3.0 cm, no major vascular invasion, no lymph node or extrahepatic metastasis). Long-term follow-up after LT in HCC patients with Milan criteria was found to have an ideal prognosis, and the 5-year survival rate was increased to 61.1% or even up to 70% (Ferreira et al., 2012). In 1998, the United Network Organ Sharing (UNOS) also uses Milan criteria as the main selection criteria. Milan criteria are currently the most widely used for LT by most countries as indicators and inclusion criteria (Kim et al., 2016). However, in clinical practice, many LT scholars found that the Milan criteria had many limitations. Some of the patients without Milan criteria can still obtain a satisfactory curative effect and prognosis (Xu et al., 2016). On the other hand, Milan criteria only consider the tumor size and the tumor number, but fail to take biological characteristics and the pathology of liver cancer into account. Milan criteria do not pay enough attention to indicators which affect the prognosis of LT such as liver cancer differentiation, invasion, and liver function. At the same time, the limit of Milan criteria for the tumor size is too strict. The number of liver cancer patients in China is so large that it will make many Chinese liver cancer patients in need of LT lose the opportunity. So the application of Milan criteria in China is restricted. In recent years, more and more international LT centers have carried out further research on Milan criteria and the expansion of LT recipients.

2.2 Up-to-seven criteria

The "Up-to-seven" criteria were proposed by Mazzaffero et al. (2009) (HCC with seven as the sum of maximum size of the largest tumor in cm and the number of tumors). In 2013, domestic scholars found that the 5-year survival rate of recipients within Up-to-seven criteria after LT was not statistically different from recipients within Milan criteria and UCSF criteria (Lei et al., 2013). Up-to-seven criteria have expanded the scope of the liver transplant recipients on Milan criteria, and have not affected the survival rate of recipients after LT.

2.3 UCSF criteria

In 2001, UCSF researchers, Yao et al. (2007), proposed the UCSF criteria, namely one tumor ≤6.5 cm or ≤3 tumors with the largest tumor diameter ≤4.5 cm and total tumor diameter ≤8 cm with no intrahepatic vascular invasion or extrahepatic metastasis. Yao et al. (2007) reported that the 5-year survival rate of HCC patients after LT under the Milan criteria and UCSF criteria was not statistically significant, and the 5-year survival rate was significantly lower in HCC patients beyond the UCSF criteria. UCSF criteria expand the scope of the LT recipients without reducing the overall survival rate. However, neither the UCSF criteria nor Milan criteria have been studied for

the factors for pathology, liver function, or tumor markers.

2.4 Hangzhou criteria

China is a large country with hepatitis B, HBV carrying rate of about 10%. Along with the development of hepatitis-liver cirrhosis-liver cancer, liver cancer is one of the most common malignant tumors in China. Using the international criteria for selection of LT recipients, there will be many patients with liver cancer who lose the opportunity for LT. It is very important to establish new criteria to screen for LT recipients, which are suitable for the present situation of China. In addition, the most widely used Milan criteria and UCSF criteria are based on tumor size and the tumor number. The biological markers and biological characteristics of liver tumors which more accurately reflect the prognosis are less studied. In 2006, the LT team led by Shu-sen ZHENG (the First Affiliated Hospital, School of Medicine, Zhejiang University) proposed the Hangzhou criteria (Zheng et al., 2008). Hangzhou criteria are defined as no portal vein tumor thrombus, tumor diameter ≤8 cm, or patients who have HCC larger than 8 cm are then eligible for transplantation if their serum alpha-fetoprotein (AFP) level is not higher than 400 ng/ml and their tumor biopsy shows only grade I and (or) II differentiation. Hangzhou criteria make up for the deficiencies of the Milan and UCSF criteria on the tumor size limit, and more importantly, factors of biological behavior, histological grade, and serum AFP level in HCC were introduced for the first time, which expands the indications of LT for HCC. The findings were published after the affirmation of the international transplantation community. The global transplantation community and multiple international transplantation centers assess the value of Hangzhou criteria by combining the results of transplantation cases through standard rigorous clinical practice. French Audet et al. (2009) believed that Hangzhou criteria are also applicable to Western countries. Comparing the 1-, 3-, and 5-year survival rates between Milan criteria and Hangzhou criteria groups, there is no statistical difference between them. Fan (2008) from the University of Hong Kong Marie Hospital reported that the addition of preoperative serum AFP of HCC in Hangzhou criteria as a biological marker is an important innovation. Hangzhou criteria expand the size of the tumor size of the liver transplant recipients, and the 1- and 3-year survival rates of HCC patients within Hangzhou criteria were found to have no significant difference from the Milan criteria.

Hangzhou criteria are the first international widely accepted criteria of LT, which put forward China's LT scheme. Without reducing the postoperative survival rate and disease-free survival rate, Hangzhou criteria increase the number of cases of LT, and effectively expand the LT recipient screening range. Hangzhou criteria are in line with the present situation of China, since more HCC patients benefit from the criteria. Hangzhou criteria proposed the biological behavior of HCC as one of the factors of LT for the first time.

3 Univariate and multivariate analyses of the prognosis of liver transplantation patients

The factors that affect the prognosis of liver cancer patients with LT are various. At present, the vast majority of prognoses after LT are focused on morphological characteristics of the tumor, such as the tumor size, number, differentiation, and vascular invasion. Tumor nodules have been widely reported as an important factor affecting tumor recurrence of HCC after transplantation. On the other hand, the biological characteristics and tumor markers have also been studied. Recent studies have found that the biological characteristics of HCC are closely related to the recurrence, metastasis, and survival rates of recipients after transplantation (Yang et al., 2007; Yao et al., 2007). AFP concentration, protein in vitamin K absence (PIVKA) level and histopathological staging were also studied as prognostic factors. Serum AFP can be used as biomarkers to predict the recurrence of HCC after LT. In recent years, studies have found that serum AFP is helpful in predicting the recurrence of liver cancer after transplantation (Wong et al., 2013). The biological markers also include the loss ratio of alleles and the expression profiles of microRNA (miRNA).

Firstly, the diameter and the number of tumors are important for screening HCC LT recipients, and are important independent risk factors for prognosis after transplantation for liver cancer (Lei et al., 2013;

Müller et al., 2013; Ahn et al., 2014; Lee et al., 2014; Balogh et al., 2016). The larger tumor diameter leads to the easier breaking of the tumor capsule and the higher recurrence rate. The factors of biological characteristics of the tumor increase the risk of tumor invasion of blood vessels, resulting in cancer cells into the blood. Kashkoush et al. (2014) also reported that a three-dimensional calculation of actual tumor volume (ATV) was of critical importance as a predictor of recurrence. Early detection of postoperative recurrence and timely treatment are the key to improving the survival rate after transplantation for HCC. The number and distribution of tumors reflect the biological behavior of malignant tumor invasion to a certain extent. A tumor number of more than two located in one liver lobe has a good curative effect early after LT, but the recurrence and metastasis of the tumor will greatly affect the long-term survival rates (Zavaglia et al., 2005). At present, scholars believe that the number and size of the tumors have a combined effect on recurrence of HCC after transplantation (Mazzaferro et al., 2009). Many LT centers screen HCC receptors considering the combined effect (Yao et al., 2001; Chan, 2013).

Secondly, when studied in all patients with HCC, AFP appears to have certain prognostic value. In some patients with HCC within the normal range, AFP levels have limited prognostic reliability. The level of AFP as an independent risk factor for prognosis should exclude pregnancy, active hepatitis, and genital embryonal neoplasms. An AFP normal value is generally less than 20 ng/ml. When the AFP is greater than 400 ng/ml or on a dynamic rise, there is a certain clinical significance. The level of AFP in patients with primary HCC may significantly increase, which may be due to the ability of the primary liver malignant tumor cells to restore the synthesis of AFP. The AFP level is related to the prediction of tumor recurrence after LT for HCC, and it is also an independent risk factor for prognosis after transplantation (Yang et al., 2007; Yao et al., 2007; Wong et al., 2013). Many different research results reported different AFP values, such as 100, 200, 210, 400, and 1000 ng/ml (Merli et al., 2005; Pawlik et al., 2005; Kwon et al., 2007; Ioannou et al., 2008; Toso et al., 2009; Xu et al., 2009; Lai et al., 2011; Ciccarelli et al., 2012; Duvoux et al., 2012; Lai et al., 2012; Grąt et al., 2014; Hameed et al., 2014; Zhang et al., 2014). More reported that a preoperative AFP >400 ng/ml was an independent risk factor for tumor recurrence and prognosis after LT. Boundary value of AFP 455 ng/ml (Ioannou et al., 2008) was also reported to be a prognostic factor for LT. There were also reports with an AFP boundary value of 1000 ng/ml or even higher (Pawlik et al., 2005).

Vascular invasion or microvascular tumor thrombus is also an influencing factor of postoperative prognosis. The results of multiple regression analysis showed that the formation of a portal vein tumor thrombus was an important factor influencing the prognosis. HCC is not only prone to invasion of portal vein tumor thrombus, but also can cause systemic dissemination of hepatic vein. The study showed that the recurrence after LT in patients with preoperative vascular invasion was higher than that without, and the prognosis was poorer (Molmenti et al., 1999; Lee et al., 2014). The vast majority of liver transplant centers in the world advocate that patients with portal vein tumor thrombus should be excluded from being LT recipients. The pathological finding of vascular invasion is that there may be a distant extra-liver metastasis. Preoperative intravascular cancer cells can retrograde to gastrointestinal venous. With hepatic arteriovenous vascular opening after LT, cancer embolus and cancer cells flow back to liver graft and reproliferate, resulting in intrahepatic recurrence of HCC. Also the traction, compression, and touch during the operation of transplantation may cause the drop of the tumor thrombus from the blood vessel, which may lead to incomplete removal of the malignant tumor cells after transplantation. Studies have shown that vascular invasion level was positively related with tumor size. The greater the tumor is, the greater the likelihood of vascular invasion. The vascular invasion rate of a tumor diameter greater than 2 cm is about 3%. Kanai et al. (1987) reported that a tumor diameter less than 3 cm of HCC has rare vascular invasion. When the tumor diameter increases, the possibility of tumor invasion of micro-vessels will be greatly increased, which leads to early recurrence, poor postoperative prognosis, and low survival rate. Kim et al. (2009) reported that tumor recurrence was not related to tumor size, but related to the microvessel density of the tumor. The more abundant and dense tumor vessels are, the more likely it is for the tumor cells to invade the blood vessels and enter the

circulatory system. In clinical practice, preoperative routine examination finds it difficult to determine a microvascular tumor embolism, but a preoperative ultrasound-guided percutaneous liver biopsy can help the diagnosis. However, with a limited liver tissue biopsy, microvascular tumor embolism detection rate is very low, and there are risks of intraperitoneal hemorrhage, bile leakage, needle tract implantation metastases, and other complications of a biopsy. Once it is confirmed by post-operation pathology, the possibility of recurrence is high. Therefore, it is of great significance to find a method that can help diagnose the vascular invasion before the operation with high sensitivity and high specificity.

A persistently high level of serum HBV DNA (Sohn et al., 2014) after radical resection of HCC is a risk factor for postoperative recurrence of HCC. The prognosis of HCC patients with HBV infection is closely related to the prognosis of patients with chronic HBV infection and HBV replication. Serum HBV DNA level is an important indicator of the reaction of HBV replication. Postoperative HBV recurrence can cause pathological liver damage, leading to a recurrence of HCC. The replication of HBV can also weaken the immune surveillance of a tumor, and even cause graft loss and death. The study of the relationship between serum HBV DNA and postoperative prognosis can be helpful to the prevention and treatment of postoperative recurrence of HCC and prolong survival.

Postoperative pathologic tumor differentiation is another independent risk factor for prognosis (Gugenheim et al., 2013; Guerrini et al., 2015; Varona et al., 2015). The higher the histological grade of the tumor is, the poorer the prognosis of LT recipients is. The survival rate of high differentiated recipients after LT is higher than that of low differentiated ones. The low differentiation of HCC cells comes with strong invasion and rapid growth, and easily breaks through the tumor capsule. Tumor differentiation degree is an independent risk factor that affects the survival time and survival rate, and it is similar in patients who received living donor LT. Therefore, it is necessary to determine the histological grade of the tumor by percutaneous biopsy guided by ultrasound or contrast-enhanced ultrasound before LT. LT should be carried out in patients with a better differentiation of HCC.

The model for end-stage liver disease (MELD) score system contains serum bilirubin level, international normalized ratio (INR), serum creatinine, and the primary cause of liver disease. It can objectively and quantitatively reflect liver and kidney function. MELD is built as the evaluation criteria of LT in benign liver disease. The modified score is suitable for HCC LT, as a non-tumor factor reflecting LT recipients' systemic condition, and also has an impact on the survival rate and prognosis after transplantation. Several reports suggested that the prognosis with high preoperative MELD score was poor, and the cutoff value of preoperative MELD score was studied by different methods with the correlation of prognosis (Ioannou et al., 2008).

The Child classification is also an important factor affecting the prognosis (Reddy and Civan, 2016). The Child-Pugh classification standard was first proposed by Child in 1964. It is the classification standard of liver function assessment for patients with liver cirrhosis, including general situation, ascites, serum bilirubin, serum albumin, prothrombin time, and liver function reserve. It has three grades A, B, and C. The higher the score is, the worse the liver reserve function is. Pugh replaced the general situation with hepatic encephalopathy, which was called Child-Pugh modified classification. It has important clinical value on the Child-Pugh grading classification. Patients with a poor Child classification cannot tolerate further treatment for a cancer recurrence, and the continuous reduction of liver function can lead to liver failure and even death.

The tumor, node, metastasis (TNM) staging system considers the comprehensive factors such as tumor size and distribution. Multivariate analysis of Cox statistics found TNM staging as independent factors in the final results. Studies reporting the TNM staging as prognostic factors are relatively rare.

Analyses of the factors in the literature include the age and gender of the patients, waiting list time, local treatment before LT (including radiofrequency ablation, microwave ablation, percutaneous ethanol injection therapy, radioactive particle implantation, selective hepatic artery chemoembolization), but do not include the history of hepatitis B or immunosuppressive therapy.

With the rapid development of surgery, study of the factors affecting the prognosis of LT has made a

series of important steps. Better surgical intervention reduces the recurrence after LT and improves the prognosis, and more and more patients with HCC benefit from LT. The studies mostly focus on the tumor number and size, extent, tumor invasion, liver function, AFP, histological tumor type, biological characteristics of tumor, and general condition of patients. However, rarely studies have been done on the influence of various factors on the prognosis. Further studies on a highly sensitive and specific evaluation tool for predicting the prognosis after LT are still needed.

4 Conclusions

It is very important to establish a tumor prognosis prediction model, with correct model parameter weight depending on further repeated verification of large clinical samples in research, and then establish early warning mechanism. It is also important to study sensitivity, specification, the positive and negative predictive values of the prediction model.

In addition, considering the great number of China's HCC patients, especially in the higher proportion of hepatitis B patients with HCC, a prognostic evaluation model for the recipients will help to reduce recurrence rate after LT. It will improve survival rate, and make full use of the limited number of donor livers, so as to achieve a major breakthrough in the treatment of liver cancer in China. After the valuable prognostic evaluation model applied to clinical practice is optimized, the prognosis of recipients will be greatly improved.

Compliance with ethics guidelines

Li-ying WANG and Shu-sen ZHENG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：肝癌肝移植术后受体预后相关因素的研究进展

概　要：研究肝癌肝移植患者术后生存与影响生存的各影响因素之间的关系，并评价各影响因素及移植标准的价值。筛选有效的预测肝癌预后的影响因素，可帮助建立肝移植术后肿瘤预后预警机制，对改善肝癌肝移植受体的术后预后具有重要意义。杭州标准是被国际移植学界广泛接受的肝癌肝移植标准，在引领肝癌肝移植领域的发展中做出了重要贡献。

关键词：肝癌；肝移植；复发；危险因子；预后