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BRIEF ARTICLE

"Metroticket" predictor for assessing liver transplantation to treat hepatocellular carcinoma: A single-center analysis in mainland China

Jian-Yong Lei, Wen-Tao Wang, Lu-Nan Yan

Jian-Yong Lei, Wen-Tao Wang, Lu-Nan Yan, Liver Transplantation Center, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China
Author contributions: Wang WT proposed the study; Lei JY and Wang WT performed the research and wrote the first draft; Lei JY collected and analyzed the data; all authors contributed to the design and interpretation of the study and to further drafts.
Correspondence to: Wen-Tao Wang, MD, PhD, Liver Transplantation Center, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China. zzphuaxiyiyuanno1@163.com
Telephone: +86-28-85422867 Fax: +86-28-85422867
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Abstract

AIM: To validate the "Metroticket" predictor using a large cohort of liver transplantation (LT) patients with hepatocellular carcinoma (HCC) in China.

METHODS: In total, 230 cases of LT for HCC treatment at our center, from July 2000 to August 2008, were included in the present study. The predicted 1-, 3- and 5-year post-LT survival rates were calculated using the Metroticket model (http://89.96.76.14/metroticket/calculator/). The predicted and observed long-term survival rates were then compared and analyzed.

RESULTS: The predicted survival rates for all 230 cases, as calculated by the Metroticket model, were 64.7% and 56.2% at 3 and 5 years, respectively, and the observed survival rates for these patients were 71.3% and 57.8%, respectively. For the 23 cases with macrovascular invasion, the predicted 5-year survival rate was 43.5%, whereas the observed 5-year survival rate was only 8.7%. For the 42 cases with microvascular invasion but an absence of macrovascular invasion, the predicted 5-year survival rate was 44.9%, and the observed 5-year survival rate was 50%. For the remaining 165 patients without any vascular invasion, the predicted 5-year survival rate was 65.8%, and the observed 5-year survival rate was 66.7%.

CONCLUSION: The Metroticket model can be used to accurately predict survival in HCC-related LT cases with an absence of macrovascular invasion.

Key words: Metroticket; Model; Survival; Hepatocellular carcinoma; Liver transplantation

Core tip: The aim of our study was to validate the "Metroticket" predictor using a large cohort of liver transplantation (LT) patients with hepatocellular carcinoma (HCC). The predicted survival rates for all 230 cases, as calculated by the Metroticket model, were 64.7% and 56.2% at 3 and 5 years, respectively, and the observed survival rates for these patients were 71.3% and 62.2%, respectively. For the 23 cases with macrovascular invasion, the predicted 5-year survival rate was 43.5%, whereas the observed 5-year survival rate was only 8.7%. The Metroticket model can be used to accurately predict survival in HCC-related LT cases with an absence of macrovascular invasion.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally[1], and this burden is heavier in China, which accounts for nearly 55% of all cases worldwide[2]. Despite the prevalence of using the hepatitis B vaccine in recent years, HCC is also the fifth most common malignancy in males and the sixth most common in females in China[3]. Liver transplantation (LT), resection and radiofrequency ablation (RFA) were once the only three potential curative treatments for early HCC[4]. LT was theoretically the best therapeutic option for HCC patients due to the procedure's overall eradication of the remnant liver with cirrhosis compared with resection and RFA[5,6]. Despite its thoroughness, LT was not suitable for all HCC cases: in that time, the very low survival rate after LT in HCC patients was mainly due to advanced HCC[7]. The Milan criteria, which were proposed in 1996 by Mazzaferro *et al*[8], resulted in excellent survival, with a 5-year survival rate of 61.1% compared with the previously observed 5-year survival rate of 25.3% in 1987. Thereafter, dozens of inclusion criteria were introduced for HCC-related LT[9-13]. However, these criteria were only inclusion criteria and could not be used to predict the results of LT, and especially the survival and recurrence rates.

In recent years, many groups have found certain risk factors that predict survival and recurrence after LT in HCC patients[14-18]. However, only few researchers have found risk factors for HCC recurrence after LT and built predictive models, such as the Metroticket[19], Alpha-fetoprotei (AFP)[20] and Markov[21] models. Derived from the largest collection of pathological data from patients with HCC (1556 overall and 1112 exceeding the Milan criteria), the Metroticket model offers individualized survival predictions based on a continuum of tumor size and number, whereby each patient is assigned an individual prognosis for 3- and 5-year survival[22]. The Metroticket model has been validated in several studies[6,21,22]. However, no analysis has been performed on the effectiveness of this predictive model using data from China with a large cohort of HCC cases, where nearly 55% of all cases worldwide[2] occurred and 24801 cases of LT were performed. Thus, in the present study, we aimed to prove the prognostic accuracy of the Metroticket model using single-center data from mainland China.

MATERIALS AND METHODS

Our study used data from a retrospective database on LT in HCC patients that was developed at our center between August 2000 and August 2008 (230 consecutive patients). All of the data from these patients, including baseline demographic data, preoperative laboratory and radiological data, intraoperative data, postoperative recovery data and long-term outcomes, were retrospectively analyzed. All of these data were collected from the China Liver Transplant Registry System. Demographic data included age, gender, height, weight and body mass index (BMI). Preoperative liver function data included underlying liver disease and liver function (Child score and MELD score). Tumor characteristics included the tumor number, diameter and differentiation. Intraoperative data included the graft type (DDLT/LDLT), operative time, blood loss and rate of transfusion. Postoperative data included mortality, complications (classified using the Clavien system), hospital stay days and overall cost. Long-term outcomes were mainly the overall survival rate.

The diagnosis of HCC was confirmed preoperatively in all patients if the patient simultaneously fulfilled the following three criteria: radiological evidence of HCC (helical triple-phase computed tomography or magnetic resonance imaging scans in arterial, portal venous and delayed venous phases; blush with washout; and a pseudocapsule), serology positive for hepatitis B or C and levels of AFP > 400 ng/mL. If the patient lacked one of these features, biopsy (histology or cytology) was performed to prove HCC. For each patient in the present study, a "Metroticket"-predicted survival score was calculated using the online calculator (http://89.96.76.14/metroticket/calculator/). All of the imaging data were based on pre-transplant radiological measurements obtained within 15 d pre-LT. The Metroticket calculator only incorporates tumors greater than 10 mm in diameter and no more than 10 nodules. We also divided all of the patients into subgroups according to the presence of micro- and macrovascular invasion. Thus, the main analysis was a comparison between the Metroticket model-predicted and observed survival rates, and the subgroup analysis also compared the Metroticket model-predicted and observed survival rates in the presence and absence of macrovascular invasion.

All of the deceased donors were brain-dead donors at our hospital, and no prisoners served as donors at our center. All of the liver donations were voluntary and altruistic. Written consent was given by the donors or their families. For all of these procedures, authorization was obtained from the donors' families, the ethics committee and the Red Cross Society of China. The surgical procedure and postoperative antiviral and immunosuppression protocols have been previously reported[23-25].

Descriptive statistics are expressed as proportion for categorical variables, and mean ± SD or median and range were used for continuous variables. The predicted survival rates at 3 and 5 years were calculated using the Metroticket online calculator for each patient, and the mean sum of the individual scores was calculated and compared with our observed survival rates at 3 and 5 years. Overall survival was defined as the time interval between LT and death from any cause. Survival rates were estimated using the Kaplan-Meier method, whereas statistical significance between survival curves was tested by the log-rank test. Statistical tests were considered to be significant when the corresponding *P*-value was less than 5%. Statistical analyses were performed using the SPSS package (SPSS 17.0, Inc., Chicago, IL).

Table 1 Complications of recipients, as classified by the Clavien system *n* (%)

	LT to treat HCC *n* = 230
Grade Ⅰ: Treated conservatively without any drugs	22 (9.6)
Pleural effusion	8
Wound infection	8
Bile leak	6
Grade Ⅱ: Treated with medication	14 (6.1)
Pneumonia	2
Ascites	2
Bile leak	2
Acute or chronic rejection	6
Hepatic artery thrombosis	2
Grade Ⅲa: Intervention using local anesthesia	25 (10.9)
Hydrothorax	11
Bile leak	6
Ileus	2
Upper gastrointestinal bleeding	3
Intra-abdominal abscess	3
Grade Ⅲb: Intervention using general anesthesia	17 (7.4)
Intra-abdominal Bleeding	6
Biliary obstruction	3
Intra-abdominal abscess	4
Portal venous thrombosis	2
Hepatic artery thrombosis	2
Grade Ⅳa: Single-organ dysfunction	6 (2.6)
Small-for-size syndrome	2
Renal dysfunction	2
Respiratory failure	2
Grade Ⅳb: Multi-organ dysfunction	2 (0.9)
Grade Ⅴ: Death	22 (9.6)
Respiratory failure	3
Graft-*vs*-host disease	1
Cardiopulmonary arrest	2
Liver failure	4
Septic shock	3
Bleeding	3
Rejection	5

LT: Liver transplantation; HCC: Hepatocellular carcinoma.

RESULTS

The baseline demographics of all patients showed that there were many more male patients (210 cases) than female ones (20 cases). The patients' mean age was 46.1 ± 10.3 years, mean height was 165.2 ± 9.1 cm, mean weight was 67.3 ± 8.8 kg and mean BMI was 23.2 ± 2.2 kg/m^2. Underlying liver disease showed that most of these patients (215 cases) were diagnosed with HBV infection. Two patients had HCV, and 13 patients did not have hepatitis B or C. There were 100 patients who were HBV-DNA positive (> 1.00E + 03 copies/mL). The preoperative liver function reflected by the MELD score of these patients was 11.1 ± 5.5 and 129 patients had Child-Pugh A, 66 patients had Child-Pugh B, and 36 patients had Child-Pugh C.

The preoperative imaging scan indicated that the mean diameter of all targets was 8.6 ± 5.0 cm and that the mean target number was 3.1 ± 2.9 for these HCC patients. In total, 26 new tumor targets were found in the explanted liver in 14 patients, and the diameter of these new targets ranged from 0.6 to 2.4 cm. The mean preoperative AFP level was 1838.2 ng/mL: < 400 ng/mL in 97 patients, 400-800 ng/mL in 12 patients, 800-1200 ng/mL in 19 patients, and > 1200 ng/mL in 102 patients. Explanted tumor histopathologic grading indicated 78 patients with good differentiation, 78 patients with moderate differentiation and 74 patients with poor differentiation.

The intraoperative and postoperative data showed that 177 patients had accepted whole-graft LT and that 53 cases had accepted living-donor LT at our center. The mean graft to recipient weight ratio was 0.81 for the 53 DDLT cases. The mean operative time was 7.8 ± 2.1 h, mean blood loss was 874.5 ± 422.5 mL, and mean length of hospital stay was 33.2 ± 12.3 d. Table 1 shows the postoperative complications for all cases. All of these postoperative complications were classified using the Clavien system. The overall complication rate was 47%, the serious (more than grade III) complication rate was 22.5%, and the mortality rate was 9.6% in the hospital.

For all 230 patients, the predicted survival rates calculated by the Metroticket model based on preoperative imaging data were 64.7% and 56.2% at 3 and 5 years, respectively, and the observed survival rates for these patients were 71.3% and 57.8%, respectively. The actuarial 3- and 5-year survival rates were 71.7% (95%CI: 62.3%-77.0%) and 64.8% (53.5%-68.4%), respectively. The Metroticket predictions of the 3- and 5-year survival rates both fell within the 95%CI of the actuarial survival. For the subgroup patients (23 cases) with macrovascular invasion, the predicted 5-year survival rate was 43.5%, whereas the observed 5-year survival rate was only 8.7%. For the subgroup patients (42 cases) with microvascular invasion but an absence of macrovascular invasion (as proven by pathological examination), the predicted 5-year survival rate was 44.9%, and the observed 5-year survival rate was 50%. For the patients (165 cases) without macro- or microvascular invasion, the predicted 5-year survival rate was 65.8%, and the observed 5-year survival rate was 66.7%. The most common recurrence site was the liver (78.6%), followed by intra-abdominal metastasis (22.1%), lung metastasis (20.2%), bone metastasis (13.2%) and brain metastasis (4.6%).

DISCUSSION

For HCC patients, LT is one of the most effective treatments. However, there are still continual pressure on limited donor resources, especially in China, and debate about what should be considered as an acceptable minimum survival outcome[22]. Since the first introduction of the Milan criteria for HCC-related LT in 1996, proposed by Mazzaferro *et al*[8], more than one decade of excellent outcomes of LT for HCC treatment was achieved with these restrictive selection criteria. However, many groups worldwide have suggested expanding the Milan criteria due to comparable survival and recurrence outcomes[9-13]. Groups everywhere have suggested adding different types of risk factors for recurrence to the inclusion criteria: for example, Toso *et al*[26] proposed a total volume

of 115 cm[3,11], and Zheng *et al*[27] proposed the AFP level and histological grade. However, most of the criteria only considered the tumor diameter or number alone[10]. The Metroticket calculator was the first to combine the tumor number with the size of the largest nodule and is a model designed to predict 3- and 5-year overall survival after transplantation on the basis of the characteristics of the HCC (the size of the largest nodule, the number of nodules and the presence or absence of vascular invasion) in a given patient. This model changes the paradigm from "one size fits all" to an individual prognosis for each patient[22]. Our key finding is that the Metroticket calculator is an accurate predictor of post-transplant survival for patients with an absence of macrovascular or microvascular invasion, but not for patients with macrovascular invasion.

The Metroticket model was built in 2009 based on data from Europe. These HCC cases were caused by alcoholic or hepatitis C virus-related liver cirrhosis. Raj *et al*[22] tried to evaluate the veracity of this model, but the study cohort was relatively small (82 cases), as mentioned as a weakness in the report, and only 40 cases included HBV. Compared with the small sample size and low rate of HBV cases in Raj's study, our study included 230 cases of HCC-related LT, and nearly all of our cases (93.5%, 215 cases) were HBV cases. Thus, our study may be more reliable and convincing. The Metroticket calculator was derived from explants' pathological data, but many reports[21,22,28] have proven the model's validity based on pre-transplant radiological criteria. Therefore, this model can be applied prospectively to patient selection.

Compared with other inclusion criteria, such as the Milan, Up-to-Seven and UCSF criteria, the Metroticket model provides a continuous range of survival probabilities rather than a dichotomous "in or out" basis for patient selection[22]. The upper limit of the tumor number is 10, and there is no upper limit for tumor diameter; the calculated tumor diameter is the largest one. Most importantly, the model also considers the presence of vascular invasion, which is a very strong risk factor for HCC recurrence after LT. This model considered all of these risk factors when it was built and thus may provide a reliable prediction of outcome for a patient who plans to accept LT for HCC treatment. However, there are certain limitations, as mentioned in Raj's study[22]. The diagnosis of microvascular invasion requires biopsy, with a risk of needle-tract seeding[29] and bleeding and false negatives[30,31]. Several other risk factors are AFP levels[32,33], the neutrophil-to-lymphocyte ratio[15,34] and the serum C-reactive protein[35] and gene[36], and all of these reported risk factors and biomarkers are available before transplantation and can be routinely used to predict recurrence and survival after HCC-related LT.

In the present study, we first examined the effectiveness of the Metroticket model in a subgroup of patients with macrovascular invasion. Our results showed that in subgroup patients with macrovascular invasion, the observed 5-year survival rate was only 8.7%, which was much lower than the predicted 5-year survival rate of 43.5%. It is known that vascular invasion is an independent risk factor for HCC recurrence after LT, especially in the presence of macrovascular invasion[16]. However, there are still certain differences between the effects of macro- and microvascular invasion on HCC recurrence. As mentioned in other studies, macrovascular but not microvascular invasion is a risk factor for HCC recurrence[37,38]. In the present study, we found that the Metroticket model can be used to predict the outcome of microvascular invasion cases but not macrovascular invasion cases. However, the Metroticket calculator website does not make a distinction between micro and macrovascular invasion. Based on our results, we believe that the Metroticket calculator needs revision on the topic of vascular invasion.

Certain potential limitations of this study are related to our single-center data analysis. The need for a 5-year follow-up limited the size of our study, as we could only include patients (230 cases) who received transplants before 2009. The retrospective nature of our study also limited the reliability. In future work, multiple-center, randomized control trials and a larger number of studies may be needed.

In conclusion, with accurately predicted 3- and 5-year survival rates, the Metroticket model should be introduced as a useful tool for selecting HCC patients for LT based on preoperative imaging examinations. However, macrovascular invasion should be considered as a contraindication to use of the Metroticket model.

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COMMENTS

Background

Liver transplantation was theoretically the best therapeutic option for hepatocellular carcinoma (HCC) patients due to the procedure's overall eradication of the remnant liver with cirrhosis compared with resection and radiofrequency ablation. Dozens of inclusion criteria were introduced for HCC-related liver transplantation (LT). However, these criteria were only inclusion criteria and could not be used to predict the results of LT, and especially the survival and recurrence rates. Recent years, many groups have found certain risk factors that predict survival and recurrence after LT in HCC patients. However, only few researchers have found risk factors for HCC recurrence after LT and built predictive models, such as the Metroticket. The Metroticket model offers individualized survival predictions based on a continuum of tumor size and number.

Research frontiers

The Metroticket model has been validated in several studies. However, no analysis has been performed on the effectiveness of this predictive model using data from China. Thus, in the present study, this study aimed to prove the prognostic accuracy of the Metroticket model using single-center data from mainland China.

Innovations and breakthroughs

The Metroticket model was introduced several years ago, but there is still no consensus about its effectiveness. 230 cases of LT for HCC treatment at our center were included in the present study. The predicted 1-, 3- and 5-year post-LT survival rates were calculated using the Metroticket model (http://89.96.76.14/metroticket/calculator/). The predicted and observed long-term survival rates

were then compared and analyzed. Due to the similar predicted and observed long-term survival rates, the Metroticket model can be used to accurately predict survival in HCC-related LT cases with an absence of macrovascular invasion.

Applications

The Metroticket model can be used to accurately predict survival in HCC-related LT cases with an absence of macrovascular invasion.

Terminology

Liver transplantation is a surgical method to cure end-stage liver disease, removing the liver with disease and implanting one or part of new liver from the donor.

Peer review

This is an interesting study to evaluate the effectiveness of the Metroticket model.

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