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CLINICAL—LIVER

Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma

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BACKGROUND & AIMS: Outcomes of liver transplantation for hepatocellular carcinoma (HCC) are determined by cancer-related and non-related events. Treatments for hepatitis C virus infection have reduced non-cancer events among patients receiving liver transplants, so reducing HCC-related death might be an actionable end point. We performed a competing-risk analysis to evaluate factors associated with survival of patients with HCC and developed a prognostic model based on features of HCC patients before liver transplantation. **METHODS:** We performed multivariable competing-risk regression analysis to identify factors associated with HCC-specific death of patients who underwent liver transplantation. The training set comprised 1018 patients who underwent liver transplantation for HCC from January 2000 through December 2013 at 3 tertiary centers in Italy. The validation set comprised 341 consecutive patients who underwent liver transplantation for HCC during the same period at the Liver Cancer Institute in Shanghai, China. We collected pretransplantation data on etiology of liver disease, number and size of tumors, patient level of α-fetoprotein (AFP), model for end-stage liver disease score, tumor stage, numbers and types of treatment, response to treatments, tumor grade, microvascular invasion, dates, and causes of death. Death was defined as HCC-specific when related to HCC recurrence after transplantation, disseminated extra- and/or intrahepatic tumor relapse and worsened liver function in presence of tumor spread. The cumulative incidence of death was segregated for hepatitis C virus status. **RESULTS:** In the competing-risk regression, the sum of tumor number and size and of $\log_{10}$ level of AFP were significantly associated with HCC-specific death ($P < .001$), returning an average c-statistic of 0.780 (95% confidence interval, 0.763−0.798). Five-year cumulative incidence of non−HCC-related death was 8.6% in HCV-negative patients and 18.1% in HCV-positive patients. For patients with HCC to have a 70% chance of HCC-specific survival 5 years after transplantation, their level of AFP should be <200 ng/mL and the sum of number and size of tumors (in centimeters) should not exceed 7; if the level of AFP was 200−400 ng/mL, the sum of the number and size of tumors should be ≤5; if their level of AFP was 400−1000 ng/mL, the sum of the number and size of tumors should be ≤4. In the validation set, the model identified patients who survived 5 years after liver transplantation with 0.721 accuracy (95% confidence interval, 0.648%−0.793%). Our model, based on patients' level of AFP and HCC number and size, outperformed the Milan; University of California, San Francisco; Shanghai-Fudan; Up-to-7 criteria ($P < .001$); and AFP French model ($P = .044$) to predict which patients will survive for 5 years after liver transplantation. **CONCLUSIONS:** We developed a model based on level of AFP, tumor size, and tumor number, to determine risk of death from HCC-related factors after liver transplantation. This model might be used to select end points and refine selection criteria for liver transplantation for patients with HCC. To predict 5-year survival and risk of HCC-related death using an online calculator, please see www.hcc-olt-metroticket.org/. ClinicalTrials.gov ID NCT02898415.

Keywords: Liver Cancer; Prognosis; Mortality; Competing-Risk Analysis.

Hepatocellular carcinoma (HCC) has become a leading indication for liver transplantation (LT), even if LT for HCC remains an unfinished product searching for perfectibility.[1] The recent introduction of effective anti-hepatitis C virus (HCV) agents[2] together with the practice to down-stage tumors originally thought to be ineligible for transplantation[3] could increase the number of HCC within the transplant waiting lists[4–7] and lead to contrasts between cancer and non-cancer indications in the current scenario of persistent organ shortage.

Cancer vs non-cancer conditions are known to affect post-transplantation outcome of individual patients, as well as liver function at the time of surgery, etiology of liver disease, comorbidities, quality of the implanted graft, and perioperative management. All of these features weight differently in determining overall survival. In fact, in case of HCC-unadjusted survival, analysis may not fully discriminate among competing

Abbreviations used in this paper: **AFP, α-fetoprotein; CI, confidence interval; CID, cumulative incidence of death; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, model for end-stage liver disease.**

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Survival of liver transplantation (LT) for hepatocellular carcinoma (HCC) is determined by cancer and non-cancer related events. Factors associated with HCC-related death after LT should be identified through competing-risk analysis.

NEW FINDINGS

The authors developed the "Metroticket 2.0" individual model of outcome prediction based on the sum of tumor size (in cm), number of tumor nodules and AFP level. The model outperformed any other current transplant criteria for HCC.

LIMITATIONS

The study is multicentric and was carried out in a relatively long time. Thus, a relative heterogeneity in pre-LT treatments and radiologic HCC assessment might be present.

IMPACT

Prognostication based on cancer-specific survival updates current recommendations for cirrhotic patients with HCC. Criteria based on AFP and tumor morphology variations recapitulate the effect of neo-adjuvant HCC treatment on post-LT outcome and favors flexibility in transplant selection for HCC.

cancer and non-cancer events, hiding the observation of the events of interest during follow-up, particularly those cancer-specific,[8] as, for example, when death for causes other than tumor precedes the recurrence of the tumor itself.

In the last 2 decades, several selection criteria for HCC have been developed on pretransplantation features or explant pathology[9–12] in order to optimize overall patients survival after transplantation. Most of them include tumor parameters (size and number of tumor nodules), as well as biology surrogates, such as serum α-fetoprotein (AFP) and response to pretransplantation neoadjuvant therapies.

Although increasingly refined, all current criteria remain elusive when searching for HCC-specific survival. Conversely, the life expectancy achievable free of tumor as the cause of death should be obtainable, to compare cancer and non-cancer patients outcomes. Available criteria accurately predict post-transplantation recurrence-free survival, but advancement in the treatment of HCC has produced significantly longer survival expectations in case of tumor recurrence: that is, HCC diagnosis after transplantation, albeit a dreaded event, often does not represent a prognosis of imminent death.[13]

All of these considerations underline the need for an appropriate analysis of competing events that occur in the natural history of LT for HCC. In competing-risk survival analysis, the risks of death due to various causes can be discriminated so to produce a more reliable estimate of cancer and non-cancer–related outcomes with respect to conventional survival analyses. To date, prognostication tools based on tumor parameters detectable preoperatively and applicable to competing-risk analysis are lacking.

In this study, we sought to investigate the end point of cancer-specific survival in the setting of liver transplantation for HCC, specifically, considering as events of interest only those deaths caused by tumor recurrence. By means of competitive-risk analysis, the independent oncologic determinants of cancer-specific survival were investigated with a prognostic model based on pretransplantation HCC features. This model and the related calculator can upgrade the current prognostic end points in this setting[14,15] and refine selection criteria for liver transplantation in patients with HCC.

Methods

To produce a robust tool to predict post-transplantation HCC-specific survival considering competing events, 2 parallel populations of patients were collected: a Western cohort (with HCV-prevailing chronic liver disease) for the training/internal validation set and an Eastern cohort (with hepatitis B virus–prevailing background) for the external/independent validation set.

Patients

The training/internal validation set was used to develop and to internally test the competing-risk regression model. This cohort included all patients who underwent LT for HCC between January 2000 and December 2013 at 3 tertiary referral hepatobiliary and transplantation centers in Italy, collected prospectively on a common database and subsequently analyzed retrospectively. The external validation set consisted of an independent consecutive cohort of patients who underwent LT for HCC during the same period at the Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China.

For both cohorts, only patients with documented preoperative diagnosis of HCC, either noninvasive[16,17] or after confirmation biopsy, were included. No particular restrictions were made on whether LT was the first treatment option or a delayed procedure after neoadjuvant therapies, including hepatic resection, according to different transplantation policies, time periods and waiting-list capabilities. Incidental HCC found on the explanted liver and patients younger than 18 years were excluded, as well as any kind of preoperative portal vein thrombosis, in order to avoid misdiagnoses of non-neoplastic portal vein thrombosis, lack of shared protocols for portal vein thrombosis, and any bias in evolution of diagnostic tools. In both cohorts, LTs were performed with grafts donated from brain-dead subjects.

Data Collection, Definitions, and End Points

In the training/internal validation cohort, data collection and analysis focused on different time points during tumor and treatment history of each patient, as follows:

1. At diagnosis of HCC: etiology of liver disease, number of HCCs, maximum diameter of nodules, AFP, model for end-stage liver disease (MELD) score;

2. Before transplantation: total number and maximum diameter of HCCs developed before LT from diagnosis to transplantation decision (Table 1), number and type of locoregional/surgical treatments (neoadjuvant therapies) performed, response to treatments, number and