A simple score for hepatocellular carcinoma risk stratification in CHC patients with cirrhosis who achieved SVR following direct acting antivirals

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ILCA 2020 — 11-13 SEPTEMBER — INTERNATIONAL LIVER CANCER ASSOCIATION VIRTUAL CONFERENCE

INTRODUCTION

Patients with advanced fibrosis or cirrhosis before achieving a sustained virologic response (SVR) to direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV) infection continue to have a high risk for hepatocellular carcinoma (HCC) for several years. However, the heterogeneity and substantial intra-individual variation in this risk have encouraged the development of scoring system that predict risk of HCC occurrence. The aim of this work was to develop a model that offer individualized patient HCC risk prediction.

AIM

To identify non-invasive parameters to predict the occurrence of HCC in a population of patients with HCV-associated advanced fibrosis or cirrhosis who achieved SVR after DAA therapy, and to develop simple HCC risk prediction model that would be available to clinicians.

METHOD

This is a prospective study including chronic hepatitis C (CHC) patients with liver cirrhosis (F4) or advanced hepatic fibrosis (F3) who achieved SVR following DAAs from January 2015 until August 2017, conducted at the Egyptian Liver Research Institute and Hospital (ELRIAH). Clinically relevant baseline parameters were collected and patients were followed up every 6 months for up to 45 months. Kaplan-Meier analysis and Log-rank test were used to evaluate effect of different predictors on cumulative hazard. Factors associated with HCC were identified through multivariable Cox regression and used to develop a scoring model for prediction of HCC risk and the performance of the model was assessed by area under the Receiver operating characteristic (ROC) curve. Other group of patients were recruited from ELRIAH clinics since September 2017 until December 2018. The same procedures used in the training group (previously mentioned) were used with this internal validation group. Other group of patients were recruited from clinics of Hepatology Department, National Liver Institute, Menoufia University, Shebeen Elkom, Egypt, since November 2015 until December 2018. The same procedures used in the training group (previously mentioned) were used with this external validation group.

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RESULTS

2372 CHC consecutive patients (1734 with F4 stage and 638 patients with F3) who achieved SVR were included. Follow up period was 23.51 ± 8.21 months (range 12-45 months). 109 patients (4.7%) developed HCC during the follow up period, out of them 101 patients had cirrhosis before initiation of DAA therapy. Age, sex, serum albumin, α feto-protein (AFP) and pre-treatment fibrosis stage were identified as risk factors for HCC (Table 1). To improve clinical utility, a simple predictive model was constructed by assigning points for each covariate in proportion to the hazard ratios in the final multivariable model: age (≤54 vs. >54 years), sex (male vs. female), serum albumin (< 3.8 vs. ≥ 3.8 g/dL), AFP (≤ 20 vs. >20 ng/ml) and pre-treatment fibrosis stage (F3 vs. F4). Using ROC analysis, patients were then stratified into three groups (low, intermediate and high risk) based on the score (AUROC = 0.824). The proposed model showed high predictive accuracy and the 2 year cumulative HCC incidence using Kaplan-Meier method was 2%, 4.5% and 10.3% in the low-risk, medium-risk and high-risk groups respectively (Fig. 1). The internal validation group showed cumulative incidence after one year of 0.21% in the low risk group, 2.11% in the intermediate risk, and 6.14% in the high risk group. Analysis of the cumulative incidence of HCC showed highly significant difference between the three risk groups (p<0.001) (Fig. 2). The external validation group showed cumulative incidence after one year of 0.0% in the low risk group, 2.05% in the intermediate risk, and 5.64% in the high risk group. Cumulative incidence after two years was 0.22% in the low risk group, 2.46% in the intermediate risk, and 6.11% in the high risk group (Fig. 3).

CONCLUSIONS

In a large cohort of HCV patients with cirrhosis or advanced fibrosis who have SVR after DAA, we developed and validated a simple score can accurately stratify patients according to HCC risk and help to identify patients who will not benefit from continued HCC surveillance based on a patient's estimated risk, enabling a personalized surveillance strategy targeting those who are at high HCC risk. GES score needs to be further replicated in an independent large cohorts of different origins before it can be further recommended for use for HCC surveillance in clinical practice.

Table 1: Predictors for the development of HCC based on Multivariate Cox Proportional Hazard Analysis

	HR	95% CI HR	P value
Age > 54 years (vs. ≤54 years)	1.072	1.042-1.104	<0.001
Male sex (vs. female)	3.608	1.998-6.517	0.011
AFP >20 ng/ml (vs. ≤20 ng/ml)	2.834	1.549-5.184	0.001
Albumin <3.8 g/dL (vs. ≥3.8 g/dL)	1.855	1.148-2.998	0.012
Fibrosis stage F4 (vs. F3)	3.481	1.689-7.173	0.001

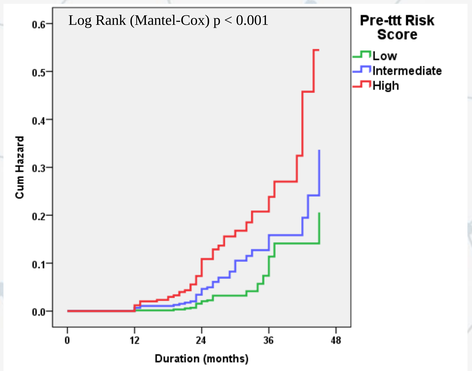

Fig. 1: Cumulative Hazard (%) of HCC in patients with HCV after end of DAA therapy, shown by Kaplan-Meier curves

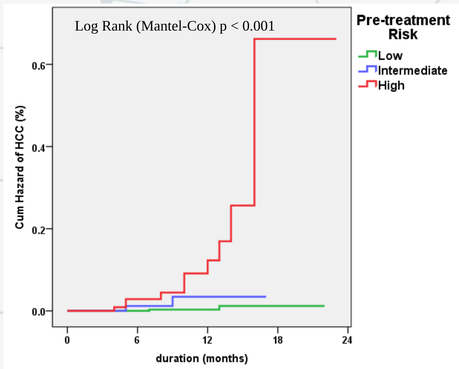

Fig. 2: Cumulative Hazard (%) of HCC in patients with HCV after end of DAA therapy for the internal validation group, shown by Kaplan-Meier curves comparing different pre-treatment risk groups

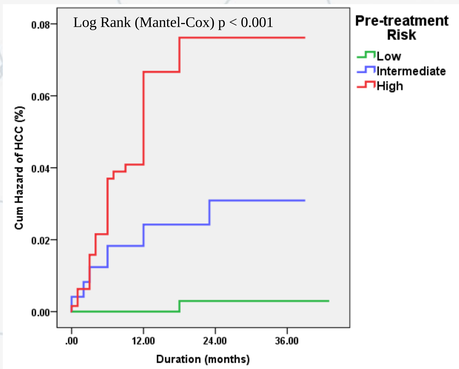

Fig. 3: Cumulative Hazard (%) of HCC in patients with HCV after end of DAA therapy for the external validation group, shown by Kaplan-Meier curves comparing different pre-treatment risk groups)

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