European Journal of Cancer 63 (2016) 25–33

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Proposal and validation of a new model to estimate survival for hepatocellular carcinoma patients☆

Po-Hong Liu [a,c], Chia-Yang Hsu [c,f], Cheng-Yuan Hsia [b,c], Yun-Hsuan Lee [a,c], Yi-Hsiang Huang [a,d], Chien-Wei Su [a,c], Fa-Yauh Lee [a,c], Han-Chieh Lin [a,c], Teh-Ia Huo [a,c,e,*]

[a] *Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[b] *Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan*
[c] *Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan*
[d] *Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan*
[e] *Institute of Pharmacology, National Yang-Ming University School of Medicine, Taipei, Taiwan*
[f] *Department of Internal Medicine, University of Nevada School of Medicine, Reno, NV, USA*

Received 30 November 2015; received in revised form 21 April 2016; accepted 28 April 2016

KEYWORDS
Hepatocellular carcinoma;
Treatment strategy;
Staging system;
Prognosis

Abstract ***Background and aims:*** The survival of hepatocellular carcinoma (HCC) patients is heterogeneous. We aim to develop and validate a simple prognostic model to estimate survival for HCC patients (MESH score).
Methods: A total of 3182 patients were randomised into derivation and validation cohort. Multivariate analysis was used to identify independent predictors of survival in the derivation cohort. The validation cohort was employed to examine the prognostic capabilities.
Results: The MESH score allocated 1 point for each of the following parameters: large tumour (beyond Milan criteria), presence of vascular invasion or metastasis, Child-Turcotte-Pugh score $\geq$6, performance status $\geq$2, serum alpha-fetoprotein level $\geq$20 ng/ml, and serum alkaline phosphatase $\geq$200 IU/L, with a maximal of 6 points. In the validation cohort, significant survival differences were found across all MESH scores from 0 to 6 (all $p < 0.01$). The MESH system was associated with the highest homogeneity and lowest corrected Akaike information criterion compared with Barcelona Clínic Liver Cancer, Hong Kong Liver Cancer (HKLC), Cancer of the Liver Italian Program, Taipei Integrated Scoring and model to estimate survival in ambulatory HCC Patients systems. The prognostic accuracy of the MESH scores remained

☆ Financial support: This study was supported by grants from the Center of Excellence for Cancer Research at Taipei Veterans General Hospital (MOHW104-TDU-B-211-124-001), Taiwan, from Taipei Veterans General Hospital (V105C-009, V104A-004, V105A-011), Taiwan, and from the Ministry of Education, Aiming for the Top University Plan (103AC-P618), Taiwan.
* *Corresponding author*: Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Taipei 11217, Taiwan. Tel: +886 2 2871 2121x2050; fax: +886 2 2873 9318.
E-mail address: tihuo@vghtpe.gov.tw (T.-I. Huo).

http://dx.doi.org/10.1016/j.ejca.2016.04.023

constant in patients with hepatitis B- or hepatitis C-related HCC. The MESH score can also discriminate survival for patients from early to advanced stages of HCC.
Conclusions: This newly proposed simple and accurate survival model provides enhanced prognostic accuracy for HCC. The MESH system is a useful supplement to the BCLC and HKLC classification schemes in refining treatment strategies.

1. Introduction

Cancer staging is a critical step in management of hepatocellular carcinoma (HCC). However, the prognosis of HCC is complex and multifaceted [1]. Although it is recognised that key predictors of prognosis include tumoural extent, degree of liver dysfunction and patient's general health condition, the optimal staging system is still under intense debate [1,2].

Over the past decades, numerous endeavours were devoted to better prognosticate HCC. Derived mostly from patients with advanced HCC, the Okuda system is renowned for its simplicity [3,4]. The widely-validated Cancer of the Liver Italian Program (CLIP) system incorporates tumoural status and liver functional reserve [5]. The Taipei integrated scoring (TIS) system takes the advantage of total tumour volume to claim superior prognostic power [6]. The model to estimate survival in ambulatory HCC patients (MESIAH) was proposed and validated externally for its better prognostic performance [7,8].

Although these survival models generally have distinct prognostic performance, they cannot guide treatment decisions directly. The Barcelona Clínic Liver Cancer (BCLC) staging system offers both management guidance and prognostic prediction. The BCLC system has been integrated in the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) HCC management guidelines [9,10]. Recently, the Hong Kong Liver Cancer (HKLC) staging system was proposed which enabled more aggressive treatment strategies [11,12].

The currently used staging systems harbour variable intrinsic deficiencies. For example, the performance status scale and the serum alpha-fetoprotein level are not included in many of the staging systems currently available [13]. It is crucially important to develop a robust yet simple prognostic model for HCC. This study aims to establish a new model to estimate survival for HCC patients (MESH score) with more precise prognostic power so that patient outcomes could be compared easily. We determined *a priori* to include only commonly-used clinical variables with a simplistic approach. We also compared the prognostic capability of MESH score with currently existing staging models.

2. Patients and methods

2.1. Patients and management

Between 2002 and 2013, 3182 patients with newly diagnosed HCC were prospectively enrolled at Taipei Veterans General Hospital. Baseline demographics, clinical information, tumoural status, and overall survival were recorded. Patients were evaluated at the multi-disciplinary HCC board for treatment guidance. Resection, ablation, and transarterial chemoembolisation were carried out under standard procedures [14–17]. Patients were randomly split into derivation and validation cohort by a 1:1 ratio. A survival model was derived from the derivation cohort and was validated in the validation cohort. The study was approved by the Institutional Review Board of the hospital. Patient information was de-identified before analysis.

2.2. Definitions of variables

HCC diagnosis was established according to EASL or AASLD HCC management guidelines [9,10]. Small tumour was defined as single tumour $\leq$5 cm or up to three tumours $\leq$3 cm in diameter (Milan criteria). Staging information for MESIAH and HKLC system was retrospectively added to the database [7,11]. Patients were classified as hepatitis B virus (HBV)-related HCC or hepatitis C virus (HCV)-related HCC, respectively, if HBV or HCV were found to be the only cause of chronic liver disease [18]. Ablation, resection, and transplantation were labelled as curative treatments. Other managements were classified as non-curative treatments.

2.3. Development of prognostic model

We constructed the model based on several principles: (1) The model should only contain clinically available variables, (2) the model should be user-friendly, and (3) the model should not include established classification systems which are subject to changes [4]. The prognostic scores were developed in the derivation cohort with all candidate predictors, including demographics, etiologies of underlying liver diseases, severity of liver