TUMOUR BURDEN AS A PREDICTOR OF EXTRAHEPATIC PROGRESSION AFTER TRANSARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA: OPTIMAL CUT-POINT DEFINITION AND PROGNOSTIC MODELLING IN AN OBSERVATIONAL MULTICENTRE STUDY

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INTRODUCTION

Hepatocellular carcinoma (HCC) typically exhibits local progression, with transarterial chemoembolization (TACE) as a common therapy [1]. This study investigates post-TACE HCC progression emphasizing extrahepatic spread, an extremely unfavourable prognostic factor that force the use of systemic treatment. We hypothesize that tumour burden score (TBS) [2] may play a pivotal role as a risk factor for extrahepatic progression (EHP).

METHODS

Derived from the Italian Liver Cancer (ITA.LI.CA) database, our TACE-treated HCC cohort was composed by 890 patients. TBS was calculated by the Pythagorean formula ($\sqrt{}$ [(maximum tumour diameter)^2 + (number of tumours)^2]); demographic, clinicopathological, and radiological data were recorded. Primary

outcomes focused on time-to-EHP at the first episode and overall post-TACE. Descriptive statistics were conducted as usual. Time-to-event curves were estimated using the Kaplan-Meier method, multivariable Cox regression models were performed to evaluate association with EHP. TBS was firstly evaluated in univariate, identifying an optimal cutpoint as the one minimizing the p-value for hazard ratio (HR) (Figure 1). To adjust for overfitting, HR estimates were calculated by shrinkage procedure with the 95%CI calculated with a bootstrap percentile method [3]. Clinically associated variables were selected with Best Subset algorithm (AIC selection), TBS was added to evaluate its incremental diagnostic improvement and Harrell C-index was calculated in cross-validated data (Figure 1).

RESULTS

The first episode occurred as intrahepatic progression in 614/890 patients, while, after a median time of 13.8 months, a *first* EHP was diagnosed in 64/890 patients. During the follow-up 232 patients overall had EHP. The median of TBS was 3.9 (IQR 2.9-5.1). The optimal cutpoint for the first EHP was 3.66, with 53% of the population above this value. In the shrunken univariate model, TBS showed an HR of 3.43 (95%CI 1.83-6.42). The Best Subset algorithm identified four clinical variables: Model for End Stage Liver Disease score, Alpha-Fetoprotein, Child-Pugh classification, and Eastern Cooperative Oncology Group performance status. TBS was associated with EHP also in the shrunken multivariable model, with an HR of 3.64 (95%CI 1.66-7.9). The c-index for the TBS plus clinical variables model improved by 0.11 points (95%CI 0.05-0.17), compared to 0.64 for only clinical variables.

CONCLUSION

Despite the pattern of progression in HCC was most commonly intrahepatic, knowledge of extrahepatic development may help with patient prognosis. TBS is associated with the risk of EHP and, with other clinical variables, may help to identify patients for whom an early use of systemic therapy may be beneficial.

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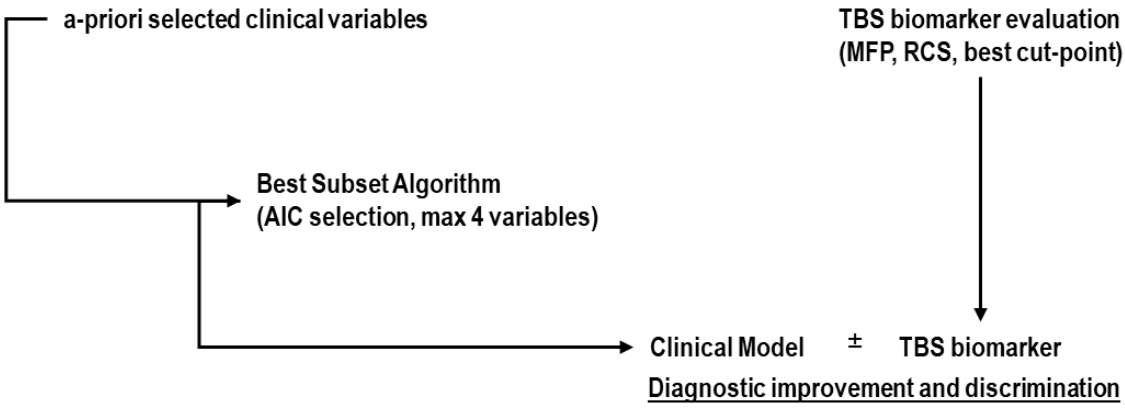
Keywords: liver cancer; transarterial chemoembolization; extrahepatic progression; tumour burden score; prognostic biomarker.

Figure 1. Proposed optimal cut-point definition and prognostic modelling.


a-priori selected clinical variables
TBS biomarker evaluation
(MFP, RCS, best cut-point)
Best Subset Algorithm
(AIC selection, max 4 variables)
Clinical Model
±
TBS biomarker
Diagnostic improvement and discrimination