CLINICAL STUDY

Validation of Clinical Scoring Systems ART and ABCR after Transarterial Chemoembolization of Hepatocellular Carcinoma

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ABSTRACT

Purpose: To perform an external validation of the Assessment for Retreatment with Transarterial Chemoembolization (ART) and α-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC), Child–Pugh, and response (ABCR) scores and to compare them in terms of prognostic power.

Materials and Methods: From 2000 to 2015, 871 patients with hepatocellular carcinoma underwent transarterial chemoembolization at a tertiary referral hospital, and 176 met all inclusion and exclusion criteria for both scores and were analyzed. Nineteen percent (n = 34) had BCLC stage A disease and 81% had stage B disease. Thirty-nine patients (22%) presented with elevated AFP levels. Overall survival was calculated. Scores were validated and compared with a Harrell C-index, integrated Brier score (IBS), and prediction error curves.

Results: Before the second chemoembolization procedure, 22 patients (12%) showed an increase of 1 point in Child–Pugh score and 51 patients (22%) had an increase of $\geq$ 2 points. Thirty-one patients (23%) showed a $>$ 25% increase in aspartate aminotransferase level, and 114 (65%) showed a response to treatment. Consequently, 127 patients (72%) had a low ART score and 49 (28%) had a high ART score. One hundred fifty-eight patients (90%) had a low ABCR score, whereas 18 (10%) had a high ABCR score. Low and high ART score groups had median survival durations of 20.8 and 15.3 mo, respectively. Harrell C-indexes were 0.572 and 0.608, and IBSs were 0.135 and 0.128, for ART and ABCR, respectively. For both scores, an increase in Child–Pugh score $\geq$ 2 points and a radiologic response were significantly associated with survival.

Conclusions: Both scores were of limited predictive value, and neither was sufficient to support clear-cut clinical decisions. Further effort is necessary to determine criteria for making valid clinical predictions.

ABBREVIATIONS

ABCR = α-fetoprotein, Barcelona Clinic Liver Cancer, Child–Pugh, and response [score], AFP = α-fetoprotein, ART = Assessment for Retreatment with Transarterial Chemoembolization [score], BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma, IBS = integrated Brier score, OS = overall survival

The point at which transarterial chemoembolization should be continued or stopped is currently not addressed by any guideline to our knowledge. Sieghart et al (1) developed a scoring system known as the Assessment for Retreatment with Transarterial Chemoembolization (ART) score. This score is calculated before the second chemoembolization procedure and used to identify patients who are likely or unlikely to benefit from further chemoembolization sessions (1). Unfavorable factors were a $>$ 25% increase in aspartate aminotransferase (AST) level, an increase of 1 or 2 points of Child–Pugh score, and no detectable radiologic tumor response. This score was developed based on a cohort of

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107 patients treated in Vienna (ART training cohort) and was subsequently validated on 115 patients treated with chemoembolization in Innsbruck (ART validation cohort).

Recently, controversy has arisen about several aspects of the ART score, and further external validation was recommended by the authors and other groups (2–4). To date, two different approaches were undertaken for validating the ART score—one by an Italian group (5) and one by a Japanese group (6)—but neither approach was successful. The Italian study included only 51 patients (5), the Japanese cohort included only 44 patients (6), and the groups presumably had entirely different patient characteristics.

Another recently published scoring system, known as the α-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC), Child–Pugh, and response (ABCR) score, also aimed to identify patients who are unlikely to benefit from continuing chemoembolization. The ABCR score was claimed to perform better than the ART score (7). The ABCR score includes the baseline BCLC stage; the unfavorable factors include an AFP level $\geq$ 200 ng/mL at baseline, an increase in Child–Pugh score by $\geq$ 2 points from baseline, and no radiologic response. Recently, considerable debate has also arisen regarding this score. The Milan group (3) criticized this model for "overfitting," and they emphasized the importance of a well-powered external validation. In response, Adhoute et al (8) reported that, in their experience, the ABCR score was a good prognostic tool. Nonetheless, they also recommended external validation.

In summary, the creators of the ART and ABCR scores, in addition to other groups, have suggested that external validation should be conducted for both scores. Therefore, the purpose of the present study was to perform an external validation of the ART and ABCR scores and to compare them in terms of prognostic power.

MATERIALS AND METHODS

This study was exempt from institutional review board approval. All patient records and information were deidentified before analysis.

Patient Recruitment

A total of 871 patients with hepatocellular carcinoma (HCC) underwent chemoembolization between 2000 and 2015 in a tertiary referral hospital. All patients who met the eligibility criteria for both scores (ART and ABCR) were included: age at least 18 years at the time of the first chemoembolization procedure, HCC diagnosis per American Association for the Study of Liver Diseases/European Association for the Study of the Liver (EASL) criteria or proof of histology, BCLC stage A or B disease with preserved liver function (Child–Pugh class A/B), and at least two chemoembolization sessions within 3 months ($\leq$ 90 d). In accordance with both scores, the exclusion criteria were previous chemoembolization or selective internal radiation therapy; previous sorafenib treatment (Nexavar; Bayer, Whippany, New Jersey), chemoembolization employed as a "bridging" therapy before liver transplantation, liver transplantation, planned resection after chemoembolization; BCLC stage C or Child–Pugh class C disease, and any portal vein thrombosis. As in the ABCR score cohort, patients who underwent bland embolization were also excluded. Patients were not excluded if they had undergone a potentially curative treatment before chemoembolization that involved a resection or local ablation (radiofrequency or microwave ablation or irreversible electroporation).

Accordingly, 695 patients were excluded for various reasons, including no second chemoembolization procedure within 90 days (n = 253), liver transplantation (n = 135), resection after chemoembolization (n = 12), Child–Pugh class C disease (n = 43), BCLC stage C disease (n = 184), extrahepatic metastases (n = 12), missing data (n = 20), and other reasons (n = 36; **Fig 1**). Therefore, a total of 176 patients were included in the final analyses. Baseline patient characteristics are shown in **Table 1**, in which they are also compared versus the original ART and ABCR cohorts.

Chemoembolization Treatment

Consistent with the ART and ABCR score cohorts, patients who received conventional Lipiodol-based (Guerbet, Roissy, France) chemoembolization as well as patients who received drug-eluting embolic agent chemoembolization were included. Chemoembolization was performed in a routine fashion by injecting embolic agents into the tumor-supplying vessels as described elsewhere (9,10). Conventional chemoembolization was conducted by using an emulsion of 10 mg mitomycin C (Mito-Medac; Medac, Hamburg, Germany) and 10 mL iodized oil (Lipiodol Ultra-Fluide; Guerbet). Drug-eluting embolic agent chemoembolization was performed by using DC Bead particles 100–300 μm, 300–500 μm, or 500–700 μm in size (BTG International, London, United Kingdom) loaded with 150 mg of doxorubicin. Additional bland embolization was not performed.

Imaging and Tumor Response

All patients underwent contrast-enhanced cross-sectional imaging with computed tomography (CT) or magnetic resonance (MR) imaging before the first chemoembolization treatment. Each patient underwent a postinterventional control CT scan immediately after conventional chemoembolization or the day after drug-eluting embolic agent chemoembolization to rule out periinterventional complications. Disease restaging with CT or MR imaging was scheduled 6 weeks later, before the second