remains unclear. Second, the other endpoints of HBV DNA suppression <1000 copies/ml and ALT normalization after 48 weeks of PegIFN treatment was unsatisfactory. These results might be worse after withdrawal of PegIFN therapy. Most of the patients had to resume ETV treatment, which is terrible news for a doctor to have to deliver to patients after a long course of PegIFN therapy. Third, sustained and profound viral suppression is the main goal of treatment. The fluctuation of ALT and HBV DNA in the sequential therapy may mimic the phenomena of viral resistance to NA. It has been reported that treatment related viral resistance blunts histologic responses [2] and increases the rate of hepatocellular carcinoma (HCC) even if rescue therapy is given [3]. Fourth, the cost of treatment should also be considered. The per capita disposable income is 18,311 RMB (≈2982 USD) in China 2013. The cost of 48 weeks of PegIFN treatment is about 50,000 RMB (≈8143 USD). Most of the treatment-naïve patients in China may find this treatment unaffordable. The cost of 48 weeks ETV is only one fifth of that. Fifth, the causative agent has not been identified in this randomized controlled study. The treatment arm underwent ETV withdrawal and PegIFN. Withdrawal of ADV after 4–5 years of therapy has been shown to result in 39% HBsAg loss in selected HBeAg negative patients [4]. To date, there has never been a parallel study in HBeAg positive patients, and there has never been a randomized control trial with PegIFN that involves a control arm with NA withdrawal only. We are anxiously waiting for such a study, we can no longer make the assumption that the treatment effect is entirely due to PegIFN. The correlation between early ALT elevation after withdrawal of ETV with HBeAg seroconversion and HBsAg loss supports this hypothesis. Finally, the benefit of HBeAg seroconversion should not be over emphasized. HBeAg seroconversion has long been regarded as an important treatment endpoint in hepatitis B therapy. However, with the prevalence of pre-core or core mutation HBV infection, HBeAg seroconversion is no longer an ideal endpoint. Recently, Jessica Liu *et al.* demonstrated that HBV DNA seroclearance, during the course of chronic hepatitis B, is the most significant factor in reducing risk for future HCC and HBeAg seroclearance will not reduce future HCC further [5]. Combination endpoint with HBeAg seroconversion and HBV DNA <1000 copies/ml may be more reasonable as the primary endpoint. We do not know if the significant difference between the two cohorts was lost with this endpoint.

In summary, as clinicians, after weighing the pros and cons, we do not think it is worthy of switching to PegIFN in patients achieving virological suppression with ETV, except if the patient refuse a long-term treatment.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Repeated transarterial chemoembolization: An overfitting effort?

To the Editor:
We read with great interest the article by Adhoute *et al.* published in *Journal of Hepatology* [1]. The authors developed a point score system, the ABCR [standing for Alpha-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC), Child-Pugh and Response], to assist in the decision making on whether to retreat hepatocellular carcinoma (HCC) patients with multiple transarterial chemoembolization (TACE) sessions. The study population consisted of HCC patients treated with repeated consecutive TACE sessions and the resulting significant parameters from regression analysis were used to build the score. In this way, the authors differentiated three groups with different survival. The score was consistently validated in training and confirmatory cohorts and a higher ABCR score after the first TACE course was found to be associated with patients at poorer prognosis who may not benefit from further TACE sessions.

Current guidelines do not specify the criteria for repeating TACE and the correct number of repeated procedures to undertake, hence the paper by Adhoute *et al.* is certainly of interest.

However, it should be noted that patients in more advanced BCLC stage and with higher baseline AFP levels, namely those requiring further treatment repetitions are considered less likely

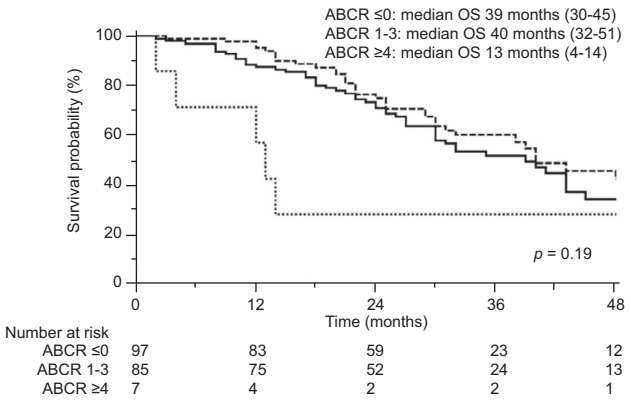

Fig. 1. Overall survival according to ABCR score in a consecutive series of 189 HCC TACE patients performed on-demand at INT-Milan. No significant difference was noted when patients were stratified by the proposed cut-off score points ($p = 0.19$).

to benefit from repeated TACE courses by the final score. This discrepancy could be explained by the fact that the accuracy of ABCR score is mostly hampered by the impact of baseline tumoral parameters (BCLC stage and AFP) on survival. Moreover, many of the features determining the score are not commonly observed in conventional intermediate patients undergoing TACE.

In our cohort of 189 consecutive HCC patients treated with repeated TACEs on demand, only 4/189 (2.1%) patients were in BCLC C and only 30 (15.8%) presented with an AFP level $\geqslant$200 IU/ml. In addition, less than 2% of patients were retreated within 6–8 weeks from original TACE in presence of Child-Pugh deterioration $\geqslant$2 points. On these premises, and in the absence of consideration of patient's performance status, variations in the ABCR will be largely influenced by only two covariates: the early treatment response and the BCLC A/B status, with consequent loss in discriminatory abilities.

In a way, the reduced weight assigned to very common clinical conditions observed in TACE could make the proposed score scarcely applicable in different contexts, particularly when current guidelines for TACE indication are more rigorously followed. At least, this was the case when the ABCR score was applied to our series (Fig. 1).

In recent years a number of scores and nomograms have been proposed to properly guide the therapeutic decision of TACE repetition in HCC patients but none of them unequivocally confirmed in clinical practice. For instance the Assessment for Repetition of TACE (ART) score seemed to properly address the need of a reliable objective tool easily applicable at bedside [2] but, despite the initial enthusiasm and the correct methodological approach, it has not been validated and to the best of our knowledge, has yet to enter clinical practice. The same can be said of other numeric scores proposed by other reputed groups [3,4].

All these efforts, although properly conducted, suffer from overfitting: a phenomenon occurring when a model maximizes its performance on some set of data but its predictive performance is not confirmed elsewhere due to random fluctuations of patients' characteristics in different clinical and demographical backgrounds. The very fact that so many different scores keep on being proposed confirms the excessive importance given to external validation in preventing overfitting.

As in the case of the study by Adhoute *et al.*, the score is tested in a different but "plausibly related" cohort and that is called external validation [1–3], although it is known that external validation shows sufficient power to detect clinically important changes in performance only when substantial sample sizes are available [5]. With smaller series, as in this study from two French groups, the sole external validation may have led to an overestimation of the performance of the model.

A possible often neglected alternative is the internal validation performed by means of bootstrap sampling, aimed at obtaining a large number of samples randomly drawn with replacement from the original population [6]. This way, the model developed in the bootstrap sample is validated in the original sample and the procedure is repeated, usually at least 100 times [6]. Recent simulation studies recommend, in the absence of substantially sized external cohorts, internal validation with bootstrapping, because this statistical procedure is able to simultaneously validate both the model building process and its performance in a broad range of random samples [5].

We think that prognostication of TACE and indication to retreatment should rely mostly on well-known clinical and tumor factors that have to be weighed properly with sounded estimation methods. On this ground, refinements of the current point scores computation seems advisable.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

Antonio Facciorusso wrote the letter and performed the analysis; Antonio Facciorusso, Sherrie Bhoori and Carlo Sposito collected the data; Vincenzo Mazzaferro revised the manuscript. All the authors approved the final version of the manuscript.

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Reply to: "Repeated transarterial chemoembolization: An overfitting effort?"

Retreatment with TACE: ABCR score and radiological response, a really tight connection

To the Editor,

We would like to thank Facciorusso *et al.* for their commentaries on our article and for applying our ABCR score to their important cohort of patients.

Transarterial chemoembolization (TACE) is recommended for intermediate stage hepatocellular carcinoma (HCC) based on the algorithm of the Barcelona–Clinic Liver Cancer (BCLC) system [1,2], and is the most widely used treatment for HCC [3].

No consensus exists for treatment methods, number of courses to be administered, objectives (complete or partial response, disease stabilization), and retreatment schedule but performing TACE guided by the radiologic response and individual tolerance appears to be the most logical option. Moreover, as suggested by Bolondi *et al.*, intermediate stage represents a heterogeneous group of patients [4] and, in our group, as in some other groups, a segmental portal vein thrombosis, corresponding to BCLC C patients was not considered as an absolute contraindication for TACE. This can certainly impact on the efficacy and tolerance, and is therefore of crucial importance to know relatively early, at least before severe toxicities, which patients will benefit from additional sessions.

Table 1. Evolution of median overall survival following ABCR score with different thresholds in a merged cohort of 186 patients treated by TACE.

ABCR	ABCR [-3] (n = 20)	ABCR [-2] (n = 3)	ABCR [-1] (n = 52)	ABCR [0] (n = 31)	ABCR [1] (n = 5)	ABCR [2] (n = 34)	ABCR [3] (n = 24)	ABCR [4] (n = 13)	ABCR [5] (n = 1)	ABCR [6] (n = 3)
Median survival months [95% CI]	38 [31-72]	31 [26-36]	38 [24-50]	25 [20-27]	24 [3-24]	18 [15-20]	13 [12-15]	7 [6-9]	8 [n.a.]	5 [4-11]
p value	<0.0001									
Median survival months [95% CI]	31 [25-38]				15 [14-19]			7 [6-9]		
p value	<0.0001									
Median survival months [95% CI]	37 [31-46]				17 [14-19]					
p value	<0.0001									
Median survival months [95% CI]	31 [25-38]				14 [12-17]					
p value	<0.0001									
Median survival months [95% CI]	31 [25-38]					14 [12-17]				
p value	<0.0001									
Median survival months [95% CI]	26 [24-31]						11 [8-13]			
p value	<0.0001									
Median survival months [95% CI]	25 [21-27]							7 [6-9]		
p value	<0.0001									