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Review article: delivering precision oncology in intermediate-stage liver cancer: advancements and challenges of novel prognostic models.

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List of Abbreviations

HCC, Hepatocellular Carcinoma; TACE, Trans-arterial chemoembolization; PS, Performance Status; BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte Pugh; OS, Overall Survival; INR, International Normalised Ratio; MELD, Model for End Stage Liver Disease; cTACE, Conventional TACE; DEB-TACE, Drug-eluting Beads TACE; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, Modified RECIST criteria; EASL, European Association for the Study of the Liver; AFP, alfa-fetoprotein; HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; HAP, Hepatic Arterial embolization prognostic score; mHAP, modified HAP score; ART, Assessment for Retreatment with TACE score; STATE, Selection for Transarterial Chemoembolisation Treatment score; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ration; IBI, Inflammation-based Index; LCSJ, Liver Cancer Study Group of Japan; JSH, Japanese Society of Hepatology.

Abstract.

Background: Intermediate-stage hepatocellular carcinoma (HCC), for which trans-arterial chemoembolization (TACE) constitutes the standard of care, is a patient subgroup with significant heterogeneity in clinical outcome. Sources of variation relate to differences in tumor burden, hepatic reserve, ethnicity and treatment modalities. Increasing research efforts have been dedicated to minimize the clinical diversity of this patient population and enhance optimal provision of treatment.

Aim: The aim of this paper is to comprehensively review the diverse prognostic models that have been proposed to refine the prognostic prediction of patients with HCC undergoing TACE.

Results: A number of prognostic algorithms (HAP, ART, ABCR score and many others) have shown potential to address the clinical heterogeneity characterizing patients with intermediate-stage HCC and facilitate early identification of patients with poor prognostic features in whom alternative treatments or best supportive care might be more appropriate than TACE.

Conclusions: Whilst an improved characterization of intermediate-stage HCC is a highly important clinical aim, current evidence suggests that **novel prognostic algorithms** in this patient population may offer potential benefits but non-negligible challenges in the provision of TACE. This review summarizes the currently available evidence to facilitate the development of a precision oncology in intermediate-stage HCC.

Keywords: TACE, prognosis, survival, hepatocellular carcinoma.

Introduction.

Approximately 60% of newly diagnosed patients with hepatocellular carcinoma (HCC) are incurable¹. Unlike other solid tumors, HCC poses a wide range of challenges stemming from the extent of spread of malignancy combined with the underlying liver dysfunction. These independent prognostic domains integrate with the patient's overall fitness, captured by the Performance Status (PS) score, to dictate the natural course of the disease. Over the past two decades, the coherent integration of individual prognostic traits into composite staging algorithms has represented a key advancement in the management of HCC. Amongst the myriad of scores in HCC, the Barcelona Clinic Liver Cancer (BCLC) is a validated and widely applied staging algorithm, due to its integration of prognostication and treatment allocation^{1, 2}.

According to the BCLC algorithm patients with liver-restricted HCC, preserved Child-Turcotte-Pugh (CTP) class and good PS who cluster into the "intermediate" (BCLC-B) stage. Whilst approximately 50% of intermediate-stage patients are alive 2 years after diagnosis even without treatment³, predicted median overall survival (OS) is highly variable, ranging between 11-45 months^{4, 5}.

It is universally recognized that such a wide variation in survival results from a significant degree

of disease heterogeneity that is not adequately captured by current staging systems, where various degrees of liver dysfunction, tumor burden and other factors including age, comorbidities and etiology of underlying chronic liver disease coexist within the unifying label of “intermediate-stage HCC”.

The issue of disease heterogeneity plays a major role in the administration of trans-arterial chemoembolization (TACE). TACE is indicated as first-line treatment in asymptomatic patients with compensated cirrhosis with a CTP score <8, PS 0 and lack of portal vein thrombosis or extra-hepatic spread. This is supported by level I evidence emerging from two randomized controlled trials showing that TACE reduces mortality by approximately 50%^{6, 7}. The beneficial effect of TACE was further consolidated by two meta-analyses⁸, where its magnitude was however re-dimensioned due to patient and procedural heterogeneity⁹.

Given the palliative intent of TACE, survival extension must be carefully weighed against treatment-related morbidity and mortality. TACE may worsen the underlying liver dysfunction and, although administered safely in most instances, it carries a potential risk of post-procedural mortality reported to be as high as 10%^{10, 11}.

Increasing clinical evidence suggests that the survival benefit deriving from loco-regional therapies is not evenly distributed across all the patients receiving TACE. Despite meeting eligibility criteria, a subset of patients may not respond to therapy, which suggests the need for more accurate prognostication. Furthermore, patients with initial radiological response to treatment may subsequently become ineligible to repeat embolization due to worsening liver failure, lack of adequate arterial access or disease progression. The lack of shared retreatment criteria across different institutions has made a harmonized definition of “TACE refractoriness” the subject of intense debate^{12, 13}.

The evolving experience in the administration of TACE has progressively widened its positioning within the treatment armamentarium of HCC to include both earlier-stage patients (ie. BCLC-A) unsuitable for curative therapies as well as a wide range of cases with BCLC-C stage tumors either due segmental, non occlusive portal vein thrombosis, extra-hepatic spread, symptomatic disease or liver dysfunction. The progressively broadening use of TACE beyond the recommended eligibility criteria has further widened the heterogeneity in treatment-induced survival benefit, making patient selection and prognostication increasing difficult tasks for clinicians.

Furthermore, the use of TACE beyond BCLC-B staging criteria relies on far less stronger evidence and such approach might potentially be futile in some patients, depriving or postponing the delivery of potentially more efficacious alternative treatments including sorafenib or radioembolization¹⁴.

Increasing research efforts have been dedicated to the identification of optimal stratifying characteristics in TACE candidates, with the intended benefit to identify patients whose survival gain following initial TACE is anticipated to be very small and migrate them to alternative, more efficacious treatments¹⁵. Some of these [models](#) are devised to provide clinicians with objective re-treatment criteria based on dynamic changes of clinical and radiological parameters following initial treatment, with the intent to spare repeat embolization for those patients displaying deteriorating scores for whom further treatment may be more harmful¹⁶.

There is no clear consensus regarding the true clinical utility of the growing number of proposed scores, nor documented evidence as to which one performs best. As a result, despite being the subject of an intense academic debate, none of the proposed clinical scores has exerted a real change in clinical practice.

Here, we portray the sources of heterogeneity affecting treatment outcomes in patients receiving TACE and review the published evidence around patient stratification in intermediate stage HCC.

Sources of clinical heterogeneity in patients treated with TACE.

[Tumour burden and liver functional reserve.](#)

Whilst a general consensus exists around the concept of optimal patient selection for TACE as a measure to optimize treatment outcomes, there are however opposing and often paradoxical messages emerging from the literature with regards to the exact positioning of TACE as a palliative treatment for HCC.

The inclusion of patients extending beyond BCLC-B criteria is common in clinical practice, amounting to 22-29% in recently published series. Life expectancy changes significantly as a function of stage, ranging from 16-18 months of stage-unselected cohorts^{17, 18} to median OS approaching 40 months in studies considering intermediate-stage disease only¹⁹.

In advanced HCC, whilst feasible, TACE is associated with reported survival outcomes that range between 6-14 months^{20, 21}, where the main determinants of survival heterogeneity are the presence of extra-hepatic disease or the extent of macro-vascular invasion, a factor that significantly deteriorates OS to <6 months, when the main branch of the portal vein is affected²².

Tumor stage is not the sole determinant influencing survival following TACE. A number of studies have now reported on outcomes of patients treated with TACE with significantly impaired liver function, describing a 30-day mortality rate of 8% and an overall morbidity rate of 11%²³.

A large retrospective study of 251 patients with hepatic dysfunction confirmed the association between decompensated liver failure with ascites, jaundice, coagulopathy or a Model for End Stage Liver Disease (MELD) score ≥ 20 with severe post-procedural complications. This included irreversible hepatotoxicity in 15% of the patients that required urgent transplantation in 2% and lead to death in 6% of the cases²⁴. Whilst accurate selection of patients with liver dysfunction might be an option when TACE is used as a bridging therapy to transplantation²⁵, the high risk of short-term morbidity and mortality generally discourages such approach in the palliative setting.

Procedure-related factors.

Since the early attempts in the therapeutic embolization of liver tumors in the 1970s, TACE has undergone significant technical advances to improve procedural efficacy and safety²⁶. Its anticancer effects rely on the trans-catheter occlusion of the tumor-feeding vessels following selective infusion of cytotoxic agents through peripheral arterial access, generally obtained by femoral puncture. TACE is however a poorly standardized technique across institutions, with a number of treatment-related variables described to influence outcome.

Selection of the dominant tumor-feeding artery is largely operator-dependent. A pre-procedural angiogram is necessary to guide selection of vessels that are likely to induce maximal tumor necrosis and minimal hepatotoxicity. Selective targeting of the tumor-feeding arteries is essential to achieve complete necrosis, especially in tumors >3 cm²⁷.

The relative effect of tumor ischemia over the cytotoxic activity of intra-arterial chemotherapy is an unresolved question in the administration of TACE. A number of cytotoxics including anthracyclines or cisplatin are currently in use, with no clear consensus as to the most efficacious compound²⁸. In a recent phase II/III trial comparing embolization alone versus chemoembolization with cisplatin using a sequential treatment schedule showed higher

response rates when cisplatin was added to the schedule (67 versus 47%) in absence, however, of significant differences in survival¹⁸. In conventional TACE (cTACE) protocols, drugs are infused in form of an emulsified suspension in iodized oil (lipiodol) prior to administration of the embolizing agent (gelfoam or polyvinyl alcohol particles) and previous studies have shown that optimal lipiodol impregnation of the target nodule preludes improved survival outcomes following TACE, making this a frequently utilized marker to identify a successful procedure in routine practice²⁹.

The use of drug-eluting beads TACE (DEB-TACE) has arisen as an alternative approach to cTACE. In DEB-TACE, embolization and drug elution into the tumor happen concurrently through the use of chemotherapy-impregnated microspheres, which yield an improved intra-hepatic delivery of cytotoxics and reduced systemic diffusion³⁰. The prospective randomized Precision V study, which evaluated cTACE versus DEB-TACE in 212 cirrhotic patients confirmed an improved tolerability and higher rates of complete response of DEB-TACE but failed in demonstrating a survival difference between the groups³¹. A second, smaller trial comparing DEB-TACE with bland embolization reported a 6.2 weeks difference in time to radiological progression, with similar adverse event profile³². Based on improved safety and local pharmacokinetics, the use of DEB-TACE has rapidly expanded, and a recently published case series of 104 patients, 60% of which were BCLC-B and 95% within Child A functional class revealed a median OS of 48.6 months following treatment⁴.

The criteria guiding the assessment of treatment response as well as the planned follow-up intervals are also highly influential in affecting the prognosis of TACE candidates. There is little evidence to inform clinicians whether TACE should be repeated periodically at fixed intervals³³, or whether patients should be treated upon evidence of radiologic progression. In the original randomized trial by Llovet, TACE was administered at study baseline, 2, 6 months, then every 6 months thereafter until “untreatable progression” defined by portal vein or systemic spread⁶, whilst in the study by Lo the re-treatment schedule was shorter, with pre-planned sessions every 2 months until unacceptable toxicity or disease progression⁷. By no means, however, these represent standard criteria for retreatment and a large number of institutions prefer adopting an “à la demande” approach, guided by the evidence of radiologically proven disease progression.

It is universally recognized that standard Response Evaluation Criteria In Solid Tumours (RECIST)³⁴ are suboptimal in identifying residual active disease following TACE, a common radiologic indication for early retreatment. For this reason, alternative paradigms insisting on the

contrast-enhancing component of the disease including the modified RECIST and the European Association for the Study of the Liver (EASL) criteria, have been adopted with comparable prognostic accuracy between the two methods in predicting long term outcome following TACE³⁵.

Stratifying prognostic algorithms in patients undergoing TACE.

The Intermediate HCC Stage Sub-classification.

In 2012, a consensus meeting held amongst experts in the management of HCC explored the applicability of a system to sub-classify intermediate-stage HCC into different prognostic strata based on the combination of common clinico-pathologic variables³⁶. The seminal paper authored by Bolondi et al. proposed a revised classification of the intermediate-stage of the BCLC algorithm into four subclasses (B1 to B4) based on CTP, tumor burden as evaluated by the Milan and up-to-seven criteria and PS (**Table 1**). Bolondi and colleagues reported significantly different survival outcomes across each subclass, suggesting that whilst the prognostically more favorable subgroups should be prioritized for TACE or even radical treatments if technically feasible, patients in the worst prognostic group might be more appropriately served by best supportive care in view of poorer CTP and PS.

This prognostic model has been further validated in independent studies. In a small retrospective, single center study including 90 BCLC-B patients with prevalent HCV/alcoholic aetiology treated with cTACE, the Bolondi sub-classification was confirmed prognostic with deteriorating OS figures ranging from 33.6 to 28.6, 19.0 and 13 months across the four strata³⁷. The observation was however limited by the scarce sample size, which yielded only 13 and 2 patients in the worse prognostic groups.

A larger study by Ha et. al was the first to appraise the prognostic value of the intermediate-stage sub-classification in 466 Korean patients, 77% of whom had cirrhosis of largely HBV-related aetiology (73%). Survival analysis did not reveal a significant difference between B3 and B4 categories, where median survival were 14.1 and 17.2 months respectively (Log rank $p=0.48$), however only 35 patients satisfied B3 criteria in the study, whilst the other subclasses were populated by at least 100 patients each³⁸. The authors therefore proposed a modification to the score by merging the B3 and B4 strata, and constructed an alternative three-tiered prognostic system describing significantly different median OS figures of 41, 22.1 and 16.6

months respectively.

In a similar, larger retrospective study of 580 patients from a single center in Taiwan, with mixed aetiologies of HCC, only 7.4 and 2.2% clustered in sub-stages B3 and B4 to suggest a recurrent difficulty of the system in capturing an adequate proportion of patients with poorer prognostic features in Asia, where the observed OS was generally poorer across each subgroup amounting to 29, 15.6, 6 and 9.6 months respectively³⁹. To improve the prognostic discrimination of each subgroup, the authors proposed a further modification of the Bolondi sub-classification by integration of alfa-fetoprotein (AFP), yielding an improved sub-stratification into 3 groups with median OS of 32.4, 22.8 and 9.6 months.

Whilst holding the advantage of being derived from routinely available clinical and laboratory parameters, the intermediate-stage HCC sub-classification may prove laborious to apply routinely because of the number of variables utilized. The model also lacks prospective validation and whilst appraised in patients with diverse ethnicity and aetiology of HCC, subsequent studies have shown the inherent difficulty of the model to capture wide enough proportions of patients with adverse prognosis, who often amounted to <10% of the overall BCLC-B population: a finding that may further limit the prospective clinical applicability of the score.

The Hepatoma Arterial-embolization Prognostic (HAP) Score and proposed modifications.

The HAP scoring system classifies patients into 4 strata (A to D) according to their risk of mortality based on the equal weighting of the strongest multivariable predictors of survival emerged from the study of 2 retrospective cohorts of patients considered for TACE collected from two independent British institutions (n= 91 and 151 respectively)¹⁵.

Patients displaying ≥ 2 adverse prognostic features should not be offered TACE due to poorer survival outcomes following treatment, whose range is reported between 3.6-9 months for stages C-D across both sets, compared with significantly improved figures of 18-24 months in stages A-B¹⁵.

However, the original qualification study suffered from some methodological constraints. Firstly, only 31% of the patients in the training set satisfied BCLC-B criteria, whilst no information was given as to BCLC stage in the validation set, potentially causing a greater heterogeneity in

survival. Secondly, presence and degree of portal vein involvement, PS or extra-hepatic disease were not documented in the analysis, a point of major consequence given that 36% of the patients utilized to derive the HAP score exceeded BCLC-B staging parameters. Lastly, a significant heterogeneity in the provision of loco-regional treatments was also reported, with <50% of the patients in the training set receiving a full cTACE treatment protocol as opposed to 100% in the validation set. Equally, the survival analysis was centered on initial TACE/TAE, and the prognostic impact of the number of re-treatments was not considered.

The HAP score was validated in a separate cohort of 131 patients from Vienna, all within BCLC-A/B criteria in whom the authors documented deteriorating median OS values ranging from 25.7 to 18.5, 12.5 and 10 months across stages A to D⁴⁰. However, given the methodological premises discussed before, it is perhaps unsurprising that external validation of the HAP score performed in a further independent, large cohort including >800 patients from 4 institutions in Europe and Asia yielded wider survival differences, with patients in stages A+B achieving significantly median OS in excess of 50 months, compared to 7.4 months of HAP D stage patients⁴¹. More importantly, in the latter study, re-assessment of each individual variable revealed a lack of significance for raised bilirubin, a prognostic factor that had in fact achieved borderline significance in the original paper¹⁵. For all these reasons, a modified version of the HAP score (mHAP) was devised by exclusion of serum bilirubin, with an improved sub-classification of the poor prognostic groups confirmed in both a training set of 124 patients from the UK and Italy, where median OS was 8 and 3.8 months in mHAP stages C and D, as well as in a validation cohort of 723 patients from Japan and Korea with similar median OS values of 13.0 and 6.5 months.

The Assessment for Retreatment with TACE (ART Score) and START strategy.

Preservation of optimal liver function stands amongst the strongest domains affecting the prognosis of patients undergoing TACE. Despite the evolving experience in delivering TACE with super-selective approaches, the combined ischemic and cytotoxic damage to the peritumoral liver parenchyma that stems from treatment carries the potential to precipitate liver failure and worsen survival. The ART score is constructed from a worsening of Aspartate Transaminase (AST) by >25%, an increase of CTP of 1 or ≥2 points and the lack of radiologic tumor response following TACE⁴². Whilst each parameter is weighted differently based on the individual hazard ratios for OS, the final computation of the ART score dichotomizes patients

into two groups (0-1.5 points; ≥ 2.5 points) with a median OS of 23.7 versus 6.6 months after initial TACE, a result that was confirmed in two independent sets of 107 and 115 patients, the majority of whom (89 and 69%) were BCLC stage B of predominant alcoholic aetiology (46%).

The analysis qualifying the ART score was limited to patients with BCLC stage A or B tumors with at least 2 TACE procedures performed within 90 days. In contrast to the HAP and the Bolondi sub-classification, the ART score takes advantage of the dynamic changes in hepatic reserve markers as well as AST, which may stand as a surrogate of post-procedural tumor necrosis (hence, tumor burden) as well as the ischemic damage suffered from the surrounding liver parenchyma. The strong linkage between a deteriorating ART score with a higher proportion of treatment-related adverse events and 30-days mortality qualifies this index as a potentially useful [surrogate of safety as well as efficacy outcomes](#) with a strong pathophysiologic relationship with survival in HCC patients treated with TACE.

It has however been argued that the score gives equal prognostic weighting to each parameter of the CTP class deterioration, some of which (ie. ascites, encephalopathy) are subjective, less reproducible and may have a stronger prognostic role compared to worsening liver biochemistry⁴³. The latter being not solely reflection of progressive hepatic failure but also intercurrent sepsis, or – in the case of hypoalbuminaemia - malnutrition⁴⁴ and cancer-related systemic inflammation⁴⁵. The confounding effect of infection has in fact not been detailed in the study, a factor that might have a transient and potentially reversible impact on the post-procedural deterioration of routine biochemistry. The time-dependence in determining the dynamic changes of liver biochemical parameters, AST elevation in particular, has been addressed by the authors given the heterogeneity in the time of blood test reassessment (13-90 days). However it is likely that, given this time window, the changes in blood parameters might reflect a condition of acute phase response following tumor necrosis and not solely liver functional deterioration. Interestingly, the presence of patients requiring retreatment in <2 weeks from initial TACE suggests inclusion of tumors requiring a two-staged embolization. Therefore, at the time of ART reassessment a proportion of patients might have been committed to retreatment due to the presence of non-embolized active disease, a situation that might have impacted on the routine blood test reassessment as well as radiologic response and survival. Patient and treatment heterogeneity was also non-negligible in the original study, both in the range of embolization techniques used (52% cTACE, 20% DEB-TACE, 28% TAE in the training set versus 99% cTACE in the validation set) and in the wide-ranging recruitment period (1999 to 2009), which corresponded to a decade of profound changes in the delivery and patient

selection for TACE, predating in part the publication of the landmark trials in 2002^{6, 7}.

Despite the uncertainties around the biologic qualification of the parameters constituting the ART score and the acknowledged limitations, the potential to identify a subset of high risk patients, whose expected survival of 7 months approaches that of advanced untreated HCC⁴⁶, is clinically appealing and potentially practice-changing feature of this model, which might favor early treatment migration of patients with poor prognostic features in an attempt to maximize survival outcomes.

Following on from the initial experience, in a separate study consisting of a pooled analysis of 109 patients derived from the same 2 retrospective cohorts, Huckle et al. explored the prognostic utility of the sequential use of the ART score in patients undergoing multiple TACE sessions⁴⁷. The reassessment of ART in patients undergoing second (n=109), third (n=77) and fourth TACE (n=29) showed adequate prognostic sub-classification at each time point despite the decreasing number of analyzed patients, allowing the investigators to conclude that worsening of the ART score to >2.5 at any stage of the sequential loco-regional retreatment of HCC is harbinger of a poorer prognosis and should preclude further TACE. When tested in a multivariate analysis of prognostic traits prior to TACE-3, the ART score outweighed the impact of tumor burden and AFP changes throughout treatment, to suggest an improved accuracy in detecting treatment-induced survival benefit over common clinico-pathologic variables.

Expanding on these findings, which supported the role of the ART score as a prognostic trait and an objective re-treatment [criterion](#), the same group investigated its positioning in the context of a compound algorithm named “START strategy” devised to select TACE candidates based on optimal prognostic features exhibited prior to initial TACE (STATE score) followed by sequential ART score reassessment to establish suitability for retreatment⁴⁰.

Based on previous observations showing that hypoalbuminaemia and elevated C-reactive protein levels are prognostic in HCC^{45, 48}, Huckle and colleagues derived the STATE prognostic score combining pre-TACE albumin levels with tumor burden classified by the up-to-seven criteria⁴⁹ and CRP levels. According to the model, a final score ≥ 18 corresponds to a median OS of 19.5 months, with a significant deterioration to 5.3 months if the STATE score is <18. The same independent Austrian cohorts (Training n=131, Validation, n=146) were utilized to qualify the STATE score. Through a combination of baseline factors and post treatment changes in routinely available clinico-pathologic variables, the START strategy lends itself as an objective prognostic marker as well as re-treatment criterion.

Whilst of potential clinical value in optimizing treatment outcomes, a comprehensive evaluation of the START strategy has not been performed externally, and the series of studies conducted in the same Austrian patient cohorts^{40, 42, 47}, which were collected retrospectively and across a wide time window might have led to overfitting of the prognostic models due to differing disease severity, treatment pathways as well as missing data⁵⁰.

In a letter published by Kudo et al.⁵¹, the ART score was externally evaluated for its prognostic role for the first time in Japanese patients. Screening of a large database of 513 patients treated with TACE between 2004 and 2011 revealed only 49 (10%) to satisfy the eligibility criteria specified in the original study by Sieghart, where, conversely, nearly 90% of the patients had >2 TACE sessions within 90 days⁴². In the 44 patients analyzed, the ART score failed to retain prognostic significance. Whilst the format of the publication precluded a comprehensive assessment of important covariates including BCLC stage, aetiology of underlying liver disease as well as number of treatments administered, it is conceivable that the heterogeneity in patient selection, stage at presentation and the differing retreatment criteria might have accounted for the lack of prognostic significance. Equally, the small sample size of 44 patients, 32 of whom displayed a high-risk ART score following TACE but without a significant difference from the 12 in the lower-risk subgroup (22.4 versus 16.5 months), might have underpowered the observation. Independent from statistical considerations, the applicability of the ART score in a minority of Asian patients due to differing re-treatment criteria is a significant finding, which is to be taken into account when evaluating the applicability of the prognostic model. It would be of important clinical value to extend the evaluation of the ART score to unselected TACE candidates in future studies, a finding that may further test the reliability and reproducibility of the model in settings where different screening policies, re-treatment intervals and various degrees of arterial embolization selectivity may influence clinical outcomes.

This point is of major consequence given the recent publication of an Italian study showing only 51 out of 344 patients (15%) to be eligible for ART score testing based on the original eligibility criteria⁴², suggesting a reduced applicability of the score that replicates the limitations noted in the Japanese study⁵¹. Furthermore, when each variable of the ART score was tested, CTP class deterioration emerged as the sole predictor of OS, with no prognostic role found for radiologic response to initial TACE or AST increase, which might the wider differences in the time of biochemical reassessment, often extending to 3-4 months post-initial TACE⁵².

Equally, patient features were different in the Italian series, which included with 47% of BCLC-B

stage HCC with mainly unilobar tumors (70%), Child A cirrhosis (82%) of predominantly viral aetiology (78%): a different setting from the Austrian cohorts, where the poorer functional reserve might have contributed to delayed AST clearance, with ongoing alcohol consumption potentially accounting as an unaddressed confounder in a population with higher proportion of alcoholic cirrhosis⁴².

Despite the optimal features displayed by the ART strategy in the selection of TACE candidates, the lack of external validity emerged from the two studies has questioned its clinical reliability. Interestingly, in an independent multicenter clinical study including >700 patients from Europe and Asia, the use of the ART score without strict application of a 90-days interval and including patients who achieved complete response after TACE – a setting that better reproduces routine clinical practice – has demonstrated a better clinical performance of the score, suggesting that patient selection and time of biochemical reassessment might be strong determinants influencing its prognostic accuracy⁵³. In light of the several issues demonstrated during external validation, prospective evaluation is a mandatory step before either the START or the ART strategies can inspire treatment changes in the clinical arena.

The ABCR score.

The criticalities emerged from the independent evaluation of the ART score broadened the interest towards prognostic scores in TACE candidates, prompting other investigators to explore novel prognostic algorithms to guide the delivery of TACE. The ABCR score is based on four established prognostic parameters in HCC including AFP>200 ng/ml at baseline (+1 point), BCLC stage (+2 and +3 points for stage B and C), increase in CTP by ≥ 2 from baseline (+2 points), and presence of radiologic response (-3 points)⁵⁴. In the derivation cohort, patients with an ABCR score ≤ 2 (n=105) achieved a median OS of 35 months, compared to 6 in patients scoring ≥ 3 (n=23). Validation was performed in an internal (n=78) and an external cohort (n=101) where incremental deterioration of the score mirrored a progressive worsening of median survival values ranging from >2 years for patients with a score ≤ 0 , 12-17 months for those classified as intermediate risk (ABCR score 1-3) and 7 months in patients with high risk score (ABCR ≥ 4).

Whilst it is undeniable that the ABCR score incorporates prognostic covariates repeatedly shown to reflect a more aggressive course of HCC, it is unclear from the initial study what is the recommended ABCR score cut-off for patient to be preserved from potentially futile TACE treatment, given that different values were utilized across the 2 studied patient subsets.

This point has in fact attracted criticism over the design of the study, where the use of relatively small and homogeneous patient cohorts from 2 centers in France, as well as the varying, non-standardized definition of “poor prognostic” group casting may have affected the reliability of the results due to over-fitting bias.

Inflammation-based prognostic models.

The presence of a cancer-related pro-inflammatory diathesis is a pathogenic and prognostic hallmark of malignancy⁵⁵. Systemic inflammation has been recognized as a stage-independent prognostic factor in most tumors⁵⁶⁻⁵⁸, including HCC^{44, 59}. Widely available, objective laboratory parameters including CRP, albumin or reactive changes in full blood count parameters including the neutrophil or platelets-to-lymphocytes ratios (NLR, PLR) are validated inflammation-based markers in HCC⁴⁵.

The interplay between inflammation and the prognosis of intermediate-stage HCC patients is complex and results from the dynamic changes in inflammatory mediators secondary to the presence of tumor-host interactions as well as treatment^{60, 61}. In a study of 145 TACE candidates, Huang et al. confirmed that a raise in the NLR 3 days post procedure correlated with improved OS, to suggest a prognostic parallelism between the acute elevation of inflammatory markers and a more efficacious post-procedural tumor necrosis⁶². In contrast to this initial finding, a second smaller study of 54 patients showed that persistent elevation of the NLR 6-8 weeks following initial TACE translated into a worsening of median OS times to 10.6 from 36.7 months of patients with normal/improved NLR after treatment⁶³. Unlike the previous study by Huang, in this, as well as in subsequent studies⁶⁴⁻⁶⁶, the delayed timing of NLR measurement dissects the unopposed, cancer-related cytokine release, from the acute post-necrotic inflammatory flare, as the main determinant of the survival deterioration seen in patients with persistently abnormal inflammatory markers after TACE. Analysis of cytokine profiles confirms the bimodal, time-dependent pattern of cytokine release, differentiating a transient interleukin (IL)-6 driven, treatment-induced pro-inflammatory response from a late-phase increase in IL-4, 5 and 10 levels to suggest chronic modulation of the T-helper-2 lymphocyte response after treatment⁶⁷.

Albumin and CRP based indices such as the Inflammation-based index (IBI)⁶⁸ following TACE have been shown to equally reflect disease-modulating effects from treatment. In a large,

multicenter study of >700 patients, normalization of albumin and CRP post TACE reflected prolonged survival and improved radiologic response, therefore sustaining the hypothesis that suppression of a systemic inflammatory response may act as a surrogate **marker** for chemoembolization failure. Such effect on survival was independent of patients' ethnicity and was validated in a small prospectively recruited patient sub-cohort within the study.

The experience with IBI has been mirrored by that of the START strategy, an alternative model that also incorporate baseline CRP and albumin, to suggest the consolidated role of these traits in HCC⁴⁰. Whilst multiple studies have confirmed the prognostic value of inflammation in HCC, the ideal positioning of inflammation-based scores in the selection process of TACE candidates remains however unclear and deserves further evaluation in future comparative studies incorporating alternative prognostic models^{15, 41, 54}.

The Liver Cancer Study Group of Japan (LCSJ) recommendations: the concept of TACE refractoriness.

In Japan, the majority of patients with HCC presenting for TACE have less advanced stage tumours comprising a limited number of small nodules, compared to Western patients. This is due to a highly effective nationwide HCC screening program and this disease pattern is also seen in other Asian countries where HCC screening programs are well-established⁶⁹. As such, Asian centres have developed their own HCC management guidelines to incorporate evidenced-based best practice and reflect regional differences in disease presentation and behaviour.

The Japan Society of Hepatology (JSH) and LCSGJ have developed guidelines for TACE treatment, which includes a definition of TACE failure or refractoriness, the point at which it is recommended to stop administering TACE therapy to patients who were unlikely to yield clinical benefit⁷⁰. The JSH proposed the concept of TACE refractoriness in its first guidelines, which were subsequently emulated by Korean guidelines and EASL guidelines for HCC management¹².

This is defined as:

- 1) ≥ 2 consecutive ineffective responses of treated tumours to TACE (defined as the persistence of >50% viable lesions), or

- 2) ≥ 2 consecutive progressive increases in total tumour number, or
- 3) Persistent elevation of tumour markers immediately after TACE, or
- 4) New vascular invasion or extra-hepatic spread

These must also occur despite a prior change in the choice of chemotherapeutic agent or re-analysis of the feeding artery to ensure TACE therapy has been optimised^{12, 71, 72}.

Globally, there is debate regarding the chosen cut-off of two ineffective TACE treatments to define TACE failure/ refractoriness. Furthermore, in some countries, the definition of ineffective TACE is considered to be progressive disease after the first and second TACE procedures, without considering the other aspects proposed by the Japanese guidelines. Therefore, the JSH definition was subsequently validated in a small retrospective study of 45 patients receiving sorafenib therapy, who had experienced TACE failure. In this study, the number of ineffectual TACE treatments received was the only significant independent variable associated with survival on multivariate analysis. Those who received up to two ineffectual TACE treatments prior to sorafenib therapy had longer overall survival compared with those who had received ≥ 3 ineffective TACE prior to sorafenib (OR 4.40, 95% CI 1.11-17.37; $p < 0.035$)⁷³.

This supports a survival benefit of swapping to other treatments once TACE proves ineffectual, rather than subjecting patients to multiple TACE treatments in the absence of survival benefit. OS was significantly shorter in those who received ≥ 2 ineffectual TACE treatments (8 months, 95% CI 5.7-10.4 months), however in this study the median survival time for those receiving ≤ 2 treatments was not calculated. Furthermore, this was a small retrospective study, and further prospective studies in mixed-ethnicity cohorts are warranted to definitively determine futility rules in HCC management.

Conclusion.

Accurate prognostic prediction is of paramount importance in oncology, especially in the palliative setting of care, where the potentially adverse effects from treatment have to be weighted against the prospect of treatment-induced survival benefit. Whilst a number of scores have claimed to improve the selection of patients and make re-treatment criteria with TACE more objective, a few criticisms need to be addressed before any of these can confidently influence clinical practice. Firstly, most of the proposed [algorithms](#) convey a prognostic (ie.

simple estimation of OS) rather than a truly predictive assessment of response to treatment (ie. treatment-induced survival benefit). As such they are maximally helpful in identifying subsets of patients with more accelerated course of the disease. However, in the absence of prospective, biomarker-driven randomised evidence, it remains impossible to ascertain whether patients with indolent as well as accelerated course of the disease might both benefit from TACE.

With radioembolization demonstrating a favourable safety and anti-tumor efficacy profile confirmed by radiologic response rates exceeding 50%⁷⁴, a process of harmonised and robust qualification of predictors of shortened survival or treatment failure in TACE candidates is a desirable aim to optimise patients' outcomes through treatment migration. Whilst a direct comparison of clinical outcomes from retrospective data is difficult due to the diverse indications and positioning of radioembolization versus TACE, randomized phase-II study data in patients with BCLC A-B HCC have shown a significantly longer time to progression following Yttrium-90 radioembolization compared to conventional TACE (>26 months versus 6.8 months, hazard ratio 0.12, 95%CI 0.02-0.55, $p=0.007$)⁷⁵. Whilst encouraging, these data were not mirrored by a consensual effect on overall survival, perhaps because of the inclusion of transplant candidates. In absence of more solid, prospectively generated evidence, which might facilitate integration of radioembolization with current treatment algorithms of HCC, the choice of depriving intermediate-stage patients from a reasonably tolerable and cost-effective option represented by TACE, should not be encouraged. The various limitations applying to the retrospective studies qualifying novel prognostic models or retreatment criteria in intermediate-stage HCC including for instance selection, recall bias and the risk of statistical over-fitting of survival analyses further reinforces the importance of this point. Study authors need to ensure that newly proposed prognostic models or biomarkers are statistically and clinically justified by presenting the preferred score and other models that have been derived in the process, thereby providing greater transparency in the choice of final model. Furthermore, validation of scores via a collaborative approach should be an integral part of presenting new prognostic scores in HCC in treatment with TACE and other therapies.

A rigorous and evidence-based approach should guide the forthcoming development of stratifying prognostic models in intermediate-stage HCC, with the prospect of fully enabling precision oncology in this highly heterogeneous patient group.

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Tables.

Table 1. Prognostic scores evaluated in patients undergoing palliative TACE treatment for unresectable HCC.

Score	Constituents	Strata	OS (months)	References
HAP Score	Albumin <35 g/L AFP >400 ng/dL Tumor diameter >7cm Bilirubin >17mmol/L	HAP A HAP B HAP C HAP D	27.6 / 25.5 18.5 / 18.1 9.0 / 8.9 3.6 / 5.9	Ref 15 (Training and Validation sets)
ART Score	Child Pugh increase following TACE (+1, +2 points) AST >25% from baseline Lack of radiologic response	High risk (>2.5) Low risk (<2.5)	6.6 / 8.1 23.7 / 27.6	Ref 46 Ref 47
STATE Score	Albumin (in g/L) -12 if CRP >1 mg/dL -12 if outside up to seven criteria	High risk (≤ 18) Low risk (>18)	5.3 / 6.1 19.5 / 20.5	Ref 40

ABCR Score	<p>AFP >200 ng/ml</p> <p>BCLC stage (B, C)</p> <p>Child Pugh increase following TACE (≥ 2 points)</p> <p>Presence of radiologic response</p>	<p>Low risk (≤ 0)</p> <p>Intermediate risk (1-3)</p> <p>High risk (≥ 4)</p>	<p>26 / 37.8</p> <p>12 / 17.1</p> <p>7 / 7.5</p>	Ref 54
IBI Score	<p>Albumin <35 g/L</p> <p>CRP >10 mg/L</p>	<p>IBI 0</p> <p>IBI 1</p> <p>IBI 2</p>	<p>33 / 49.6</p> <p>18.2 / 35.0</p> <p>8.6 / 20.0</p>	<p>Ref 67</p> <p>(Training and Validation sets)</p>

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