**ASSESSMENT OF SURVIVAL AFTER INTRA-ARTERIAL TREATMENT OF HEPATOCELLULAR CARCINOMA: IMPACT OF LIVER DYSFUNCTION, TUMOUR-RELATED FACTORS AND VASCULAR INVASION.**

 **AN INTERNATIONAL COLLABORATIVE STUDY**

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***Abbreviations***

AFP, alpha fetoprotein; C-P, Child-Pugh; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KM, Kaplan-Meier; VI, vascular invasion; TACE, Transarterial chemo-embolisation

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***Abstract***

***Background and aims:*** TransArterial Chemo-Embolisation (TACE) is recommended for patients with BCLC intermediate stage HCC (stage B) particularly in patients with good underlying liver function and minimal symptoms. The HAP score combines measures of liver function and tumour-related factors to offer a simple prognostic scoring system. The ALBI grade permits assessment of the impact of liver function on survival. We aimed to investigate the performance of these two models and vascular invasion (VI) in patients undergoing TACE.

 ***Methods:*** We accrued patient level data on an international cohort of 3030 patients undergoing TACE and examined the impact of liver function as assessed by the Child-Pugh grade or the ALBI score on survival. The performance of the HAP score and the importance of vascular invasion was also assessed.

***Results:*** Overall, 60% had Child-Pugh (C-P) grade ‘A’ and 15% had vascular invasion (VI). Classification according to ALBI grade resulted in non-overlapping survival curves in the overall dataset and all regional cohorts. Results were remarkably consistent across regions. The HAP score was also validated. Tumour number, aetiology and vascular invasion were identified as additional independent prognostic risk factors not currently included in the HAP score. Survival was particularly poor for patients with vascular invasion.

***Conclusion:*** The ALBI grade categorised patients receiving TACE into three clear prognostic groups thereby emphasising the importance of underlying liver function in the outcome of TACE. The HAP score has been validated internationally and the serious adverse impact of vascular invasion is clearly shown.

***Keywords:*** Hepatocellular carcinoma; Transarterial Chemo-embolisation; ALBI

***Introduction***

International guidelines recommend TransArterial Chemo-Embolisation (TACE) for patients with hepatocellular carcinoma (HCC) at the BCLC intermediate stage (B) or for those patients in the early stage that are not candidates for percutaneous ablation, liver resection or transplantation.[1](#_ENREF_1) This recommendation was based upon two randomised trials and a subsequent systematic review.[2-4](#_ENREF_2) However the benefits from TACE remain controversial.[5-7](#_ENREF_5) A recent Cochrane review concluded that there was no firm evidence to support or refute the benefit of TACE for patients with unresectable HCC[8](#_ENREF_8) although this conclusion has, itself, been robustly challenged.[9](#_ENREF_9)

Nonetheless, there is little argument that the degree of underlying liver (dys) function is an important factor determining survival and hence in defining the patient groups most likely to benefit from this form of treatment. International guidelines suggest that TACE should be confined to those with Child-Pugh (C-P) ‘A’ disease and that patients with vascular invasion (VI) should receive Sorafenib rather than TACE although VI was not excluded in one of the original RCTs1,[3](#_ENREF_3). However it is now well-established that TACE can be performed safely in the presence of some degree of VI and, in current clinical practice, a significant proportion of patients undergoing TACE do, in fact, have VI. We have previously developed and validated a simple model, the **H**epatoma **A**rterial embolisation **P**rognostic (HAP) score[10](#_ENREF_10), based on a cohort of UK patients, that permits assessment of prognosis after TACE. The model was built on the clinical parameters of bilirubin, albumin, tumour size and AFP, the former two presumably reflecting the impact of liver function and the latter two, the impact of tumour-related factors, on survival.

We have now assembled a comprehensive global dataset that includes patient level data from more than 3000 patients undergoing TACE and undertaken a rigorous statistical analysis of the factors influencing survival. We placed particular emphasis on underlying liver function and the presence or absence of vascular invasion (VI) and, in the process thereof, we sought to validate the HAP score. Liver function was assessed by applying the recently developed ALBI score[11](#_ENREF_11), a simple objective and extensively validated[12-14](#_ENREF_12), approach.

***Patients and methods***

The cohorts comprised patients undergoing TACE in four different regions namely Europe, Japan, China (Hong Kong) and Egypt (Table 1). The European cohort comprised 413 patients from the UK (Birmingham, Liverpool and London), 768 from Germany (Hannover and Freiburg) and 88 patients from Pamplona, Spain. Some of the data from the UK (London and Birmingham) came from those on which the HAP score was originally derived and validated. These patients were excluded for the HAP score validation. The Japanese cohort (n=655) were recruited from five institutions in the Western part of Japan, as previously reported by Toyoda et al[15](#_ENREF_15). The Chinese patients (n=145) were from those attending the Joint Hepatoma Clinic at the Prince of Wales Hospital, Hong Kong and the Egyptian cohort (n=998) were from those referred to the Oncology department of the National Liver Institute (NLI) in Shebeen El-Kom, Egypt. Detailed demographic data is given in Table 1. Data recorded in each cohort include age, gender, albumin (g/l), bilirubin (µmol/l), tumour number (solitary or multiple), tumour size (cm), vascular invasion (VI), AFP (ng/ml), Child-Pugh grade and aetiology (HCV, HBV or ‘other’). ‘Other’ comprised mainly patients with alcoholic liver disease. Laboratory data were recorded within the six week period prior to the first TACE procedure which was, in turn, undertaken within 6 weeks of diagnosis. Vascular invasion (including portal vein, hepatic vein and inferior vena cava involvement) was assessed in the portal phase of computed tomography and by arterial portography by the superior mesenteric artery.  Assessments were made within the six week period prior to treatment.

The centres involved had extensive experience in the management of HCC and the use of TACE. We included all patients that were classified by the local investigator as undergoing TACE as their primary treatment excluding only those where TACE was used as a bridge to transplantation or other potentially curative treatment options. Neither the response, nor any specific aspects of the procedure such as type of cytotoxic drug or embolic agent used or frequency of repeat TACE, or other treatment after the primary treatment, were recorded for the purpose of this study. All data was analysed in the UK (University of Liverpool) and used exactly as presented by the contributing investigator. Liver function was assessed by the Child-Pugh grade (as graded by the local investigator) and the ALBI score, the latter being graded according to the published cut-off points. Grade 1, 2 and 3 refer to good, intermediate and poor liver function respectively.

***Statistical methods***

All statistical analyses were undertaken using Stata/SE 14.1. The HAP score[10](#_ENREF_10) and ALBI grade[11](#_ENREF_11) were calculated as previously described. Survival (in months) was calculated from date of TACE treatment until date of death or date of last-follow up. Survival according to HAP score or ALBI grade was plotted using the Kaplan-Meier method. The different classification systems were compared using the Harrell’s C (a measure of predictive power)[16-18](#_ENREF_16) and Akaike information criterion (AIC) (a measure of model fit)[19](#_ENREF_19). Higher values of the former and lower values of the latter indicates a better prognostic utility of the model. Log-rank tests were used to compare between the survival curves within each staging group. AFP and bilirubin were log-transformed due to extreme skewness. Variables that influence survival were identified using univariable Cox proportional hazards model. Using forward selection of variables at the p=0.05 level (and likelihood ratio test at each step), a multivariable Cox proportional hazards model was built to explain survival in TACE patients. For the Cox regression models, all the cohorts were merged and “region” was used as a frailty term. The proportional hazards assumption was tested on the basis of scaled Schoenfeld residuals after fitting the Cox regression model. For all tests, statistical significance level was set at 5%.

***Results***

The results from the univariable Cox regression analysis (Table 2) showed that albumin, bilirubin, tumour number, tumour size, vascular invasion, and aetiology were prognostic in patients undergoing TACE (all p≤0.0001). The multivariable Cox regression model (Table 3) showed that the key variables influencing survival were related to tumour characteristics (tumour size, tumour number, AFP and VI) (p<0.0001), liver function (albumin and bilirubin) (p<0.0001), aetiology (p=0.0082) and age (p=0.002) (Table 3). Most patients had Child-Pugh (CP) grade ‘A’ grade liver function; the remainder had CP grade B with only a small percentage (4%) having CP grade C (Table 1). Assessing liver function by the two variables of bilirubin and albumin as defined in the ALBI score revealed a clear discrimination in survival between each ALBI grade in all separate regions (Figure 1a-d) and overall (Figure 2a). The model also revealed clear separation within C-P ‘A’ patients (Figure 2b and Supplementary figure 1a-d). Assessing liver function with the C-P score also showed separation by grade in each individual region (Supplementary figure 2a-d). There was no clear difference between C-P B and C-P C particularly amongst the European, Japanese and Hong Kong cohorts but, as expected, the numbers in the C-P C group were low. Results after merging the datasets from all four regions showed clear separation between the three C-P grades (Figure 2c). Both by visual inspection and formal statistical analysis (via Harrell’s C statistic), the ALBI score is at least as effective as C-P in discriminating between prognostic groups. Harrell’s C statistic was 0.5661 and 0.5586 for ALBI and C-P respectively. The corresponding AIC values were 26963.33 and 26548.21 respectively.

The HAP score was originally developed using the UK datasets only (London and Birmingham). Applying the HAP score to each of the other cohorts – Europe (Liverpool, Spain and Germany), Japan, Egypt and Hong Kong – produced four prognostic groups in each region (Supplementary figure 3a-d) and overall (Figure 2d), thereby validating the score internationally, although it should be noted that there was considerable overlap between HAP 2 and 3 in the Egyptian (Supplementary figure 3c), and to a lesser extent the Hong Kong cohorts (Supplementary figure 3d). Merging all the cohorts, however, generated four clear prognotic groups (log-rank tests, p<0.0001 for all combinations) (Figure 2d).

Overall 15% of patients had vascular invasion and there was a very clear difference in survival according to presence or absence thereof, in all regions (Supplementary figure 4a-d) and overall (Figure 2e). Among those with VI survival was particularly poor, ranging for 2.7-10.7 months in the various regions and 8.2 months overall (Supplementary figure 4a-d and 2e).

Median survival (and 95% CI) for each of the above sub-groups as well as the Harrell’s C and AIC scores are summarised in Table 4 and Supplementary table 1. Log-rank test outcomes for each combination of the survival curves in all the figures is summarised in supplementary table 2.

***Discussion***

Our multivariable analysis showed that the key variables influencing survival were related to tumour characteristics (tumour size, tumour number, AFP and VI) and liver function (albumin and bilirubin) and aetiology. These results were largely in agreement with the literature[20-24](#_ENREF_20) and our previous analysis (based largely on the current UK dataset). In the latter we used bilirubin, albumin, tumour size and AFP to develop a score (the HAP score) that gave accurate and nationally-validated prognostication.[10](#_ENREF_10) The present study validates the HAP score internationally, although it should be noted that there is no reason to believe that it is specific for patients treated by TACE.

However, the dataset on which the HAP score was originally developed did not contain information on tumour number and the number of patients with different aetiologies and VI was too small for meaningful statistical analysis; these parameters did not, therefore, enter the model. Thus, it became apparent in the present, much larger and international dataset, that VI, tumour number and aetiology were also important. These factors could be added to the HAP score to increase its prognostic utility or it would be possible to build a more rigorous, but inevitably more complex, multivariable model in the same way we have done for combining tumour markers for HCC diagnosis and prognosis and indeed[25-27](#_ENREF_25), in building the ALBI model[28](#_ENREF_28). Our datasets were accrued before the recent publication of other scoring systems designed to facilitate identification of patients appropriate for TACE and we have not therefore collected the variables that would be required for comparison with HAP[29](#_ENREF_29), [30](#_ENREF_30).

Our results also give particular insight into two of the key prognostic variables that are integral to the model namely liver function and vascular invasion. Thus albumin and bilirubin are clear measures of liver (dys) function and form the basis of our ALBI score. In all regions there is clear discrimination in survival according to ALBI and this was also maintained within patients classified as C-P ‘A’. Despite this clear discrimination within regional groups, the percentage falling into each ALBI group and the survival within each group was different. This presumably reflects the different availability of, and indication for, various therapeutic options and treatment algorithms in the different regions and the different aetiologies. For example, Sorafenib was not available in Egypt and liver transplantation was not available in the Japanese or Hong Kong cohorts.

Our current analysis suggests that the ALBI score is at least as discriminatory, in prognostic terms, as the CPS in the TACE setting and in a recent study on a similar population but including those undergoing radio-embolisation, Hickey et al concluded that the ALBI score ‘outperformed’ the CPS in discriminating survival[31](#_ENREF_31). Even without any claim to superiority over the CPS, the ALBI score/grade has several advantages. Specifically, it does not require three of the five parameters involved in the CPS (including the two which are most subjective, ascites and encephalopathy) thereby making the classification more reliable between observers. A less obvious advantage is that it was built on an extensive evidence base, specifically for assessment of liver function in HCC and made no prior assumptions as to the presence or absence of cirrhosis. By contrast, the CPS is advocated for assessment of liver function in patients with cirrhosis and, at least by convention, it should only be applied to such patients. This convention is generally not applied to patients with HCC being used widely, even with the knowledge that many patients with HBV-related HCC will not have cirrhosis. In our recent study, where we examined the extent of fibroses in resected HCC specimens and even among the Japanese patients, most of whom had HCV-related HCC, only 52% had cirrhosis[32](#_ENREF_32). It should not be assumed therefore that, because all patients with HCC were assigned a CPS by their local investigator, that all had cirrhosis.

The prevalence of vascular invasion (15%) is in line with reports in the literature[33-36](#_ENREF_33) (10-40%) and confirms that despite guidelines suggesting that patients with vascular invasion should receive sorafenib, a significant proportion of those undergoing TACE did in fact have VI. The prognostic importance of VI is also seen in patients treated with curative intent.[37](#_ENREF_37) Although the AASLD/EASL guidelines[38](#_ENREF_38) suggest treatment with Sorafenib rather than TACE for those with any degree of vascular invasion there is no explicit statement that suggests that VI is a contraindication to TACE1. Quirk et al.[36](#_ENREF_36), have noted that overall survival after TACE in patients with VI ranges from 7.4 to 10.2 months in the literature (and in the series reported here), figures that are only marginally better than those obtained with systemic Sorafenib[39](#_ENREF_39). Although we cannot be certain that patients with VI do not gain some benefit from TACE, the very poor overall survival figures suggest that any benefit is likely to be outweighed by the cost and toxicity of the procedure. However, this observation does not exclude the possibility that some patients with minor degrees of VI might achieve benefit from TACE.[40](#_ENREF_40), [41](#_ENREF_41)

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***Figure legends***

**Figure 1:** Kaplan-Meier curves depicting survival according to ALBI grade in patients undergoing TACE from (a) Europe, (b) Japan, (c) Egypt and (d) Hong Kong, China.

**Figure 2:** Kaplan-Meier curves depicting survival in all the patients undergoing TACE according to (a) ALBI grade, (b) ALBI grade within C-P grade A, (c) C-P grade, (d) HAP class and (e) the presence or absence of macrovascular invasion.

***Supplementary figure legends***

**Supplementary figure 1:** Kaplan-Meier curves depicting survival according to ALBI grade (within C-P A) in patients undergoing TACE from (a) Europe, (b) Japan, (c) Egypt and (d) Hong Kong, China.

**Supplementary figure 2:** Kaplan-Meier curves depicting survival according to C-P grade in patients undergoing TACE from (a) Europe, (b) Japan, (c) Egypt and (d) Hong Kong, China.

**Supplementary figure 3:** Kaplan-Meier curves depicting survival according to HAP class in patients undergoing TACE from (a) Europe, (b) Japan, (c) Egypt and (d) Hong Kong, China.

**Supplementary figure 4:** Kaplan-Meier curves depicting survival according to macrovascular invasion in patients undergoing TACE from (a) Europe, (b) Japan, (c) Egypt and (d) Hong Kong, China.

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| **Table 1** |
| **Variables** | **Europe** **(n=1232)** | **Japan****(n=655)** | **Egypt****(n=998)** | **Hong Kong****(n=145)** | **All (n=3030)** |
| **% Male** | 83.12n=1232 | 74.66n=655 | 83.27n=998 | 85.52n=145 | 81.45n=2769 |
| **Age (median, IQR)** | 66.48 (59.00 – 73.18)n=1230 | 65.00 (58.00 – 73.00)n=655 | 57.00 (51.00 – 62.00)n=998 | 65.00 (56.00 – 71.00)n=145 | 62.77 (55.00 – 70.07)n=3028 |
| **Albumin g/l (median, IQR)** | 37.00 (33.00 – 41.00)n=1214 | 32.00 (28.00 – 36.00)n=653 | 33.00 (29.00 – 37.00)n=998 | 35.00 (32.00 – 39.00)n=145 | 35.00 (30.00 – 39.00)n=3010 |
| **Bilirubin µmol/l (median, IQR)** | 16.00 (10.94 – 26.00)n=1213 | 15.39 (11.97 – 23.94)n=653 | 22.23 (13.68 – 32.49)n=998 | 14.00 (9.00 – 22.00)n=145 | 17.10 (11.97 – 27.36)n=3009 |
| **Tumour size cm (median, IQR)** | 5.00 (3.40 – 7.60)n=1180 | 3.50 (2.20 – 5.40)n=594 | 6.00 (4.00 – 8.00)n=998 | 6.00 (3.80 – 10.00)n=141 | 5.00 (3.40 – 7.60)n=2913 |
| **% Multifocal** | 66.24n=1161 | 69.27n=654 | 75.75n=998 | 58.33n=144 | 69.73n=2957 |
| **AFP ng/ml (median, IQR)** | 46.00 (6.70 – 534.50)n=1045 | 45.45 (12.40 – 510.00)n=614 | 129.00 (17.00 – 600.00)n=998 | 92.00 (10.00 – 1365.00)n=145 | 70.45 (11.00 – 584.00)n=2802 |
| **INR (median, IQR)** | 1.10 (1.01 – 1.20)n=851 | NA | 1.40 (1.20 – 1.70)n=998 | 1.14 (1.07 – 1.22)n=145 | 1.20 (1.10 – 1.40)n=1994 |
| **ALBI score (median, IQR)** | -2.34 (-2.72 – -1.91)n=1203 | -1.97 (-2.36 – -1.55)n=653 | -1.91 (-2.34 – -1.55)n=998 | -2.29 (-2.59 – -1.90)n=145 | -2.10 (-2.53 – -1.67)n=2999 |
| **% ALBI grade (1:2:3)** | 32.09 : 60.93 : 6.98n=1203 | 13.02 : 70.75 : 16.23n=653 | 15.63 : 69.14 : 15.23n=998 | 24.83 : 67.59 : 7.59n=145 | 22.11 : 66.12 : 11.77n=2999 |
| **% Child-Pugh (A:B:C)** | 73.94 : 24.62 : 1.45n=1174 | 52.06 : 41.22 : 6.72n=655 | 47.60 : 46.89 : 5.51n=998 | 77.24 : 21.38 : 1.38n=145 | 60.43 : 35.60 : 3.97n=2972 |
| **% HAP class (A : B : C : D)** | 18.72 : 34.42 : 31.95 : 14.91n=892(Liverpool, Birmingham, Germany and Spain only) | 13.49 : 32.40 : 38.53 : 15.59n=571 | 9.02 : 22.55 : 41.08 : 27.35n=998 | 12.06 : 37.59 : 29.79 : 20.57n=141 | 13.49 : 29.59 : 36.78 : 20.14n=2602 |
| **% Vascular invasion** | 10.61n=1225 | 30.28n=654 | 10.32n=998 | 11.03n=145 | 14.79n=3022 |
| **% HCV : HBV : Other** | 24.29 : 12.19 : 63.52n=1165 | 56.66 : 18.42 : 24.92n=646 | 98.39 : 1.10 : 0.50n=996 | 8.33 : 79.86 : 11.81n=144 | 55.61 : 13.11 : 31.28n=2951 |
| **Overall Survival (months, 95% C.I.)** | 16.6 (15.4 – 18.0)n=1226 | 22.3 (20 – 24.5)n=655 | 18.0 (17.0 – 19.0)n=998 | 19.9 (14.2 – 25.6)n=143 | 18.6 (17.9 – 19.5)n=3022 |

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| **Table 2 – Univariable Cox regression** |
| **Variable** | **Hazard ratio (95% C.I.)** | **p-value** | **LR test of theta=0** |
| **Age** | 0.999 (0.994 – 1.003) | 0.630 | 0.003 |
|  |  |  |  |
| **Gender** |  |  |  |
|  Female | 1 |  |  |
|  Male | 1.099 (0.980 – 1.234) | 0.108 | 0.005 |
|  |  |  |  |
| **Albumin, g/l** | 0.958 (0.951 – 0.966) | <0.0001 | <0.0001 |
| **Log 10 Bilirubin** | 1.894 (1.608 – 2.231) | <0.0001 | 0.007 |
|  |  |  |  |
| **Tumour number** |  |  |  |
|  Solitary | 1 |  |  |
|  Multiple | 1.279 (1.158 – 1.412) | <0.0001 | 0.005 |
|  |  |  |  |
| **Tumour size, cm** | 1.072 (1.059 – 1.086) | <0.0001 | 0.084 |
|  |  |  |  |
| **Vascular invasio**n |  |  |  |
|  No | 1 |  |  |
|  Yes | 2.282 (2.024 – 2.573) | <0.0001 | <0.0001 |
|  |  |  |  |
| **Log 10 AFP** | 1.263 (1.215 – 1.312) | <0.0001 | <0.0001 |
|  |  |  |  |
| **Aetiology** |  |  |  |
|  HCV | 1 |  |  |
|  HBV | 1.211 (1.055 – 1.391) | 0.007 |  |
|  Other | 1.276 (1.138 – 1.432) | <0.0001 | 0.077 |

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| **Table 3 – Multivariable Cox regression** |
| **Variable** | **Hazard ratio (95% C.I.)** | **p-value** |
| **Vascular invasion** |  |  |
|  No | 1 |  |
|  Yes | 1.744 (1.508 – 2.016) | <0.0001 |
|  |  |  |
| **Albumin, g/l** | 0.959 (0.950 – 0.968) | <0.0001 |
| **Log10 AFP** | 1.206 (1.156 – 1.259) | <0.0001 |
| **Tumour size, cm** | 1.054 (1.038 – 1.070) | <0.0001 |
| **Log10 Bilirubin**  | 1.671 (1.373 – 2.034) | <0.0001 |
|  |  |  |
| **Tumour number** |  |  |
|  Solitary | 1 |  |
|  Multiple | 1.283 (1.151 – 1.431) | <0.0001 |
|  |  |  |
| **Age** | 1.009 (1.003 – 1.014) | 0.002 |
|  |  |  |
| **Aetiology** |  |  |
|  HCV | 1 |  |
|  HBV | 1.212 (1.032 – 1.423) | 0.019 |
|  Other | 1.212 (1.060 – 1.387) | 0.005 |
|  |  |  |
| Theta=0.0206259 (?sd=0.0165923), LR test of theta=0, chibar2(01)=20.46, p<0.0001 |

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| **Table 4:** Median survival according to each classification system in the various cohorts  |
| **Figure** | **Cohort** | **Classification system** | **N** | **Median survival in months (95% C.I.)** | **Harrell’s C** | **AIC** |
| Figure 1 | Europe | ALBI grade 1 | 384 | 26.18 (22.93, 28.09) | 0.5749 | 11269.51 |
| ALBI grade 2 | 731 | 14.61 (13.39, 15.92) |
| ALBI grade 3 | 82 | 9.70 (5.80, 14.01) |
| Japan | ALBI grade 1 | 85 | 38.91 (27.27, 51.35) | 0.566 | 5816.714 |
| ALBI grade 2 | 462 | 22.43 (19.61, 25.39) |
| ALBI grade 3 | 106 | 15.33 (9.34, 20.46) |
| Egypt | ALBI grade 1 | 156 | 30.00 (20.00, .) | 0.5808 | 4443.527 |
| ALBI grade 2 | 690 | 18.00 (17.00, 20.00) |
| ALBI grade 3 | 152 | 13.00 (9.00, 14.00) |
| Hong Kong (China) | ALBI grade 1 | 34 | 30.20 (16.84, 47.17) | 0.5898 | 995.5034 |
| ALBI grade 2 | 98 | 18.65 (12.60, 25.59) |
| ALBI grade 3 | 11 | 6.05 (1.22, 14.18) |
| Figure 2 | All | ALBI grade 1 | 659 | 27.60 (25.53, 29.90) | 0.5661 | 26963.33 |
| ALBI grade 2 | 1981 | 17.76 (16.94, 18.62) |
| ALBI grade 3 | 351 | 12.40 (9.61, 14.18) |
| All | ALBI grade 1 (within C-P A) | 626 | 27.86 (25.95, 30.00) | 0.5478 | 14901.81 |
| ALBI grade 2 (within C-P A) | 1146 | 19.05 (17.99, 20.63) |
| ALBI grade 3 (within C-P A) | 12 | 18.09 (6.88, . ) |
| All | C-P A | 1791 | 21.78 (20.00, 23.65) | 0.5586 | 26548.21 |
| C-P B | 1055 | 15.20 (14.00, 16.28) |
| C-P C | 118 | 8.26 (5.00, 12.40) |
| All | HAP class A | 349 | 32.96 (28.00, 37.57) | 0.6121 | 22273.51 |
| HAP class B | 768 | 23.49 (20.00, 26.22) |
| HAP class C | 955 | 18.00 (16.81, 19.14) |
| HAP class D | 523 | 11.91 (9.34, 12.00) |
| All | Without macrovascular invasion | 2567 | 20.39 (19.51, 22.00) | NA | NA |
| With macrovascular invasion | 447 | 8.22 (7.34, 9.87) | NA | NA |

**Figure 1**

**(b)**

**(a)**





**(c)**

**(d)**

**(c)**





**Figure 2**

**(b)**

**(a)**









**(c)**

**(d)**

**(e)**



**Supplementary tables**

|  |
| --- |
| **Supplementary Table 1:**  Median survival according to each classification system in the various cohorts |
| **Figure** | **Cohort** | **Classification system** | **N** | **Median survival in months (95% C.I.)** | **Harrell’s C** | **AIC** |
| Supplementary figure 1 | Europe | ALBI grade 1 (within C-P A) | 366 | 26.45 (23.22, 28.09) | 0.5661 | 7524.7 |
| ALBI grade 2 (within C-P A) | 487 | 15.39 (13.59, 17.27) |
| ALBI grade 3 (within C-P A) | 5 | . |
| Japan | ALBI grade 1 (within C-P A) | 83 | 38.91 (27.27, 51.97) | 0.542 | 2582.401 |
| ALBI grade 2 (within C-P A) | 257 | 24.51 (19.90, 28.32) |
| ALBI grade 3 (within C-P A) | 1 | . |
| Egypt | ALBI grade 1 (within C-P A) | 143 | 30.00 (20.00, .) | 0.5422 | 1558.429 |
| ALBI grade 2 (within C-P A) | 326 | 22.00 (18.00, 24.00) |
| ALBI grade 3 (within C-P A) | 6 | . |
| Hong Kong (China) | ALBI grade 1 (within C-P A) | 34 | 30.20 (16.84, 47.17) | 0.5568 | 722.9373 |
| ALBI grade 2 (within C-P A) | 76 | 21.61 (14.41, 25.92) |
| ALBI grade 3 (within C-P A) | 0 | . |
| Supplementary figure 2 | Europe | C-P A | 865 | 18.68 (17.27, 20.72) | 0.5446 | 10877.14 |
| C-P B | 286 | 13.26 (11.32, 15.03) |
| C-P C | 17 | 5.30 (2.73, 26.84) |
| Japan | C-P A | 341 | 26.32 (23.49, 31.55) | 0.5662 | 5849.668 |
| C-P B | 270 | 19.77 (15.89, 22.20) |
| C-P C | 44 | 15.00 (7.47, 27.04) |
| Egypt | C-P A | 475 | 24.00 (20.00, 27.00) | 0.6161 | 4392.089 |
| C-P B | 468 | 15.00 (14.00, 17.00) |
| C-P C | 55 | 5.00 (4.00, 9.00) |
| Hong Kong (China) | C-P A | 110 | 23.16 (16.88, 30.07) | 0.5684 | 1003.309 |
| C-P B | 31 | 7.53 (3.09, 20.13) |
| C-P C | 2 | . |
| Supplementary figure 3 | Europe | HAP class A | 165 | 27.27 (25.07, 32.96) | 0.603 | 8251.555 |
| HAP class B | 307 | 18.26 (15.26, 23.03) |
| HAP class C | 283 | 16.05 (13.68, 17.43) |
| HAP class D | 132 | 7.96 (5.92, 9.61) |
| Japan | HAP class A | 77 | 40.53 (32.66, 51.35) | 0.6382 | 4788.528 |
| HAP class B | 185 | 31.12 (26.81, 36.88) |
| HAP class C | 220 | 20.66 (19.14, 23.55) |
| HAP class D | 89 | 8.65 (7.20, 13.52) |
| Egypt | HAP class A | 90 | 32.00 (24.00, . ) | 0.5951 | 4432.884 |
| HAP class B | 225 | 19.00 (18.00, 26.00) |
| HAP class C | 410 | 18.00 (16.00, 20.00) |
| HAP class D | 273 | 13.00 (12.00, 14.00) |
| Hong Kong (China) | HAP class A | 17 | 45.13 (22.20, 79.14) | 0.6651 | 949.9856 |
| HAP class B | 51 | 25.59 (15.63, 31.55) |
| HAP class C | 42 | 15.89 (7.89, 22.83) |
| HAP class D | 29 | 3.65 (1.81, 7.89) |
| Supplementary figure 4 | Europe | Without macrovascular invasion | 1089 | 17.60 (16.25, 19.38) | NA | NA |
| With macrovascular invasion | 130 | 7.53 (6.35, 11.84) | NA | NA |
| Japan | Without macrovascular invasion | 456 | 27.96 (25.56, 30.99) | NA | NA |
| With macrovascular invasion | 198 | 10.69 (8.22, 12.93) | NA | NA |
| Egypt | Without macrovascular invasion | 895 | 18.00 (18.00, 20.00) | NA | NA |
| With macrovascular invasion | 103 | 7.00 (6.00, 9.00) | NA | NA |
| Hong Kong (China) | Without macrovascular invasion | 127 | 22.83 (16.88, 28.39) | NA | NA |
| With macrovascular invasion | 16 | 2.70 (1.74, 9.01) | NA | NA |

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| **Supplementary Table 2:**  Log-rank tests for the different KM plots presented in the manuscript |
| **Figure** | **ALBI 1 vs ALBI2** | **ALBI 2 vs ALBI3** | **ALBI 1 vs ALBI3** | **CP-A vs CP-B** | **CP-B vs CP-C** | **CP-A vs CP-C** | **HAP A vs HAP B** | **HAP A vs HAP C** | **HAP A vs HAP D** | **HAP B vs HAP C** | **HAP B vs HAP D** | **HAP C vs HAP D** | **VI vs no VI** |
| 1A | <0.0001 | 0.003 | <0.0001 | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| 1B | 0.0006 | <0.0001 | <0.0001 | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| 1C | 0.0001 | <0.0001 | <0.0001 | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| 1D | 0.0407 | <0.0001 | 0.0025 | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| 2A | <0.0001 | <0.0001 | <0.0001 | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| 2B | <0.0001 | NA | NA | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| 2C | NA | NA | NA | <0.0001 | 0.0001 | <0.0001 | NA | NA | NA | NA | NA | NA | NA |
| 2D | NA | NA | NA | NA | NA | NA | <0.0001 | <0.0001 | <0.0001 | 0.0001 | <0.0001 | <0.0001 | NA |
| 2E | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | <0.0001 |
| s.1A | <0.0001 | NA | NA | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| s.1B | 0.0092 | NA | NA | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| s.1C | 0.0165 | NA | NA | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| s.1D | 0.0328 | NA | NA | NA | VA | NA | NA | NA | NA | NA | NA | NA | NA |
| s.2A | NA | NA | NA | 0.0002 | 0.6356 | 0.1901 | NA | NA | NA | NA | NA | NA | NA |
| s.2B | NA | NA | NA | <0.0001 | 0.1590 | 0.0001 | NA | NA | NA | NA | NA | NA | NA |
| s.2C | NA | NA | NA | <0.0001 | <0.0001 | <0.0001 | NA | NA | NA | NA | NA | NA | NA |
| s.2D | NA | NA | NA | 0.0754 | 0.3428 | 0.0084 | NA | NA | NA | NA | NA | NA | NA |
| s.3A | NA | NA | NA | NA | NA | NA | 0.0015 | <0.0001 | <0.0001 | 0.1009 | <0.0001 | <0.0001 | NA |
| s.3B | NA | NA | NA | NA | NA | NA | 0.0805 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 | NA |
| s.3C | NA | NA | NA | NA | NA | NA | 0.0043 | 0.0003 | <0.0001 | 0.2771 | <0.0001 | <0.0001 | NA |
| s.3D | NA | NA | NA | NA | NA | NA | 0.0534 | 0.0029 | 0.0001 | 0.1024 | 0.0005 | 0.0194 | NA |
| s.4A | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | <0.0001 |
| s.4B | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | <0.0001 |
| s.4C | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | <0.0001 |
| s.4D | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | <0.0001 |
| CP, Child-Pugh; VI, vascular invasion; NA, not applicable; s.1A, supplementary figure 1A |

**SUPPLEMENTARY FIGURES**

**Supplementary figure 1**

**(a)**

**(b)**





**(d)**

**(c)**





**Supplementary figure 2**

**(a)**

**(b)**









**(c)**

**(d)**

**Supplementary** **Figure 3**

**(c)**

**(a)**

**(b)**





**(c)**

**(d)**

**(c)**





**Supplementary Figure 4**



**(a)**

**(b)**



**(c)**

**(d)**



