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Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy

Short title:

Identification of PBC patients in need of new therapies

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List of abbreviations

PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; LLN, lower limit of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, AST to platelet ratio index; NL, natural logarithm; IQR, interquartile range; NRI, net reclassification improvement

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Disclosure of potential conflicts of interest

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Authors contributions

Willem J. Lammers, Bettina E. Hansen and Henk R. van Buuren had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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ABSTRACT

Background & Aims: Approaches to risk stratification for patients with primary biliary cirrhosis (PBC) are limited, single-center based, and often dichotomous. We aimed to develop and validate a better model for determining prognoses of patients with PBC.

Methods: We performed an international, multicenter meta-analysis of 4119 patients with PBC treated with ursodeoxycholic acid (UDCA) at liver centers in 8 European and North American countries. Patients were randomly assigned to derivation (n=2488, 60%) and validation cohorts (n=1631, 40%). A risk score (GLOBE score) to predict transplantation-free survival was developed and validated with univariate and multivariable Cox regression analyses using clinical and biochemical variables obtained after 1 y UDCA therapy. Risk score outcomes were compared with the survival of age-, sex-, and calendar time-matched members of the general population. The prognostic ability of the GLOBE score was evaluated alongside those of the Barcelona, Paris-1, Rotterdam, Toronto, and Paris-2 criteria.

Results: Age (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.04–1.06; *P*<.0001); levels of bilirubin (HR, 2.56; 95% CI, 2.22–2.95; *P*<.0001), albumin (HR, 0.10; 95% CI, 0.05–0.24; *P*<.0001), and alkaline phosphatase (HR, 1.40; 95% CI, 1.18–1.67; *P*=.0002); and platelet count (HR/10 units decrease, 0.97; 95% CI, 0.96–0.99; *P*<.0001) were all independently associated with death or liver transplantation (C statistic derivation, 0.81; 95% CI, 0.79–0.83, and validation cohort, 0.82; 95% CI, 0.79–0.84). Patients with risk scores >0.30 had significantly shorter times of transplant-free survival than matched healthy individuals (*P*<.0001). The GLOBE score identified patients who would survive for 5 y and 10 y (responders) with positive predictive values of 98% and 88%, respectively. Up to 22% and 21% of events and non-events, respectively, 10 y after initiation of treatment were correctly reclassified in comparison with earlier proposed criteria. In subgroups of patients <45 y, 45–52 y, 52–

58 y, 58–66 y, and ≥66 y old, age-specific GLOBE-score thresholds beyond which survival significantly deviated from matched healthy individuals were –0.52, 0.01, 0.60, 1.01 and 1.69, respectively. Transplant-free survival could still be accurately calculated by the GLOBE score with laboratory values collected at 2–5 y after treatment.

Conclusions: We developed and validated scoring system (the GLOBE score) to predict transplant-free survival of UDCA-treated patients with PBC. This score might be used to select strategies for treatment and care.

KEYWORDS: cholestasis; autoimmune liver disease; prognosis; predictive factor

INTRODUCTION

Primary biliary cirrhosis (PBC) is the most common of the autoimmune liver diseases, with 1 in 1000 women over the age of 40 affected.[1] Prognosis largely depends on the development of liver cirrhosis and its complications.[2] Presently, treatment with ursodeoxycholic acid (UDCA) represents the global standard of care,[2, 3] and can delay histological progression[4-6] and can improve long-term survival.[7, 8] However, UDCA is not an uniformly effective drug and the prognosis of patients insufficiently responding to treatment is markedly worse compared with the general population.[9] Reliable identification of such individuals is of key importance to clinical management, particularly for selecting those who could benefit from additional second-line medical therapies, but equally for identification of patients at low risk of developing end-stage liver disease.

A number of existing stratification tools, using biochemical liver tests applied after one or two years of UDCA exposure, will readily identify patients with or without sufficient treatment response.[9-13] Paris-1 criteria is generally considered as the one with best predictability of transplant-free survival as validated in large studies, such as the UK-PBC consortium and our own group.[11, 14-16] However, Paris-1 and other criteria were all based on dichotomized variables, potentially leading to loss of important predictive information. And even more important there is a relatively high disagreement between the different criteria in classifying someone among low- and high risk groups.[17]

The Global PBC Study Group has representative data from an international PBC research collaboration that has already evaluated biochemical surrogates of disease progression and liver cancer risk.[16, 18] The aim of present study was to utilise our unique dataset, alongside representative healthy population data, to develop a new unifying score with optimal ability to identify UDCA treated patients with an insufficient treatment effect, based on readily obtainable, biochemical and clinical variables.

METHODS

Study population and design

Patients were derived from the Global PBC Study Group database. This study group is an international and multicenter collaboration between 15 liver centers from 8 North American and European countries, which combined individual patient data from major long-term follow-up cohorts. Most cohorts included prospectively collected follow-up data. All patients had an established diagnosis of PBC[2, 3] and characteristics of the study population have been previously described elsewhere.[18] For the current study only those patients treated with UDCA were included. Patients were excluded if follow-up data were insufficient or unavailable, the start date of treatment or the exact date of major clinical events was unknown or in case of concomitant liver disease. Collected clinical and laboratory data included gender, age, PBC diagnosis, liver histology, treatment (type of medication, dosage and duration), duration and last date of follow-up, baseline antimitochondrial antibody status, baseline and yearly laboratory values (serum alkaline phosphatase, total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelets and outcomes (death and cause of death, liver transplantation, hepatocellular carcinoma, ascites and variceal bleeding).

Ethical approval

This study was conducted in accordance with the protocol and the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Research Board of the corresponding center, and at each participating center, in accordance with local regulations.

Statistical analysis

The study population was divided into a two cohorts, a derivation series comprising a randomly selected group of 2488 patients (60%), with the remainder serving as of a validation cohort (n=1631,

40%). Follow-up commenced at the start of UDCA therapy. Clinical outcome consisted of a composite endpoint of liver transplantation and all-cause mortality with the first event considered. Patients failing to reach a clinical endpoint were censored at time of last follow-up.

For development of our risk score only easily and readily available clinical and laboratory variables were considered: sex, baseline age, and serum bilirubin, alkaline phosphatase, AST, ALT, albumin, platelet count, AST/ALT ratio, and AST to platelet ratio index (APRI) at one year follow-up. Where indicated, continuous variables underwent natural logarithmic transformation to correct for non-linearity. Multiple imputation was also applied to account for missing data wherein ten complete datasets were constructed by imputing missing values (SAS Proc MI, MCMC method; SAS 9.3).[19]

Time-to-event analysis was conducted using univariate and multivariable cox proportional hazard regression, and a final model was selected by comparing the goodness of fit criteria (Akaike Information Criteria and maximum-likelihood estimation). The final model was checked for potential confounding factors and interactions between the included variables. A penalised maximum likelihood estimation was used to account for over fitting of the model.[20 21]

A prognostic index (GLOBE score) was calculated with the beta coefficients of variables included in the final penalized multivariable model, along with a baseline survival estimate $S_0(t)$, t=time. The GLOBE score was centered on the median in the derivation set.

The overall discriminative ability of the GLOBE score was measured with C statistic in both the derivation and validation cohort. To visualise the discriminate ability Kaplan-Meier curves were plotted of 5 risk groups according to the 10^{th}, 40^{th}, 60^{th} and 90^{th} percentiles of the GLOBE score.

Calibration of the GLOBE score was tested within the validation set.[22] The calibration slope was calculated by estimating the regression coefficient on the GLOBE score. The necessity of recalibration was further tested by performing a Cox regression analysis on the variables included in the final model and including the GLOBE score with the regression coefficient constrained to 1. A good model fit was reached when the joint test of all beta coefficients did not significantly differ

from 0. The accuracy of the baseline survival estimate $S_0(t)$ was investigated by comparing the predicted survival probabilities of the 5 risk groups as defined above in the validation set with the observed Kaplan-Meier survival probabilities.

In order to identify patients in whom prognosis significantly deviates from normal, the score was calculated beyond which prognosis was significantly worse than of a normal population. To determine this threshold, survival of patients with GLOBE scores below the tenth percentile was compared with that of an age-, sex- and calendar time matched Dutch population. During subsequent steps patients with scores within the next ten percentiles were added to the population and calculations were repeated until survival significantly deviated from that of the matched normal population (non-responders). Data of the matched population, a population with a life-expectancy comparable with that of the other participating countries, were retrieved from a Dutch registry (Statistics Netherlands, www.cbs.nl). The performance of the GLOBE score using this threshold was assessed with sensitivity, specificity, negative predictive value and positive predictive value at 5- and 10-year follow-up. For this purpose a GLOBE score below the aforementioned threshold was considered as a positive test and the absence of adverse outcome was considered as an event.

The overall predictive performance of previously reported tools (the Barcelona,[9] Paris-1,[10] Rotterdam,[11] Toronto[12] and Paris-2 criteria[13]) was assessed with C statistic. To quantify the improvement in discriminative ability the net reclassification improvement (NRI) for both events and non-events[23, 24] during the first 5 and 10 years follow-up was calculated.

All analyses were 2 sided. P <.05 was considered statistically significant if not otherwise specified. Statistical analyses were performed with IBM SPSS Statistics 22.0 (SPSS Inc, Chicago, IL, USA) and SAS 9.3 (SAS institute, Cary, NC, USA).

RESULTS

Clinical characteristics of the derivation cohort

The derivation cohort consisted of 2488 subjects with PBC, with a median age of 54.6 years at the time of diagnosis (**Table 1**). During a median follow-up of 7.8 years (interquartile range (IQR) 4.0-12.1) 558 patients reached a clinical endpoint; 369 patients died and 189 patients underwent liver transplantation (center specific characteristics are described in **Supplementary Table 1**). The 5-, 10- and 15-year transplant-free survival rates were 90.0%, 77.5% and 65.6% respectively, as shown in **Figure 1**.

Construction of the GLOBE score

Following univariate Cox regression analyses older age at start of UDCA therapy, male sex, elevated serum bilirubin, alkaline phosphatase, AST and ALT levels, lower serum albumin levels and thrombocytopenia and higher AST/ALT and APRI ratios after one year of UDCA therapy were all associated with higher risk of liver transplantation or death (**Table 2**). The final penalized multivariable model comprised age, bilirubin, albumin, alkaline phosphatase and platelet count as independent predictors of liver transplantation or death (**Table 2**). No significant interactions were found between these variables (**Supplementary Table 2).**

The GLOBE score was calculated as follows:

GLOBE score = (0.044378 * age at start of UDCA therapy + 0.93982 * LN(bilirubin times the upper limit of normal (ULN) at 1 year follow-up)) + (0.335648 * LN(alkaline phosphatase times the ULN at 1 year follow-up)) – 2.266708 * albumin level times the lower limit of normal (LLN) at 1 year follow-up – 0.002581 * platelet count per 10^9/L at 1 year follow-up) + 1.216865.

The distribution of the GLOBE score is plotted in **Supplementary Figure 1**. The baseline survival curve at the mean GLOBE score $S_0(t)$ was: 0.9652, 0.9385, 0.8429, 0.7361 at 3-, 5-, 10- and 15-year follow-up respectively. The survival S(t) for any given patients was then calculated by $S(t) = S_0(t)^{\exp(\text{GLOBE score})}$.

Example:

For a 50-year old patient with a bilirubin level of 1 time the ULN, an alkaline phosphatase level of 3 times the ULN, an albumin level of 1.5 time the LLN and a platelet count of 250 per 10^9/L:
GLOBE score = 0.64; transplant-free survival at 5-year, S(5) = 88.6% and at 10-year, S(10) = 72.2%.

The overall predictive ability of the GLOBE score for transplantation or death, calculated with C statistic, was 0.81 (95% CI, 0.79-0.83).

Validation of the GLOBE score

The clinical characteristics of the validation cohort (n=1631) are described in **Table 1**. During a median follow-up time of 7.5 years (IQR 3.8-11.8) 328 patients reached a clinical endpoint; 197 died and 131 received a liver transplant (center specific characteristics are described in **Supplementary Table 1**). The 5-, 10- and 15-year transplant-free survival rates were 90.0%, 79.6% and 66.3% respectively and not significantly different from those observed in the derivation cohort (**Figure 1**).

A comparable overall discriminative ability was found as in the derivation cohort (C statistic 0.82, 95% CI 0.79-0.84). To explore to what extent the GLOBE score might be influenced by the imputation process for missing variables, the discriminative ability of the GLOBE score was additionally tested in cases with complete data. These analysis showed comparable results (C statistic derivation cohort: 0.82, 95% CI 0.78-0.86 and validation: 0.83, 95% CI 0.79-0.86).

The discriminative ability of the GLOBE score was visualised by plotting the transplant-free survival curves for 5 risk groups according to the 10th, 40th, 60th and 90th percentiles of the score (**Figure 2**). Good separation was shown for the survival curves of the 5 risk groups.

There was a good agreement between the curves in the derivation and validation cohort as shown in **Figure 2,** with a good model fit (calibration slope, P value=0.64). No re-calibration of the GLOBE score was necessary, when calculating the regression coefficient on the prognostic index (P value=0.22). Further, the predicted survival probabilities corresponded well with the observed survival probabilities (**Supplementary Table 3**).

Application of the GLOBE score

An overall threshold was determined for the GLOBE score in the derivation cohort beyond which prognosis of patients significantly deviated from a normal life-expectancy (non-responders). Patients with a GLOBE score above 0.30, which applied to 40% of cases, had a significantly diminished survival compared with a matched general population (HR 5.51, 95%CI 4.52-6.72, P value <.0001), with 5-, 10- and 15-year transplant-free survival rates of 79.7%, 57.4%, 42.5% respectively. Patients with a GLOBE score of 0.30 or less (responders) had a life-expectancy comparable with a matched general population; the 5-, 10- and 15-year transplant-free survival rates were 98.0%, 92.0%, 82.3% respectively (p-value: <.0001) (**Figure 3**). Non-responders were significantly more often at a late stage of disease at baseline than responders (**Supplementary Table 4).**

The performance of the GLOBE score was assessed using the aforementioned threshold. A high positive predictive value was found at 5-year follow-up (1057/1084, 98%) and at 10-year follow-up (588/669, 88%), implying that the probability of reaching an adverse outcome is very low for patients identified as a responder. Also a high specificity was found at 5-year follow-up (193/220, 88%) and 10-year follow-up (328/409, 80%) which means that the majority of patients with an adverse outcome were identified as non-responder. Additionally, we found a sensitivity of 65%

(1057/1623) at 5-year and 69% at 10-year (588/857) follow-up and a low negative predictive value at 5-year (193/759, 25%) and at 10-year (328/597, 55%) follow-up.

The performance of the GLOBE score compared with other criteria

The overall discriminative ability of the GLOBE score was superior in comparison with previously proposed stratification tools[9-13] (**Table 3)**. To quantify the improvement in discriminative ability the NRI for both events and non-events in the validation set was calculated.[23] The percentage of patients with an event at 5- and 10-year follow-up that were correctly reclassified with the GLOBE score as compared with existing criteria ranged from 3% to 25% and 1% to 22% respectively, and in patients without an event at 5- and 10-year follow-up the NRI ranged from -15% to 18% and -14% to 21% respectively (**Table 4**).

The performance of the GLOBE score among different age groups, disease severity groups and at different time points

Additionally, we created five equal age groups (<45, 45-52, 52-58, 58-66 and ≥66 years), to perform an in-depth analysis of the threshold per age group. Patients within these groups were separately matched with an age- and sex-matched population and thresholds of -0.52, 0.01, 0.60, 1.01 and 1.69 respectively were determined. When using these thresholds 70%, 50%, 30%, 20% and 10% respectively of patients had a diminished survival compared with a matched population. Importantly, this implies that older patients inevitably may derive les impact ultimately from additional therapies.

Within the derivation cohort the performance of the GLOBE score was tested within a subgroup of patients with histological early stage PBC (n=673), defined as stage I or II and a subgroup of patients with histological late stage PBC (n=309), defined as stage III or IV. In the early stage subgroup 280/1090 (26%) patients had a survival significantly deviating from that of a matched population and this were 373/540 (69%) patients in the advanced stage subgroup. In both subgroups

the predictive ability of the score was satisfactory with a C statistic of 0.81 (95% CI 0.76-0.86) in the early stage subgroup and 0.78 (95% CI 0.74-0.83) in the late stage. Comparable results were found when repeating these analyses in the validation cohort; with a C statistic in the early stage (n=448) of 0.85 (0.79-0.91) and in the late stage (n=212) of 0.79 (0.72-0.86).

Importantly, the risk score was calculated based on lab values collected 1 y after UDCA therapy, but transplant-free survival could still be accurately calculated by the GLOBE score with laboratory values collected at 2–5 y after treatment (**Supplementary Table 5**).

DISCUSSION

In this study of over 4000 UDCA treated patients with PBC from across Europe and North America we present the GLOBE score, an internationally relevant and validated risk assessment tool, able to accurately stratify patients to high and low risk. The score comprises five simple, readily available and objective variables: age, bilirubin, albumin, alkaline phosphatase and platelet count. Moreover, through robust evaluation and validation we demonstrate appropriate test characteristics in subgroups with early and advanced disease. Most importantly, the prognostic ability of the score was found to be markedly superior to previously proposed criteria for (non-)response to UDCA. The score has utility for patients managed with PBC internationally, as a means to more readily stratify risk of adverse outcomes, and hence tailor patient education. In particular, in an era of potential new therapies the GLOBE score is better able than current stratification tools to highlight patients at greatest need for new therapies. Of further relevance to the health economics of PBC, the GLOBE score improves capacity to identify individuals in whom UDCA mono-therapy should be continued, with opportunities to de-escalate care back to their primary care provider.

Previous studies have extensively documented the prognostic importance of the individual components of the GLOBE score. In particular, age, bilirubin and albumin have been recognized as important predictors of survival in PBC, irrespective of UDCA treatment[7, 8, 25, 26] In general, age and mortality are strongly correlated and not surprisingly age proved to be an independent predictor of liver transplantation or death in present study. Serum bilirubin is generally considered the strongest and most independent predictor of outcome in PBC,[18, 27-29] and is a main component of prognostic models[25, 30-32] and response criteria in PBC.[10, 11, 13, 33] Serum bilirubin levels normally increase relatively late in the course of disease. However, its predictive value is not limited to late stage disease, as suggested by our previous finding that even in patients with normal levels, prognosis improves as levels fall.[18] Alkaline phosphatase levels are of key importance in establishing the diagnosis PBC.[2, 3] Changes in alkaline phosphatase levels have previously been documented to

provide significant prognostic information, both in UDCA treated[9, 10, 12, 13, 18, 34] and untreated PBC.[18] Finally, the platelet count, generally considered as a marker of portal hypertension,[35] has been validated as an independent predictor of outcome in addition to current biochemical response criteria.[15, 36]

Although some of the factors comprising the score, such as bilirubin and albumin, will change relatively late in the course of disease, the GLOBE score performed well in patients with early stage disease. This is probably largely explained by the well-documented strong predictive significance of alkaline phosphatase values, even in cases with normal bilirubin.[18]

Our score provides improved identification of patients insufficiently responding to UDCA in comparison with previously reported criteria (**Table 3**). As reflected by the high positive predictive value, responders to UDCA according to the GLOBE score are at low risk for future adverse events. Therefore these patients can reliably be advised to continue with UDCA mono-therapy. The GLOBE score also allows more reliable identification of patients likely to have a future unfavourable health outcome. Thus, for healthcare providers the GLOBE score provides an improved instrument for selecting candidate patients for additional, second-line therapies. The superior performance of our score is likely attributable to the effect of dichotomization of every single variable in previously proposed response criteria. Dichotomization of continuous variables inevitably will have led to loss of predictive ability.[37] Moreover, age, as a recognized major predictor of survival, was included in our score. Importantly, we confirm that younger patients have the potential to benefit more from additional PBC therapies than older patients.[14] Finally, the methodological approach to base the score on a prognostic index, corresponding with a continuum of possible outcomes, is an important factor explaining improved ability to reliably estimate prognosis using the GLOBE score.

Other predictors of outcome in PBC have been suggested, including liver histology and elastography.[38, 39] Liver histology has important prognostic meaning,[38] but in the majority of cases liver biopsy is not considered necessary for diagnosis.[3] Moreover, given other disadvantages, such as its invasive character, sampling error and inter-observer variation, liver biopsy is no longer routinely

performed in the management of PBC patients. Non-invasive assessment of liver fibrosis with transient elastography is an interesting alternative,[39] but data supporting this technique as an important clinical tool are still limited and further validation is required. Elastography may be less suitable for assessing the response to medical treatment, especially after a relatively short duration of treatment, as PBC is a slowly progressive disease, suggesting it might take longer before reliably detectable changes in liver stiffness will ensue.[4-6] Biochemical markers are routinely checked during yearly check-up of PBC patients, and levels of biochemical variables after a short period of UDCA treatment are strongly associated with long-term outcome.[9-13, 18, 34] Considering the fact that biochemical markers are easily obtainable and readily available, they seem more attractive and preferable for first-line patient stratification.

A potential limitation to our study is the use of reference population data originating from only one country, namely the Netherlands, for developing the Global PBC Study Group Score. However, according to life table data of the World Health Organisation (WHO) life expectancy was comparable among the countries involved in this study.[40] Therefore, this may not be a factor of major relevance. Further, we were not able to take into account other laboratory variables of potential interest in PBC, such as gamma-GT, IgM, IgG and prothrombin time. Due to the nature of our study laboratory data were also not always fully complete, especially when inclusion in the original cohort studies occurred more than 15-20 years ago. However, considering the exceptionally large dataset, we believe our results are sufficiently robust, as well as notably representative. Finally, the reliability of our findings is supported by the validation of the prognostic model in a separate population of considerable size. The complex calculation of the GLOBE score has been simplified by the development of a web application to improve its usage in clinical practice (www.globalpbc.com).

In conclusion, we demonstrate that the prognosis of patients with PBC, irrespective of the stage of disease, who have been treated with UDCA for one year can be readily determined using a *de novo* derived and validated, risk calculation. Our score performs significantly better than thus far proposed criteria for response to UDCA thereby providing internationally representative data to

quantify the needs of low- and high-risk patients with PBC. The GLOBE score therefore complements efforts to develop and implement a more stratified, evidence-based, approach to the care of patients with PBC.

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Authors names in **bold** designate shared co-first authors

FIGURE LEGENDS

Figure 1. Liver transplant-free survival probability.

Transplant-free survival probability of patients with primary biliary cirrhosis in the derivation cohort (N = 2488, solid line) and the validation cohort (N = 1631,dotted line).

Figure 2. Liver transplant-free survival probability of risk groups according to the GLOBE score.

A). Transplant-free survival probability of 5 predefined risk groups according to percentiles of the GLOBE score: (1) <10^{th}, (2) 10^{th}-40^{th}, (3) 40^{th}-60^{th}, (4) 60^{th}-90^{th} and (5) >90^{th}, and B). accompanying hazard ratios between the risk groups in the derivation (N = 2488, solid line) and validation cohort (N = 1631, dotted line).

Figure 3. Liver transplant-free survival probability using a GLOBE score threshold.

Transplant-free survival probability of patients with a GLOBE score of 0.30 or less compared with an age-, sex- and calendar-time matched population for patients within (A) the derivation and (C) the validation cohort, and for those with a GLOBE score greater than 0.30 this probability significantly deviated for patients within (B) the derivation and (D) the validation cohort.

Table 1. Baseline characteristics

	Derivation cohort (n=2488)	Validation cohort (n=1631)
Age, years, mean (SD)	54.6 (11.7)	54.8 (11.9)
Female, n (%)	2253 (90.6%)	1453 (89.1%)
AMA+, n (%)	2208 (88.7%)	1425 (87.4%)
Year of diagnosis	1997 (1991-2003)	1998 (1992-2004)
Year of diagnosis, time frame	1961-2012	1970-2012
Histological disease stage, n (%)*		
Stage I	336 (27.9%)	237 (28.6%)
Stage II	337 (28.0%)	211 (25.5%)
Stage III	171 (14.2%)	125 (15.1%)
Stage IV	138 (11.5%)	87 (10.5%)
Not available	222 (18.4%)	167 (20.2%)
Serum bilirubin (xULN)	0.65 (0.45-1.00)	0.67 (0.45-1.05)
Serum alkaline phosphatase (xULN)	2.11 (1.37-3.79)	2.16 (1.33-3.78)
Serum AST (xULN)	1.46 (0.94-2.20)	1.45 (0.94-2.27)
Serum ALT (xULN)	1.68 (1.05-2.59)	1.63 (1.00-2.67)
Serum albumin (xLLN)	1.14 (0.15)	1.14 (0.17)
Platelet count	246 (90)	240 (96)
AST/ALT ratio	0.90 (0.72-1.16)	0.92 (0.73-1.18)
APRI	0.60 (0.34-1.01)	0.62 (0.36-1.09)
Laboratory data after one year		
Serum bilirubin (xULN)	0.57 (0.41-0.86)	0.59 (0.41-0.90)
Serum alkaline phosphatase (xULN)	1.34 (0.93-2.26)	1.36 (0.93-2.25)
Serum AST (xULN)	0.90 (0.67-1.40)	0.90 (0.67-1.42)
Serum ALT (xULN)	0.90 (0.60-1.53)	0.90 (0.59-1.47)
Serum albumin (xLLN)	1.14 (0.15)	1.14 (0.17)
Plateletcount	237 (90)	237 (96)
AST/ALT ratio	1.03 (0.79-1.33)	1.03 (0.81-1.33)
APRI	0.38 (0.25-0.66)	0.39 (0.26-0.72)

*Baseline biopsies (obtained within one year of start of UDCA) were available in 1204/2488 (48%) patients of the derivation cohort and in 827/1631 (51%) patients of the validation cohort.

Table 2. Univariate and multivariable cox regression analysis for liver transplantation or death within the derivation cohort (n=2488)

	Univariate analyses			Multivariable analyses[1]		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age at baseline, *per year*	1.038	1.030-1.046	<.0001	1.045	1.035-1.056	<.0001
Male sex	1.913	1.510-2.425	<.0001	-	-	-
Bilirubin xULN[2]	3.215	2.903-3.562	<.0001	2.560	2.219-2.952	<.0001
Alkaline phosphatase xULN[2]	1.929	1.687-2.204	<.0001	1.399	1.175-1.665	.0002
AST xULN[2]	2.560	2.220-2.952	<.0001	-	-	-
ALT xULN[2]	1.401	1.232-1.594	<.0001	-	-	-
Albumin xLLN	0.014	0.007-0.028	<.0001	0.104	0.045-0.238	<.0001
Platelet count (*10^9/L), *per 10 units*	0.993	0.992-0.995	<.0001	0.970	0.961-0.990	<.0001
AST/ALT ratio[2]	2.537	1.998-3.223	<.0001	-	-	-
APRI[2]	2.235	1.985-2.518	<.0001	-	-	-

Abbreviations: HR, hazard ratio; LLN, lower limit of normal; ULN, upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index.

[1]A P-value of <0.01 was considered as statistically significant.

[2]These biochemical variables were transformed with natural logarithm.

Table 3. Performance of biochemical response criteria and the GLOBE score

Criteria[a*]	Derivation cohort (n=2488)					Validation cohort (n=1631)				
	HR	95% CI	P-value	C statistic	95% CI	HR	95% CI	P-value	C statistic	95% CI
Barcelona[9]	1.69	1.39-2.06	<.0001	0.58	0.55-0.61	1.84	1.42-2.38	<.0001	0.57	0.54-0.61
Paris-1[10]	3.64	3.03-4.36	<.0001	0.69	0.66-0.71	4.61	3.61-5.90	<.0001	0.70	0.67-0.73
Rotterdam[11]	4.11	3.32-5.08	<.0001	0.69	0.66-0.71	4.10	3.11-5.42	<.0001	0.68	0.65-0.71
Toronto[12, b]	2.13	1.76-2.56	<.0001	0.61	0.58-0.63	2.46	1.90-3.18	<.0001	0.62	0.59-0.65
Paris-2[13]	2.82	2.29-3.47	<.0001	0.63	0.61-0.65	2.89	2.17-3.85	<.0001	0.63	0.61-0.66
GLOBE score	-	-	-	0.81	0.79-0.83	-	-	-	0.82	0.79-0.84

[a]Response assessed after one year UDCA treatment. Response according to Toronto criteria calculated after 2 years.

[b]After 2 years follow-up 2335/2488 patients of the derivation cohort and 1521/1631 patients of the validation cohort were at risk.

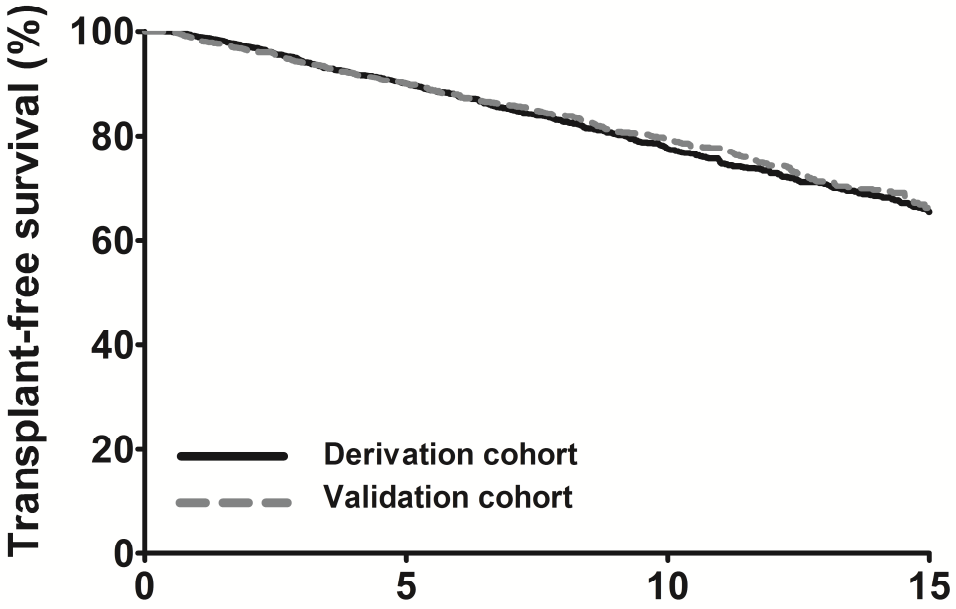
Table 4. Net reclassification improvement of the GLOBE score compared with existing response criteria for events and non-events at 5-year follow-up

	Derivation cohort				Validation cohort		
	5-year		10-year		5-year		
Criteria[a]	*Events NRI*[b]	*Non-events NRI*[b]	*Events NRI*[b]	*Non-events NRI*[b]	*Events NRI*[b]	*Non-events NRI*[b]	*Events*
Barcelona	25%	10%	21%	13%	26%	9%	22%
Paris-1	12%	-8%	15%	-6%	17%	-7%	13%
Rotterdam	21%	-15%	22%	-14%	23%	-13%	23%
Toronto	21%	2%	21%	6%	28%	0%	20%
Paris-2	3%	18%	1%	21%	5%	18%	0%

Abbreviation: Net reclassification improvement, NRI

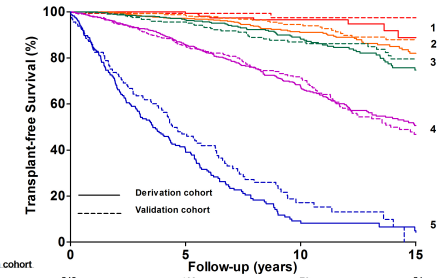
[a]All criteria were calculated after 1 year follow-up except Toronto criteria which was calculated after 2 years follow-up.

[b]The event NRI and non-event NRI were calculated as following: event NRI = (number of events classified up – number of events classified down) / number of events and non-event NRI = (number of non-events classified down – number of non-events classified up) / number of non-events.[22]



Patients at risk				
Derivation cohort	2488	1688	886	345
Validation cohort	1631	1091	567	202

A



Derivation cohort				
<10th perc	249	162	73	21
10-40th perc	746	509	253	97
40-60th perc	498	342	187	71
60-90th perc	747	449	216	82
>90th perc	248	67	10	3 Numbers at risk
Validation cohort				
<10th perc	154	99	41	17
10-40th perc	492	339	170	56
40-60th perc	326	216	114	47
60-90th perc	474	283	140	43
>90th perc	185	49	10	0 Numbers at risk

B

	Derivation cohort			Validation cohort		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
<10th percentile	1			1		
10th-40th percentiles	2.26	1.13-4.53	.0214	4.20	1.00-17.59	.0499
40th-60th percentiles	3.18	1.58-6.38	.0011	9.22	2.23-38.16	.0022
60th-90th percentiles	8.96	4.60-17.46	<.0001	25.48	6.30-103.15	<.0001
>90th percentile	58.50	29.87-114.57	<.0001	129.89	31.95-528.05	<.0001

Derivation cohort

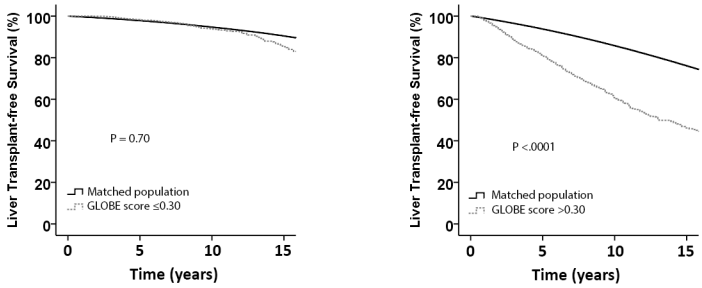


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FIGURE LEGENDS

Supplementary Figure 1. Distribution of the GLOBE score within the derivation and validation cohort

TABLES

Supplementary Table 1. Center specific characteristics of the study population.

	Derivation cohort							Validation cohort						
		Year of diagnosis		Follow-up (years)		End points			Year of diagnosis		Follow-up (years)		End points	
	N	*Median (IQR)*		*Median (IQR)*		*Death*	*LTx*	*N*	*Median (IQR)*		*Median (IQR)*		*Death*	*LTx*
USA, (*Rochester*)	349	2000	1997-2006	4.9	2.6-10.1	70	30	241	2000	1997-2007	4.1	2.1-9.7	32	36
The Netherlands, *(Nationwide cohort*)	515	1998	1992-2005	9.1	4.9-14.6	96	19	323	2000	1994-2006	8.5	4.5-13.1	57	12
Canada, (*Toronto*)	301	1999	1994-2003	7.6	4.4-11.4	24	15	228	1999	1995-2004	7.5	4.6-11.7	10	12
Italy, (*Padua*)	166	1997	1991-2005	8.0	4.3-14.3	40	2	110	2000	1995-2006	6.1	3.1-11.9	19	2
UK, (*Birmingham*)	175	2003	2000-2007	5.7	3.1-9.7	29	27	110	2003	2000-2007	6.8	4.2-10.0	21	14
French, (*Paris*)	221	1988	1986-1993	5.3	2.1-8.8	26	25	127	1987	1985-1992	6.2	2.1-9.2	12	15
USA, (*Dallas*)	191	1993	1990-1996	9.1	7.1-11.7	11	18	135	1993	1991-1996	8.5	6.4-11.5	4	14
Italy, (*Milan, 2 centers*)	232	1990	1984-1997	8.7	4.7-12.9	39	15	154	1989	1985-1994	8.2	5.0-13.5	29	6

Supplementary Table 1 (continued). Center specific characteristics of the study population.

	Derivation cohort							Validation cohort						
		Year of diagnosis		Follow-up (years)		End points			Year of diagnosis		Follow-up (years)		End points	
	N	*Median (IQR)*		*Median (IQR)*		*Death*	*LTx*	*N*	*Median (IQR)*		*Median (IQR)*		*Death*	*LTx*
Spain, (*Barcelona*)	156	1995	1991-2000	12.3	7.7-16.5	22	16	110	1996	1992-2000	12.2	8.1-16.3	9	7
Belgium, (*Leuven*)	95	2000	1992-2006	7.9	3.9-13.1	9	15	41	2004	1995-2009	5.3	2.6-11.1	2	4
UK, (*London*)	36	1994	1990-1999	9.0	4.8-13.7	1	4	20	1996	1991-2001	8.8	5.1-11.1	1	3
Canada, (*Edmonton*)	30	2004	2001-2006	5.9	4.9-8.3	2	3	23	2003	1995-2006	6.5	3.8-9.2	1	6
USA, (*Seattle*)	21	2008	2002-2010	2.7	1.6-9.5	0	0	9	2008	2006-2010	2.9	1.6-6.2	0	0
Total	2488	1997	1991-2003	7.8	4.0-12.1	369	189	1631	1998	1992-2004	7.5	3.8-11.8	197	131

Supplementary Table 2. Interactions tested between individual variables of the GLOBE score

	Bilirubin	Albumin	Alkaline phosphatase	Platelet count
Age	0.94*	0.25*	0.97*	0.75*
Bilirubin	-	0.54*	0.63*	0.74*
Albumin	-	-	0.95*	0.89*
Alkaline phosphatase	-	-	-	0.03*

*P values of interaction terms tested in the final multivariable Cox regression model; a P <.01 was considered statistically significant

Supplementary Table 3. Predicted against observed probability of transplant-free survival in the validation cohort (n=1631)

Risk groups according to percentiles of the GLOBE score	Years of follow-up	Predicted probability[1]	Observed probability[2]
<10th percentile	3-year	0.993	0.993
	5-year	0.988	0.993
	10-year	0.968	0.975
	15-year	0.943	0.975
10th – 40th percentiles	3-year	0.982	0.993
	5-year	0.968	0.985
	10-year	0.918	0.949
	15-year	0.857	0.882
40th – 60th percentiles	3-year	0.965	0.975
	5-year	0.937	0.956
	10-year	0.840	0.864
	15-year	0.732	0.789
60th – 90th percentiles	3-year	0.915	0.924
	5-year	0.854	0.854
	10-year	0.660	0.720
	15-year	0.484	0.478
>90th percentiles	3-year	0.617	0.638
	5-year	0.460	0.474
	10-year	0.183	0.181
	15-year	0.067	0.069

[1]The predicted transplant-free survival probabilities for each risk group were assessed by first applying the GLOBE score of each individual in the validation cohort to the baseline survival estimate $S_0(t)$ derived from the derivation cohort: $S_{GLOBE\ SCORE}(t) = S_0(t)^{\exp(GLOBE\ SCORE)}$. Than, the average of $S_{GLOBE\ score}(t)$ across each risk group was calculated.

[2]The observed probabilities are observed from Kaplan-Meier estimation.

Supplementary Table 4. Baseline characteristics of responders vs non-responders according to the threshold GLOBE score of 0.30 in the derivation cohort.

	Responders (n=1493) GLOBE score ≤0.30	**Non-responders (n=995) GLOBE score >0.30**	
Age, years, mean (SD)	49.14 (10.47)	57.95 (11.51)	<.0001
Female, n (%)	1395 (94%)	858 (86%)	0.0049
AMA+, n (%)	1493	894	0.52
Year of diagnosis, median (IQR)	1998 (1992-2004)	1996 (1989-2002)	<.0001
Year of diagnosis, time frame	1961-2012	1971-2012	
Histological disease stage, n (%)	816	389	<.0001
Stage I	269 (33%)	67 (17%)	
Stage II	251 (31%)	86 (22%)	
Stage III	88 (11%)	83 (21%)	
Stage IV	61 (7%)	78 (20%)	
Not available	148 (18%)	75 (19%)	
Biochemical disease stage, n (%)			<.0001
Early stage	1262 (85%)	422 (42%)	
Moderately advanced stage	209 (14%)	410 (41%)	
Advanced stage	22 (1%)	163 (16%)	

Supplementary Table 5. Predictive performance of the GLOBE score calculated after *n* years of UDCA therapy.

	Validation cohort n=1630	
Follow-up	**C statistic**	**95% CI**
1 year	0.82	0.79-0.84
2 years	0.83	0.80-0.85
3 years	0.83	0.80-0.85
4 years	0.83	0.80-0.86
5 years	0.84	0.81-0.87