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# Ursodeoxycholic Acid Treatment–Induced GLOBE Score Changes Are Associated With Liver Transplantation-Free Survival in Patients With Primary Biliary Cholangitis

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**INTRODUCTION:** Treatment of primary biliary cholangitis (PBC) can improve the GLOBE score. We aimed to assess the association between changes in the GLOBE score ( $\Delta$ GLOBE) and liver transplantation (LT)–free survival in patients with PBC who were treated with ursodeoxycholic acid (UDCA).

**METHODS:** Among UDCA-treated patients within the Global PBC cohort, the association between  $\Delta$ GLOBE ( $\Delta$ GLOBE<sub>0–1</sub>: during the first year of UDCA,  $\Delta$ GLOBE<sub>1–2</sub>: during the second year) and the risk of LT or death was assessed through Cox regression analyses.

**RESULTS:** Overall, 3,775 UDCA-treated patients were included; 3,424 (90.7%) were female, the median age was 54.0 (interquartile range [IQR] 45.9–62.4) years, and the median baseline GLOBE score was 0.25 (IQR –0.47 to 0.96). During a median follow-up of 7.2 (IQR 3.7–11.5) years, 730 patients reached the combined end point of LT or death. The median  $\Delta$ GLOBE<sub>0–1</sub> was –0.27 (IQR –0.56 to 0.02). Cox regression analyses, adjusted for pretreatment GLOBE score and  $\Delta$ GLOBE<sub>0–1</sub><sup>2</sup>, showed that  $\Delta$ GLOBE was associated with LT or death (adjusted hazard ratio 2.28, 95% confidence interval 1.81–2.87,  $P < 0.001$ ). The interaction between baseline GLOBE score and  $\Delta$ GLOBE<sub>0–1</sub> was not statistically significant ( $P = 0.296$ ). The  $\Delta$ GLOBE<sub>1–2</sub> was associated with LT or death (adjusted hazard ratio 2.19, 95% confidence interval 1.67–2.86,  $P < 0.001$ ), independently from the baseline GLOBE score and the change in GLOBE score during the first year of UDCA.

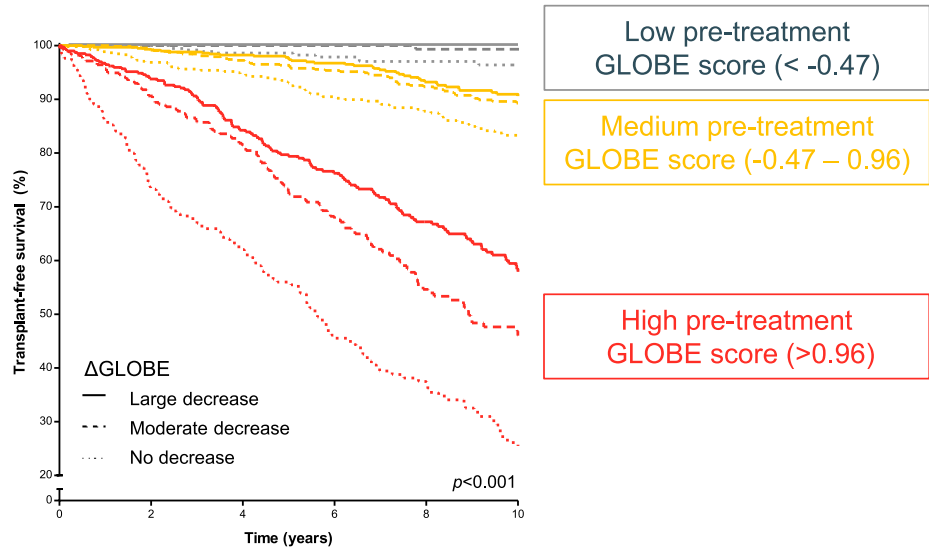
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## UDCA-induced $\Delta$ GLOBE is associated with LT-free survival in patients with PBC

$n=3775$

$\Delta$ GLOBE =  
GLOBE score after one  
year of UDCA –  
pretreatment GLOBE  
score



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**DISCUSSION:** UDCA-induced changes in the GLOBE score were significantly associated with LT-free survival in patients with PBC. While the relative risk reduction of LT or death was stable, the absolute risk reduction was heavily dependent on the baseline prognosis of the patient.

**KEYWORDS:** primary biliary cholangitis; ursodeoxycholic acid; GLOBE score; prognosis

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/AJG/C825>

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### INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic and usually slowly progressive liver disease with autoimmune features (1). Managing patients with PBC is important because the disease may silently progress toward cirrhosis, and the survival of the affected patients is substantially impaired. Ursodeoxycholic acid (UDCA) is currently recommended as the first-line therapy (2,3), which is associated with an improved liver transplantation (LT)-free survival (4).

The GLOBE score is an externally validated continuous prognostic model, which includes age, bilirubin, alkaline phosphatase (ALP), albumin, and platelets, to accurately assess the absolute risk of LT or death among patients with PBC after 1 year of UDCA therapy (5,6). The GLOBE score also showed an adequate prognostic performance among patients who were not treated with UDCA, indicating it can be considered an objective predictor of the natural history of PBC (4).

Nowadays, the GLOBE score is frequently used to assess the potential impact of new drugs in development for PBC. Add-on treatment with obeticholic acid (OCA) or fibrates resulted in a

treatment-induced decline of the GLOBE score, based on which clinical benefit was suggested (7–11). However, the change in GLOBE score (delta GLOBE:  $\Delta$ GLOBE) has never been assessed in relation to the LT-free survival among patients with PBC who were treated with UDCA. Therefore, the aim of this study was to assess how UDCA-induced changes in GLOBE score were related to LT-free survival in PBC, also according to different risk groups based on the expected natural history.

### METHODS

#### Study population and design

Patients were derived from the GLOBAL PBC Study Group database, an international and multicenter collaboration between liver centers across 10 countries in Europe and Northern America. All patients had an established diagnosis of PBC according to the international accepted guidelines (2,3). For this study, patients were excluded for analysis in case they were not treated with UDCA and in case of autoimmune overlap syndrome according to the Paris criteria (12), concomitant liver diseases, an insufficient follow-up (<1 year), unknown UDCA treatment

**Table 1. Baseline characteristics**

	Total cohort (n = 3,775)
Age at diagnosis, yr <sup>a</sup>	52.1 (11.7)
Female, n (%)	3,424/3,775 (90.7)
AMA positive, n (%)	3,394/3,732 (90.9)
Year of diagnosis <sup>b</sup>	1997 (1991–2004)
Histological disease stage, n (%) <sup>c</sup>	
Stage I	827/2,191 (37.7)
Stage II	676/2,191 (30.9)
Stage III	355/2,191 (16.2)
Stage IV	333/2,191 (15.2)
Serum bilirubin (ULN) <sup>b</sup>	0.66 (0.47–0.98)
Serum ALP (ULN) <sup>b</sup>	2.35 (1.51–3.83)
Serum AST (ULN) <sup>b</sup>	1.60 (1.12–2.29)
Serum ALT (ULN) <sup>b</sup>	1.82 (1.20–2.69)
Serum albumin (LLN) <sup>b</sup>	1.16 (1.09–1.23)
Platelet count ( $\times 10^9/\text{mm}^3$ ) <sup>b</sup>	251 (203–298)
GLOBE score before UDCA <sup>b</sup>	0.25 (–0.47 to 0.96)
Biochemical disease stage, n (%) <sup>d</sup>	
Early	2,732/3,775 (72.4)
Moderate/advanced	1,043/3,775 (37.6)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; AST, aspartate aminotransferase; LLN, lower limit of normal; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.  
<sup>a</sup>Data are expressed as mean and SD.  
<sup>b</sup>Data are expressed as median and interquartile range.  
<sup>c</sup>Histological disease stage according to Ludwig and Scheuer classification (17,18).  
<sup>d</sup>Biochemical disease stage according to Rotterdam criteria (14).

start date, or unknown dates of clinical events. Data on liver histology were included only if the liver biopsy was performed within 1 year of study entry, except in case of an earlier biopsy showing cirrhosis. Further details about the study population and methodology of the data collection have been described in detail elsewhere (13).

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the international research board of the corresponding center and at each participating center, in accordance with their local regulations. During the observation period of this retrospective study, OCA was not available and alternative second-line treatment options for PBC were not generally prescribed, but data on off-label medication use were not available.

### Statistical analyses

The primary outcome measure of this study was defined as a composite end point of LT and all-cause mortality. Baseline was considered as the start of UDCA treatment. Patients were followed up until LT or death or censored at their last visit in case no event occurred. The GLOBE score was calculated with the following formula:  $0.044378 \times \text{age at baseline} + 0.93982 \times \text{LN (bilirubin)} + 0.335648 \times \text{LN (ALP)} + 2.266708 \times \text{albumin} + 0.002581 \times \text{platelets (per } 10^9/\text{L)} + 1.216865 \times \text{(bilirubin and ALP}$

in “times upper limit of normal” and albumin in “times lower limit of normal”). The change in GLOBE score during the first year ( $\Delta\text{GLOBE}_{0-1}$ ) was calculated by subtracting the GLOBE score at baseline from the GLOBE score after 1 year of UDCA. The delta of the individual laboratory parameters within the GLOBE score was calculated accordingly. In line with the Rotterdam criteria, early biochemical disease stage was defined as normal albumin ( $\leq 1.0 \times \text{ULN}$ ) and normal bilirubin ( $\leq 1.0 \times \text{ULN}$ ) (14). Advanced biochemical disease stage was defined as abnormal albumin and/or abnormal bilirubin. Disease activity at baseline was defined according to the POISE criteria: below POISE (ALP  $< 1.67 \times \text{ULN}$  and bilirubin  $< 1.0 \times \text{ULN}$ ) and above POISE (defined as ALP  $\geq 1.67 \times \text{ULN}$  or bilirubin  $> 1.0 \times \text{ULN}$ ). In addition, the change in the GLOBE score during the second year of UDCA ( $\Delta\text{GLOBE}_{1-2}$ ) was assessed.

Data are presented as mean values with SD, median with interquartile range (IQR), or as proportions. Biochemical markers were log-transformed in case of non-normality. Cox proportional hazards regression analyses were performed to assess the association between  $\Delta\text{GLOBE}_{0-1}$  and the risk of LT or death, which was adjusted for the baseline GLOBE score and all other sufficiently available individual baseline parameters considering the power of the data set. Linearity was assessed by using polynomial terms of  $\Delta\text{GLOBE}_{0-1}$ , where appropriate. The  $\Delta\text{GLOBE}_{1-2}$  was added to the model and thus assessed in the subgroup of patients with at least 2 years of follow-up. The cumulative LT-free survival rates were based on the Kaplan-Meier method and compared with a log-rank test. To visualize the relationship between  $\Delta\text{GLOBE}_{0-1}$  and the LT-free survival, patients were stratified according to their baseline GLOBE score into a “low,” “medium,” and “high” group (based on the IQR of the GLOBE score before the start of UDCA therapy). For each group, cumulative LT-free survival curves were plotted based on categories of the  $\Delta\text{GLOBE}_{0-1}$ : no decrease and a moderate or large decrease (cutoff at the median GLOBE decline). A similar approach was used to visualize the relationship between the  $\Delta\text{GLOBE}_{1-2}$  and clinical outcome, which was stratified for the IQR of the GLOBE score at 1 year of UDCA.

Missing biochemical data at baseline and during UDCA therapy were handled by means of multiple imputation (10 databases) using SAS software, version 9.4 (SAS Institute, Cary, NC), as described in previous reports from our study group (4,5,15). Rubin rules were used to obtain pooled parameters and corresponding SEs (16). For the cumulative LT-free survival estimates and survival figures, patients were categorized into specific subgroups based on their individual mean GLOBE score over the 10 imputed databases, either at baseline or at 1 year of UDCA therapy. In this data set that includes the mean of the 10 imputed values for each missing variable, the bootstrapping method with 5,000 replications was applied to the primary Cox model as a sensitivity analysis.

All statistical tests were 2-sided, and a  $P$  value  $< 0.05$  was considered statistically significant. Statistical analyses were performed in SPSS Statistics, version 25.0 (IBM, Armonk, NY).

## RESULTS

### Cohort characteristics

In total, 3,775 UDCA-treated patients with PBC were included. The mean (SD) age was 52.1 (11.7) years, and most of the patients were female ( $n = 3,424$ ; 90.7%). Clinical and biochemical characteristics are summarized in Table 1 and were consistent with

**Table 2.** Cox proportional hazards regression analysis for LT or death

	Model 1		Model 2 <sup>a</sup>	
	HR (95% CI)	P value	aHR (95% CI)	P value
Pretreatment GLOBE score	3.05 (2.77–3.35)	0.001	2.82 (2.51–3.16)	0.001
$\Delta$ GLOBE <sub>0-1</sub>	2.36 (1.92–2.90)	<0.001	2.28 (1.81–2.87)	<0.001
$\Delta$ GLOBE <sub>0-1</sub> <sup>2</sup>	1.05 (1.01–1.10)	0.020	1.05 (1.01–1.10)	0.021

$\Delta$ GLOBE<sub>0-1</sub>, delta GLOBE during the first year of UDCA therapy; CI, confidence interval; HR, hazard ratio; LT, liver transplantation.  
<sup>a</sup>Adjusted for gender, year of diagnosis, and baseline AST and ALT

previous reports of PBC epidemiology. Patients were followed up for a median of 7.2 (IQR 3.7–11.5) years, during which a total of 253 patients underwent LT and 477 patients died (composite end point). The cumulative 10-year LT-free survival rate was 79.5% (95% confidence interval [CI] 77.9–81.1).

### Changes in GLOBE score during UDCA treatment and clinical outcome

The median GLOBE score was 0.25 (IQR –0.47 to 0.96) before treatment and –0.05 (IQR –0.72 to 0.66) after 1 year of UDCA therapy ( $P < 0.001$ ). The calculated median  $\Delta$ GLOBE<sub>0-1</sub> was –0.27 (IQR –0.56 to 0.02). Cox proportional hazards regression analyses, adjusted for the pretreatment GLOBE score, showed that  $\Delta$ GLOBE<sub>0-1</sub> was associated with the risk of LT or death (hazard ratio [HR] 2.36, 95% CI 1.92–2.90,  $P < 0.001$ ), which was not linear because  $\Delta$ GLOBE<sub>0-1</sub><sup>2</sup> was statistically associated with LT or death as well (Table 2). There was no statistically significant interaction between the pretreatment GLOBE score and  $\Delta$ GLOBE<sub>0-1</sub> for the occurrence of LT or death ( $P = 0.296$ ). The association between  $\Delta$ GLOBE<sub>0-1</sub> and LT or death remained stable, when gender, year of diagnosis, baseline alanine aminotransferase, and aspartate aminotransferase were added to the model (adjusted HR [aHR] 2.28, 95% CI 1.81–2.87,  $P < 0.001$ ). After applying the bootstrapping method with 5,000 replications as a sensitivity analysis, the  $\Delta$ GLOBE<sub>0-1</sub> remained independently associated with the primary end point (aHR 1.85, 95% CI 1.61–2.25,  $P < 0.001$ ). When stratified by baseline disease severity according to the Rotterdam score,  $\Delta$ GLOBE<sub>0-1</sub> was associated with LT-free survival in both patients with early (aHR 2.20, 95% CI 1.57–3.07,  $P < 0.001$ ) and advanced (aHR 2.31, 95% CI 1.76–3.03,  $P < 0.001$ ) disease (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/AJG/C825>). The  $\Delta$ GLOBE<sub>0-1</sub> also remained associated with the LT-free survival (aHR 2.67, 95% CI 1.54–4.63,  $P < 0.001$ ) among patients who were already below the POISE criteria (ALP  $< 1.67 \times$  ULN and bilirubin  $< 1.0 \times$  ULN) before the start of UDCA therapy (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/AJG/C825>).

As a sensitivity analysis, the baseline albumin and platelet levels were held stable for the calculation of the GLOBE score at 1 year of UDCA therapy, considering that the actual stage of disease is unlikely to change within 1 year. In this analysis, the  $\Delta$ GLOBE<sub>0-1</sub> showed a comparable independent association with the risk of LT or death (aHR 2.33, 95% CI 1.89–2.88,  $P < 0.001$ ). In addition, allowing the age to increase by 1 year had no impact on the estimated association between  $\Delta$ GLOBE<sub>0-1</sub> and clinical outcome (aHR 2.28, 95% CI 1.80–2.88,  $P < 0.001$ ).

After 1 year of UDCA, the median  $\Delta$ ALP was  $-0.79 \times$  ULN (IQR –1.56 to –0.29), median  $\Delta$ bilirubin was  $-0.08 \times$  ULN (IQR –0.21 to 0.05), median  $\Delta$ albumin was  $0.0 \times$  LLN (IQR –0.05 to 0.06), and median  $\Delta$ platelets was  $-6 \times 10^9/L$  (IQR –25 to 11).

Multivariate Cox regression analysis showed that  $\Delta$ ALP (aHR 1.32, 95% CI 1.05–1.66,  $P = 0.020$ ),  $\Delta$ bilirubin (aHR 2.13, 95% CI 1.67–2.72,  $P < 0.001$ ),  $\Delta$ albumin (aHR 0.27, 95% CI 0.11–0.63,  $P = 0.004$ ), and  $\Delta$ platelets (aHR 0.54, 95% CI 0.32–0.91,  $P = 0.023$ ) were all statistically significantly associated with the risk of LT or death.

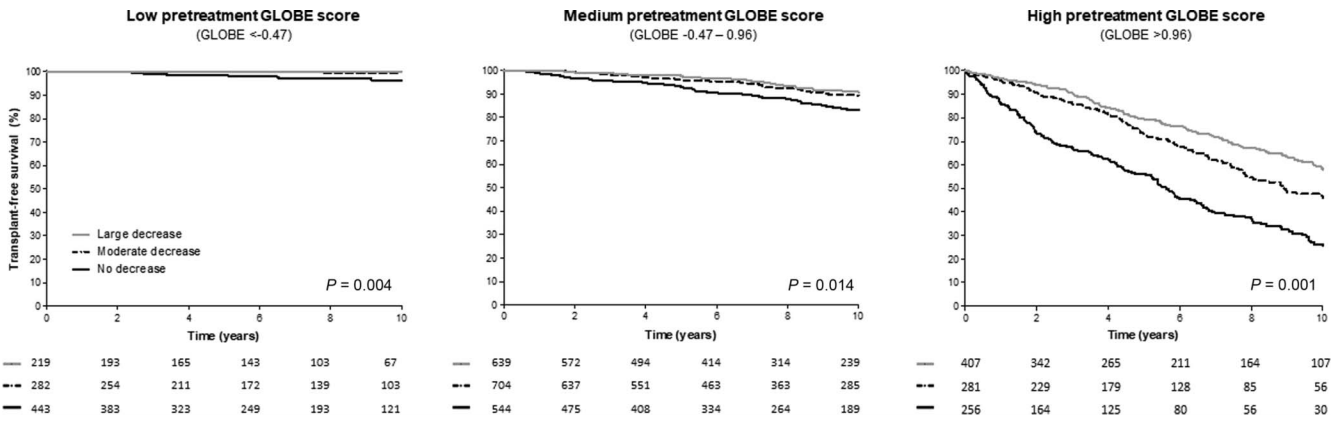
### Clinical outcome according to pretreatment GLOBE score and $\Delta$ GLOBE<sub>0-1</sub>

Patients were categorized into 3 groups according to the IQR of the pretreatment GLOBE score. The low GLOBE score group included 944 (25%) patients with a median-predicted 10-year LT-survival at baseline of 93.1% (IQR 91.4–94.9); the medium GLOBE score group included 1,887 (50%) patients with a median-predicted 10-year LT-free survival of 80.3% (IQR 73.8–85.6); and the high GLOBE score group included 944 (25%) patients with a median-predicted 10-year LT-free survival of 43.3% (IQR 23.0–55.4). Among patients in the low GLOBE score group, the cumulative 10-year LT-free survival was 100% for those with a  $\Delta$ GLOBE<sub>0-1</sub>  $< -0.42$  (large decrease,  $n = 219$ ; 23.2%), 99.3% (95% CI 97.9–100) for patients with a  $\Delta$ GLOBE<sub>0-1</sub> between –0.42 and 0 (moderate decrease,  $n = 282$ ; 29.9%), and 96.4% (95% CI 94.0–98.8) for those with a  $\Delta$ GLOBE<sub>0-1</sub>  $\geq 0$  (no decrease,  $n = 443$ ; 46.9%) ( $P = 0.004$ ) (Figure 1). Patients in the high GLOBE score group showed the largest differences in the absolute cumulative LT-free survival over the 3  $\Delta$ GLOBE<sub>0-1</sub> groups. The cumulative survival rates were 58.4% (95% CI 52.3–64.5), 46.0% (95% CI 38.6–53.4), and 26.1% (95% CI 19.2–33.0) for those with a large decrease ( $n = 407$ ; 43.1%), moderate decrease ( $n = 281$ ; 29.8%), and no decrease ( $n = 256$ ; 27.1%) in GLOBE score at 1 year of UDCA therapy, respectively ( $P < 0.001$ ). Table 3 summarizes the differences in cumulative 5-year and 10-year LT-free survival in comparison with a stable/increased GLOBE score, according to the baseline prognosis and change in GLOBE score at 1 year of UDCA therapy.

### Changes in GLOBE score during the second year of UDCA in relation to clinical outcome

Two years after the start of UDCA therapy, 3,524 (93.4%) patients were still in follow-up without LT. Among these patients, the median GLOBE score was –0.55 (IQR –0.72 to 0.66) at 1 year of UDCA therapy and –0.10 (IQR –0.80 to 0.67) at 2 years. The median  $\Delta$ GLOBE<sub>1-2</sub> was –0.04 (IQR –0.34 to 0.28). Adjusted for the baseline GLOBE score and the  $\Delta$ GLOBE<sub>0-1</sub>, the  $\Delta$ GLOBE<sub>1-2</sub> was independently associated with the LT-free survival (aHR 2.19, 95% CI 1.67–2.86,  $P < 0.001$ ). This association remained similar in the full Cox model (aHR 2.11, 95% CI 1.58–2.82,  $P < 0.001$ ). Supplementary Figure S1 (see Supplementary Digital Content 1, <http://links.lww.com/AJG/C825>) visualizes these results according to the IQR of the GLOBE score at 1 year and the predefined  $\Delta$ GLOBE<sub>1-2</sub> categories.





**Figure 1.** Transplant-free survival in patients with a low, medium, and high pretreatment GLOBE score, stratified according to  $\Delta\text{GLOBE}_{0-1}$  category. A  $\Delta\text{GLOBE}_{0-1} \geq 0$  was included in the group of no decrease. Patients with  $\Delta\text{GLOBE}_{0-1} < 0$  were separated into 2 groups based on their median  $\Delta\text{GLOBE}_{0-1}$  of  $-0.42$  as cutoff. Patients with a  $\Delta\text{GLOBE}_{0-1}$  between  $-0.42$  and  $0$  were considered to have a moderate decrease, whereas patients with a  $\Delta\text{GLOBE}_{0-1} < -0.42$  were considered to have a large decrease.

**DISCUSSION**

In this large retrospective international cohort study, we showed how treatment-induced changes in the GLOBE score were associated with the LT-free survival among UDCA-treated patients with PBC. This association remained in patients who already had a beneficial biochemical profile at the start of UDCA therapy. The relative reduction of the hazard of LT or death per UDCA-induced change in GLOBE score was stable over the baseline prognosis of patients. However, with a similar GLOBE score reduction, the absolute LT-free survival improved substantially more in patients with a higher baseline risk of LT or death (indicated by higher pretreatment GLOBE scores). The decline of the GLOBE score after 1 year of UDCA therapy was mainly due to a reduction in ALP, but the deltas of the individual biochemical parameters in the GLOBE score were all independently related to the time to LT or death. These findings support the hypothesis of long-term clinical gain with therapeutic agents for PBC based on their short-term impact on the GLOBE score. In addition, the results are helpful for physicians to counsel patients with PBC on their projected clinical benefit with UDCA therapy, for instance, to improve compliance in case of mild symptoms during UDCA use, especially in case of an unclear causal relation.

The GLOBE score has proven to be an accurate continuous prognostic model to predict the overall LT-free survival of

patients with PBC treated with UDCA (link to online calculator in the acknowledgments) (5). Subsequently, authors have concluded on the clinical benefit of new PBC treatment options based on the drug-induced GLOBE score improvements (9,10,19,20). While changes in prediction scores (i.e., deltas) are often used to assess clinical benefit, which is indeed helpful for patients, physicians, and policymakers, it is important to assess whether this approach is valid. For example, there has been conflicting results regarding the predictive value of MELD score changes in relation to clinical outcome among patients with liver cirrhosis (21,22). For PBC, several studies reported on the change in GLOBE score with second-line therapy. In their open-label prospective trial, Gomez et al. (7) found that the mean GLOBE score decreased from 0.31 to 0.14 among the 78 patients who completed 1 year of OCA. According to the GLOBE score estimates, this translated into an improvement of the projected 10-year risk of LT or death from 20.8% to 17.9% (risk reduction of approximately 14%). This is in line with our estimated 9% risk reduction per 0.1 decline of the GLOBE score. For this long-term clinical benefit, the recently shown maintenance of biochemical response to OCA over many years of combination therapy is likely to be an important precondition (23). In a smaller Spanish cohort of 47 patients, the mean GLOBE score had reduced from 0.13 to  $-0.16$  ( $\Delta\text{GLOBE} = 0.29$ ) at the end of 1 year of OCA add-on therapy (24). The 23.4% relative reduction of the projected risk of LT or death was again in line with our estimates regarding the  $\Delta\text{GLOBE}$ . For bezafibrate (BZF), cohort reports from Spain and Japan showed mean  $\Delta\text{GLOBE}$  scores of  $-0.36$  and  $-0.38$ , respectively, after 1 year of add-on therapy (8,24). These estimates were remarkably similar despite the differences in background population and mean baseline GLOBE scores (0.5 and  $-0.2$ , respectively). Because of this difference, however, the absolute risk reduction was twice as high in the Japanese cohort (6.9%) as opposed to the Spanish cohort (3.7%). Our study also highlights that the relative reduction of the risk of LT or death was stable over the baseline prognosis ( $P = 0.296$  for the interaction between  $\Delta\text{GLOBE}_{0-1}$  and pretreatment GLOBE score), while the absolute risk reduction was strongly dependent of the GLOBE score at baseline. Besides the biochemical response of new treatment options, our study indicates that it is important to consider the potential survival gain and side effects of these new drugs in relation to the

**Table 3.** Difference in LT-free survival in comparison with  $\Delta\text{GLOBE} \geq 0$  after 1 year of UDCA

Pretreatment GLOBE score	$\Delta\text{GLOBE}_{0-1}$ -0.42 to 0 (50% with lowest decrease)		$\Delta\text{GLOBE}_{0-1}$ <-0.42 (50% with largest decrease)	
	5 yr	10 yr	5 yr	10 yr
Low (GLOBE <-0.47) (%)	1.4	2.9	1.4	3.6
Medium (GLOBE -0.47 to 0.96) (%)	3.3	6.0	4.4	7.6
High (GLOBE >0.96) (%)	16.9	19.9	23.4	32.3

$\Delta\text{GLOBE}_{0-1}$ , delta GLOBE during the first year of UDCA therapy; LT, liver transplantation; UDCA, ursodeoxycholic acid.

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target population. For instance, in real-life cohorts, OCA seems to be prescribed to those with more severe PBC-related liver disease when compared with BZF (24,25), perhaps because currently OCA is the only approved second-line treatment option and there were toxicity concerns with fibrates. The absolute survival gain with these treatment options should therefore be assessed separately from the biochemical response.

The change in GLOBE score during the second year of UDCA therapy ( $\Delta$ GLOBE<sub>1-2</sub>) was associated with the risk of LT or death independently from the GLOBE score at baseline and the change in GLOBE score during the first year of treatment. This is relevant considering the previously described biphasic biochemical response to UDCA; an initial steep ALP decline is followed by a more gradual reduction of this cholestatic parameter to a maximum response at approximately 2 years of therapy (26,27). While it is frequently suggested to evaluate the need of adding second-line therapy such as OCA or BZF after 1 year of UDCA, our results indicate that a continued biochemical improvement after the first year of UDCA is clinically relevant (2). This may argue to postpone the decision to add second-line drugs in selected patients, especially considering the potential side effects and associated costs. This could be relevant, for instance, for patients not in urgent need of add-on treatment because of slowly progressive PBC who are just above the biochemical threshold for add-on therapy at 1 year of UDCA. Further validation of these results is needed, however, before such an approach can be generally advised.

It is important to consider that all GLOBE score-related estimates for clinical outcome are based on follow-up among patients with PBC treated with UDCA (5). Activation of the farnesoid X receptor or peroxisome proliferator-activated receptor, however, is considered to have multiple favorable effects besides improvement of cholestasis (28,29). Therefore, not all potential long-term clinical benefits of peroxisome proliferator-activated receptor and farnesoid X receptor agonism may be captured by the reduction of the GLOBE score (8). For instance, OCA therapy led to substantial alanine aminotransferase declines (which was also more pronounced when compared with the BZF therapy) (25). Despite being relevant prognostic markers, the hepatic transaminases are not included in the GLOBE score. More recently, the first long-term data on BZF add-on therapy showed an even greater reduction in mortality (aHR 0.33) as what may have been based on the BZF-associated GLOBE score decline (described above) (30). This may also hint toward additional benefit beyond the decline in ALP or bilirubin, which remains our main surrogate markers in clinical trials. Future cohort studies are needed to assess the validity of the GLOBE score LT-free survival estimates in long-term combination treatments. A benefit beyond the improvement of cholestasis has been shown for UDCA as well because patients with PBC without any reduction in ALP or bilirubin with UDCA therapy still had favorable long-term outcome compared with those untreated (31). Thus, even in case the GLOBE score is not reduced with UDCA, patients should generally continue treatment.

Limitations of this study mostly relate to the nature of this cohort. The Global PBC cohort is a largely retrospectively constructed data set, in which (biochemical) data are not always fully complete. Nonetheless, by using the multiple imputation method, we were able to correct for these missing laboratory data. Second, data collection in our cohort did not exceed beyond 2015. Further efforts are needed to assess the relationship between biochemical

status and long-term solid clinical end points in those with combination therapy. Third, we lacked detailed data on the cause of mortality, and therefore, we were unable to repeat our analysis with the change in the UK-PBC score. It may be anticipated, however, that the results with this alternative continuous risk model will be similar. Last, we recognize that this cohort is pre-dominated by patients treated in tertiary liver centers, which may have led to a potential selection bias. A strength of this study is that it was conducted with the use of a large, internationally, well-characterized cohort with a long-term follow-up and many clinical end points, resulting in substantial statistical power.

In conclusion, we showed how short-term UDCA-induced changes in GLOBE score were related to the long-term risk of LT or death among patients with PBC. Importantly, among patients with an unfavorable prognosis at baseline, a similar reduction in the GLOBE score resulted in a larger absolute improvement of their LT-free survival. This should be considered when assessing the value of treatment for PBC.

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Link to online GLOBE score calculator of the GLOBAL PBC Study Group: <https://www.globalpbc.com/globe>.

#### CONFLICTS OF INTEREST

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## Study Highlights

### WHAT IS KNOWN

- ✓ The GLOBE score is a validated and accurate continuous prognostic model to determine the patients' individual long-term liver transplantation (LT)–free survival.
- ✓ New drugs in development for primary biliary cholangitis (PBC) have shown to reduce the GLOBE score shortly after treatment initiation.

### WHAT IS NEW HERE

- ✓ Ursodeoxycholic acid–induced changes in the GLOBE score were associated with an improved clinical outcome.
- ✓ The relative risk reduction of the risk of LT or death was stable over the predicted prognosis before treatment, while the absolute risk reduction was strongly dependent of the GLOBE score at baseline.

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