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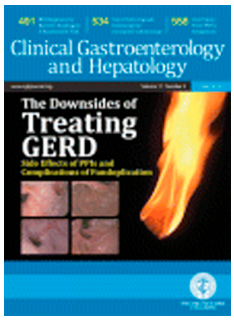

Effects of Age and Sex of on Response to Ursodeoxycholic Acid and Transplant-free Survival in Patients With Primary Biliary Cholangitis

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Short title:

Prognostic value of age and sex

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Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; PBC, primary biliary cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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Willem J. Lammers, Carla F. Murillo Perez and Bettina E. Hansen had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analyses.

Study concept and design: All authors.

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ABSTRACT (word count: 333)

Background & Aims: Primary biliary cholangitis (PBC) predominantly affects middle-aged women; there are few data on disease phenotypes and outcomes of PBC in men and younger patients. We investigated whether differences in sex and/or age at the start of ursodeoxycholic acid (UDCA) treatment are associated with response to therapy, based on biochemical markers, or differences in transplant-free survival.

Methods: We performed a longitudinal retrospective study of 4355 adults in the Global PBC Study cohort, collected from 17 centers across Europe and North America. Patients received a diagnosis of PBC from 1961 through 2014. We evaluated the effects of sex and age on response to UDCA treatment (based on GLOBE score) and transplant-free survival using logistic regression and Cox regression analyses, respectively.

Results: Male patients were older at the start of treatment (58.3±12.1 years vs 54.3±11.6 years for women; *P*<.0001) and had higher levels of bilirubin and lower circulating platelet counts (*P*<.0001). Younger patients (45 years or younger) had increased serum levels of transaminase than older patients (older than 45 years). Patients older than 45 years at time of treatment initiation had increased odds of a biochemical response to UDCA therapy, based on GLOBE score, compared to younger patients. The greatest odds of response to UDCA were observed in patients older than 65 years (odds ratio compared to younger patients 45 years or younger, 5.48; 95% CI, 3.92–7.67; *P*<.0001). Risk of liver transplant or death (compared to a general population matched for age, sex, and birth year) decreased significantly with advancing age: hazard ratio for patients 35 years or younger, 14.59 (95% CI, 9.66–22.02) vs hazard ratio for patients older than 65 years, 1.39 (95% CI, 1.23–1.57) (*P*<.0001). On multivariable analysis, sex was not independently associated with response or transplant-free survival.

Conclusion: In longitudinal analysis of 4355 adults in the Global PBC Study, we associated patient age, but not sex, with response to UDCA treatment and transplant-free survival. Younger age at time of PBC diagnosis is associated with increased risk of treatment failure, liver transplant, and death.

Keywords: Risk stratification; Stratified Medicine; Cholestatic Liver Disease; Mortality

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease in which patient outcome is largely dictated by the development of cirrhosis and portal hypertension.[1, 2] Between 83 to 95% of patients are women, most often presenting between 40 and 60 years of age.[3]

Several studies have demonstrated that the clinical impact of PBC differs according to sex and age group.[3, 4] Compared to male patients, females are more frequently symptomatic, with an increased burden of pruritus[5, 6] and greater scores in the fatigue domain of the PBC-40 quality of life questionnaire.[7] In contrast, male PBC patients are more likely to present with advanced disease[5-7], harbor an increased risk for hepatocellular carcinoma[8], and appear to have significantly worse transplant-free survival.[4,9] Male sex has also recently been identified as a risk factor for non-response to ursodeoxycholic acid (UDCA) independent of age at presentation, presence of portal hypertension, and biochemical indices of disease severity[7], alluding to the possibility of a more rapidly progressive disease course. Age appears to add another layer of complexity to clinical phenotypes, as a study conducted by the UK-PBC consortium recognized that younger patients are affected by more severe pruritus and fatigue. Furthermore, there was a positive correlation between older age at presentation and response to UDCA in females; with a lesser impact evident in patients of male sex.[7]

The aim of this study was to validate the prognostic impact of presenting age and sex on treatment responses and transplant-free survival using a large, internationally representative cohort of patients with PBC.

PATIENTS AND METHODS

Subjects and study design. This was a longitudinal study of treatment response and transplant-free survival according to age and sex in a well-defined cohort from the Global PBC Study Group. Demographic, clinical, and outcome data were collected from 17 centers across Europe and North America. Patients with a short follow-up (<6 months), overlap syndrome, or another concomitant liver disease were excluded. This study included adult (≥18 years of age) patients diagnosed between 1961 and 2014 with PBC as defined by published criteria[1,10] and who were treated with UDCA.

Baseline was defined as the date of UDCA initiation. The primary endpoints were biochemical response as per the GLOBE score criteria[11] (GLOBE score below the age-specific threshold) and liver transplant-free survival. Secondary endpoints included biochemical response according to the following response criteria: Barcelona, Paris-I, Rotterdam, Toronto, and Paris-II. Patients who did not meet clinical endpoints (liver transplant or death) were censored at their last date of available follow-up. The protocol was reviewed and approved by all local Institutional Review Boards across the 17 centers.

Statistical analysis. Continuous data are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate, and categorical data as proportions. Unpaired t-test, Mann-Whitney U test, or analysis of variance was used to determine whether there was a significant difference for continuous data, and differences in categorical data were analyzed using the Chi-square test. Life table analysis was conducted to assess the effect of age on transplant-free survival in PBC patients when compared to a control Dutch population. PBC

patients were stratified into various age groups, after which they were independently analyzed relative to the control population matched for age, sex, and birth year. Unadjusted differences in transplant-free survival between males and females were assessed using Kaplan-Meier estimates and compared using the log-rank test. Univariable and multivariable associations were computed using a logistic regression for biochemical response (odds ratio [OR] and 95% confidence interval [CI]) and Cox proportional hazards regression for transplant-free survival (hazard ratio [HR] and 95% CI). Univariable analysis included: sex, age at UDCA initiation, year of diagnosis, histologic stage at baseline as defined by Scheuer's[12] and Ludwig's criteria[3], biochemical stage at baseline as defined by ter Borg et al.[14] (mild: normal bilirubin and albumin, moderately advanced: either abnormal bilirubin or albumin, advanced: abnormal bilirubin and albumin), biochemical response, and surrogates of portal hypertension (platelet count $<150\times10^9$/L).[15,16] Age at UDCA initiation was analyzed as a continuous and categorical variable (grouped as ≤35, 36-45, 46-55, 56-65, and >65) to allow for an equitable distribution during analysis. In order to account for the lack of an adequate threshold of response for the age group ≤35, age was analyzed in the following age groups for response to UDCA (≤45, 46-55, 56-65, >65). The association of age with response was further assessed with a restricted cubic spline function with three knots. In order to determine whether age was an independent determinant of response in various subgroups, patients were categorized into two groups, according to whether their GLOBE score at baseline was below or above the age-specific threshold (GLOBE score status at baseline). An interaction between age and sex, and age and GLOBE score status at baseline were included in the analysis.

All analyses were performed using multiple imputation by Markov chain Monte Carlo

method for missing data (Proc MI in SAS version 9.3). Multiple imputation was based on the assumption that data were missing at random, with ten imputed datasets created from iterations to reduce sampling variability. Rubin's rules were used for the estimation of parameters of interest and standard error.[17,18] The variables included in the process of imputation were: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, albumin, and platelet count.

A two-sided *P*-value of <.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA) and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics. For the current study, a total of 4355 UDCA-treated PBC patients were analyzed after excluding those <18 years of age (n=3) and with no (n=647) or unknown treatment status (n=96). 446 (10%) were male and 3909 (90%) were female with a median follow-up of 7.7 years (IQR 3.9-12.0); 576 patients died (276 deaths were liver-related) and 330 patients were transplanted.

Clinical differences at baseline between sexes and age groups. At the time of UDCA initiation, males were older than females (58.3 ± 12.1 years vs 54.3 ± 11.6 years, *P*<.0001), exhibited greater median serum bilirubin values (0.82 ×ULN [IQR 0.59-1.49] vs 0.62 ×ULN [IQR 0.44-1.00], *P*<.0001) and were more often thrombocytopenic (platelet count $<150\times10^9$/L, 21% vs 14%, *P*=.001) (**Table 1**). Concurrently, patients presenting at a younger age more often manifest

an earlier disease stage, both biochemically and histologically, albeit with significantly greater serum transaminases and ALP values than older patients (*P*<.0001) (**Table 2**). The ALP levels in age groups 36-45 and 46-55 were significantly lower from that of 56-65 and >65 (P<.001). Furthermore, there was significantly higher ALP in the group 56-65 compared to the age group >65 (P=.001). Younger patients were more likely to present with an ALP>4×ULN: 27%, 31%, 27%, 18%, and 14%, in order from youngest to oldest (P<.001).

***Effect of age on biochemical response to UDCA*.** Across the cohort in its entirety, laboratory data after one year of UDCA therapy was available for 4200 (96%) patients. On univariable analysis, an older age at UDCA initiation was associated with a higher likelihood of achieving biochemical response according to the GLOBE score (per 10-year increase in age: OR 1.25, 95% CI 1.18-1.32, *P*<.0001). After adjusting for additional baseline factors, older patients appeared to have significantly better response than younger patients (**Table 3**). The same relationship was observed when age was analyzed as a categorical variable in multivariable analysis: ≤45 years (reference group), 46-55 years (OR 2.67, 95% CI 2.06-3.46, *P*<.0001), 56-65 years (OR 4.91, 95% CI 3.68-6.56 *P*<.0001), >65 years (OR 5.48, 95% CI 3.92-7.67, *P*<.0001). When analyzing the effect of age on biochemical response to UDCA in males and females separately, age had a similar effect in both (**Supplementary Figure 1**). In independent multivariable logistic regressions, the OR per a 10-year increase in age was comparable for males and females (Males: OR 1.65, 95% CI 1.27-2.12, P<.001; Females: OR 1.49, 95% CI 1.36-1.64, P<.001). Furthermore, the interaction term between age and sex was not significantly different (*P*=.66) and there was no evidence of an additive interaction. Age was also a significant predictor for the other response criteria, except Rotterdam criteria (**Supplementary Table 1**). Older patients had a

higher probability of response than younger patients irrespective of whether their GLOBE score at baseline was below or above the age-specific thresholds (**Figure 1**). The effect of age was additionally assessed with a restricted cubic spline function, which suggested the positive effect of age is less pronounced after the age of 65 (P=.004) (**Supplementary Figure 2**).

Since younger patients were more likely to have elevated ALT and AST levels, we assessed whether these biochemical markers were independently associated with response to UDCA in separate multivariable models while adjusting to center, sex, age, year of diagnosis, response at baseline and log bilirubin. AST but not ALT was an independent predictor of response (ALT [log]: OR 1.15, 95% CI 0.84-1.58, P=.39; AST [log]: OR 0.57, 95% CI 0.39-0.84, P=.004).

Effect of sex on biochemical response to UDCA. Overall, males had significantly lower biochemical response compared to females (62% [n=263] vs 72% [n=2732], *P*<.0001) and were associated with lower response (OR 0.62, 95% CI 0.50-0.76, *P*<.0001). However, after adjusting for parameters corresponding to disease severity (baseline bilirubin, ALP, albumin, and platelet count), age at UDCA initiation, year of diagnosis, GLOBE score status at baseline, and center, male sex was no longer an independent predictor of response (OR 0.77, 95% CI 0.57-1.04, *P*=.09) (**Table 3**). Comparable results were found for the other response criteria (**Supplementary Table 2**).

Transplant-free survival amongst different age groups.

The 10-year transplant-free survival rate decreased with age in the corresponding age groups from youngest to oldest: 89.4%, 87.0%, 82.4%, 77.7%, and 64.1% (*P*<.001). To gain additional insight into the effect of age on transplant-free survival of PBC patients, they were assessed relative to a general population (matched according to age, sex, and birth year) within each age group. On life table analysis, the PBC population within each age group had significantly lower transplant-free survival than the matched general population (**Figure 2A**). Interestingly, the transplant-free survival hazard ratio relative to a general population significantly decreased with advancing age (*P*<.0001) (**Figure 2B**). PBC patients ≤35 years old had the highest hazard ratio (HR 14.59, 95% CI 9.66-22.02, *P*<.0001) and patients >65 years of age had the lowest (HR 1.39, 95% CI 1.23-1.57, *P*<.0001). The distribution of clinical events from the 5-year transplant-free survival (n=67) was also significantly variable with age, as younger patients more often received a liver transplant and older patients experienced increased mortality that was primarily liver-unrelated (*P*<.0001) (**Supplementary Figure 3A**).

Transplant-free survival amongst males and females. On crude analysis of overall transplant-free survival, males had a significantly lower 10-year transplant-free survival rate than females (67.7% vs 80.1%, *P*<.0001) (**Supplementary Figure 4A**). However, after adjusting for age at UDCA initiation, year of diagnosis, bilirubin, ALP, platelet count, and center, the increased risk for liver transplantation or death in males was no longer significant (HR 1.19, 95% CI 0.99-1.44, *P*=.07) (**Table 4, Supplementary Figure 4B**). There was also no significant difference in the distribution of clinical events from the 5-year transplant-free survival between males and females (**Supplementary Figure 3B**).

DISCUSSION

The results of our study confirm that a younger age at presentation confers an impaired biochemical response to UDCA compared with older patients, even after adjusting for sex and disease severity. Despite manifesting less severe biochemical and histological disease, younger patients exhibit more pronounced biochemical hepatitic activity, as evident by significantly greater serum transaminases levels.[19] Moreover, younger age is also associated with markedly lower transplant-free survival relative to a matched general population. Conversely, patient sex does not appear to be an independent determinant of biochemical response or transplant-free survival, but rather male patients present with more advanced disease; a known cause of diminished treatment response and prognosis in PBC.[2,20]

Similar to other diseases of autoimmune origin, the pathogenesis of PBC appears to be driven by fundamental differences in susceptibility across males and females, as well as different age groups. The inherent challenges posed by the epidemiology of PBC have led to an elusive understanding of whether males or younger patients have a more aggressive disease phenotype. Owing to the size of the cohort and statistical validation through the use of center-specific stratification and multiple imputation, our study is strongly positioned to explore outcomes in small subgroups while minimizing bias.

In line with our study's findings, Carbone *et al.* found that when response was stratified by sex, it appeared that older female patients have significantly better response than their younger counterparts, whereas males have weak age-associated response rates.[7] However, we found that the effect of age on response to UDCA is similar in both sexes. There are several

potential reasons for lower rates of biochemical response in younger patients. One possibility is that younger patients may have reduced compliance, or alternatively, disparities in response may be related to underlying disease pathology. While the relationship between age and medication compliance is complex, one possibility is that younger patients have reduced compliance, as demonstrated in other chronic disease literature.[21,22] Patients with ductopenia have been previously demonstrated to have diminished response to UDCA[23], and descriptions of a severe ductopenic variant of PBC all involved patients younger than 50 years of age.[24] Thus, it is possible that younger patients have a predominantly ductopenic phenotype which is particularly resistant to UDCA treatment. Younger patients were more likely to present with severe disease, as determined by ALP levels above 4×ULN and it is possible that they also have a predominantly ductopenic phenotype that is particularly resistant to UDCA treatment. Additionally, in our cohort, patients under the age of 45 appeared to have higher AST and ALT, which may suggest more exuberant histologic inflammation. Interestingly, Carbone *et al*. found that younger patients were more likely to fail therapy based on transaminase criteria[7], which collectively implies a more hepatitic phenotype. Alternatively, it may reflect a more advanced disease given the AST elevations associated with cirrhosis. Indeed, AST was an independent predictor of response in our cohort. Further, we demonstrate that the effect of age on response rates do not vary according to their status at baseline (criteria for response evaluated at baseline).

The life expectancy of asymptomatic patients diagnosed at 55 years or older has been shown to be comparable with a matched population.[25] Similarly, we found that when our cohort of PBC patients was matched to a general population, the risk for liver transplantation and death incrementally decreased with increasing age. Taking into account our data demonstrate that

younger patients are less likely to respond to UDCA, this suggests that younger patients could have lower transplant-free survival than their older counterparts as a consequence of diminished treatment response.

Earlier studies have demonstrated that males present with more advanced disease, reflected by their higher rates of jaundice, variceal bleeding, and thrombocytopenia at presentation.[5, 7] Asymptomatic males also present at an older age than females, with a mean difference of approximately five years.[5, 7] The UK-PBC cohort also showed that male sex was an independent predictor of biochemical response. In contrast, our study demonstrated that sex was not independently associated with biochemical response or transplant-free survival. In a previous study of a Dutch population, sex was also not an independent predictor of response to UDCA.[26] The lack of association between male sex and clinical outcomes in PBC suggests that sex is not an inherent determinant of treatment response or prognosis, but rather that males are at greater risk of presenting with more advanced disease, with a greater degree of hepatic synthetic dysfunction and portal hypertension. A possible factor explaining this finding could be that the diagnosis of PBC is not sufficiently considered in males presenting with features of liver disease. However, this is highly speculative and it may well be that male patients develop less frequent or less severe symptoms and therefore remain undiagnosed until later in the course of the disease. Lastly, though this is the largest study of the impact of male sex on transplant-free survival, it is possible that we were insufficiently powered to detect a small effect size. This would suggest that despite adequate biochemical response, additional factors are leading to decreased transplant-free survival in males. This highlights the need for further research evaluating sex-specific factors in the outcome of PBC patients, both from an epidemiologic standpoint, as well

as clinical trials.

In conclusion, patient age irrespective of sex has significant impact on biochemical response and transplant-free survival. Our data suggests that younger patients should be monitored carefully, with early consideration for additional therapies, as they appear to be at greatest risk of biochemical non-response to UDCA, liver transplantation, and death. The presence of more overt biochemical hepatitic activity suggests a more aggressive and inflammatory phenotype in younger, compared to older patients. Conversely, males appear to be diagnosed at a more advanced disease stage, putatively accounting for the differences in biochemical response rates compared to females. It is thus important to prevent diagnostic delays by maintaining a high index of suspicion for PBC in male patients and aggressively managing any potential concomitant causes of progressive fibrosis. Further studies are required to unravel the mechanisms underlying the diminished treatment response to UDCA and transplant-free survival in young patients.

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FIGURE LEGENDS

Figure 1. Predicted probability of GLOBE response according to age at the start of ursodeoxycholic acid (UDCA) treatment stratified by GLOBE status at baseline.

Predicted probability of GLOBE response according to age at UDCA initiation in (A) patients whose GLOBE score at baseline is below the age-specific threshold (n=2621) and (B) patients whose GLOBE score at baseline is above the age-specific threshold (n=1579). Predicted probabilities obtained from a logistic regression correspond to a PBC patient diagnosed in 2000 with median laboratory values after adjusting for diagnosis year, sex, bilirubin, albumin, and platelet count. Odds ratios (OR) and 95% confidence intervals (CI) are with respect to a 10-year increase in age.

Figure 2. Transplant-free survival according to age at the start of ursodeoxycholic acid of PBC patients compared to an age-, sex-, and birth year-matched general population.

(A) Life table analysis of transplant-free survival in different age groups relative to a matched general population. (B) Transplant-free survival hazard ratios (95% CI) obtained from Cox regression analyses of PBC patients relative to a matched general population and in different age groups. Age was a significant determinant of the transplant-free survival hazard ratio relative to a matched general population ($P<.001$).

Table 1. Baseline characteristics of the total cohort of PBC patients and according to sex

Parameter	All patients n=4355	Male n=446	Female n=3909	P-value
Age at beginning of follow-up, mean ± SD	54.7 ± 11.7	58.3 ± 12.1	54.3 ± 11.6	<.0001
AMA-positive, no. (%)[a]	3849 (90.7)	410 (92.8)	3439 (90.5)	.12
Year of diagnosis, no. (%)				.44
<1990	816 (18.7)	79 (17.7)	737 (18.9)	
1990-2000	1678 (38.5)	161 (36.1)	1517 (38.8)	
2000-2010	1655 (38.0)	181 (40.6)	1474 (37.7)	
>2010	206 (4.7)	25 (5.6)	181 (4.6)	
Biochemical disease stage, no. (%)[b]				<.0001
Early	1731 (67.9)	146 (52.9)	1585 (69.8)	
Moderate	618 (24.3)	91 (33.0)	527 (23.2)	
Advanced	199 (7.8)	39 (14.1)	160 (7.0)	
Histological disease stage, no. (%)[c]				.84
Early stage disease (F1-2)	1225 (68.3)	121 (67.6)	1104 (68.4)	
Late stage disease (F3-4)	569 (31.7)	58 (32.4)	511 (31.6)	
Portal hypertension, no. (%)[d]	368 (14.8)	59 (21.2)	309 (13.9)	.001
Laboratory parameters, median (IQR)[e]				
AST (×ULN)	1.43 (0.94-2.23)	1.40 (0.92-2.13)	1.45 (0.94-2.23)	.42
ALT (×ULN)	1.64 (1.00-2.60)	1.65 (1.00-2.61)	1.64 (1.00-2.60)	.96
ALP (×ULN)	2.07 (1.30-3.71)	2.00 (1.30-3.40)	2.10 (1.30-3.74)	.26
Albumin (×LLN)	1.14 (1.06-1.23)	1.14 (1.03-1.24)	1.14 (1.06-1.23)	.05
Total bilirubin (×ULN)	0.65 (0.45-1.04)	0.82 (0.59-1.49)	0.62 (0.44-1.00)	<.0001
Platelets ($x10^9$/L)	244 (186-297)	216 (162-262)	248 (190-300)	<.0001

PBC, primary biliary cholangitis; SD, standard deviation; AMA, anti-mitochondrial antibody; IQR, interquartile range; AST, aspartate aminotransferase; ULN, upper limit of normal; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LLN, lower limit of normal

[a] AMA status was unavailable for 112 patients (4 males, 108 females).

[b] Biochemical disease stage defined as per ter Borg et al. [13] (early: normal serum bilirubin and albumin levels, moderate: abnormal serum bilirubin or albumin levels, advanced: abnormal serum bilirubin and albumin levels). Insufficient data for determination in 41.5% (n=1807, all patients); 38.1% (n=170, males) and 41.9% (n=1637, females).

[c] Baseline biopsy was performed in 51.5% (2244 patients; 232 males and 2012 females). Baseline histological disease stage was unavailable in 20.1% (n=450, all patients), 22.8% of male patients (n=53) and 19.7% of female patients (n=397).

[d] Portal hypertension defined as a platelet count $<150x10^9$/L. Platelet count was available for 57.2% (2494 patients; 278 males and 2216 females).

[e] Due to differences in normal thresholds between centres, laboratory values are listed as factors of the upper and lower limit of normal.

Table 2. Baseline characteristics according to age at UDCA initiation

Parameter	≤35 n=199	36-45 n=727	46-55 n=1305	56-65 n=1234	>65 n=890	P-value
Male sex	15 (7.5)	55 (7.6)	97 (7.4)	140 (11.3)	139 (15.6)	<.0001
AMA-positive	172 (87.8)	634 (90.7)	1139 (89.9)	1094 (90.6)	810 (92.8)	.11
Diagnosis year						<.0001
<1990	28 (14.0)	112 (15.4)	239 (18.3)	268 (21.7)	169 (19.0)	
1990-1999	64 (32.2)	330 (45.4)	530 (40.6)	460 (37.3)	294 (33.0)	
2000-2010	101 (50.8)	259 (35.6)	482 (36.9)	444 (36.0)	369 (41.5)	
>2010	6 (3.0)	26 (3.6)	54 (4.1)	62 (5.0)	58 (6.5)	
Biochemical Disease stage[a]						.003
Early	71 (67.6)	238 (63.1)	496 (69.5)	549 (71.6)	377 (64.4)	
Moderate	30 (28.6)	116 (30.8)	164 (23.0)	159 (20.7)	149 (25.5)	
Advanced	4 (3.8)	23 (6.1)	54 (7.6)	59 (7.7)	59 (10.1)	
Histological Disease stage[b]						.03
Early (F1-2)	74 (77.1)	250 (69.6)	443 (70.8)	288 (64.4)	170 (63.9)	
Late (F3-4)	22 (22.9)	109 (30.4)	183 (29.2)	159 (35.6)	96 (36.1)	
Portal hypertension[c]	8 (7.4)	29 (7.5)	81 (11.6)	117 (15.8)	133 (23.8)	<.0001
Laboratory values						
AST (×ULN)	1.67 (1.03-2.75)	1.89 (1.15-2.80)	1.53 (1.00-2.40)	1.30 (0.90-2.00)	1.23 (0.83-1.87)	<.0001
ALT (×ULN)	2.25 (1.43-3.89)	2.46 (1.37-3.80)	1.87 (1.20-2.86)	1.49 (1.00-2.20)	1.20 (0.79-1.84)	<.0001
ALP (×ULN)	2.01 (1.12-4.22)	2.55 (1.49-4.83)	2.33 (1.45-4.13)	2.00 (1.30-3.31)	1.15 (1.20-2.76)	<.0001
Albumin (×LLN)	1.17 (1.09-1.27)	1.16 (1.06-1.25)	1.16 (1.08-1.26)	1.14 (1.06-1.24)	1.11 (1.01-1.20)	<.0001
Total bilirubin (×ULN)	0.64 (0.42-1.06)	0.71 (0.48-1.23)	0.60 (0.41-1.00)	0.67 (0.48-1.00)	0.67 (0.48-1.05)	.003
Platelet count ($x10^9$/L)	261 (224-302)	277 (222-331)	253 (202-304)	233 (177-284)	216 (151-272)	<.0001

UDCA, ursodeoxycholic acid; AMA, anti-mitochondrial antibody; IQR, interquartile range; AST, aspartate aminotransferase; ULN, upper limit of normal; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LLN, lower limit of normal.

All data presented as no. (%), expect laboratory values, which are expressed as median (IQR).

[a] Biochemical disease stage defined as per ter Borg et al. [13] - early: normal serum bilirubin and albumin levels, moderate: abnormal serum bilirubin or albumin levels, advanced: abnormal serum bilirubin and albumin levels. Insufficient data for determination in 41.5% (94, 350, 591, 467, and 305 for each age group).

[b] Baseline histological disease stage was not available in 23% (n=28), 21% (n=95), 15% (n=114), 23% (n=135), 23% (n=266) in each respective age group (listed from youngest to oldest).

[c] Portal hypertension defined as a platelet count $<150x10^9$/L. Platelet count was unavailable for 57.3% (91, 339, 608, 493, 330 for each respective age group listed from youngest to oldest).

Table 3. Multivariable logistic regression for factors affecting biochemical response to UDCA according to the GLOBE score criteria

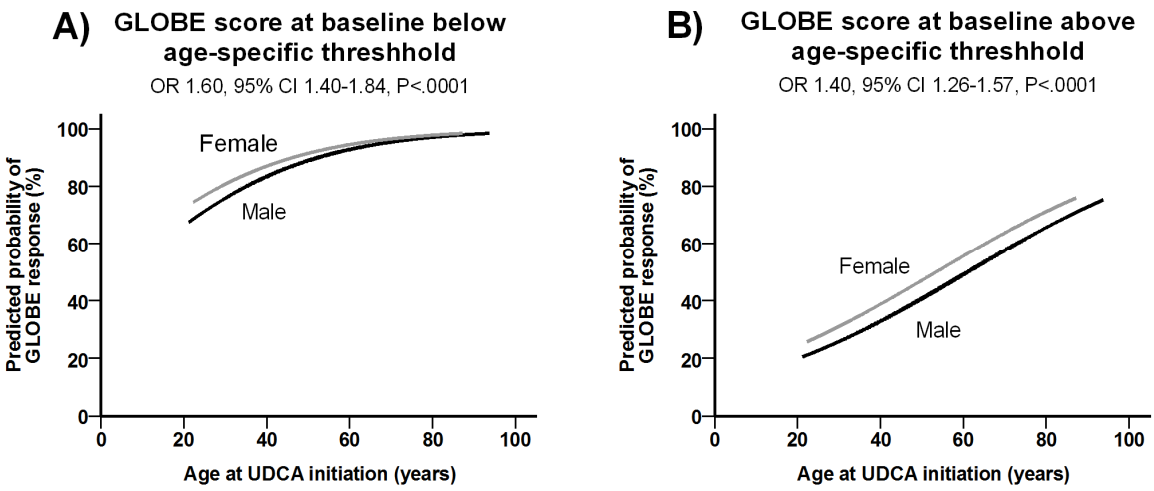
Baseline variable	Entire cohort (n=4200)		
	OR	95% CI	P-value
Male sex	0.77	0.57-1.04	.09
Age at UDCA initiation (per 10-year increase)	1.51	1.37-1.64	<.0001
Year of diagnosis (per 10-year increase)	1.11	0.96-1.27	0.16
Baseline log bilirubin (×ULN)	0.06	0.03-0.09	<.0001
Baseline log ALP (×ULN)	0.28	0.19-0.40	<.0001
Baseline albumin (×LLN) (per 0.5 increase)	3.75	2.57-5.49	<.0001
Baseline platelet count (per 50×10^9/L increase)	1.49	1.42-1.57	<.0001
GLOBE score below threshold at baseline	3.76	2.85-4.95	<.0001

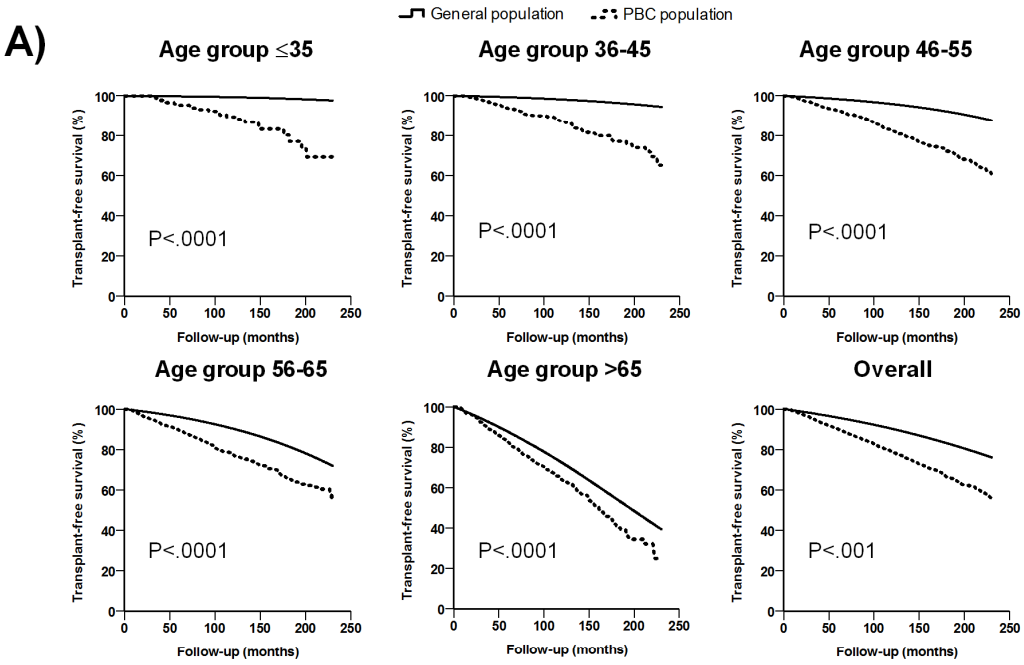
UDCA, ursodeoxycholic acid; OR, odds ratio; CI, confidence interval; ULN, upper limit of normal; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

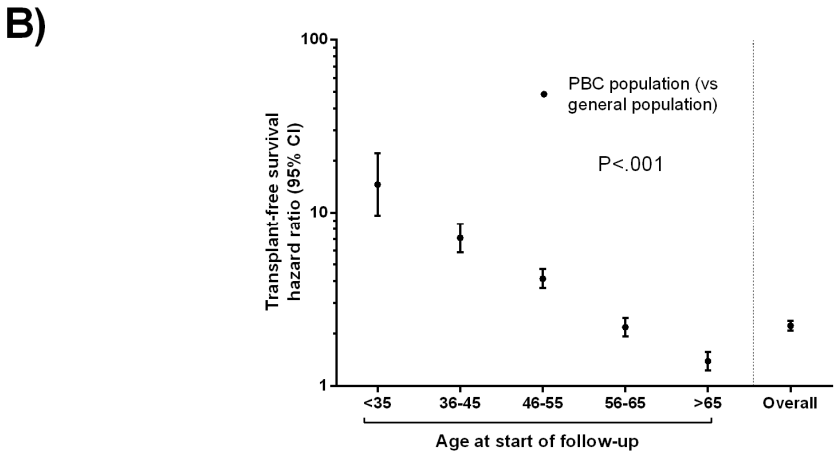
Table 4. Multivariable Cox regression for factors affecting transplant-free survival

Baseline variable	Entire cohort (n=4349)		
	HR	95% CI	P-value
Male sex	1.19	0.99-1.44	.07
Age at UDCA initiation (per 10-year increase)	1.55	1.47-1.66	<.0001
Year of diagnosis (per 10-year increase)	0.83	0.75-0.92	.001
Baseline log bilirubin (×ULN)	7.34	6.03-8.93	<.0001
Baseline log ALP (×ULN)	1.88	1.47-2.40	<.0001
Platelet count (per 50×10^9/L increase)	0.88	0.83-0.93	<.0001

HR, hazard ratio; CI, confidence interval; ULN, upper limit of normal; ALP, alkaline phosphatase.




A)
General population
PBC population
Age group ≤35
Age group 36-45
Age group 46-55
Age group 56-65
Age group >65
Overall
Transplant-free survival (%)
Follow-up (months)
P<.0001
P<.0001
P<.0001
P<.0001
P<.0001
P<.001


B)
Transplant-free survival hazard ratio (95% CI)
PBC population (vs general population)
P<.001
<35
36-45
46-55
56-65
>65
Overall
Age at start of follow-up

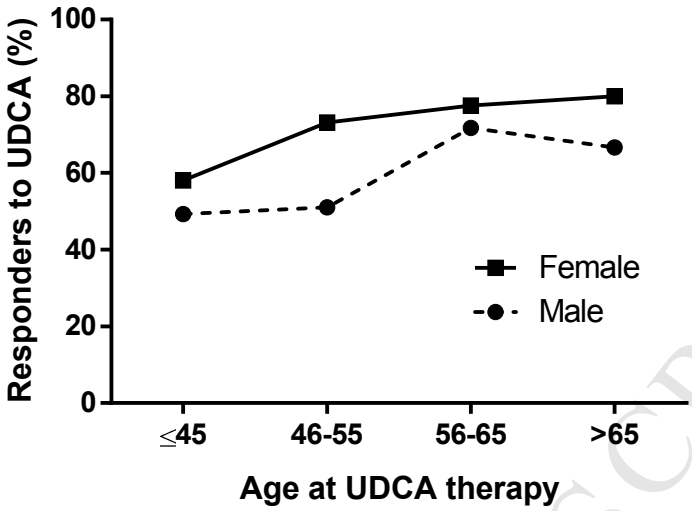
What You Need to Know

Background: Primary biliary cholangitis (PBC) mostly affects middle-aged women—there are few data from men and younger patients. We investigated whether differences in sex and/or age at the start of ursodeoxycholic acid (UDCA) treatment are associated with differences in response to therapy or transplant-free survival.

Findings: In longitudinal analysis of 4355 adults from the Global PBC Study Group, we found that younger age at treatment initiation is associated with increased risk of treatment failure, liver transplant, and death. However, patient sex was not associated with outcome.

Implications for patient care: Younger patients with PBC are at higher risk for failure to respond to UDCA, liver transplantation, and death.

SUPPLEMENTARY DATA



Supplementary Figure 1. The impact of age on response to UDCA according to GLOBE score stratified by sex.

Supplementary Table 1. Multivariable logistic regression of the effect of age on biochemical response to UDCA according to various published criteria

Criteria	OR[a]	95% CI	P-value
Barcelona	1.12	1.05-1.18	<.0001
Paris-I	1.15	1.06-1.23	.001
Rotterdam	0.94	0.88-1.02	.14
Toronto	1.25	1.16-1.34	<.0001
Paris-II	1.15	1.08-1.23	<.0001

UDCA, ursodeoxycholic acid; OR, Odds ratio; CI, confidence interval.

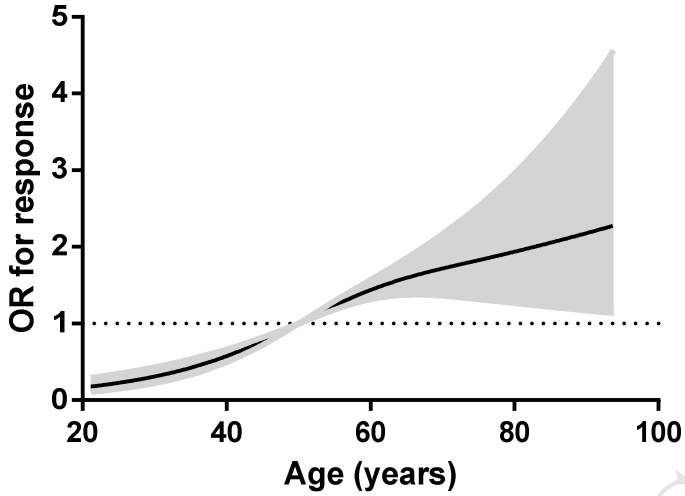
[a] OR corresponds to a 10-year increase in age.

Supplementary Table 2. Multivariable logistic regression of the effect of sex on biochemical response to UDCA according to various published criteria

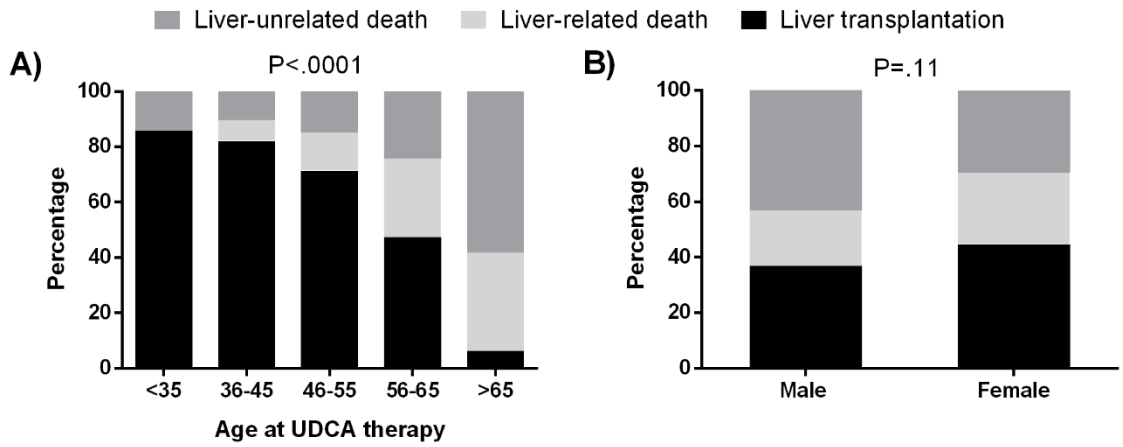
Criteria	OR[a]	95% CI	P-value
Barcelona	1.05	0.84-1.31	.66
Paris-I	0.88	0.66-1.16	.35
Rotterdam	0.80	0.61-1.05	.10
Toronto	0.80	0.60-1.05	.10
Paris-II	1.06	0.82-1.37	.67

UDCA, ursodeoxycholic acid; OR, Odds ratio; CI, confidence interval.

[a] OR corresponds to male sex.

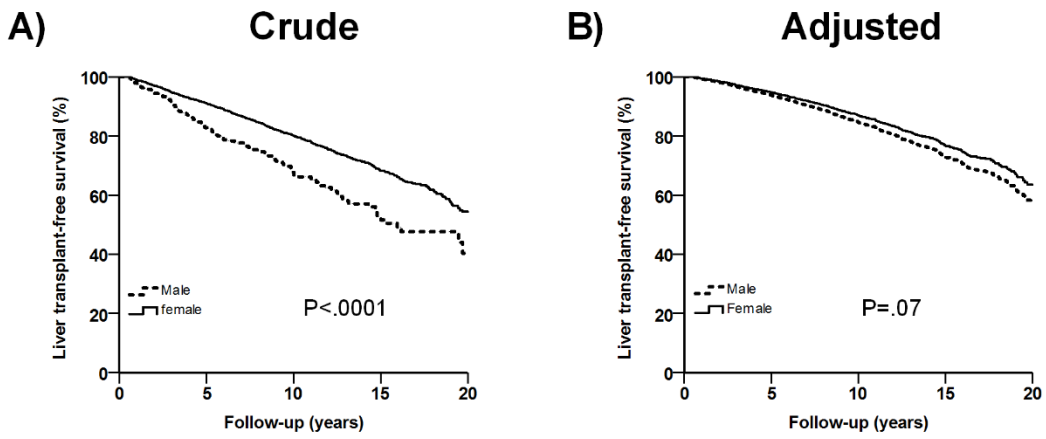


Supplementary Figure 2. The association between age and the odds for response to UDCA according to the GLOBE score modelled by a restricted cubic spline function. The age reference is 50 years. The test for curvature was curvature was significant (P=.004).



Supplementary Figure 3. The distribution of clinical events at 5 years stratified by age at the start of ursodeoxycholic acid and sex.

The distribution of liver-unrelated death, liver-related death, and liver transplantations at 5 years (n=67) according to (A) age at the start of ursodeoxycholic acid and (B) sex were compared by Chi-square tests.



Supplementary Figure 4. Crude and adjusted transplant-free survival curves of males and females.

Survival curves of (A) unadjusted (crude) transplant-free survival and (B) adjusted transplant-free survival between males and females. Cox regression analysis (n=4349) was adjusted for center, age at the start of ursodeoxycholic acid, year of diagnosis, serum alkaline phosphatase levels, serum bilirubin levels, and platelet count.