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Biochemical Response to Ursodeoxycholic Acid Predicts Survival in a North American Cohort of Primary Biliary Cirrhosis Patients

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Abstract

Background—Biochemical response to Ursodeoxycholic Acid among patients with Primary Biliary Cirrhosis remains variable and there is no agreement of an ideal model. Novel assessment of response coupled to histologic progression was recently defined by the Toronto criteria. We retrospectively assessed transplant-free survival and clinical outcomes associated with Ursodeoxycholic Acid response to evaluate the Toronto criteria using a large North American cohort of PBC patients.

Methods—398 PBC patients from the Mayo Clinic PBC Genetic Epidemiology (MCPGE) Registry were assessed for Ursodeoxycholic Acid treatment and biochemical response per the Toronto criteria. Responders were defined by reduction in alkaline phosphatase to less than or equal to 1.67 times the upper normal limit by 2 years of treatment, whereas non-responders had alkaline phosphatase values greater than 1.67 times the upper normal limit. Probability of survival was estimated using the Kaplan-Meier method.

Results—302 (76%) patients were responders and 96 (24%) were non-responders. Significantly more non-responders developed adverse events related to chronic liver disease compared to responders (Hazard Ratio (HR): 2.77, $P = 0.001$). Biochemical responders and early-stage disease at treatment start was associated with improved overall transplant-free survival compared to non-responders (HR: 1.9) and patients with late stage disease (HR: 2.7) after age and sex adjustment.

Conclusions—The Toronto criteria are capable of identifying Ursodeoxycholic Acid-treated Primary Biliary Cirrhosis patients at risk of poor transplant-free survival and adverse clinical outcomes. Our data reveal that despite advanced disease at diagnosis, biochemical response per the Toronto criteria associates with improved overall transplant-free survival.

Keywords

Toronto Criteria; Cholestasis; Autoimmune; Outcomes

INTRODUCTION

Primary biliary cirrhosis (PBC) is a complex autoimmune disease that is likely caused by environmental interaction with genetically determined predisposition [1, 2]. PBC is characterized by the destruction of small intrahepatic bile ducts, subsequently causing biliary cholestasis. This sustained chronic injury may ultimately lead to the development of end-stage liver disease requiring liver transplantation. Currently, Ursodeoxycholic Acid (UDCA) is the only FDA approved treatment for PBC, resulting in the reduction of biochemical markers of cholestasis and leading to the normalization of survival in most patients [3–6].

The extent of biochemical response to UDCA differs among PBC patients [7, 8] and may be associated with the underlying genetic variation of individual patients. Future studies examining the genetic differences between UDCA responders and non-responders will be dependent on accurate and reliable biochemical assessment after the initiation of therapy. Several groups have published different biochemical response criteria that predict overall survival and progression of liver disease among PBC patients with both early- and late-stage disease, including the Barcelona and Paris I criteria [8–12]. However, there has been no consensus defining the ideal response criteria. Recently, Kumagi et al [12] published the Toronto criteria, the only biochemical response criteria defined according to progression assessed by paired liver biopsies over time. We find this model of response intriguing given these criteria are the first to incorporate disease stability or progression at the level of hepatic parenchyma, and thus may reflect a response to UDCA that relates to the pathogenetic progression of disease.

In this study, we aimed to evaluate transplant-free survival and clinical outcomes of the Mayo Clinic PBC Genetic Epidemiology (MCPGE) Registry utilizing the Toronto criteria. This diverse patient cohort is strongly positioned to evaluate the primary aims of the study given a prolonged duration of clinical follow-up and easily accessible electronic medical record documenting serologic and procedural data for the past 18 years. The referral nature of our institution has also provided the inclusion of individuals with advanced disease or outside hospital evidence of poor response to therapy, thereby enriching the cohort with a spectrum of PBC cases. Lastly, our medical center contains a high volume liver transplant program, therefore it is common for patients to continue close clinical follow-up because of disease advancement despite appropriate therapy.

METHODS

PBC Patients

613 PBC patients from the MCPGE Registry, recruited between January 2004 and March 2010, were included in this study. The details regarding the establishment of this registry are discussed previously [13]. Our study was reviewed and approved by our institutional review board, identified by institution number: 670-02. All study participants provided written informed consent prior to the inclusion of the study. The diagnosis of PBC was completed per clinically accepted standards [3] and study inclusion required documented treatment

with UDCA of at least 13–15 mg/kg for 2 uninterrupted years after diagnosis without concurrent use of other therapeutic compounds for the treatment of PBC. Patients were excluded if there was evidence of an autoimmune overlap syndrome on biopsy or laboratory testing. Clinically relevant data and normal laboratory ranges within 6 months of diagnosis were collected by automated query of the electronic medical record and/or manual curating of the paper medical record including: antimitochondrial antibody (AMA) level, alkaline phosphatase (AP), total bilirubin (TB), and biopsy stage (if available). Adequate liver biopsies with evidence of Ludwig stage II or less were defined as early-stage disease, whereas Ludwig stage III or higher were classified as late-stage disease. Follow-up was completed via retrospective chart review and details regarding significant adverse events related to chronic liver disease were collected via detailed assessment of clinical notes, radiographic and ultrasonography imaging, and luminal endoscopic findings. These adverse outcomes included development of abdominal ascites, esophageal varices, hepatic encephalopathy, and hepatocellular cancer after classification of biochemical response at 2 years.

Definition of Biochemical Response to UDCA

Ascertainment of biochemical response to UDCA of the included PBC patients was defined according to the Toronto criteria [12]. These criteria identify biochemical responders as having an AP value of less than or equal to 1.67 times the upper normal limit by 2 years of treatment with dose appropriate UDCA, whereas biochemical non-responders are identified as having AP values greater than 1.67 times the upper normal limit. In our study, application of the Toronto criteria to define biochemical response to UDCA was chosen not only because previous associated performance with concordant parenchymal changes, but also given the retrospective nature of this assessment and available pertinent lab data including liver biopsies dating back to the 1980s. Nonetheless, every effort was made to collect laboratory data including normal laboratory ranges to further assess other UDCA response models including the Barcelona [8] and Paris I criteria [9]. Biochemical response according to the Barcelona criteria was defined as a reduction in UDCA pretreatment levels of AP of more than 40% (normalized by the upper limit normal) or normal AP levels by 1 year of UDCA treatment. Responders according to the Paris I criteria were defined by concurrent AP $\leq$ 3 times upper normal limit, aspartate aminotransferase (AST) $\leq$ 2 times upper normal limit, and a normal total bilirubin (TB) level.

Itching and Health Assessment

To assess symptoms associated with PBC among responders and non-responders to UDCA, a short 7-page scannable survey with prepaid return envelope was mailed to included MCPGE Registry patients. The questionnaire, developed in association with the Mayo Clinic Survey Research Center, assessed common patient symptoms including dry mouth and eyes, itching, and overall health. Current symptoms of dry mouth, dry eyes, and itching were assessed on a 5-point frequency scale: never, rarely, occasionally, frequently, all the time. Overall health was assessed on a 5-point wellness scale: excellent, very good, good, fair, and poor. MCPGE Registry patients that subsequently underwent liver transplantation since biochemical response assessment were excluded from analysis.

Statistical Analysis

Categorical data were analyzed using the chi-square test and continuous data were analyzed using the Wilcoxon rank sum test. Survival was estimated starting at 2 years following initiation of UDCA treatment when subjects were classified as responders or non-responders. Subjects were followed until death or transplant (event) or were censored at last follow-up. The probability of survival was estimated for up to 15 years using the Kaplan-Meier method. Expected death rates were estimated using the US population, and observed and expected survival curves were compared using the log-rank test [14]. The Cox proportional hazard assumptions were checked. The Cox model was used to assess survival differences for biochemical responses (responder/non-responder) after adjusting for age and sex. Multivariable Cox models were also fit to evaluate the effect of corresponding histologic class (early/late stage), an interaction between biochemical responses and histologic class, and TB. The analysis for this paper was generated using SAS and R software; a p -value < 0.05 was considered significant [15].

RESULTS

Biochemical Response to UDCA

Among the 613 PBC patients identified within the MCPGE Registry, a total of 398 (65%) patients met inclusion criteria for analysis, whereas 215 patients were excluded because of unknown treatment status, inadequate and/or unidentified duration of follow-up or insufficient laboratory parameters to assess biochemical response per the Toronto criteria (Figure 1). The application of the Toronto criteria at 2 years of treatment with UDCA identified 302 (76%) patients as responders and 93 (24%) patients as non-responders. All 613 PBC patients within the MCPGE Registry were further assessed for biochemical response according to the Barcelona and Paris I criteria (Table 1). Strict application of these individual criteria revealed a significantly reduced number of patients with definition specific UDCA biochemical response compared to the Toronto criteria within our cohort: 282 patients per Barcelona (46%) and 252 (41%) per Paris I criteria. Nonetheless, application of the Barcelona and Paris I criteria identified 146 (52%) and 178 (71%) patients as responders, respectively. The lower number of patients with available biochemical assessments within the MCPGE Registry was a result of inadequate clinical follow-up within one year with associated pertinent laboratory values. Therefore, we pursued further clinical assessment of PBC patients within MCPGE Registry utilizing the Toronto criteria definition for biochemical responders and non-responders.

The patients assessed using the Toronto criteria were of similar age at diagnosis (median = 52 years) compared with those who could not be assessed for the Toronto criteria (median = 51 years, $P = 0.83$). There were slightly more males among those included in the study versus those not (12% vs. 6% respectively, $P = 0.02$) and more early stage histologic class (65% vs. 55% respectively, $P = 0.04$).

Among the patients assessed with the Toronto criteria, age at PBC diagnosis was higher among biochemical responders (median = 52.7 years) vs. non-responders (median = 47.2 years, $P < 0.001$). The response groups were no different according to AMA level

(responders: median = 1.7 vs. non-responders = 1.8, $P = 0.19$) and AMA positivity (responders: 86% vs. non-responders: 93%, $P = 0.09$). There was also no statistical difference of sex composition among the groups; the responders included 90% females and non-responders 83% females ($P = 0.09$).

Regardless of the limitation of available data for Barcelona and Paris I criteria, we felt it was important to assess TB among included patients because of a history as strong predictor of poor outcomes in PBC. TB within 6 months of UDCA therapy initiation was available for 195 (65%) included responders and 68 (71%) non-responders. Among these patients, 15% of responders and 41% of non-responders had a TB higher than the upper normal limit ($P < 0.001$). Available liver biopsy stage within 6 months of diagnosis was available for 343 (86%) included patients. There were a total of 254 liver biopsies in responders, 69% of which showed evidence of early-stage and 31% late-stage disease on histology. In comparison, 89 biopsies were available for non-responders, 54% with early- and 46% with late-stage findings ($P = 0.04$).

Survival Analysis

Using the Toronto criteria, clinical follow-up was available for a median of 84 months for the responders and 99 months for the non-responders. The median transplant-free survival (the estimated time at which half of the subjects in the group have had a transplant or have died) was 244 months and 285 months for responders and non-responders. During the follow-up period, 9 responders underwent liver transplantation and 21 responders died from any cause (2 after transplantation). In comparison, among non-responders 22 patients received liver transplantation and 6 patients died (2 after transplantation). As shown in Figure 2, the survival rate of non-responders was significantly lower than that of responders (HR: 2.4, CI: 1.4–4.1, $P = 0.001$). The probability of survival without transplantation or death in responders was 96%, 90%, and 83% at 5, 10, and 15 years, whereas among non-responders the probability of survival without liver transplantation or death was 88%, 77%, and 57%, respectively.

Further analysis of transplant-free survival was completed accounting for stage of liver disease at diagnosis (available in 86% of included patients) among the different response groups. Among this subset of PBC patients with available stage data, transplant-free survival was significantly worse for non-responders compared to responders (HR: 2.0, CI: 1.1–3.7, $P = 0.02$, Figure 2) after adjusting for age, sex, and stage. Moreover, patients with late stage disease at PBC diagnosis had an worse transplant-free survival compared to those with early stage disease, regardless of the response status per the Toronto criteria (HR: 2.8, CI: 1.67–5.0, $P = 0.001$).

Responders and non-responders presenting with early stage disease at time of diagnosis did not differ statistically in regards to survival, although there was a trend for improved outcome among the responders ($P = 0.09$). Transplant-free survival for responders presenting with early stage disease was 99% at 5 years, 93% at 10 years, and 87% at 15 years. Comparatively, survival in non-responders presenting with early stage disease was 92%, 89%, and 53%, respectively. Patients presenting with late stage disease did show improved survival if they were responders to UDCA therapy ($P = 0.03$). Transplant-free

survival for responders presenting with late stage disease was 85% at 5 years, 80% at 10 years, and 61% at 15 years. Comparatively, among non-responders presenting with late stage disease it was 83%, 67%, and 48%, respectively (Figure 3). However, there was no evidence that the survival difference between responders and non-responders among those presenting with early stage disease was different from those presenting with late stage disease ($P = 0.32$). TB above normal limits prior to treatment start was also associated with worse transplant-free survival, yet available only in 231 (57%) of assessed PBC patients. A multivariable model including elevated TB revealed it also predicted transplant-free survival when controlling for age at diagnosis, sex, and disease stage at diagnosis (HR: 4.9, CI: 2.4 – 9.7, $P < 0.001$).

Adverse Events

Within the first two years following onset of treatment, 14 responders (5%) had developed an adverse event related to chronic liver disease. 8 (3%) developed varices, 4 (1%) developed ascites, 2 (1%) had evidence of encephalopathy, and none (0%) had diagnosis of hepatocellular cancer. Among non-responders, 5 (5%) developed varices, 1 (1%) developed ascites, and none had evidence of encephalopathy or hepatocellular cancer. The occurrence of any adverse event prior to Toronto assessment was not significantly different between responders and non-responders (6.0% vs. 6.3%, respectively; $P = 0.89$). After the two years following the onset of treatment (the time of Toronto assessment), an additional 31 responders developed varices, 13 developed ascites, 12 had evidence of encephalopathy, and 9 had diagnosis of hepatocellular cancer, whereas among non-responders an additional 21 developed varices, 18 developed ascites, 11 had evidence of encephalopathy, and 3 had diagnosis of hepatocellular cancer. Using only those subjects who had an adverse event within the first two years of treatment onset, and treating death and transplant as competing risks to the occurrence of adverse events, the 10 year cumulative incidence of adverse events among the responders was 15% and among the non-responders was 32% ($P = 0.06$). When adverse events were combined with death and transplant as the event of interest, non-responders had a higher event rate compared with responders (HR: 1.6, CI: 1.02 – 2.6, $P = 0.04$) after adjusting for age and sex. Non-responders had significantly more events compared to responders in regards to varices ($P = 0.04$) and ascites ($P < 0.001$).

In regards to stage, patients with early stage disease had a total of 37 adverse events seen in study follow-up compared to 67 events in patients with late stage no matter the biochemical response status. Interestingly, only 14 adverse events occurred among included patients without known liver stage at diagnosis.

Multivariate Analysis

Table 2 shows the multivariate analysis to assess independent predictors of transplant-free survival among factors shown to be associated with worse outcome at baseline including: younger age at PBC diagnosis, female sex, late stage disease at diagnosis, and biochemical nonresponse per the Toronto criteria ($n = 343$).

Itching and Health

29 (32%) non-responders and 157 (53%) responders returned the survey tool within 2 months of mailing ($P < 0.001$). Twelve patients (7%), 3 responders and 9 non-responders, were removed because of liver transplantation since assessment of biochemical response. The median time from biochemical response assessment and the itching and health survey was 9.8 years for responders and 12 years for the non-responders ($P = 0.52$). There were no difference between response groups according to assessment of overall health ($P = 0.49$) or frequency of dry mouth ($P = 0.54$) or eyes ($P = 0.9$). Non-responders had higher itching frequency ($P < 0.001$) as well as itching that made the skin raw ($P = 0.004$) compared to responders.

DISCUSSION

Our survival analysis demonstrates significant improvement of transplant-free survival among PBC patients of the MCPGE Registry if biochemical response to UDCA according to the Toronto criteria is met. Baseline factors associated with worse transplant-free survival include younger age at diagnosis, female sex, late-stage disease at diagnosis, and TB above upper normal limits within 6 months of treatment start. Our data reveal that despite advanced disease at diagnosis, achievement of biochemical response per the Toronto criteria will still improve overall transplant-free survival. This study also provides further analysis of stage and biochemical response to UDCA, revealing that the biochemical response does not differ by histologic stage (i.e., there was no evidence of an interaction) in a multivariable model. Finally, we show biochemical responders via the Toronto criteria have significantly fewer adverse events (i.e. ascites and varices) and have less clinical symptoms of itching in prolonged clinical follow-up.

We utilized the Toronto criteria; this easily applicable model was developed with histologic evidence of disease stability or progression in paired liver biopsies after dose appropriate UDCA therapy. The MCPGE Registry represents a large population of both early and late-stage presentations of PBC with extended and detailed clinical follow-up, as well as the only reported findings from the United States. Our results demonstrate that biochemical response to UDCA, as determined by the Toronto criteria, is significantly associated with transplant-free survival. As shown in Figure 2, biochemical non-responders had approximately 2.4 times the risk of progression to transplant or death over the follow-up period. Moreover, survival among biochemical responders was not statistically different from the expected North American survival rates ($P = 0.28$). We attempted to collect data to assess other published UDCA biochemical response criteria, however, the available laboratory data revealed a high degree of incompleteness. Only 46% and 41% of patients within our cohort had data sufficient to complete assessment of the Barcelona and Paris I criteria respectively (Table 1). Nonetheless, application of the Toronto criteria among our cohort did identify similar predictive factors of worse transplant-free survival as a recent large cohort of PBC patients from the United Kingdom (Paris I criteria) including male sex and younger age at diagnosis [16].

Histologic stage was available within 6 months of treatment start in 88% of included PBC patients. The extent of clinical follow-up along with histologic completeness makes this

population well suited to analyze for interactions between stage and biochemical response in regards to overall survival. Similar to prior reports [11], we show findings of late-stage histology (Ludwig stage III or higher) at diagnosis is an independent predictor of diminished transplant-free survival in PBC patients. However, there was no interaction between biochemical response and histologic stage ($P = 0.23$) and UDCA's effect on transplant-free survival remained independent of presenting histology. Selection bias in our study remains possible, however the proportion early- (64%) and late-stage (36%) of included patients were similar to that of those excluded (early, 55% vs. late, 45%, $P = 0.08$) (Figure 1). Our findings support a previous study by Corpechet [9], strongly reinforcing patients presenting with advanced liver disease at time of PBC diagnosis should start and continue dose appropriate UDCA therapy to improve transplant-free survival. Dissociation of the response and histologic stage before therapy initiation may highlight other contributory mechanisms by which UDCA exhibits its overall benefit to PBC patients.

Our study also provides evidence supporting a reduction in total overall adverse events related to liver disease (including ascites and varices) among UDCA biochemical responders (HR: 0.54, $P = 0.001$). However, 36% of all UDCA-treated patients were excluded due to inadequate clinical follow-up. Among this group, a total of 21 transplants, 2 deaths, and 0 adverse liver disease outcomes were recorded during a limited follow-up period. We believe study endpoints within this group are not necessarily comparable to patients included in our analysis given the possibility of advanced presentation resulting in a short duration (therefore exclusion) to liver transplant or poor follow-up resulting in less laboratory and clinical investigations. Our institution is a tertiary care facility; therefore patients seeking further evaluation after PBC diagnosis with evidence of early robust biochemical response likely do not return for follow-up and are managed at local facilities.

Prior studies evaluating biochemical response have not fully evaluated clinical outcomes and only focus on models that predict liver transplantation and death [8–10]. We found evidence of significant reduction in varices and development of ascites among patients identified as responders. However, we realize that physician clinical biases may exist in patients that do not have evidence of biochemical response or late-stage disease. It is feasible that patients with early-stage disease and biochemical response were screened (esophagogastroduodenoscopy and radiologic imaging) less often than their counterparts. The retrospective approach in our study limited the comparisons of total clinical assessments between these groups. This may have created a biased perspective, specifically since portal hypertensive outcomes have been seen in any stage of fibrosis in PBC patients [17].

Despite limitations with adverse event assessment, a small Canadian study [18] has shown a reduction in portohepatic gradient can be utilized to delineate UDCA responders. We were not surprised by less adverse events related to the development of portal hypertension seen in the biochemical response group when extrapolating this principle to our population. UDCA in responders may directly impact effective inflammation within the portal tract limiting portal venopathy and nodular regenerative hyperplasia, thereby decreasing portal pressures. Nonetheless, delineation of response to UDCA among PBC patients is critical, and our data suggests biochemical response may help identify patients that may require more intense clinical follow-up and screening measures.

Optimal clinical or biochemical response criteria that correlate to overall PBC patient survival continue to be paramount, although no clear criteria have been proven superior. These response models have been proposed as key in determining patients that may require novel therapies to improve clinical outcomes. We show that the Toronto criteria perform well to define biochemical responders and non-responders in the MCPGE Registry, however other predictors of transplant-free survival including age at PBC diagnosis, sex, stage at diagnosis, and total bilirubin before treatment have important predictor properties. Nonetheless, utilization of these models to ascertain responders and non-responders is an integral step for further elucidating PBC pathogenesis. PBC has been hypothesized a result of complex interactions between both environment and individual genetic factors. Therefore a better approach to discerning underlying pathways of biochemical response, or even predicting the course of disease pathogenesis, may lie within the assessment of individual genetic variants and environmental exposures.

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Abbreviations

PBC	Primary Biliary Cirrhosis
UDCA	Ursodeoxycholic Acid
MCPGE	Mayo Clinic PBC Genetic Epidemiology Registry
AMA	antimitochondrial antibody
AP	alkaline phosphatase
TB	Total Bilirubin
AST	Aspartate Aminotransferase

References

1. Gershwin ME, Mackay IR. The causes of primary biliary cirrhosis: Convenient and inconvenient truths. *Hepatology*. 2008; 47:737–45. [PubMed: 18098322]
2. Hirschfield GM, Invernizzi P. Progress in the genetics of primary biliary cirrhosis. *Semin Liver Dis*. 2011; 31:147–56. [PubMed: 21538281]
3. Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis. *Hepatology*. 2009; 50:291–308. [PubMed: 19554543]
4. Poupon RE, Balkau B, Eschwege E, et al. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. *N Engl J Med*. 1991; 324:1548–54. [PubMed: 1674105]
5. Lindor KD, Therneau TM, Jorgensen RA, et al. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. *Gastroenterology*. 1996; 110:1515–8. [PubMed: 8613058]
6. Poupon RE, Bonnand AM, Chretien Y, et al. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. *Hepatology*. 1999; 29:1668–71. [PubMed: 10347106]
7. Poupon R. Primary biliary cirrhosis: a 2010 update. *J Hepatol*. 2010; 52:745–58. [PubMed: 20347176]

8. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. *Gastroenterology*. 2006; 130:715–20. [PubMed: 16530513]
9. Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology*. 2008; 48:871–7. [PubMed: 18752324]
10. Kuiper EM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology*. 2009; 136:1281–7. [PubMed: 19208346]
11. Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *J Hepatol*. 2011; 55:1361–7. [PubMed: 21703194]
12. Kumagi T, Guindi M, Fischer SE, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. *Am J Gastroenterol*. 2010; 105:2186–94. [PubMed: 20502446]
13. Lazaridis KN, Juran BD, Boe GM, et al. Increased prevalence of antimitochondrial antibodies in first-degree relatives of patients with primary biliary cirrhosis. *Hepatology*. 2007; 46:785–92. [PubMed: 17680647]
14. Kalbfleisch, J.; Prentice, R. *The Statistical Analysis of Failure Time Data*. 2. Wiley; Interscience: 1980.
15. R Development Core Team. A language and environment for statistical computing. The R Project for Statistical Computing. 2011. www.r-project.org/
16. Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. *Gastroenterology*. 2013; 144:560–9. [PubMed: 23246637]
17. Ali AH, Sinakos E, Silveira MG, et al. Varices in early histological stage primary biliary cirrhosis. *J Clin Gastroenterol*. 2011; 45:e66–71. [PubMed: 20856137]
18. Huet PM, Vincent C, Deslaurier J, et al. Portal hypertension and primary biliary cirrhosis: effect of long-term ursodeoxycholic acid treatment. *Gastroenterology*. 2008; 135:1552–60. [PubMed: 18722374]

Figure 1. PBC patients included in analysis as biochemical responders and non-responders to UDCA therapy per the Toronto criteria

* AP value greater than 1.67 times the upper normal limit after 2 years of treatment with dose-appropriate UDCA. ** AP value of less than or equal to 1.67 times the upper normal limit after 2 years of treatment with dose appropriate UDCA

Figure 2. Transplant-free survival between responders and non-responders to UDCA according to the Toronto criteria

The HR (95% Confidence Interval) for non-responders, after adjusting for age at diagnosis and sex, is 2.4 (1.3–4.3). There was no significant difference comparing responders with the expected death rates of the US population assuming the same age and sex distribution ($p=0.28$).

Figure 3. Transplant-free survival between responders and non-responders to UDCA according Toronto criteria and disease stage at diagnosis

The HR for non-responders, after adjusting for age at diagnosis and sex, is 2.8 among those with an early stage of diagnosis and 1.4 among those with a late stage of diagnosis, though this difference between the HR is not statistically significant ($p=0.23$).

Table 1
Complete assessment of PBC patients according to biochemical response criteria

Biochemical response according to the Barcelona criteria was defined as a reduction in UDCA pretreatment levels of AP of more than 40% (normalized by the upper limit normal) or normal AP levels by 1 year of UDCA treatment. Responders according to the Paris I criteria were defined by concurrent AP $\leq$ 3 times upper normal limit, AST $\leq$ 2 times upper normal limit, and a normal TB level.

Biochemical Response Criteria	Number of Patients Meeting Individual Assessment Criteria within the MCPGE Registry	Number of Biochemical Responders per Criteria
Toronto	398 (65%)	302 (76%)
Barcelona	282 (46%)	146 (52%)
Paris I	252 (41%)	178 (71%)

Table 2

Multivariable time-to-event analysis including UDCA response per the Toronto criteria.

Variable	Hazard Ratio	95% Confidence Interval	P-value
Age at PBC diagnosis, per 10 year increase	0.95	0.70 – 1.29	0.75
Sex, male	2.01	1.002 – 3.98	0.04
Late stage disease at diagnosis	2.74	1.52 – 4.94	< 0.001
Elevated total bilirubin at diagnosis	4.9	2.4 – 9.7	< 0.001
Biochemical non-responder	1.87	1.02 – 3.41	0.04