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Ursodeoxycholic Acid Therapy in Pediatric Primary Sclerosing Cholangitis: Predictors of Gamma Glutamyltransferase Normalization and Favorable Clinical Course

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Abstract

Objective: To investigate patient factors predictive of gamma glutamyltransferase (GGT) normalization following Ursodeoxycholic acid (UDCA) therapy in children with primary sclerosing cholangitis (PSC).

Study design: We retrospectively reviewed patient records at 46 centers. We included patients with a baseline serum GGT level ≥50 IU/L at PSC diagnosis, who initiated UDCA therapy within one month and continued therapy for at least 1 year. We defined 'normalization' as a GGT level < 50 IU/L without experiencing portal hypertensive or dominant stricture events, liver transplantation or death during the first year.

Results: We identified 263 patients, median age 12.1 years at diagnosis, treated with UDCA at a median dose of 15 mg/kg/day. Normalization occurred in 46%. Patients with normalization had a

lower prevalence of Crohn's disease, lower total bilirubin level, lower AST to Platelet Ratio Index, higher platelet count, and higher serum albumin level at diagnosis. The 5-year survival with native liver was 99% in those patients who achieved normalization vs 77% in those who did not

Conclusions: Less than half of the patients treated with UDCA have a complete GGT normalization in the first year after diagnosis, but this subset of patients has a favorable five-year outcome. Normalization is less likely in patients with a Crohn's disease phenotype or a laboratory profile suggestive of more advanced hepatobiliary fibrosis. Patients who do not achieve normalization could reasonably stop UDCA, as they are likely not receiving clinical benefit. Alternative treatments with improved efficacy are needed, particularly for patients with already-advanced disease.

Keywords

Juvenile; Cholestasis; Autoimmune; Surrogate Endpoint; Treatment

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease characterized by progressive destruction of the bile ducts.[1] Within 10 years of diagnosis, 30% of children with PSC will require liver transplantation and 50% of children will develop complications, including biliary stricturing and portal hypertension[2]. To date there is no medical intervention proven to prolong patient survival[3]. PSC is recognized as one the largest unmet needs in hepatology[4].

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid with hepatobiliary cytoprotective and immune-modulating effects[5–7]. The role of UDCA in modifying disease behavior in PSC and prolonging patient survival is controversial. UDCA has not been shown to improve patient survival in adult clinical trials[8–12]. Given the unclear benefit, as well as a possibility that higher doses of UDCA may cause harm[12], the current practice guideline of the American Association of the Study of Liver Diseases (AASLD) recommends against the use of UDCA in adults with PSC[13]. There are no formal guidelines for the use of UDCA in children with PSC.

A subset of adults normalize serum alkaline phosphatase levels during UDCA therapy and have improved survival compared with those with persistently elevated levels[14–16]. We showed an analogous effect in children with PSC using gamma glutamyl transferase (GGT) as a biomarker[17]. Children whose GGT declined to < 50 IU/L at one year after PSC diagnosis had favorable long-term outcomes. Untreated patients who spontaneously normalized serum GGT levels also had good outcomes. The proportion of patients who achieved GGT normalization was higher in those treated with UDCA however, with an approximate number needed to treat of four patients to achieve one normalization that would not have occurred on its own. Thus, there appears to be a subgroup of children treated with UDCA who have a favorable response. UDCA is the most common medication used in children with PSC, with over 80% currently receiving long-term therapy[2,18]. More data is needed to better define which patients may be receiving a clinical benefit from UDCA therapy. There are presently no predictors of which patients will respond. The aim of this study was to identify baseline differences between children with complete vs. incomplete biochemical normalization on UDCA.

Methods:

The Pediatric PSC Consortium is an active research collaboration that includes 49 centers in Europe, North America, the Middle East, and Asia. We retrospectively reviewed medical records on all known PSC patients with disease onset prior to 18 years of age at each institution, as previously described[2]. For each patient we collected data on basic demographics, and diagnostic cholangiography and histopathology studies. We collected laboratory data at liver disease diagnosis and approximately one year later (within 46–58 weeks after diagnosis). To account for the wide range of normal alkaline phosphatase (ALP) values in children at various ages due to bone turnover and growth, we normalized all values for age using Mayo Medical Laboratories reference values[19].

The diagnosis of PSC required elevated hepatobiliary inflammatory markers (GGT or aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) and/or bilirubin. When characteristic changes on cholangiography were seen, large duct PSC was diagnosed. When cholangiography was normal but liver histopathology showed typical changes, small duct PSC was diagnosed[13]. Cases of sclerosing cholangitis secondary to any other cause were excluded.

Autoimmune hepatitis (AIH) was diagnosed in patients who met the simplified AIH criteria, which have been validated in children[20], based on histopathology, positive autoantibodies, elevated serum globulins and exclusion of viral hepatitis. We documented the presence and type of associated inflammatory bowel disease (IBD).

We created a retrospective cohort of all patients followed from date of PSC diagnosis to the date of several clinical endpoints: 1. the development of portal hypertensive complications (ascites, hepatic encephalopathy, or esophageal varices with or without bleeding); 2. biliary complications (a clinical picture of biliary obstruction as evidenced by a biliary stricture requiring an intervention in the form of endoscopic or percutaneous stenting, balloon dilation, or drainage); 3. Cholangiocarcinoma; 4. liver transplantation; or 5. death from liver disease. Survival free of any of these endpoints was termed event-free survival. Patients were censored at the date of last known follow-up. We excluded patients who presented with portal hypertensive or biliary complications within 3 months of PSC diagnosis from this analysis, because their baseline laboratory studies were likely reflective of the outcomes of interest already being present. Data was abstracted and de-identified at local study sites and reviewed and stored centrally. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Utah[21].

In this analysis, we included patients with baseline serum GGT level > 50 IU/L, who started UDCA within one month of PSC diagnosis and continued taking it for at least one year. We defined ‘normalization’ as a decline in GGT to ≤ 50 IU/L without experiencing clinical endpoints during the first year. The threshold of 50 IU/L for GGT represents 1–2 times the upper limit of normal for most non-infant pediatric age groups at most laboratories and was validated as an endpoint in our prior study[17]. We compared baseline demographic, phenotypic and laboratory data between these 2 groups. We assessed differences in the

change in laboratory studies between diagnosis and at one year. We compared transplant-free survival after 1 year between groups.

The Wilcoxon rank sum and chi squared tests were used to assess differences between groups. We used the Kaplan-Meier method to calculate annual outcome probabilities. The Logrank test assessed survival differences between groups. Logistic regression was used to assess the association between baseline predictor variables and treatment success or failure. Variables with *P* value < .1 in univariate analyses were included in a multivariate model. The model was optimized using variance inflation factor diagnostics, removing any collinear variables. Calculations were done using Stata version 15 (StataCorp, College Station, TX). All research work was approved by the institutional review board of each participating center.

Results:

We identified 344 patients with a serum GGT level > 50 IU/L at diagnosis who had laboratory data one year later. We excluded 63 patients who did not receive UDCA treatment and 18 patients with clinical complications at or within 3 months after diagnosis. The remaining 263 patients (60% male, median age 12.1 years old, median GGT 290 (IQR 163–431) were followed for a median of 5.4 years with a total of 1736 person-years of observation. The median UDCA dose administered was 15 mg/kg/day [IQR: 15–19].

Serum GGT normalization occurred in 46% (122/263) of patients. In the remainder, non-normalization occurred in 16% (23/141) due to occurrence of clinical events and in 84% due to persistently elevated GGT at one year. Patients with normalization vs. non-normalization had similar PSC phenotypes. At diagnosis however, the response group had a lower prevalence of Crohn's disease, lower total bilirubin, lower AST to Platelet Ratio Index (APRI), higher platelet count, and higher serum albumin (Table 1). In addition to the primary endpoint of GGT reduction, the normalization group experienced larger improvements in ALT, AST, ALP and APRI compared with those with non-normalization in the year after PSC diagnosis (Table 2).

The presence or absence of a Crohn's disease IBD phenotype, as well as baseline platelet count, total bilirubin and albumin at diagnosis showed significant univariate correlation with treatment response (Table 3; available at www.jpeds.com). After regression diagnostics including all variables with p<0.10 in univariate analysis, hemoglobin was removed for excessive covariance. In the final multivariate model, a Crohn phenotype decreased the odds of normalization. Increased platelet count and serum albumin significantly increased the odds of a normalization (Table 4; available at www.jpeds.com).

Long-term survival with native liver after one year was better in the normalization group than the incomplete response group (Figure 1). Following the first year of UDCA treatment, the annual event rate (deaths or liver transplants per group per year) was 0.7%/year in the normalization group vs. 4.3%/year in the non-normalization group, Logrank p<0.001. The 5-year survival with native liver was 99% [95%CI 94–100] in those with normalization, compared with 77% [95%CI 68–84] in those who did not normalize, p<0.001.

Amongst those who did not normalize GGT on UDCA who did not experience an adverse clinical event within the first year, event-free survival from years 1–6 was different based on the percentage GGT reduction achieved by one year (Figure 2). There was a trend towards the best event-free survival for patients with the largest relative GGT reductions between diagnosis and year one. Those with a > 75% reduction in GGT, compared with a < 25% reduction in GGT, had an 88% vs. 52% event-free survival over the next five years, p=0.055.

Discussion:

Although only a minority of children experience normalization of their serum GGT level in response to UDCA therapy, those who do show a decreased likelihood of liver transplant or death during follow-up. We identified clinically-relevant patient factors at baseline associated with non-normalization on UDCA treatment including a Crohn's disease IBD phenotype, relative thrombocytopenia, hypoalbuminemia, or hyperbilirubinemia, and increased APRI, a surrogate marker of fibrosis.

The 46% normalization rate observed in this study is similar to a 41% biochemical response seen in an adult prospective trial of UDCA[15]. In our pediatric cohort, outcomes were best in those with GGT < 50 IU/L at one year after diagnosis. Even amongst those with GGT ≥ 50 IU/L at one year, outcomes were better with progressively larger reductions in GGT between diagnosis and one year. Those who had a reduction in GGT of .> 75% had nearly the same long-term survival as those with GGT < 50 IU/L at one year. This data further supports the utility of GGT reduction as a candidate surrogate endpoint for future clinical trials. Clinically, children with PSC on long-term UDCA who have not had a >75% reduction in GGT or complete normalization of GGT can stop the medicine as they are unlikely to be receiving a clinical benefit and could minimize unnecessary drug exposure.

Of note, we do not know how many of the UDCA-treated patients would have had spontaneous GGT normalization and no adverse liver events without UDCA therapy. We previously showed that nearly one third of children who are UDCA-naïve have spontaneous GGT normalization by one year. These untreated patients' long-term survival outcomes are indistinguishable from UDCA-treated patients with GGT normalization[17]. A larger proportion of UDCA-treated patients achieved GGT normalization however. The number of PSC patients who would need to be treated with UDCA to achieve one case of GGT normalization that would not have occurred spontaneously without treatment was approximately four (number needed to treat = 4). A recent clinical trial evaluated the impact of UDCA withdrawal from children with PSC who had been on chronic therapy with normal liver biochemistries. Upon complete withdrawal of the medication for 12 weeks, one third of patients maintained serum GGT level < 29 IU/L[22]. Whether the third of patients who may have spontaneously normalized GGT and the third of patients who maintained a normal GGT upon complete withdrawal of UDCA represent the same group is speculative, but it is likely that a large proportion of children on chronic UDCA are receiving no clinical benefit. More data on the natural history of GGT in UDCA-exposed and unexposed patients within the first 3 to 6 months after diagnosis are needed to determine the optimal length of a trial of UDCA therapy.

Liver disease phenotype was not associated with normalization: patients with large and small duct disease had equivalent normalization rates, and the presence of autoimmune hepatitis overlap features did not affect outcome. Similarly, no phenotypic differences were observed in UDCA complete vs. incomplete biochemical changes in an adult randomized-controlled trial[10]. Biochemical differences between groups at baseline suggest that patients with more extensive hepatobiliary fibrosis were less likely to achieve normalization on UDCA. There was a consistent trend across several markers: decreased serum albumin and platelet count, and increased APRI and bilirubin in non-normalizers. Length of time with PSC before diagnosis is likely an important, but ultimately unmeasurable, factor. Patient age at diagnosis was similar in response and incomplete response groups. We speculate that there may be additional subphenotypes of PSC that are more slowly-progressive and more responsive to therapy, perhaps based on microbiome or metabolome profiles.

Crohn's disease had a negative impact on the probability of normalization. This was in contrast to the association between Crohn's disease and a favorable PSC prognosis in general. The presence of IBD overall (either ulcerative colitis or a Crohn's disease phenotype) is a favorable predictor of outcome in pediatric PSC[2], and a Crohn's disease phenotype was a favorable predictor in adult PSC[23]. patients with Crohn's disease may be more likely to receive immunomodulatory or biologic medicines than patients with ulcerative colitis (UC) or those with no IBD, though such medicines have not shown a survival detriment or benefit in PSC[24,25]. Differences in the microbiome of patients with Crohn's disease may not favor useful, disease-modifying metabolism of UDCA in some patients. Indeed, PSC-Crohn, PSC-UC, and PSC patients with no IBD each have distinct microbiota signatures[26], with underrepresentation of Butyricoccus species in PSC-Crohn compared with the others. the microbiome may impact for PSC progression itself and, metabolism of and potential responsiveness to UDCA. Additional research is needed to more fully characterize the relative effectiveness of medical therapies for PSC in patients with different microbiome profiles and across the spectrum of objectively-staged hepatobiliary fibrosis and duct stricturing.

A strength of this study was its large size and inclusion of patients from a diverse mix of secondary and tertiary referral centers. There are weaknesses to this study. The retrospective design prevented a standardized diagnostic and therapeutic algorithm, and misclassification bias may be present. We did not have data on compliance with prescribed UDCA, which may have been poor especially in teenage patients. GGT and general biochemistry was only available at the time of diagnosis and one year later. Data at earlier time points to report on rapidity of GGT improvement was not available. Similarly, longer-term data are needed to define the durability of GGT normalization on and off chronic UDCA therapy. Future studies should control for the severity of intestinal disease and concomitant immunosuppression for IBD and autoimmune hepatitis, which we were unable to do here. Finally, objective markers of disease severity and response are needed, including performing liver biopsy and cholangiography before and during therapy. These data are part of a larger, more extensive data collection that is currently underway within the Pediatric PSC Consortium to address these shortfalls.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations (in order of appearance):

PSC	primary sclerosing cholangitis
UDCA	ursodeoxycholic acid
GGT	gamma glutamyl transferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ALT	alanine aminotransferase
AIH	autoimmune hepatitis
IBD	inflammatory bowel disease
APRI	aspartate aminotransferase to platelet ratio index
UC	ulcerative colitis

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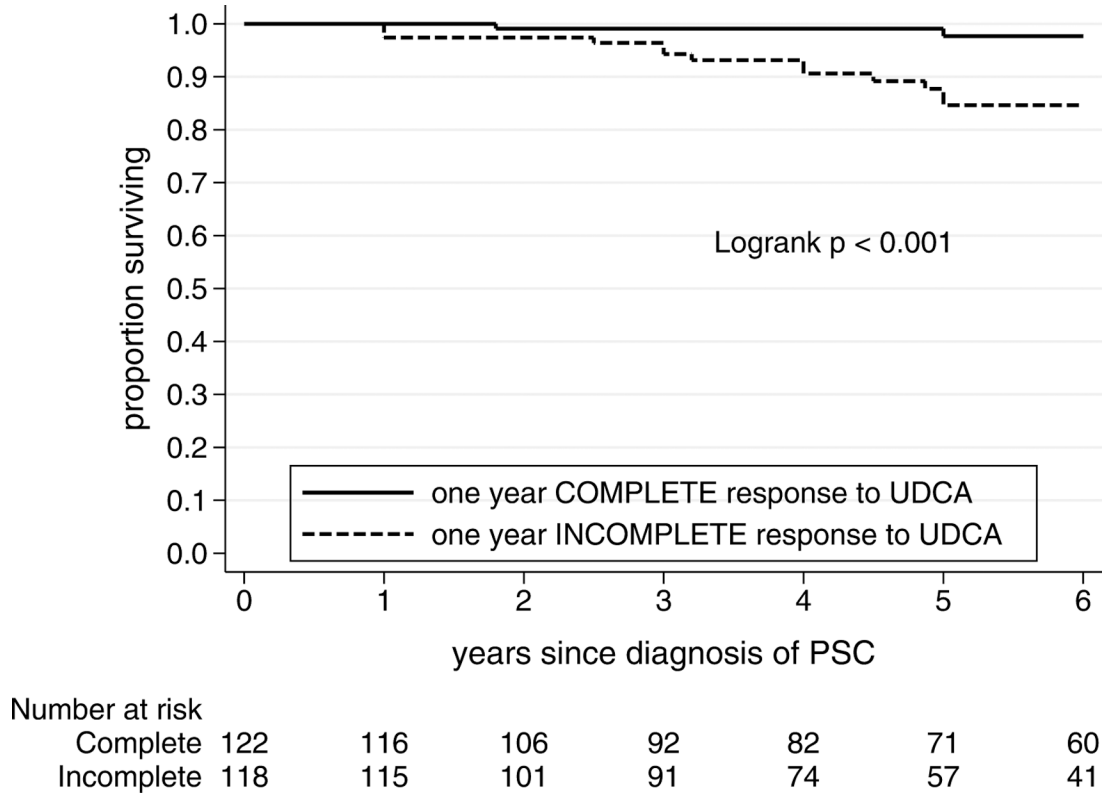
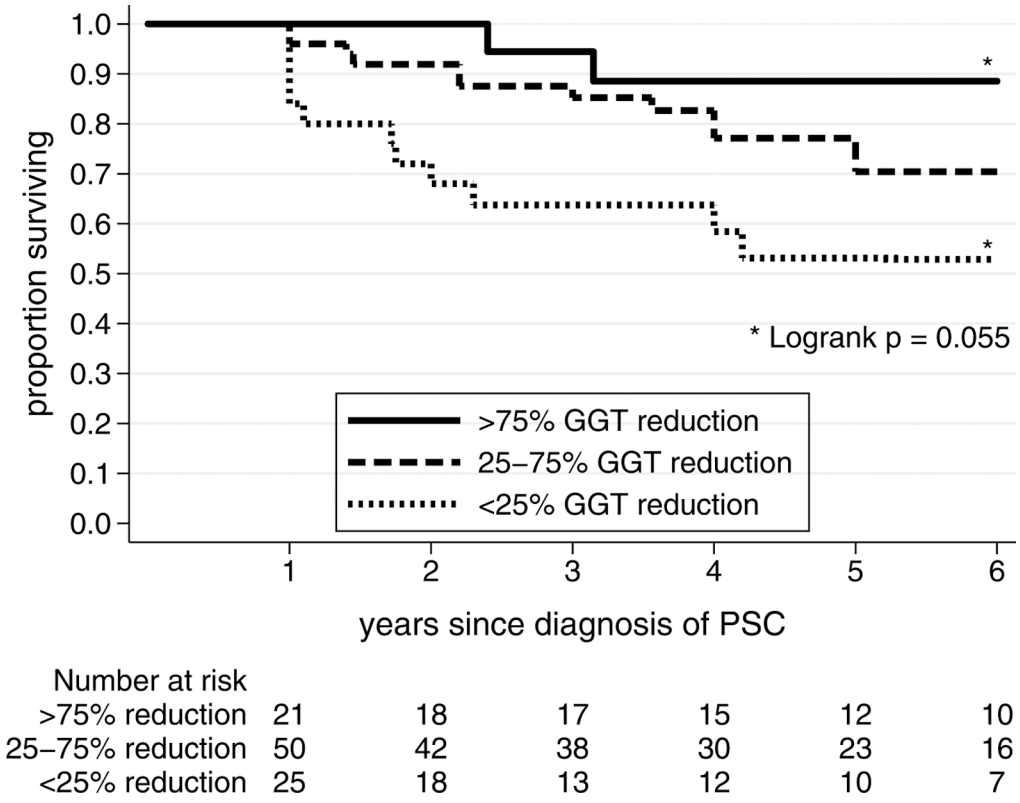


Figure 1.
Long-term survival with native liver in ursodeoxycholic acid treated patients



Number at risk						
>75% reduction	21	18	17	15	12	10
25–75% reduction	50	42	38	30	23	16
<25% reduction	25	18	13	12	10	7

Figure 2:

Event-free survival after one year in patients with incomplete biochemical response to ursodeoxycholic acid, stratified by percentage reduction in GGT from baseline.

Table 1:

Baseline phenotypic and laboratory data

	Normalization n=122	Non-normalization n=141	p
Age (years)	12.0 [7.8–15]	12.4 [8.6–15]	0.416
Gender (% male)	60%	60%	0.941
Ulcerative colitis (% with)	**74%**	**59%**	**0.012**
Crohn disease (% with)	**10%**	**18%**	**0.017**
No IBD (% with)	16%	23%	0.203
Autoimmune hepatitis (%)	39%	39%	0.955
Large duct phenotype	73%	76%	0.586
Hemoglobin (g/dL)	12.4 [11.5–13.2]	12.1 [11–13.4]	0.137
Platelet count (k/uL)	**325 [260–438]**	**298 [196–375]**	**<0.001**
INR	1.1 [M.2]	1.1 [1–1.2]	0.331
ALT(U/L)	167 [87–297]	146 [87–229]	0.278
AST (U/L)	125 [71–226]	140 [78–192]	0.697
ALP (U/L)	406 [281–720]	448 [275–717]	0.918
ALP (× ULN)	1.0 [0.7–1.6]	1.0 [0.6–1.5]	0.461
GGT (U/L)	290 [148–427]	290 [192–465]	0.158
Total Bilirubin (mg/dL)	**0.7 [0.4–1]**	**0.9 [0.5–1.6]**	**0.002**
Albumin (g/L)	**4.1 [3.7–4.5]**	**3.9 [3.6–4.3]**	**0.008**
APRI	**0.9 [0.5–1.9]**	**1.3 [0.7–2.3]**	**0.023**

Table 2:

Change in biochemistry over one year of ursodeoxycholic acid treatment

	Normalization n=122	**Non-normalization n=141**	**p**
Hemoglobin (g/dL)	+0.8 [−0.4 to +1.6]	+0.6 [−0.4 to +1.5]	0.382
Platelet count (k/uL)	−34 [−114 to +5]	−32 [−87 to +22]	0.132
INR	0 [−0.1 to +0.1]	0 [−0.1 to +0.2]	0.600
ALT (U/L)	**−141 [−266 to −59]**	**−70 [−165 to +3]**	**<0.001**
AST (U/L)	**−92 [−197 to −40]**	**−62 [−151 to −7]**	**<0.001**
ALP (U/L)	**−278 [−411 to +2]**	**−129 [−618 to +80]**	**<0.001**
ALP(× ULN)	**−0.6 [−1.3 to −0.2]**	**−0.3 [−0.9 to 0]**	**<0.001**
GGT (U/L)	**−258 [−406 to −127]**	**−142 [−271 to −42]**	**<0.001**
Total Bilirubin (mg/dL)	−0 [−0.4 to +0.2]	+0.1 [−0.7 to +0.2]	0.567
Albumin (g/L)	+0.2 [−0.1 to +0.6]	+0.1 [−0.3 to +0.4]	0.038
APRI	**−0.7 [−1.6 to −0.2]**	**−0.4 [−1.3 to 0]**	**0.023**

Table 3:

Univariate regression analysis of baseline predictors of normalization on ursodeoxycholic acid

	Univariate Odds Ratio	p
Age	0.97	0.328
Gender	0.98	0.941
UC	1.35	0.235
Crohn	**0.41**	**0.026**
No IBD	0.57	0.094
AIH	1.01	0.955
Large duct phenotype	0.84	0.586
Hemoglobin	1.15	0.071
Platelet count	**1.43**	**<0.001**
INR	0.82	0.795
ALT	1.00	0.660
AST	1.00	0.710
ALP	0.99	0.943
ALP	1.01	0.906
GGT	0.99	0.092
Total Bilirubin	**0.87**	**0.005**
Albumin	**1.84**	**0.008**
APRI	0.95	0.155

Table 4:

Multivariate model of baseline predictors of normalization on ursodeoxycholic acid

	Multivariate Odds Ratio	p
Crohn (vs. UC or no IBD)	**0.33**	**0.012**
Platelet count (per 100,000 k/uL)	**1.55**	**<0.001**
GGT (per U/L)	0.99	0.119
Total Bilirubin (per mg/dL)	0.88	0.167
Albumin (per g/dL)	**1.98**	**0.009**