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Original Article

Clinical Outcomes and Validation of Ursodeoxycholic Acid Response Scores in Patients with Korean Primary Biliary Cholangitis: A Multicenter Cohort Study

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Background/Aims: The ursodeoxycholic acid (UDCA) response score (URS) was developed to identify poor responders to UDCA before treatment, in order to offer timely and proactive intervention. However, validation of the URS in Asian population is warranted.

Methods: A total of 173 Asian patients diagnosed with primary biliary cholangitis (PBC) between 2007 and 2016 at seven academic institutions in Korea who started UDCA treatment were analyzed to validate the performance of URS. UDCA response was defined as an alkaline phosphatase level less than 1.67 times the upper limit of normal after 1-year of UDCA treatment. In addition, prognostic performance of URS for liver-related events, defined as newly developed hepatic decompensation or hepatocellular carcinoma was evaluated.

Results: After 1 year of UDCA treatment, 133 patients (76.9%) achieved UDCA response. UDCA response rate was 98.7% for those with URS ≥1.41 (n=76) and 58.8% for those with URS <1.41 (n=97). The area under the receiver operating characteristic curve of URS in predicting UDCA response was 0.84 (95% confidence interval, 0.78 to 0.88). During a median follow-up of 6.5 years, liver-related events developed in 18 patients (10.4%). Among 117 patients with PBC stage I-III by histological evaluation, the 5-year liver-related event-free survival rate differed according to the URS; 100% for URS ≥1.41 and 86.5% for URS <1.41 (p=0.005).

Conclusions: URS demonstrated good performance in predicting a UDCA treatment response in Asian PBC patients. In addition, the risk of liver-related events differed according to the URS for the PBC stage. Thus, URS can be used to predict the response and clinical outcome in patients with PBC. **(Gut Liver 2023;17:620-628)**

Key Words: Primary biliary cholangitis; Ursodeoxycholic acid; Ursodeoxycholic acid response score; Prognosis

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic inflammatory autoimmune cholestatic liver disease that can result in end-stage liver disease with associated complications and increase the risk of developing hepatocellular carcinoma (HCC).[1-4] PBC should be suspected if a patient shows persistent alkaline phosphatase (ALP) elevation. It can be diagnosed based on biochemical evidence of cholestasis, positive immunological markers and/or histological evi-

dence.[1,2] Although liver biopsy is not mandatory for the diagnosis of PBC,[5] histological features of PBC can stratify the risk of liver transplantation and liver-related mortality in PBC patients since advanced stages are associated with poor prognosis.[6,7]

Ursodeoxycholic acid (UDCA) is the first-line treatment of PBC. Several studies have shown that UDCA can delay histologic progression and improve transplantation-free survival.[8-10] Current guidelines recommend that all patients should begin treatment with UDCA, and those with an inadequate biochemical response after 1 year should be considered for second-line therapies.[1,2] Multiple biochemical response criteria of UDCA treatment have been reported. GLOBE and UK-PBC scores were developed to predict the risk of liver transplantation or liver-related mortality of PBC.[11-13] However, these scores use laboratory parameters after 1 year of UDCA treatment.

At present, there are no reliable means to identify patients before treatment who are unlikely to respond to UDCA and determine who might benefit from an early introduction of second-line therapy. UDCA response score (URS) is a recently developed scoring system that uses only pretreatment parameters to predict UDCA treatment response without waiting for 1 year to see a biochemical response.[14] URS was developed and validated in Caucasians.[14] However, there has been limited information on Asian patients. Therefore, we conducted a multicenter cohort study to validate URS for predicting UDCA response and evaluated whether URS could predict prognosis as well.

MATERIALS AND METHODS

1. Study design, setting, and participants

This is a retrospective cohort study performed at seven academic institutions in South Korea. Between January 2007 and December 2016, a total of 234 newly diagnosed PBC patients who started UDCA treatment were screened. PBC was defined by the presence of at least two of the following diagnostic criteria:[2] (1) elevated serum ALP levels, defined as more than 1.5 times of the upper limit of normal (ULN); (2) serum antimitochondrial antibody (AMA) positive; and (3) nonsuppurative cholangitis and destruction of small bile ducts on histologic evaluation. Among them, we excluded 37 patients who met the following exclusion criteria: (1) age less than 18 years; (2) patients with chronic hepatitis B or chronic hepatitis C; (3) excessive alcohol intake, defined as consuming more than the threshold of one drink per day for women and two drinks per day for men; (4) history of malignancy or liver transplantation; (5) patients with overlap syndrome who presented at least two of the Paris criteria: (a) alanine aminotransferase (ALT) >5×ULN, (b) immunoglobulin G >2×ULN and/or positive anti-smooth muscle antibody, (c) liver histology with moderate or severe interface hepatitis; and (6) presence or history of hepatic decompensation (ascites, variceal bleeding and/or hepatic encephalopathy). In addition, we excluded 24 patients who were lost to follow-up within a year from diagnosis of PBC. Finally, a total of 173 adult PBC patients without hepatic decompensation or

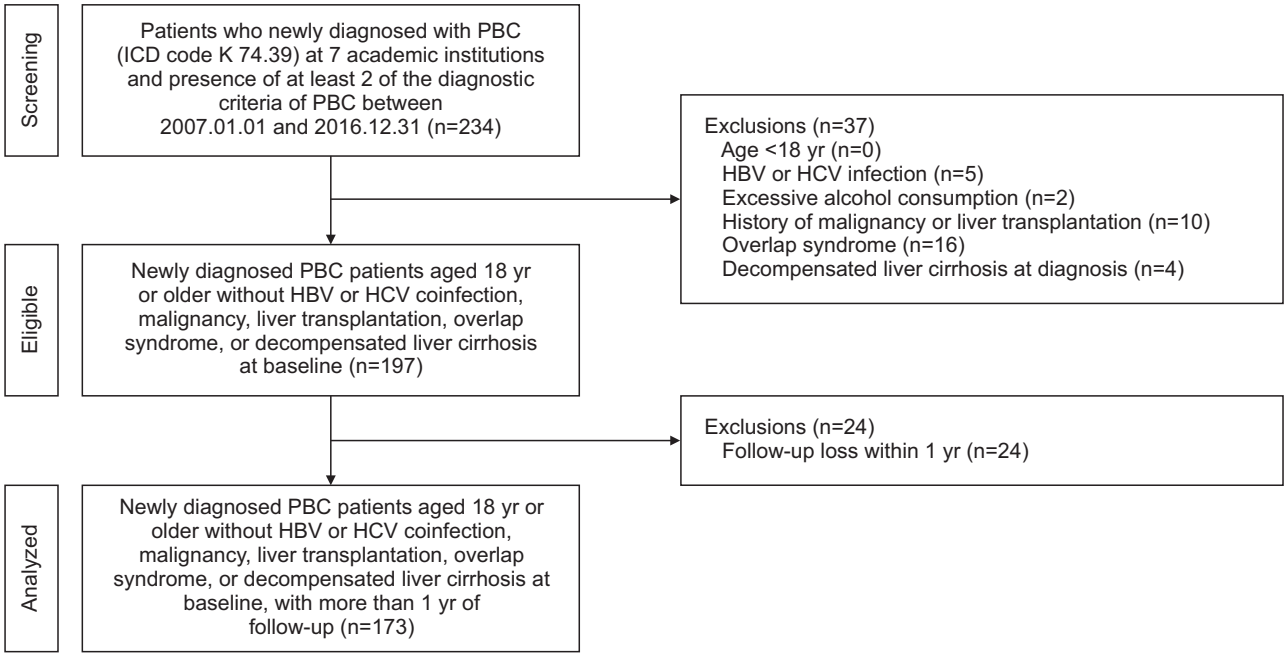

Fig. 1. Flowchart showing the study population.
PBC, primary biliary cholangitis; ICD, International Classification of Diseases; HBV, hepatitis B virus; HCV, hepatitis C virus.

malignancy who started UDCA treatment were analyzed (Fig. 1). The study protocol was reviewed and approved by each institutional review board including Samsung Medical Center (IRB number: 2021-10-145). Because this study was based on a retrospective analysis of existing clinical data, the institutional review board waived the requirement for informed patient consent.

2. Study outcome, variables, and definitions

The primary outcome was UDCA response, defined as an ALP level less than 1.67 times the ULN after 1 year of UDCA treatment.[14] Secondary outcomes were UDCA response, defined as ALP level less than 1.0, 1.5, or 2.0 times ULN after 1 year of UDCA treatment, and liver-related event-free survival, defined as development of hepatic decompensation and/or HCC during follow-up. Hepatic decompensation was defined as newly developed ascites requiring diuretics or paracentesis, hepatic encephalopathy necessitating hospitalization, or esophagogastric variceal bleeding. For liver-related event-free survival, the follow-up period was defined as the time between PBC diagnosis and the occurrence of liver-related events or the end of the study, whichever came first. The reference date was June 30, 2021.

The original URS formula is as follows:[14] URS=0.77+0.60×($\sqrt{\text{total bilirubin at diagnosis [× ULN]}}$)$^{-1}$–2.73×ln (ALP at diagnosis [×ULN])+0.35×ln (ALT at diagnosis [×ULN])+0.03×age [yr]–0.15×(time from diagnosis to the start of treatment [yr])–0.56×(change in ALP concentration from diagnosis to the start of treatment [×ULN]).

In our cohort, all patients started UDCA at the time of PBC diagnosis. Consequently, we used URS with a time lag set to 0 and a change in ALP set to 0. We also calculated the modified URS developed using only data from the treatment start date. The formula is as follows:[14] modified URS=0.76+0.56×($\sqrt{\text{total bilirubin at diagnosis [× ULN]}}$)$^{-1}$–2.77×ln (ALP at diagnosis [×ULN])+0.49×ln (ALT at diagnosis [×ULN])+0.03×age (yr). The following variables were extracted from electronic medical records: age at diagnosis, sex, body weight, initial dose of UDCA per day, AMA positivity, histologic findings, serum platelet counts, prothrombin time, albumin, total bilirubin, aspartate aminotransferase, ALT, ALP, and gamma-glutamyl transferase at diagnosis, and serum platelet counts, albumin, total bilirubin, ALT, and ALP at 1 year after UDCA treatment. Based on histologic findings, PBC was classified as stages I-IV: stage I, portal inflammation and florid ductal lesions; stage II, portal inflammation, focal interface hepatitis, and bile ductular proliferation; stage III, distortion of the hepatic architecture with numerous fibrous septa; and stage IV, cirrhosis.[2] For the upper or lower limit of the normal value of albumin, bilirubin, aspartate aminotransferase, ALT, ALP, and gamma-glutamyl transferase levels, we used normal ranges of each variable provided by each institution.

3. Statistical analysis

Values are presented as median (interquartile range) or frequency (percentage). For comparing continuous variables such as laboratory parameters before and after UDCA treatment, the Wilcoxon rank-sum test was applied because a substantial deviation from normality was detected. Categorical variables were compared using the chi-square test. The Kaplan-Meier method was used to calculate and plot liver-related event-free survival probability. The difference in survival rates between groups was analyzed using log-rank tests. The predictive performance was assessed by calculating and plotting the area under the receiver operating characteristic curve (AUROC) and estimating the 95% confidence interval (CI) with stratified bootstrapping. Optimal cutoff values of URS for UDCA response were determined according to the Youden index (maximum sum of sensitivity and specificity). All analyses were two sided. Statistical significance was defined at p-value less than 0.05. Statistical analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Clinicopathological characteristics

The clinicopathological characteristics of study participants are shown in Table 1. The median age of the study population was 55 years. Women accounted for 88%. AMA was positive in 95% of patients. Data of liver biopsies were available for 125 patients. Of them, eight had stage IV cirrhosis at the time of diagnosis. Seventy patients (40.5%) took the recommended UDCA dose (13 to 15 mg/kg/day), 52 patients (30.1%) took an underdose (13 mg/kg/day), and 51 patients (29.5%) took an overdose (>15 mg/kg/day).[2] When laboratory parameters before and after 1 year of UDCA treatment were compared, the median ALP level decreased from 2.27 times to 1.06 times of the ULN.

2. Performance of URS in predicting UDCA response

After 1 year of UDCA treatment, 76.9% achieved UDCA response (ALP <1.67 times ULN). When stratified according to quartile of URS, UDCA response rate was 46.5%, 67.4%, 90.9% and 100% for those with URS of –3.20 to 0.13, 0.13 to 1.05, 1.05 to 2.03, and 2.03 to 4.67, respectively (Table 2). The AUROC of URS in predicting UDCA response (ALP <1.67 times ULN) was 0.84 (95% CI, 0.78

Table 1. Subject Clinicopathological Characteristics

Characteristic	At diagnosis (n=173)	At 1 yr (n=173)	p-value
Age, yr	55.2 (49.1–63.0)	-	-
Female sex	152 (87.9)	-	-
Body weight at diagnosis, kg	57.0 (52.8–63.0)	-	-
AMA positive	164 (94.8)	-	-
Platelet counts, ×10³/μL	214 (170–260)	204 (155–255)	<0.001
PT INR	0.98 (0.91–1.04)	-	-
Albumin, ×LLN	1.20 (1.14–1.26)	1.23 (1.17–1.28)	<0.001
Total bilirubin, ×ULN	0.58 (0.42–0.83)	0.50 (0.42–0.71)	<0.001
AST, ×ULN	1.71 (1.24–2.80)	-	-
ALT, ×ULN	1.67 (1.03–2.48)	0.70 (0.48–1.12)	<0.001
ALP, ×ULN	2.27 (1.56–3.20)	1.06 (0.82–1.62)	<0.001
GGT, ×ULN	5.75 (3.40–9.95)	-	-
UDCA dose, mg/kg	14.0 (12.0–16.0)	-	-
<13	52 (30.1)		
13–15	70 (40.5)		
>15	51 (29.5)		
Liver biopsy (n=125)	125 (72.3)	-	-
PBC stage I	26 (20.8)		
PBC stage II	37 (29.6)		
PBC stage III	54 (43.2)		
PBC stage IV	8 (6.4)		

Data are presented as median (interquartile range) or number (%).
AMA, antimitochondrial antibody; PT INR, prothrombin time and international normalized ratio; LLN, lower limit of normal; ULN, upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; UDCA, ursodeoxycholic acid; PBC, primary biliary cholangitis.

Table 2. Proportion of Patients with a UDCA Response 1 Year after UDCA Treatment

URS	UDCA responder, %*
1Q (–3.20 to 0.13)	46.5
2Q (0.13 to 1.05)	67.4
3Q (1.05 to 2.03)	90.9
4Q (2.03 to 4.67)	100
<1.41 (n=97)	58.8
≥1.41 (n=76)	98.7

UDCA, ursodeoxycholic acid; URS, UDCA response score.
*UDCA responders were defined as patients with alkaline phosphatase <1.67×upper limit of normal.

to 0.88) (Supplementary Fig. 1). The best cutoff of URS to identify UDCA response was 1.41, meaning 80% probability of response to UDCA. UDCA response rate was 98.7% for those with URS ≥1.41 and 58.8% for those with URS <1.41 (Table 2). Proportion of patients achieving ALP <1.0, <1.5, and <2.0 times ULN after 1 year of UDCA treatment were 47.4%, 71.7%, and 86.7%, respectively (Supplementary Fig. 2). The AUROC of URS for predicting UDCA response (ALP <1.0, <1.5, and <2.0 times ULN) was 0.76 to 0.81 (Supplementary Table 1). We also calculated modified URS. The AUROC of modified URS in predicting UDCA response (ALP <1.67 times ULN) was 0.84 (95% CI, 0.77 to 0.88) (Supplementary Table 2).

In this real-life study, many patients did not receive recommended UDCA dose (13 to 15 mg/kg/day). Nevertheless, there was no difference in UDCA response between patients receiving the recommended dose (80.0%), underdose (76.9%), and overdose (70.6%, p=0.52). URS from all three dose groups predicted UDCA response well. The AUROC of URS in predicting UDCA response (ALP <1.67 times ULN) was 0.85, 0.78, and 0.87 for underdose, recommended dose, and overdose, respectively (comparison of AUROC: underdose vs recommended dose, p=0.49; underdose vs overdose, p=0.81; recommended dose vs overdose, p=0.27).

3. URS and liver-related event-free survival

During a median of 6.5 years of follow-up (range, 1.0 to 14.1 years), 18 patients (10.4%) experienced newly developed liver-related events. Most liver-related events were hepatic decompensation (n=16, 9.2%). Ascites, hepatic encephalopathy, and variceal bleeding were observed in eight (4.6%), seven (4.0%), and seven (4.0%) patients, respectively. Six patients experienced more than one hepatic decompensation events. Three patients developed HCC. One patient who developed HCC also experienced hepatic decompensation. The 5- and 10-year liver-related event-free survival rates for the whole study population were 91.1% and 85.0%, respectively. Among 125 patients with

available histological information, liver-related event-free survival rates at 5 years for PBC stage IV (n=8), PBC stage III (n=54), PBC stage II (n=37), and PBC stage I (n=26) were 62.5%, 96.1%, 88.4%, and 95.8%, respectively (Fig. 2). Mortality was observed in five patients. The causes of death were liver cirrhosis-related complications in three patients and unknown in two patients. The 5- and 10-year overall survival rates for the whole study population were 98.2% and 95.3%, respectively.

When stratified with ALP endpoints as responders (<1.67 times ULN) or nonresponders (ALP ≥1.67 times ULN), responders had a higher probability of liver-related event-free survival (Supplementary Fig. 3). The 5-year and 10-year liver-related event-free survival rates of the responders were 95.9% and 91.7%, respectively, while those of nonresponders were 77.8% and 74.1% (p<0.001), respectively.

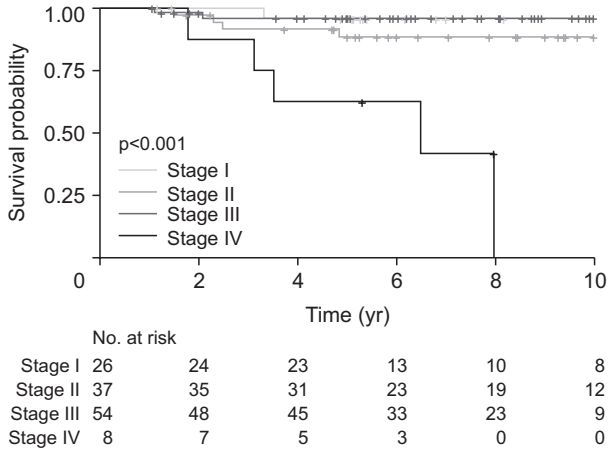

Fig. 2. Probability of liver-related event-free survival of patients with available histologic data stratified by fibrosis stage (n=125).

Liver-related events of responders and nonresponders defined by URS and other biochemical response criteria in 5 years are shown in Table 3. Patients with URS ≥1.41 did not develop any liver-related events in 5 years. The 5-year liver-related event-free survival rates for patients with URS ≥1.41 were 100%, while for patients with URS <1.41 was 85.5% (p=0.001) (Fig. 3A). The 5-year AUROC of the URS for liver-related events in the overall cohort was 0.69 (Table 4). Among 117 non-cirrhotic PBC patients by histological evaluation (PBC stages I-III), the 5-year AUROC of the URS for the liver-related events was 0.72 (Table 4). The 5-year liver-related event-free survival rate for patients with URS ≥1.41 were 100%, while for patients with URS <1.41 was 86.5% (p=0.005) (Fig. 3B). We also compared the predictive performance of URS to other biochemical response criteria and risk scoring systems. Both UK-PBC and GLOBE showed high discriminative ability. However, AUROCs of biochemical response criteria, Paris I, Paris II, and Rotterdam were not significantly different from those of URS (Table 4). We further investigated and found that the patients who did not meet any of the biochemical response criteria, including Paris I, Paris II, Rotterdam, and Barcelona, after 1 year of UDCA treatment were 75

Table 3. Liver-Related Event Rates at 5 Years

	Overall cohort (n=173)		Non-cirrhotic patients (n=117)*	
	Response, No.	Event, No. (%)	Response, No.	Event, No. (%)
URS				
≥1.41	97	0	59	0
<1.41	76	13 (17.1)	58	7 (12.1)
ALP <1.67×ULN at 1 yr				
Responder	132	5 (3.8)	92	2 (2.2)
Nonresponder	41	8 (19.5)	25	5 (20.0)
Paris I				
Responder	139	5 (3.6)	99	3 (3.0)
Nonresponder	34	8 (23.5)	18	4 (22.2)
Paris II†				
Responder	108	3 (2.8)	77	1 (1.3)
Nonresponder	65	10 (15.4)	40	6 (15.0)
Rotterdam				
Responder	152	5 (3.3)	107	3 (2.8)
Nonresponder	51	8 (15.7)	10	4 (40.0)
Barcelona				
Responder	130	8 (6.2)	93	5 (5.4)
Nonresponder	43	5 (11.6)	24	2 (8.3)

URS, ursodeoxycholic acid response score; ALP, alkaline phosphatase; ULN, upper limit of normal.
*Only patients with histologic evaluation were included; †Paris II criteria had been developed for early primary biliary cholangitis. Therefore, the analysis of Paris II was excluded for cirrhotic patients.

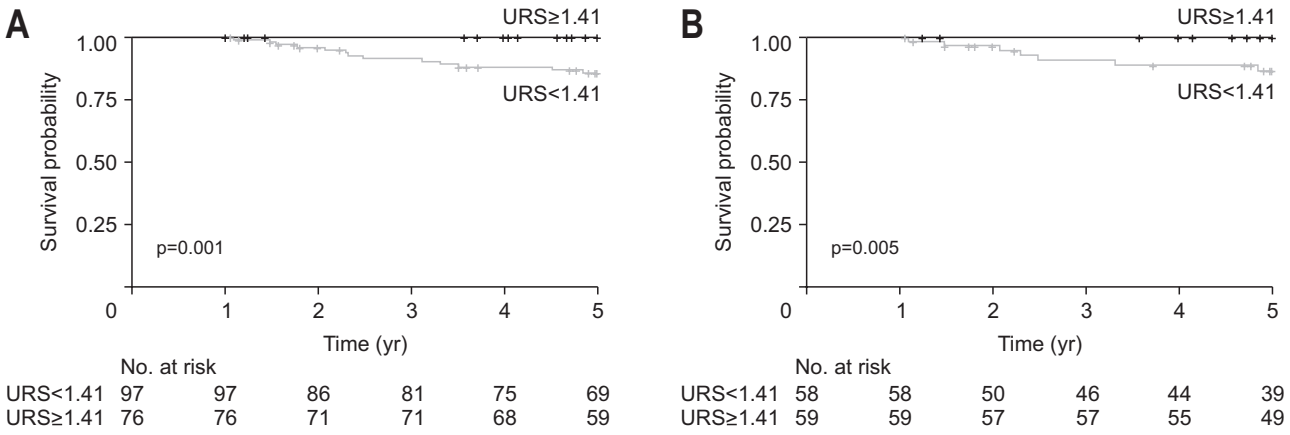

Fig. 3. Probability of liver-related event-free survival stratified by ursodeoxycholic acid response score (URS). (A) Overall patients (n=173). (B) Non-cirrhotic patients (stages I-III, n=117).

Table 4. Predictive Performance At 5 Years of the URS and Biochemical Response Criteria/Risk Scoring Systems

Scoring systems	Overall cohort (n=173)		Non-cirrhotic patients (n=117)	
	AUROC (95% CI)	p-value*	AUROC (95% CI)	p-value*
URS	0.69 (0.61–0.79)		0.72 (0.60–0.82)	
ALP <1.67×ULN at 1 yr	0.70 (0.58–0.81)	0.76	0.77 (0.59–0.91)	0.59
UK-PBC	0.90 (0.84–0.95)	<0.001	0.91 (0.82–0.07)	0.004
GLOBE	0.91 (0.81–0.97)	<0.001	0.92 (0.83–0.99)	0.004
Paris I	0.72 (0.60–0.85)	0.62	0.72 (0.57–0.91)	0.99
Paris II†	0.71 (0.58–0.81)	0.66	0.77 (0.63–0.88)	0.47
Rotterdam	0.77 (0.66–0.90)	0.34	0.76 (0.57–0.91)	0.70
Barcelona	0.43 (0.27–0.55)	<0.001	0.46 (0.30–0.62)	0.004

URS, ursodeoxycholic acid response score; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ALP, alkaline phosphatase; ULN, upper limit of normal.
*p-value was obtained after comparing AUROC of URS to each biochemical response criteria/risk scoring system; †Paris II criteria were developed for early primary biliary cholangitis. Therefore, the analysis of Paris II was excluded for cirrhotic patients.

(44.3%). Among them, 54 patients (72%) were not changed with the treatment, 19 patients (25.3%) received increased doses of UDCA, and two patients (2.7%) received immunosuppressants such as steroids.

DISCUSSION

In this multicenter study of PBC, we aimed to validate the performance of URS in Asian patients and assess whether URS could be used as a prognostic scoring system. We found that the predictive performance of URS was good in Asian PBC patients. The AUROC of URS for predicting UDCA response was 0.84 (95% CI, 0.78 to 0.88). We also found that the risk of liver-related events could be differentiated by URS for non-cirrhotic patients.

The primary endpoint of this study was UDCA response defined as an ALP level less than 1.67 times the ULN at 1 year after UDCA treatment. Carbone *et al.*[14] have made different models for each different definition of ALP endpoints because there had been disagreements regarding the optimal ALP cutoff value for the response to UDCA. In the present study, we also calculated models with varying ALP endpoints, and found that the model with 1.67 times the ULN of ALP showed the highest discrimination ability in our cohort (Supplementary Table 1). In Toronto criteria, 1.67 times the ULN of ALP was used as the endpoint of UDCA response and for predicting histological progression.[15] Also, the study of Momah *et al.*[16] about optimizing biochemical markers for PBC patients demonstrated that patients with ALP ≤1.67 times the ULN after 1 year of UDCA treatment also showed bilirubin ≤1 mg/dL and these patients were more likely to experience treatment success.

In the present study, we set treatment time lag and delta ALP to be zero with the original URS score because all patients in our cohort began UDCA immediately after being diagnosed with PBC. In addition, we calculated a modified

URS. However, both the original and modified URS accurately predicted UDCA response, showing no significant difference in AUROC between the two methods. Carbone *et al.*[14] have demonstrated that even if fixing the treatment time lag to zero, URS still showed high discrimination ability with an AUROC of 0.87 (95% CI, 0.85 to 0.89). The AUROC of modified URS in their cohort was 0.83 (95% CI, 0.82 to 0.85). There have been some studies on the validation of URS. Yagi *et al.*[17] have reported that the AUROC of modified URS (0.79; 95% CI, 0.74 to 0.83) was higher than that of the original URS (0.74; 95% CI, 0.70 to 0.79) in their cohort. The authors explained the difference between the two models was due to the large variability in the treatment time lag. To reflect actual clinical practice, we used the original URS instead of modified URS based on the following facts: (1) there was no treatment time lag in our cohort, which differed from other cohorts; (2) the original URS in the study of Carbone *et al.*[14] showed good performance even after fixing the time lag to zero; and (3) both the original URS with fixed time lag as zero and modified URS showed good performance in our cohort.

When AUROC was analyzed, we found that URS of 1.41 was the cutoff value based on the Youden index in our cohort, which meant 80% of the probability of response to UDCA. In the group of patients with a URS of equal or greater than 1.41, about 99% of patients achieved ALP endpoints. UDCA responders had higher liver-related event-free survival probability. We hypothesize that if URS could accurately predict UDCA response, it could also predict prognosis because previous studies demonstrated that biochemical response to UDCA is a predictor of clinical outcome of PBC patients.[10,18-23] The calculated AUROC of URS for predicting the survival of liver-related events in overall cohorts was not favorable. However, when we subdivided patients into non-cirrhotic groups based on histologic evaluation, the predictive performance was better for the non-cirrhotic group. In the overall population, risk scoring systems such as UK-PBC and GLOBE scores showed high discriminative ability, while the biochemical response criteria such as Paris I, Paris II, and Rotterdam showed insignificant differences from URS. The reason that risk scoring systems showed better performance might be due to markers of synthetic liver function and fibrosis such as albumin and platelets.[11,13] However, URS could stratify the risk of liver-related events in histologically proven non-cirrhotic patients. Further study will be needed to develop the prognostic scoring systems using data at the beginning of treatment.

Although histologic evaluation is not mandatory in the diagnosis of PBC, it is known that histology is one of the prognostic factors of PBC.[1,2] Murillo Perez *et al.*[6] have found that advanced fibrosis was an independent factor associated with survival and the patients with advanced fibrosis had a lower survival rate despite having a favorable biochemical response at 1 year. UDCA can reduce inflammation and ductular proliferation. However, it cannot reverse fibrosis.[24] Therefore, obtaining a sufficient UDCA treatment response in patients with advanced stage of PBC is difficult.[21,25] When we stratified the patients with fibrosis stage, stage IV cirrhosis was found to be the decisive factor for poor prognosis. However, the patients with higher URS did not develop any liver-related events in 5 years in histologically proven non-cirrhotic group.

This study has some limitations due to its retrospective design. Firstly, we only included patients who met the inclusion criteria, which were more stringent than those of other cohorts. If patients showed elevated ALP less than 1.5 ULN, AMA positive, but without results of liver biopsy could be excluded even if they had true PBC. However, in the setting of a retrospective design, it was the only way to convince a patient's diagnosis in the absence of histologic analysis. Secondly, more than half of patients took either under dose or overdose of UDCA. This is probably because there are three different dosages (100, 200, and 300 mg) of UDCA pills. Physicians usually prescribe 300 mg three times a day for normal or overweight patients and 200 mg three times a day for underweight patients. Therefore, prescriptions might be inadequate or excessive for certain patients. Interestingly, the proportion of patients achieving ALP endpoints did not differ significantly between groups. Moreover, when we analyzed the AUROC to predict the response to UDCA with URS, despite the fact that doses of UDCA varied, the performance for predicting UDCA response was good for all groups. Thirdly, even if URS could predict clinical outcomes in our study, further studies will be needed to validate it in other populations for prognosis and develop new prognostic scoring systems with data from the treatment start date. Moreover, even if URS could predict prognosis, it would be hard to switch the treatment plan from UDCA to other therapeutic options at present. Therefore, URS should be validated for other PBC treatment options as well.

In conclusion, URS demonstrated good performance in predicting the UDCA treatment response before starting UDCA in Asian PBC patients. In addition, the risk of liver-related events differed by URS. These findings suggest URS can be a tool to identify a high-risk subgroup of Asian patients with PBC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study concept and design: D.H.S., J.I.C. Data acquisition, analysis, and interpretation: J.I.C., J.H.K., J.Y.C., K.M.K., J.H.O., Y.P., W.S., M.J.G. Writing and drafting of the manuscript: J.I.C., J.H.K., J.Y.C., D.H.S. Critical revision of the manuscript for important intellectual content: W.K., Y.H.P., M.S.C., J.H.L., K.C.K. Statistical analysis: J.I.C., D.H.S. Study supervision: D.H.S., G.Y.G., S.W.P. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220420.

REFERENCES

1. European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145-172.
2. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2019;69:394-419.
3. Shah RA, Kowdley KV. Current and potential treatments for primary biliary cholangitis. Lancet Gastroenterol Hepatol 2020;5:306-315.
4. Liang Y, Yang Z, Zhong R. Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis. Hepatology 2012;56:1409-1417.
5. Zein CO, Angulo P, Lindor KD. When is liver biopsy needed in the diagnosis of primary biliary cirrhosis? Clin Gastroenterol Hepatol 2003;1:89-95.
6. Murillo Perez CF, Hirschfield GM, Corpechot C, et al. Fibrosis stage is an independent predictor of outcome in primary biliary cholangitis despite biochemical treatment response. Aliment Pharmacol Ther 2019;50:1127-1136.
7. Tan D, Goodman ZD. Liver biopsy in primary biliary cholangitis: indications and interpretation. Clin Liver Dis 2018;22:579-588.
8. Harms MH, van Buuren HR, Corpechot C, et al. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol 2019;71:357-365.
9. Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology 2000;32:1196-1199.
10. Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. Gastroenterology 2006;130:715-720.
11. Carbone M, Sharp SJ, Flack S, et al. The UK-PBC risk scores: derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology 2016;63:930-950.
12. Cheung AC, Gulamhusein AF, Juran BD, et al. External validation of the United Kingdom-primary biliary cholangitis risk scores of patients with primary biliary cholangitis treated with ursodeoxycholic acid. Hepatol Commun 2018;2:676-682.
13. Lammers WJ, Hirschfield GM, Corpechot C, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology 2015;149:1804-1812.e4.
14. Carbone M, Nardi A, Flack S, et al. Pretreatment prediction of response to ursodeoxycholic acid in primary biliary cholangitis: development and validation of the UDCA Response Score. Lancet Gastroenterol Hepatol 2018;3:626-634.
15. Kumagi T, Guindi M, Fischer SE, et al. Baseline ductopenia and treatment response predict long-term histological pro-

gression in primary biliary cirrhosis. Am J Gastroenterol 2010;105:2186-2194.
16. Momah N, Silveira MG, Jorgensen R, Sinakos E, Lindor KD. Optimizing biochemical markers as endpoints for clinical trials in primary biliary cirrhosis. Liver Int 2012;32:790-795.
17. Yagi M, Matsumoto K, Komori A, et al. A validation study of the ursodeoxycholic acid response score in Japanese patients with primary biliary cholangitis. Liver Int 2020;40:1926-1933.
18. Zhang LN, Shi TY, Shi XH, et al. Early biochemical response to ursodeoxycholic acid and long-term prognosis of primary biliary cirrhosis: results of a 14-year cohort study. Hepatology 2013;58:264-272.
19. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147:1338-1349.e5.
20. Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol 2011;55:1361-1367.
21. Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology 2008;48:871-877.
22. John BV, Khakoo NS, Schwartz KB, et al. Ursodeoxycholic acid response is associated with reduced mortality in primary biliary cholangitis with compensated cirrhosis. Am J Gastroenterol 2021;116:1913-1923.
23. 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;136:1281-1287.
24. Poupon RE, Lindor KD, Parés A, Chazouillères O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. J Hepatol 2003;39:12-16.
25. Kawata K, Joshita S, Shimoda S, et al. The ursodeoxycholic acid response score predicts pathological features in primary biliary cholangitis. Hepatol Res 2021;51:80-89.