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Evaluation of renal arterial resistive index in patients with extrahepatic cholestasis

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Abstract. – OBJECTIVE: Biliary obstruction has been shown to cause acute renal failure. The Renal Resistive Index (RRI) has been recognized to be an important index for evaluating changes in renal plasma flow and renal damage in cholestatic patients. We aimed to investigate the effects of cholestasis on renal hemodynamics in patients with extrahepatic cholestasis by RRI.

PATIENTS AND METHODS: The prospective study included patients with extrahepatic cholestasis due to benign biliary stricture, choledocholithiasis, or periampullary tumor between January 1, 2022, and December 31, 2022. Renal and liver function tests, as well as renal doppler ultrasound for RRIs, were conducted before and after cholestasis treatment.

RESULTS: Patients who experienced cholestasis resolution after treatment showed lower cholestasis enzymes and bilirubin values and higher glomerular filtration rates compared to pre-treatment values. RRI values significantly decreased in patients with resolved cholestasis compared to pre-treatment levels (p=0.009). Patients with malignant cholestasis had higher RRI values than those with benign cholestasis (p=0.006). Bilirubin levels were higher (p=0.001), and glomerular filtration rates were lower (p=0.046) in patients with malignant cholestasis compared to those with benign cholestasis.

CONCLUSIONS: Acute renal injury in cholestatic patients can be demonstrated non-invasively by RRI and is reversible once cholestasis has resolved. Patients with benign cholestasis had lower RRI values than those with cholestasis due to periampullary tumors.

Key Words:
Renal arterial resistive index, Benign extrahepatic cholestasis, Malign extrahepatic cholestasis, Acute renal injury.

Introduction

Cholemic nephropathy, or biliary nephropathy, is an impaired renal function with characteristic histomorphological changes in cholestatic patients[1]. Tubular obstruction caused by bile salts, tubular and interstitial inflammation, and altered renal blood flow are blamed for the etiopathogenesis of colemic nephropathy[2]. However, its role is controversial, as both harmful and kidney-protective effects of bilirubin have been reported[3-6]. Despite this controversy, bile acid and bilirubin levels correlate well[7]. Biliary obstruction has been shown to increase renal complications by causing an increase in endothelin-1 and prostaglandin E2[8]. Also, elevated bilirubin may increase renal hypoperfusion by causing systemic endotoxemia[9]. In addition, severe cholestasis, which can cause acute renal failure, may be reversible by removing the biliary obstruction[10]. In the differential diagnosis with other causes of acute renal injury, colemic nephropathy is a neglected clinical entity. Because kidney damage can be rapidly reversed as bilirubin levels fall, early diagnosis and treatment are crucial[7].

Renal Doppler ultrasound has been used for many years to evaluate renal perfusion. The Renal Resistive Index (RRI) has been recognized as an important index for evaluating changes in renal plasma flow[11]. The calculation of the RRI is based on the propagation of the velocity waveform, where arterial pulsation gradually declines[12], which is associated with permanent acute kidney injury[13]. The correlation of RRI with renal parameters such as glomerular filtration rate and

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serum cystatin C has been evaluated[14] previously in cirrhotic patients. Although biopsy is required to diagnose colemic nephropathy, evaluating the renal functions of these patients with a non-invasive and easy method such as RRI can predict permanent renal damage in cholestatic patients. In light of the information above, RRI as an indicator of kidney function has been employed safely as a noninvasive method. Acute kidney damage may be seen in cases with cholestasis, and renal functions may be reversible with the elimination of cholestasis. There appears to be a lack of literature on assessing renal function in cholestatic patients using the RRI.

In the present study, we aimed to investigate the effects of cholestasis on renal hemodynamics by RRI in patients with extrahepatic cholestasis and after cholestasis has resolved.

Patients and Methods

Patients

The study was in a prospective design and included patients who underwent ERCP (Endoscopic Retrograde Cholangio Pancreatography) or PTC (Percutaneous Transhepatic Cholangiography) with extrahepatic cholestasis due to benign biliary stricture, choledocholithiasis, or periampullary tumor in Zonguldak Bulent Ecevit University Gastroenterology clinic between January 1, 2022, and December 31, 2022. Before these procedures and after the bilirubin level fell below 3 mg/dl (at least three weeks later), the RRIs were evaluated by renal Doppler ultrasound. In addition, renal and liver function tests were recorded before ERCP/PTC and after the bilirubin level decreased.

Patients with chronic kidney disease, acute or chronic respiratory failure, severe heart failure with an ejection fraction lower than 35%, chronic liver disease, renal artery stenosis, ectopic or malrotated kidneys, renal scarring, intrahepatic cholestasis, total bilirubin level lower than 3 g/dL, malignancy other than a periampullary tumor, pregnant women, those under 18 years of age, and those who could not cooperate with breathing during ultrasonography were excluded from the study.

Renal Ultrasonography

The ultrasound device calculated RRI and acceleration time (AT). RRI was calculated as peak systolic velocity-end diastolic velocity/peak systolic velocity, and AT was the time between the starting point of systole to the top of systolic peak velocity (Figure 1). Three measurements were obtained from interlobar arteries at each kidney's upper, mid, and lower parts. The mean values of RRI and AT were recorded. Also, each kidney's dimensions and parenchymal thickness were measured (Figure 2). All measurements were done at the supine position, and patients were asked to hold their breath at the measurement time. Measurements were made by a single specialist radiologist with three years of post-specialist experience, blinded to patients' clinical data to avoid interobserver variability, using Siemens Acuson S2000™ (Siemens Healthcare GmbH, Erlangen, Germany) with an abdominal probe (6C-1 HD™).

Statistical Analysis

The statistical analyses were performed using SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±SD or median with interquartile range (IQR). The Chi-square test was used to compare categorical variables. Shapiro-Wilk and Kolmogorov-Smirnov tests evaluated the normal distribution of continuous variables. Paired-sample *t*-test and independent-sample *t*-test were used for normally distributed data. Mann-Whitney U and Wilcoxon Signed Rank tests were used for data that did not show normal distribution. Covariance analysis was conducted to eliminate the influence of other variables on RRI values in the malignant and benign cholestasis groups. ROC curve analysis was used to distinguish RRI levels in malignant and benign cholestasis patients. Statistical significance was determined at $p<0.05$.

Results

Eighty-four patients with extrahepatic cholestasis, including choledocholithiasis, benign biliary stricture, and periampullary tumors, were included in the study. Six patients were excluded during renal doppler ultrasonography. In the follow-up of 78 patients, 36 patients whose cholestasis was treated with ERCP or PTC and whose total bilirubin level fell below three at follow-up volunteered to continue the study (Figure 3).

After treatment, patients with resolved cholestasis showed lower cholestasis enzymes and bilirubin levels. Additionally, their urea and creatinine levels were lower, and glomerular filtration rates were higher compared to pre-treatment levels (Table I). RRI values significantly decreased in patients with resolved cholestasis

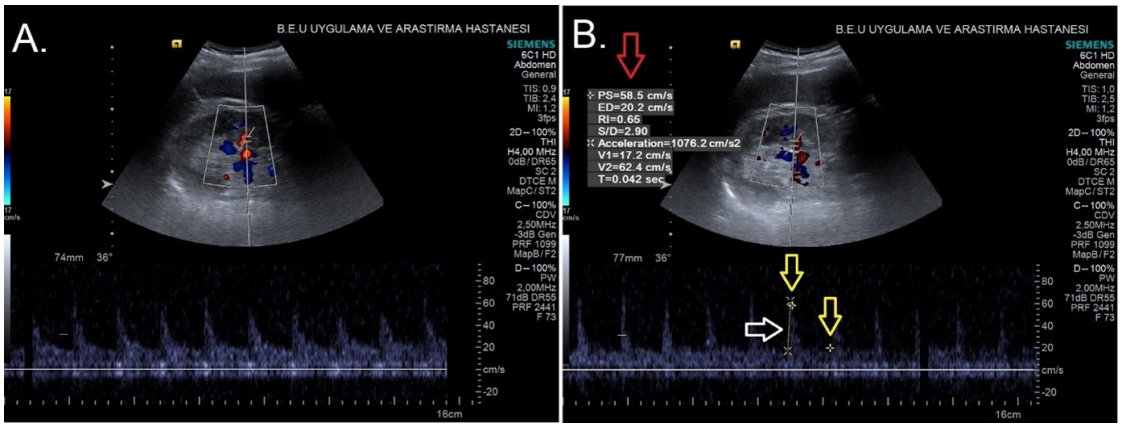

Figure 1. Measurement of Renal Resistive Index by renal doppler ultrasonography. **A**, Renal color and spectral Doppler at interlobar artery. **B**, Renal Resistive Index (RRI) and Acceleration Time (AT) measurements, the white arrow shows AT, the yellow arrows show RRI, and the red arrow shows automated calculations which ultrasound device made.

compared to pre-treatment levels (p=0.009). AT values remained similar in patients with improved cholestasis after treatment (p=0.764) (Table II).

Patients with benign and malignant extrahepatic cholestasis had similar demographic characteristics, including age, gender, and comorbidity (Table III). Bilirubin levels were significantly higher (p=0.001), and glomerular filtration rates were significantly lower (p=0.046) in patients with malignant cholestasis compared to those with benign cholestasis (Table IV). Patients with malignant cholestasis had significantly higher RRI values than those with benign cholestasis (p=0.006).

Upon examination of other variables such as age, diabetes mellitus, hypertension, and cardiovascular diseases, it was observed that being over 65 and having hypertension significantly affected RRI values. After conducting covariance analysis to eliminate the influence of these variables on RRI values between the malignant and benign cholestasis groups, it was found that the RRI values were still significantly different between the two groups (p=0.016).

During the ROC curve analysis to distinguish RRI levels between patients with malignant and benign cholestasis, a cut-off value of 0.6933 was identified with a sensitivity of 0.941 and a specificity of 0.481 (Youden index=0.42, AUC=0.708, p=0.01). Patients with malignant cholestasis had a significantly higher RRI value than the reference value (p=0.001).

Patients with malignant and benign cholestasis had similar AT values (p=0.979) (Table V).

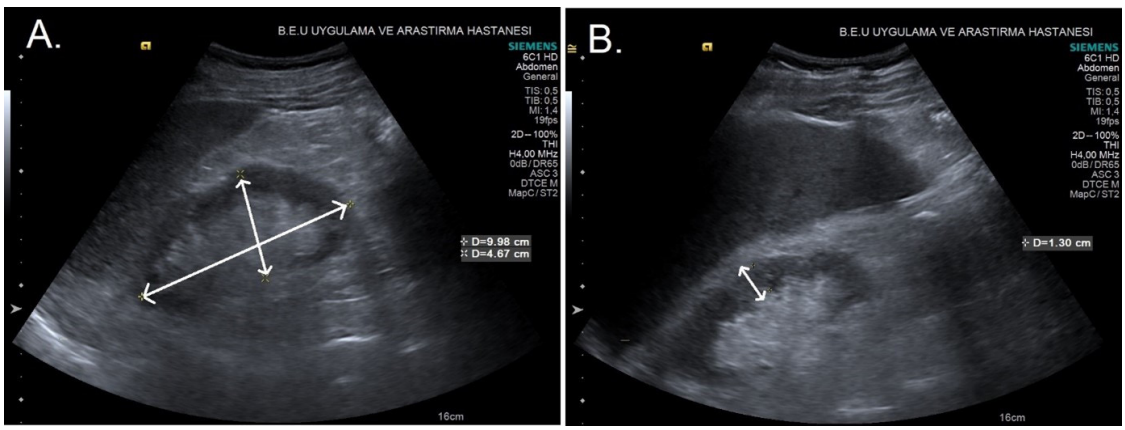

Figure 2. Measurement of kidney size and renal cortical thickness by renal ultrasonography. **A**, Long and short axis dimensions of the kidney. **B**, Renal cortical parenchymal thickness measurement.

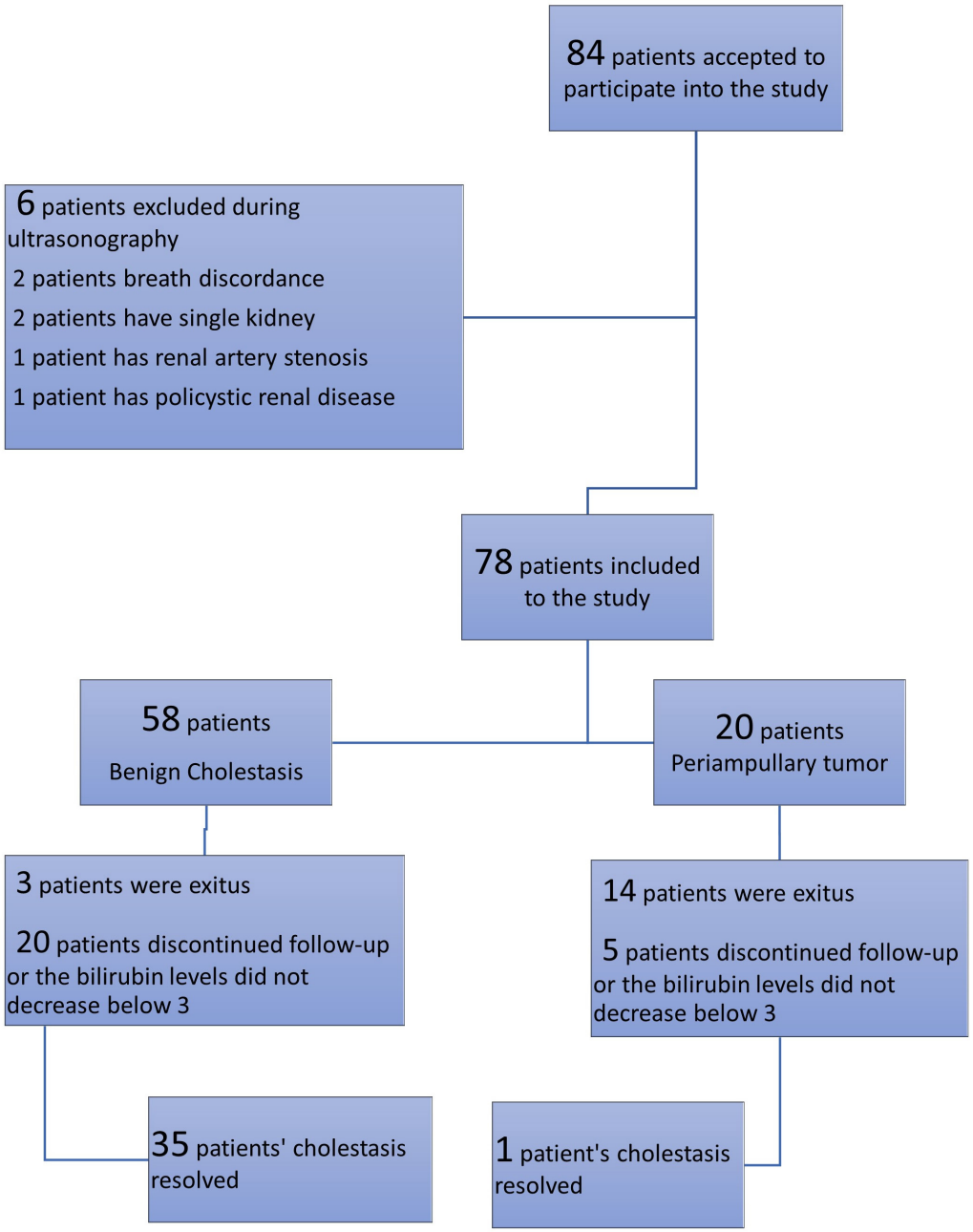

Figure 3. Study flow diagram.

Discussion

To our knowledge, this is the first study to analyze the relationship between cholestasis and RRI. The present study found that resolving cholestasis reduces RRIs in patients with extrahepatic cholestasis during follow-up. RRI measurement is a highly sensitive parameter for detecting changes in renal plasma flow. Increased RRI is considered a marker of intrarenal arterial stiffness associated with worsening renal function[15]. RRI has previously been shown[13] to predict the occurrence of acute kidney injury. Improvement in renal functions was also observed after the resolution of cholestasis of cholestatic patients in the present study. Therefore, the higher RRI in cholestatic patients suggests that acute kidney injury is associated with increased resistance in renal blood

Table I. Laboratory findings of patients with extrahepatic cholestasis and those whose cholestasis resolved after treatment.

	Patients with cholestasis n=36			Patients with resolved cholestasis n=36			
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	*p*-value
Hemoglobin (gr/dl)	12.1	10.9	13.2	12.8	11.2	13.6	0.771
Albumin (gr/dl)	3.5	3.1	3.8	3.8	3.5	4.4	0.081
Platelet count (10^3/ml)	223	160	271	242.5	211.5	330	**<0.001**
Lymphocyte count (mcl)	1300	700	1900	1650	1300	2000	**0.001**
Blood urea nitrogen (mg/dl)	32	22	43	27	17	33	**0.008**
Creatinine (mg/dl)	0.9	0.7	1.1	0.7	0.6	0.9	**0.015**
Alanine transaminase (U/L)	126.5	63	269	31	26	52.5	**<0.001**
Aspartate transaminase (U/L)	95	59	165	26.5	18	32	**<0.001**
Total bilirubin (mg/dL)	5.91	4.35	10.86	1.18	0.9	1.36	**<0.001**
Direct bilirubin (mg/dL)	5.1	3.37	8.99	0.81	0.52	1.04	**<0.001**
Gamma-glutamyl-transferase (U/L)	435	250	769	145.5	66.5	258.5	**<0.001**
Alkaline phosphatase (U/L)	346	210	534	147	112	233.5	**<0.001**
Glomerular filtration rate (ml/min)	91	72	106	105	83	126.5	**0.037**

Table II. Renal Doppler ultrasonography findings of patients with extrahepatic cholestasis and whose cholestasis resolved after treatment.

	Patients with cholestasis n=36		Patients with resolved cholestasis n=36		
	Mean	Standard Deviation	Mean	Standard Deviation	*p*-value
Renal resistive index	0.71	0.1	0.66	0.04	**0.009**
Renal acceleration time (m/s)	61.37	21.62	58.48	17.31	0.764
Kidney length (cm)	106.22	12.76	110.79	11.66	0.266
Kidney width (cm)	48.91	7.34	50.46	6.94	0.784

Table III. Demographic characteristics of patients with benign extrahepatic cholestasis and malignant extrahepatic cholestasis.

		Benign extrahepatic cholestasis n=58				Periampullary tumor n=20				
		Mean	SD	n	%	Mean	SD	n	%	*p*-value
Age		63.6	16			70	9.2			0.097
Gender	Male			34	58.60%			13	65.00%	0.615
	Female			24	41.40%			7	35.00%	
Diabetes Mellitus	No			43	74.10%			16	80.00%	0.598
	Yes			15	25.90%			4	20.00%	
Hypertension	No			36	62.10%			12	60.00%	0.87
	Yes			22	37.90%			8	40.00%	
Cardiovascular Disease	No			43	74.10%			18	90.00%	0.138
	Yes			15	25.90%			2	10.00%	

Table IV. Laboratory findings of patients with benign extrahepatic cholestasis and malignant extrahepatic cholestasis.

	Benign extrahepatic cholestasis n=58			Periampullary tumor n=20			
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	*p*-value
Hemoglobin (gr/dl)	12.3	11.5	13.5	10.9	10.3	11.7	**<0.001**
Albumin (gr/dl)	3.6	3.3	4	3.2	2.8	3.7	**0.004**
Platelet count (10^3/ml)	194	155	252	268	221	359.5	**0.001**
Lymphocyte count (mcl)	1200	700	1700	1550	1000	4350	**0.023**
Blood urea nitrogen (mg/dl)	32	20	41	42	27.5	48	**0.031**
Creatinine (mg/dl)	0.8	0.7	1	0.9	0.7	1.2	0.576
Alanine transaminase (U/L)	158.5	77	318	87.5	62	166.5	0.091
Aspartate transaminase (U/L)	95	59	174	102	60	135.5	0.706
Total bilirubin(mg/dL)	5.44	4.12	7.72	11.05	6.68	17.4	**0.001**
Direct bilirubin (mg/dL)	4.42	3.26	6.7	8.55	5.95	15.04	**0.001**
Gamma-glutamyl transferase (U/L)	449	272	708	293	155.5	960	0.407
Alkaline phosphatase (U/L)	318.5	198	437	542.5	416.5	733	**<0.001**
Glomerular filtration rate (ml/min)	93.5	77	109	85.5	55.5	94.5	**0.046**

Table V. Renal Doppler ultrasonography findings of patients with benign extrahepatic cholestasis and malignant extrahepatic cholestasis.

	Benign extrahepatic cholestasis n=58		Periampullary tumor n=20		
	Mean	Standard Deviation	Mean	Standard Deviation	*p*-value
Renal resistive index	0.70	0.06	0.77	0.16	**0.006**
Renal acceleration time (m/s)	61.41	21.77	61.25	21.79	0.979
Kidney length (cm)	106.1	12.94	106.61	12.54	0.882
Kidney width (cm)	48.88	7.23	49	7.85	0.95

flow and is reversible. In adults, a resistive index value below 0.70 is considered normal[15]. We observed a decrease in mean RRI from 0.71 to 0.66 in patients with resolved cholestasis. Based on the results, it can be inferred that the renal blood flow of patients with resolved cholestasis has returned to normal. It is thought that increased bile acids in obstructive jaundice cause direct oxidative damage to tubular cell membranes, followed by the release of vasoactive mediators, which reduces the glomerular filtration rate through renal vasoconstriction[7], and patients have shown[16] an improvement in proximal renal tubular damage with remission of jaundice. Obstructive jaundice can lead to reversible renal dysfunction consequently.

In the present study, patients with malignant cholestasis had higher RRIs than those with benign cholestasis. Patients with periampullary tumors often experience more severe and persistent obstructive jaundice, resulting in a higher RRI. In the study of Bairaktari et al[16], proximal tubular dysfunction was shown in all patients with obstructive jaundice, regardless of the underlying cause (malignant, benign), but no comparison was made regarding the etiology of the patients. No data on RRI change in extrahepatic cholestasis were found in the literature, but early RRI changes can be used to obtain useful clinical prognostic information in cirrhotic patients. High RRI values (RRI>0.70) are a sensitive marker of premature renal functional deterioration. It predicts the development of hepatorenal syndrome even before renal failure becomes clinically apparent in cirrhotic patients[17]. Our study found no change in AT levels in patients with resolved cholestasis and no difference between malignant and benign

cholestatic patients, in contrast to RRI. The lack of difference in AT could be due to its reflection of changes in the renal artery, while RRI reflects changes in the renal parenchymal arteries[17].

A total bilirubin level above three was considered a criterion to accept our patients as cholestatic in our study. There is currently no direct evidence linking high bilirubin levels to tubular epithelial damage or loss of renal function in patients with cholestasis[18]. Furthermore, bilirubin has been shown[6] to improve vascular resistance, tubular function, and mitochondrial integrity, and higher serum bilirubin levels were associated with a lower risk of developing chronic kidney disease[19]. In cholestatic patients, bile acids accumulate in the serum, exceeding the renal excretion capacity, resulting in tubular epithelial damage, tubular casts, basement membrane defects, and obstruction of the collecting ducts, which has been associated[18] with cholemic nephropathy. Although we could not measure bile acids in patients with high bilirubin, we observed higher ALP and GGT levels pre-treatment than post-treatment.

Cholestatic patients in this study were more likely to have accompanying septic components such as cholangitis, which may have contributed to their higher RRI values compared to post-treatment. In patients with septic shock, measurement of RRI in the first 24 hours helps predict sepsis-induced acute kidney injury[20].

Limitations

The main limitation of our study was the absence of age- and sex-matched healthy controls in cholestatic patients. Future studies may compare cholestatic patients and healthy controls. Another study limitation is the inability to exclude septic components that may affect RRI in cholestatic patients. Finally, only a small number of patients experienced cholestasis improvement after treatment, possibly due to patient dropouts, deaths, or lack of bilirubin level decrease, particularly in cases of malignancy.

Conclusions

This study is the first to evaluate the relationship between RRI and extrahepatic cholestasis. The results showed that RRI values significantly decreased when patients' cholestasis improved. Patients with benign cholestasis had lower RRI values than those with cholestasis due to periampullary tumors. Acute renal injury in cholestatic patients can be demonstrated non-invasively by RRI and is reversible once cholestasis has resolved.

Conflict of Interest
The authors declare that they have no conflicts of interest.

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Authors' Contributions
ZGS, MB, ID, UC, YU: Concept and design of study or acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published.

Ethics Approval
The study received approval from the Zonguldak Bulent Ecevit University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee. (Protocol No: 2021/25, Approval date: 29/12/2021). The study protocol meets the 1964 Declaration of Helsinki's ethical principles and its latest amendments.

Data Availability
The data underlying this article are available within the article. Any additional information will be shared on reasonable request to the corresponding author.

Informed Consent
An informed consent form was obtained from the patients before participating in the study.

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