



Original Research

Can simple Non-Invasive Fibrosis Models Determine Prognostic Indicators (Fibrosis and Treatment Response) of Primary Biliary Cholangitis?

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ABSTRACT

Objective: The fibrosis stage during diagnosis and the response to ursodeoxycholic acid in the 1st year of treatment are considered to be prognostic indicators in primary biliary cholangitis (PBC). Determining these indicators with non-invasive models can enable the risk of liver failure to be monitored with continuous variables from the moment of diagnosis. The aim of this study was to evaluate the diagnostic performance of non-invasive models for determining the prognostic indicators in patients with PBC.

Materials and Methods: Data from patients with PBC were screened retrospectively. Patients were divided into early (≤ 2) and advanced (≥ 3) fibrosis groups. In addition, treatment response status according to the Paris-II criteria and liver failure risk (LFR) according to the UK-PBC score were determined. The S-Index consisting of gamma-glutamyltransferase (GGT), platelets (PLT), and albumin, (S-index: $1000 \times \text{GGT} + [\text{PLT} \times \text{Albumin}^2]$), other non-invasive models were calculated. The diagnostic effectiveness of non-invasive indicators to determine the fibrosis stage, response to treatment, and low LFR was analyzed.

Results: Fifty-three patients were included in the study. The overall mean age at diagnosis was 49.6 ± 13.6 years and 86.8% of the patients ($n=46$) were female. The S-Index was able to determine fibrosis stage, treatment responded, and patients with low LFR (AUC: 0.747, 0.823, and 0.752; $p=0.006$, <0.001 , and 0.0007, respectively). Furthermore, S-Index found to superior to other non-invasive indicators in terms diagnosis of prognostic indicators of PBC.

Conclusion: S-index is a practical and inexpensive non-invasive model that can identify liver fibrosis and treatment response in patients with PBC. It can be used as a continuous variable prognostic model in PBC.

Keywords: Liver fibrosis; non-invasive marker; primary biliary cholangitis; S-Index.

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Introduction

Primary biliary cholangitis (PBC) is a slowly progressive disease that is characterized by immune-mediated and non-suppurative chronic destructive cholangitis of the intra-hepatic biliary tract.^[1] The fibrosis stage during diagnosis and

the response to ursodeoxycholic acid (UDCA) in the 1st year of treatment are considered to be prognostic indicators.^[2]

During diagnosis, liver biopsy may not be necessary, and it is also an invasive procedure.^[3] However, the degree of liver fibrosis at the time of diagnosis is important because

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it is an essential prognostic indicator. Therefore, in cases where biopsy cannot be performed and/or the diagnosis is not changed by biopsy, determining the stage of fibrosis using non-invasive fibrosis indicators can be useful.^[4]

The aspartate aminotransferase (AST)-to-platelet ratio index (APRI), fibrosis index based on four factors (Fib-4), and RDW-to-platelet ratio (RPR) are models that were proposed to detect the fibrosis stage in PBC patients.^[5] In addition, there are models that have no literature data in PBC but that were reported to have a better diagnostic performance in chronic hepatitis B than APRI and Fib-4 scores. One of these models is the S-Index, which is calculated using gamma-glutamyltransferase (GGT) and albumin levels and the platelet count.^[6] However, the literature data regarding the prognostic value of these non-invasive indicators are scarce. Furthermore, determining prognostic indicators of PBC with non-invasive models can enable the risk of liver failure to be monitored with continuous variables.

The aim of this study was to evaluate the diagnostic performance of the APRI, Fib-4, RPR, and S-index to determine the prognostic indicators (fibrosis at diagnosis and response to treatment at month 12 after starting treatment) in patients with PBC.

Materials and Methods

Between January 2010 and April 2019, the follow-up charts and data recorded in the computer database for patients with PBC were retrospectively screened.

PBC was diagnosed when there was the presence of one of the following criteria in patients with ALP elevation: Antimitochondrial antibody (AMA) positivity or the presence

of histopathological non-suppurative destructive cholangitis and interlobular bile duct destruction.^[7] Demographic and laboratory test results within 1 month before biopsy and treatment, biopsy findings, treatment data at diagnosis, and laboratory test results from the patients at months 12 after starting treatment were recorded.

Patients with concomitant viral hepatitis, alcohol consumption of more than 20 g/day, malignancy, primary sclerosing cholangitis, hemochromatosis, or autoimmune or toxic hepatitis were excluded from the study. Patients with missing laboratory test results that were used to calculate the non-invasive indicators within 1 month before biopsy and treatment were excluded from the study. In addition, patients with missing data that were used to determine the treatment response or prognostic criteria at month 12 of treatment were excluded from the study. Patients diagnosed at another center and who lacked histopathological, clinical, laboratory, and treatment-related data were excluded from the study. The flowchart of the study is shown in Figure 1.

Non-invasive indicators were calculated separately using data from before biopsy (to evaluate the performance in diagnosing fibrosis) and at month 12 of treatment (to evaluate the relationship between non-invasive indicators in terms of the treatment response and liver failure risk [LFR]).^[4,8,9] Calculation methods of these indices are shown in Table 1.

Patients were divided into the following two groups based on liver biopsy results: Early stage (Scheuer Stages I and II) and advanced stage (Scheuer Stages III and IV) PBC.^[10] Treatment responses from the patients at month 12 were determined according to the Paris-II criteria. In addition, prognostic scores (for 10 years) were analyzed using the UK-PBC risk score.^[11,12] According to the UK-PBC score,

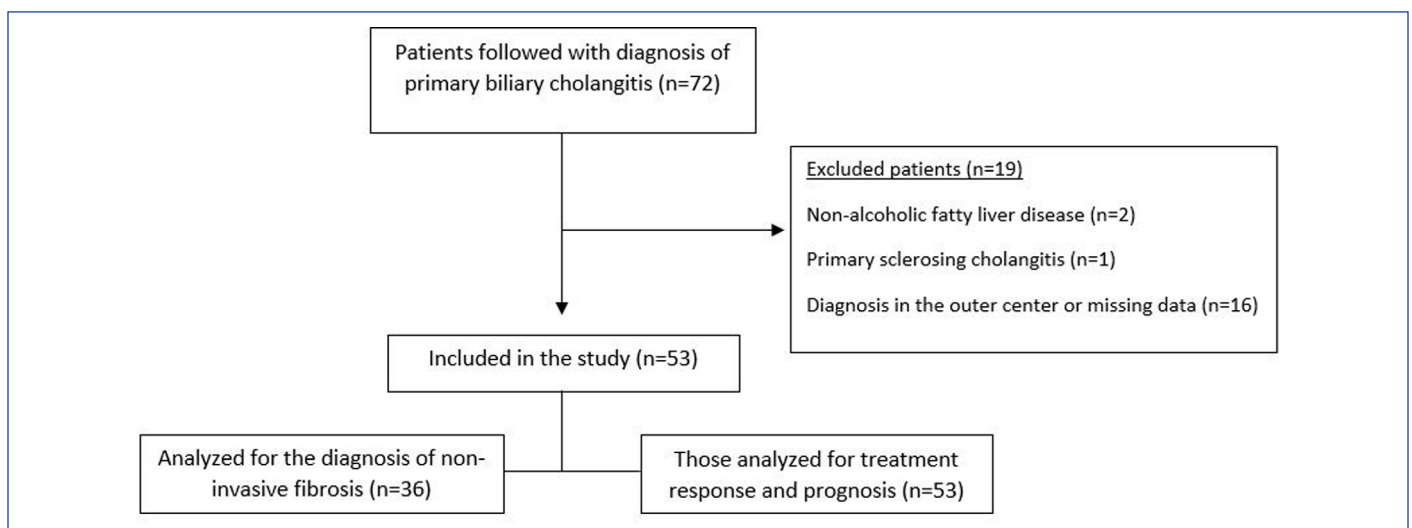


Figure 1. Flowchart of the study.

Table 1. Calculation methods for non-invasive models

Non-invasive model	Formula
APRI	$[\text{AST}/(34^*) \div \text{plt} (10^9/\text{L})] \times 100$
FIB-4	$\text{Age (year)} \times \text{AST} \div \text{PLT}(10^3/\text{L}) \times \sqrt{\text{ALT}}$
RPR	$\text{RDW} \times 100/\text{PLT} (10^9/\text{L})$
S-Index	$1000 \times \text{GGT} (\text{IU/L}) \div [\text{PLT}(10^9/\text{L}) \times \text{Albumin}^2(\text{g/dL})]$

*Upper limit of normal of AST=34 U/L. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet count; GGT: Gamma-glutamyl transferase; RDW: Red blood cell distribution width; FIB-4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index; RPR: RDW-to-platelet ratio.

those with a 10-year risk probability <3% were considered to have a low LFR.

The diagnostic effectiveness of non-invasive indicators in terms of diagnosing fibrosis (at diagnosis), determination of the treatment response, and patients with a low LFR (at month 12 of treatment) was analyzed.

This study approved by local ethics committee (Decision number and date: B.10.1.TKH.4.34.H.GP.0.01/225;12.06.2020) of our hospital.

Statistical Analysis

Patient data were analyzed with the IBM SPSS 25.0 program. Descriptive statistics (mean, standard deviation, minimum, median, and maximum) were used to define continuous variables. The distribution of data according to the number of samples was evaluated using the Shapiro–Wilk and Kolmogorov–Smirnov tests. The relationship between independent two-categorical variables was evaluated using Fisher's exact test. The Mann–Whitney *U*-test was used to compare two continuous variables with a non-normal distribution and a paired *t*-test was used for normally distributed data. Diagnostic performance of non-invasive fibrosis markers was evaluated using receiver operating curve (ROC) analysis. Significance was set at $p < 0.05$, and the results are given within a 95% confidence interval.

Results

Fifty-three patients were included in the study. They had an overall mean age at the time of diagnosis of 49.6 ± 13.6 years and 86.8% of the patients ($n=46$) were female. At the time of diagnosis, 64.1% ($n=34$) of the patients had weakness, 37.7% ($n=20$) had itching, and 18.8% ($n=10$) were asymptomatic. AMA and anti-nuclear antibody positivity were found in 83% ($n=44$) and 67.9% ($n=36$) of the patients, respectively. Liver biopsy was performed in 67.9% of the patients ($n=36$) before diagnosis and treatment, and

33.2% ($n=12$) and 66% ($n=24$) of the patients had early and advanced fibrosis, respectively. All patients were taking 13–15 mg/kg/day UDCA after diagnosis. The median follow-up time was 34.5 (interquartile range, 30.5) months.

Non-invasive indicators were compared in early and advanced stage fibrosis groups. The S-Index was found to be significantly lower in patients in the early stages compared to later stages ($p=0.02$). Comparison of non-invasive markers between the fibrosis groups is shown in Table 2. The diagnostic performance of the S-Index in determining the fibrosis stage is shown in Table 3. ROC curve analysis is shown in Figure 2.

After 1 year of treatment, AST, ALT, ALP, and GGT levels and the APRI, Fib-4, and S-Index values were significantly lower, and albumin values were significantly higher ($p < 0.05$) than before treatment. However, there was no significant difference in terms of total bilirubin, international normalized ratio, creatinine levels, platelet count, and RPR before and after treatment ($p > 0.05$). The comparison of laboratory parameters and non-invasive scores before and after UDCA treatment is shown in Table 4.

The response rate to UDCA was 43.4% ($n=23$) according to the Paris-II criteria. The S-Index value (at month 12 of treatment) was significantly lower in patients who were responders compared to non-responders ($p=0.001$). These findings are shown in Table 5. In addition, the diagnostic performance of the S-Index (at month 12 of treatment) to determine the patients who responded to UDCA is shown in Table 3. The ROC analysis curve is shown in Figure 3.

According to the UK-PC score, 52.8% ($n=28$) of patients had a low risk at 10 years. The S-Index value was significantly lower in patients with a low risk ($p=0.02$). The diagnostic efficiency of the S-Index in determining low-risk patients is shown in Table 3. The ROC analysis curve is shown in Figure 4.

Table 2. Comparison of non-invasive markers between fibrosis groups

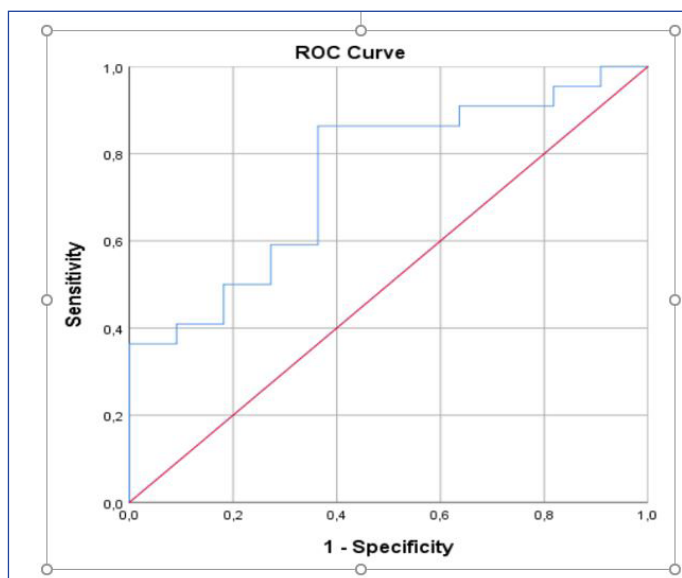
Index	Early stage ($n=12$)	Advanced stage ($n=24$)	<i>p</i> -value
APRI	0.47* (IQR:0.64)	0.76* (IQR:0.46)	0.099***
Fib-4 Index	0.96* (IQR:1.36)	1.99* (IQR:2.48)	0.092***
RPR	6.46	7.25	0.430**
S-Index	29.06	66.74	0.021***

*Median values; **Student's *t*-test (independent sample); ***Mann–Whitney *U*-test; IQR: Interquartile range; FIB-4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index; RPR: RDW-to-platelet ratio.

Table 3. Diagnostic performance of S-Index in determining fibrosis (at diagnosis), treatment response (at month 12), and patients with low LFR (month 12)

Analysis parameters	Fibrosis (Early-Advanced)	Response to treatment (Paris II)	Low LFR (UK-PBC score – 10 years)
Cutoff	37.9 (CI: 0.569–0.926)	13.9 (CI: 0.708–0.937)	27.6 (CI: 0.606–0.899)
AUC	0.747	0.823	0.752
Sensitivity	0.864	0.759	0.667
Specificity	0.636	0.826	0.893
PPV	0.826	0.846	0.842
NPV	0.700	0.731	0.758
P-value	0.006	<0.001	0.0007

LFR: Low liver failure risk; AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value.

**Figure 2.** ROC analysis of the S-Index (at diagnosis) for detecting fibrosis.

Discussion

PBC usually occurs as a slow progressive liver disease. An advanced stage of fibrosis at diagnosis is associated with a reduction in transplant-free survival. Thus, determination of the fibrosis stage at diagnosis, by liver biopsy or non-invasive methods, has been proposed to predict the prognosis and establish the risk stratification of patients.^[13] Liver biopsy is considered to be the gold standard for diagnosing the fibrosis stage. However, it is an invasive procedure that requires expert interpretation and there is some sampling error. It is also difficult to repeat and may not always be accepted by patients. However, different non-invasive diagnostic tools have been proposed that are useful for diagnosing fibrosis in PBC.^[4,14] Transient elastography is superior to other simple non-invasive indicators for diagnosing liver fibrosis.^[15] However, it is not easily accessible, and it is also

an expensive method. Therefore, using non-invasive methods that are easily accessible, inexpensive, and practical remain an important topic for diagnosing fibrosis.^[4]

Expected survival in patients with UDCA responders is that similar to a matched control population. On the contrary, UDCA non-responders have an increased risk of progression of liver disease and decreased transplant-free survival.^[16] These patients should be long term monitored regarding cirrhosis and its complications.^[17] Pre-treatment higher ALP, higher bilirubin levels, lower transaminases, younger age, the longer interval from diagnosis to the start of UDCA (treatment time lag), and worsening of ALP from diagnosis were found to have been associated with non-response to UDCA.^[18]

It is important that ideally, non-invasive model can identify both fibrosis and treatment response in PBC. In this study, we evaluated the diagnostic performance of non-invasive models, which have mostly been studied in other liver diseases and for which there are limited data in PBC, to determine fibrosis and UDCA responders. Among the indices, we found that the S-Index was the only model with a favorable performance that could significantly determine both fibrosis and UDCA responders.

The S-Index is a non-invasive fibrosis model that was first described by Zhou *et al.*, and it has been reported to have good performance in determining fibrosis in chronic hepatitis B. However, to the best of our knowledge, there are no data about the diagnostic efficacy of the S-Index in PBC. The S-Index is calculated using GGT levels, platelet count, and albumin parameters.^[8] High GGT levels and low albumin levels and platelet count have also been reported to be associated with advanced fibrosis in other chronic liver diseases.^[8,19] In animal models with intrahepatic cholestasis, increased serum GGT was found to be of cholangiocyte origin and increased serum GGT levels reflect biliary injury and cholangiolar proliferation.^[20] The GGT level is often

Table 4. Comparison of laboratory parameters and non-invasive scores before and after UDCA treatment

Parameters	Before treatment	12th month after treatment	p-value
ALP (IU/L)	264* (IQR:282)	133* (IQR:103.5)	<0.001**
GGT (IU/L)	210* (IQR:275.5)	62* (IQR:114.5)	<0.001**
ALT (IU/L)	53* (IQR:48)	26* (IQR:23)	<0.001**
AST (IU/L)	56* (IQR:45.5)	27* (IQR:25.5)	<0.001**
Total bilirubin (mg/dL)	0.7* (IQR:0.90)	0.69* (IQR:0.77)	0.068**
INR	0.98* (IQR:0.13)	1* (IQR:0.14)	0.943**
Platelet (/µL)	243* (IQR:112)	240 (IQR:127)	0.141**
Albumin (g/dL)	4.0* (IQR:0.60)	4.1* (IQR:0.40)	0.001**
Creatinine (mg/dL)	0.72 (IQR:0.15)	0.73* (IQR:0.14)	0.213**
APRI	0.64* (IQR:0.51)	0.36* (IQR:0.42)	<0.001**
FIB-4 index	1.61* (IQR:2.15)	1.11* (IQR:1.34)	0.002**
RPR	6.44* (IQR:3.01)	6.38* (IQR:3.47)	0.666**
S-Index	59.79* (IQR:93.84)	12.89* (IQR:51.25)	<0.001**

*Values are median; **Wilcoxon signed-rank test; ***paired t-test; IQR: Interquartile range; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; PLT: Platelet count; GGT: Gamma-glutamyl transferase; INR: International normalized ratio; RDW: Red blood cell distribution width; FIB-4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index; RPR: RDW-to-platelet ratio; UDCA: Ursodeoxycholic acid.

Table 5. Comparison of non-invasive markers according to treatment response (Paris II criteria)

Index	Responders	Non-responders	p-value
APRI	0.59* (IQR:0.46)	0.76* (IQR:0.45)	0.056**
Fib-4 index	1.39* (IQR:2.10)	1.73* (IQR:2.22)	0.482**
RDW/platelet	6.55* (IQR:2.77)	6.42* (IQR:3.55)	0.648**
S-Index	31.07* (IQR:52.0)	85.94* (IQR:176.5)	0.001**

*Values are median; **Mann-Whitney U-test. FIB-4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index; RPR: RDW-to-platelet ratio.

used to confirm increased ALP levels during diagnosis, but it has been reported to be used rarely to evaluate the UDCA response.^[21] However, to the best of our knowledge, there are insufficient data about a relationship between serum GGT levels and the treatment response or prognosis in PBC.

Some literature data regarding diagnosing fibrosis in PBC showed that the APRI, Fib-4 score, and RPR can favorably predict fibrosis. However, we found that these scores could not determine early or advanced stage fibrosis.^[5,22] Among the studies, sample size, distribution differences for patients according to the fibrosis stage, and variations in the general patient characteristics may affect the diagnostic performance of these non-invasive indicators.

Recently, Murillo Perez *et al.* reported that UDCA unresponsiveness and the presence of advanced fibrosis are two independent poor prognostic factors in patients with PBC. Therefore, the diagnostic effectiveness of non-invasive methods based on the fibrosis stage and treatment response could be important to predict transplant-free survival and the necessity for novel treatment.^[13]

In our study, we found that the S-Index has good diagnostic performance in identifying patients who are UDCA responders. In addition, the S-Index was able to predict patients with low LFR. The UK-PBC score is a continuous prognostic score that was validated in different cohorts, and it predicts patients' prognosis with high accuracy. It has also been shown to be superior to the dichotomous models that were previously used to predict a patient's prognosis (Barcelona, Paris I, Paris II, Rotterdam, and

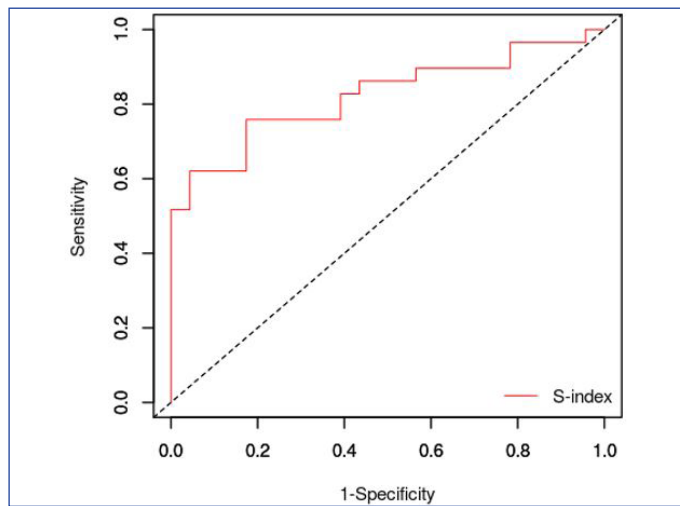


Figure 3. ROC analysis of the S-Index (at month 12 of treatment) to determine the patients' response to ursodeoxycholic acid treatment according to the Paris II criteria.

Toronto), which were based solely on treatment response. [23] However, estimation of the prognosis can be made at the earliest in the 1st year of treatment according to these models.

There are important limitations to our study including the retrospective, single-center design. However, because of the slow natural course of PBC and relatively short follow-up period for our patients, the prognostic performance of the indices was analyzed based on validated prognostic scores rather than objective clinical outcomes.

Conclusion

S-index is a practical and inexpensive non-invasive model that can identify liver fibrosis and treatment response in patients with PBC. It can be used as a continuous variable prognostic model in PBC. However, these findings should be supported by larger cohort studies.

Disclosures

Ethics Committee Approval: This study was approved by the Umraniye Training and Research Hospital Ethics Committee (Date:12.06.2020, Decision number:B.10.1.TKH.4.34.H).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.S.; Design – S.S., H.A., P.G.; Supervision – G.A.; Materials – S.S., P.G., H.A.; Data collection &/or processing – S.S., P.G., H.A.; Analysis and/or interpretation – S.S., H.A., G.A., K.O.; Literature search –S.S., G.A.; Writing – S.S.; Critical review – H.L.D., K.O., G.A.

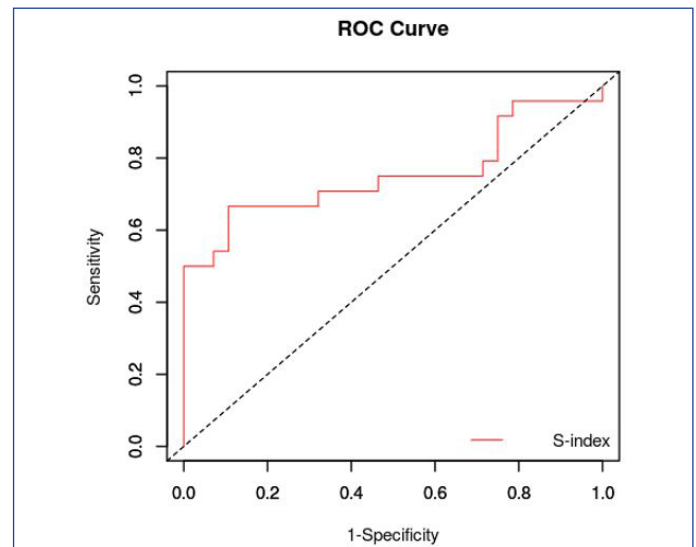


Figure 4. ROC analysis of the S-Index (at month 12) to determine the patients with low LFR according to the UK-PBC score (10 years).

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