# Associations Between Biomarkers and Magnetic Resonance Imaging-Derived ANALI Score in Patients With Primary Sclerosing Cholangitis: Analysis from the Phase 3 PRIMIS Study

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**Oral presentation at AASLD The Liver Meeting 2024, November 15–19, 2024, San Diego, CA, USA**

# Disclosures

MT has received research grants, travel grants, speaker fees, and advised for Gilead Sciences, Inc.; received consultancy fees from Agomab Therapeutics, Boehringer Ingelheim, Chemomab, Dr Falk Pharma, Ipsen, Mirum Pharmaceuticals, and Pliant Therapeutics; research funding from Alnylam, Dr Falk Pharma, and Genentech; travel grants from Dr Falk Pharma; speaker fees from Albireo, Boehringer Ingelheim, Dr Falk Pharma, Ipsen, and Madrigal Pharmaceuticals; and the Medical Universities of Graz and Vienna have filed patents on medical use of norUDCA and MT is listed as co-inventor (service inventions as employee)

# Background and Aims

- Magnetic resonance cholangiopancreatography (MRCP) is the imaging standard for the diagnosis and follow up of patients with primary sclerosing cholangitis (PSC)[1]
- Magnetic resonance (MR) risk scoring systems, such as the ANALI score[2], have been developed to provide risk evaluation and predict disease progression in patients with PSC

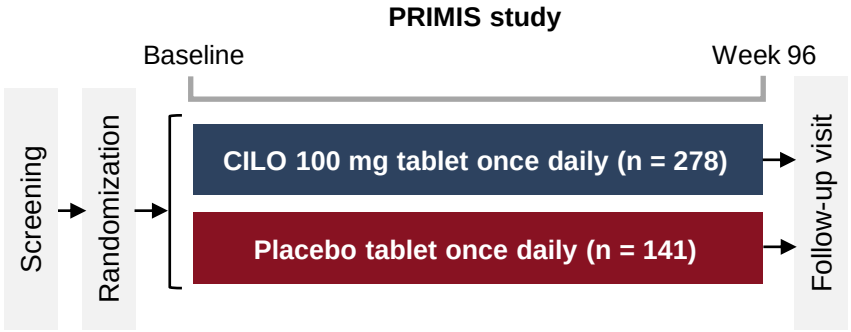
**Aim 1: evaluate baseline associations between ANALI score and other noninvasive biomarkers in patients with PSC in the phase 3 PRIMIS study**

**Aim 2: evaluate ANALI score for prediction of PSC-related clinical events in patients with PSC in the phase 3 PRIMIS study**

1. Venkatesh SK, *et al. Eur Radiol.* 2022;32:923–37. 2: Ruiz A, *et al. Hepatology.* 2014;59:242–50.

# Methods: Evaluation of Baseline Noninvasive Biomarkers and PSC-Related Clinical Events in the Phase 3 PRIMIS Study

- In the phase 3 PRIMIS study, 419 adults (aged 18–75 years) with large-duct PSC and F0–F3 liver fibrosis were randomized 2:1 to receive cilofexor 100 mg or placebo for 96 weeks




**Baseline imaging and NIT biomarkers**

- Liver stiffness measurement (LSM) was assessed by transient elastography
- Serum biomarkers, including Enhanced Liver Fibrosis (ELF) score, bile acid, and liver biochemistry were measured individually
- MR features and categorical scores were assessed by a central reader
- ANALI score without gadolinium was calculated from the intrahepatic dilation, dysmorphy, and portal hypertension scores

**PSC-related clinical events (baseline to week 96)**

- Acute cholangitis
- Other clinical events (adjudication-confirmed progression to cirrhosis, hepatic decompensation, liver transplantation, qualification for transplantation, or death)

**CILO**, cilofexor; **MR**, magnetic resonance; **NIT**, non-invasive test; **PSC**, primary sclerosing cholangitis.

# Methods: Evaluation of ANALI Score in the PRIMIS Study

- ANALI score[1] without gadolinium:
  - intrahepatic bile duct dilatation (IHBD) (0–2) x 1 +
  - liver dysmorphy (0–1) x 2 +
  - portal hypertension (0–1) x 1
- Total score range: 0–5
- Patients with ANALI score > 2 have been shown to have a higher risk of PSC-related clinical events[2]

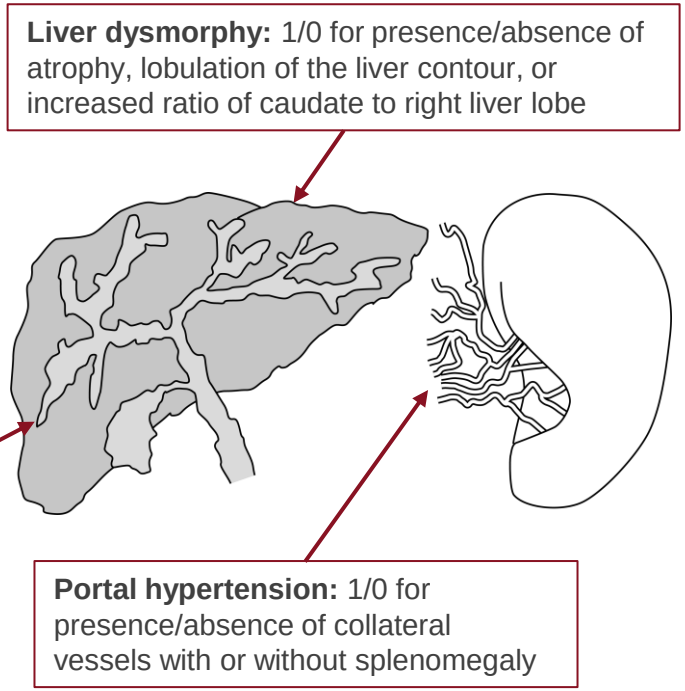
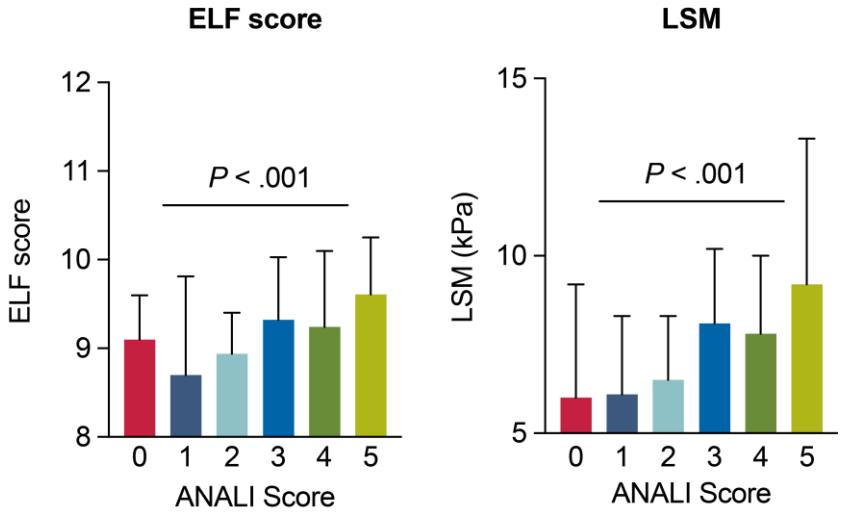



Image adapted from Poetter-Lang *et al.*, 2024[2]

1. Ruiz A, *et al. Hepatology*. 2014;59:242–50. 2. Poetter-Lang, *et al. Eur Radiol*. 2024. doi: 10.1007/s00330-024-10787-4.

# At Baseline, ANALI Score was Significantly Associated With ELF Score and LSM, With an Increasing Trend




| | ANALI = 0 (n = 50) | ANALI = 1 (n = 45) | ANALI = 2 (n = 152) | ANALI = 3 (n = 29) | ANALI = 4 (n = 92) | ANALI = 5 (n = 20) |
|---|---|---|---|---|---|---|
| **ELF score** | 9.1 (8.5, 9.6) | 8.7 (8.0, 9.8) | 8.9 (8.3, 9.4) | 9.3 (8.8, 10.0) | 9.2 (8.6, 10.1) | 9.6 (9.2, 10.3) |
| **LSM, kPa** | 6.0 (5.0, 9.2) | 6.1 (5.0, 8.3) | 6.5 (5.1, 8.3) | 8.1 (5.2, 10.2) | 7.8 (6.0, 10.0) | 9.2 (6.9, 13.3) |

Statistical associations were assessed using Kruskal–Wallis test. Data shown are median (Q1, Q3).

**ELF**, Enhanced Liver Fibrosis; **LSM**, liver stiffness measurement; **Q**, quartile.

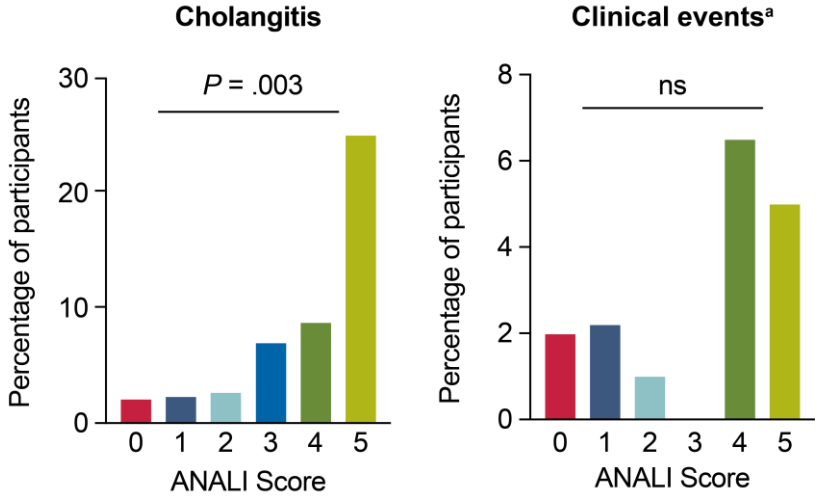
# At Baseline, Higher ANALI Score was Not Significantly Associated With Increased Levels of Liver Enzymes, IBD Status, or Fecal Calprotectin

| | ANALI = 0 (n = 50) | ANALI = 1 (n = 45) | ANALI = 2 (n = 152) | ANALI = 3 (n = 29) | ANALI = 4 (n = 92) | ANALI = 5 (n = 20) | *P* value |
|---|---|---|---|---|---|---|---|
| **ALT, IU/L** | 50 (26, 95) | 49 (22, 100) | 42 (26, 88) | 67 (30, 109) | 54 (26, 91) | 69 (30, 106) | 0.49 |
| **AST, IU/L** | 38 (23, 63) | 35 (24, 64) | 37 (24, 61) | 60 (33, 84) | 41 (26, 71) | 43 (22, 70) | 0.32 |
| **GGT, IU/L** | 143 (52, 343) | 125 (37, 329) | 124 (43, 298) | 207 (51, 522) | 186 (77, 400) | 246 (122, 423) | 0.15 |
| **ALP, IU/L** | 164 (100, 297) | 124 (94, 218) | 161 (99, 270) | 196 (121, 272) | 187 (129, 330) | 202 (154, 410) | 0.068 |
| **IBD, n (%)** | 30 (60.0) | 31 (68.9) | 109 (71.7) | 16 (55.2) | 68 (73.9) | 15 (75.0) | 0.27 |
| **Fecal calprotectin µg/g** | 42 (29, 139) | 68 (29, 206) | 75 (29, 255) | 93 (44, 199) | 104 (29, 288) | 520 (29, 1056) | 0.29 |

Statistical associations were assessed using Kruskal–Wallis test, except for IBD (Pearson's Chi-square test).
Data shown are median (Q1, Q3) unless otherwise specified.

**ALP**, alkaline phosphatase; **ALT**, alanine transaminase; **AST**, aspartate transferase; **GGT**, γ-glutamyl transferase; **IBD**, inflammatory bowel disease; **Q**, quartile.

# ANALI Score At Baseline was Significantly Associated With Cholangitis Events During the Study, With an Increasing Trend




| | ANALI = 0 (n = 50) | ANALI = 1 (n = 45) | ANALI = 2 (n = 152) | ANALI = 3 (n = 29) | ANALI = 4 (n = 92) | ANALI = 5 (n = 20) |
|---|---|---|---|---|---|---|
| **Cholangitis, n (%)** | 1 (2.0) | 1 (2.2) | 4 (2.6) | 2 (6.9) | 8 (8.7) | 5 (25.0) |
| **Clinical events,[a] n (%)** | 1 (2.0) | 1 (2.2) | 1 (0.7) | 0 | 6 (6.5) | 1 (5.0) |

Statistical associations were assessed using Fisher's exact test.

[a]Clinical events included adjudication-confirmed progression to cirrhosis, hepatic decompensation, liver transplantation, qualification for transplantation, or death.
**ns**, not significant.

# At Baseline, ANALI Score > 2 (High Risk) was Significantly Associated With Increased Fibrosis Biomarkers and Liver Enzyme Levels

| | ANALI > 2 (n = 141) | ANALI ≤ 2 (n = 247) | *P* value |
|---|---|---|---|
| **ELF score** | **9.3 (8.7, 10.1)** | **8.9 (8.3, 9.5)** | **< 0.001** |
| **LSM, kPa** | **8.1 (6.1, 10.4)** | **6.4 (5.0, 8.5)** | **< 0.001** |
| ALT, IU/L | 57 (28, 104) | 46 (25, 94) | 0.073 |
| **AST, IU/L** | **43 (27, 74)** | **36 (24, 63)** | **0.032** |
| **GGT, IU/L** | **189 (79, 429)** | **125 (43, 322)** | **0.0061** |
| **ALP, IU/L** | **190 (128, 344)** | **156 (98, 271)** | **0.0035** |
| **Total bile acids,[a] ng/mL** | **2376 (1156, 4882)** | **1565 (697, 4273)** | **0.014** |
| IBD, n (%) | 99 (70.2) | 170 (68.8) | 0.78 |
| Fecal calprotectin, µg/g | 104 (29, 336) | 62 (29, 235) | 0.089 |
| **Cholangitis, n (%)** | **15 (10.6)** | **6 (2.4)** | **< 0.001** |
| **Clinical events,[b] n (%)** | **7 (5.0)** | **3 (1.2)** | **0.041** |

| | | ANALI > 2 (n = 141) | ANALI ≤ 2 (n = 247) |
|---|---|---|---|
| **IHBD dilatation** | **0** | 0 | 61 (24.7) |
| | **1** | 25 (17.7) | 44 (17.8) |
| | **2** | 116 (82.3) | 142 (57.5) |
| **Dysmorphy** | **0** | 7 (5.0) | 238 (96.4) |
| | **1** | 134 (95.0) | 9 (3.6) |
| **Portal hypertension** | **0** | 111 (78.7) | 244 (98.8) |
| | **1** | 30 (21.3) | 3 (1.2) |

Data shown are n (%)

Statistical comparisons were assessed using Wilcoxon test, except for IBD (Pearson's Chi-square test), and cholangitis and clinical events (both Fisher's exact test owing to small patient numbers).
Data shown are median (Q1, Q3) unless otherwise specified.

[a]Total bile acids after removing UDCA and UDCA conjugates. [b]Clinical events included adjudication-confirmed progression to cirrhosis, hepatic decompensation, liver transplantation, qualification for transplantation, or death.
**ALP,** alkaline phosphatase; **ALT**, alanine transaminase; **AST**, aspartate transferase; **ELF**, Enhanced Liver Fibrosis; **GGT**, γ-glutamyl transferase; **IBD**, inflammatory bowel disease; **IHBD**, intrahepatic bile duct; **LSM**, liver stiffness measurement; **Q**, quartile; **UDCA**, ursodeoxycholic Acid.

# At Baseline, Liver Dysmorphy was Significantly Associated With Increased Fibrosis Biomarkers and Liver Enzymes

| | Liver Dysmorphy = 1 (n = 143) | Liver Dysmorphy = 0 (n = 245) | *P* value |
|---|---|---|---|
| **ELF score** | **9.3 (8.7, 10.1)** | **8.9 (8.3, 9.5)** | **< 0.001** |
| **LSM, kPa** | **7.8 (6.1, 10.3)** | **6.4 (5.0, 8.5)** | **< 0.001** |
| ALT, IU/L | 55 (30, 94) | 46 (25, 95) | 0.10 |
| **AST, IU/L** | **43 (27, 73)** | **36 (24, 63)** | **0.032** |
| **GGT, IU/L** | **185 (79, 402)** | **128 (43, 322)** | **0.013** |
| **ALP, IU/L** | **188 (128, 333)** | **156 (98, 271)** | **0.0061** |
| **Total bile acids,[a] ng/mL** | **2376 (1124, 4535)** | **1606 (691, 4392)** | **0.014** |
| IBD, n (%) | 100 (69.9) | 169 (69.0) | 0.84 |
| Fecal calprotectin, µg/g | 104 (29, 298) | 63 (29, 233) | 0.14 |
| **Cholangitis, n (%)** | **15 (10.5)** | **6 (2.4)** | **0.002** |
| **Clinical events,[b] n** (%) | **7 (4.9)** | **3 (1.2)** | **0.042** |

Statistical comparisons were assessed using Wilcoxon test, except for IBD (Pearson's Chi-square test), and cholangitis and clinical events (both Fisher's exact test owing to small patient numbers). Data shown are median (Q1, Q3) unless otherwise specified.

[a]Total bile acids after removing UDCA and UDCA conjugates. [b]Clinical events included adjudication-confirmed progression to cirrhosis, hepatic decompensation, liver transplantation, qualification for transplantation, or death. **ALP,** alkaline phosphatase; **ALT**, alanine transaminase; **AST**, aspartate transferase; **ELF**, Enhanced Liver Fibrosis; **GGT**, γ-glutamyl transferase; **IBD**, inflammatory bowel disease; **LSM**, liver stiffness measurement; **Q**, quartile; **UDCA**, ursodeoxycholic Acid.

# At Baseline, Portal Hypertension was Significantly Associated With Increased Fibrosis Biomarkers and Cholestasis Markers

| | Portal Hypertension = 1 (n = 33) | Portal Hypertension = 0 (n = 355) | *P* value |
|---|---|---|---|
| **ELF score** | **9.7 (9.2, 10.3)** | **9.0 (8.4, 9.6)** | **< 0.001** |
| **LSM, kPa** | **8.8 (6.9, 12.4)** | **6.8 (5.2, 8.9)** | **0.0016** |
| ALT, IU/L | 70 (31, 118) | 49 (26, 93) | 0.12 |
| AST, IU/L | 54 (25, 75) | 38 (25, 63) | 0.23 |
| **GGT, IU/L** | **278 (135, 522)** | **140 (51, 329)** | **0.027** |
| **ALP, IU/L** | **237 (158, 422)** | **167 (104, 285)** | **0.018** |
| Total bile acids,[a] ng/mL | 2724 (1481, 5073) | 1790 (796, 4327) | 0.12 |
| IBD, n (%) | 24 (72.7) | 245 (69.0) | 0.66 |
| **Fecal calprotectin, µg/g** | **266 (90, 763)** | **72 (29, 245)** | **0.018** |
| **Cholangitis, n (%)** | **5 (15.2)** | **16 (4.5)** | **0.025** |
| Clinical events,[b] n (%) | 1 (3.0) | 9 (2.5) | 0.59 |

Statistical comparisons were assessed using Wilcoxon test, except for IBD (Pearson's Chi-square test), and cholangitis and clinical events (both Fisher's exact test owing to small patient numbers). Data shown are median (Q1, Q3) unless otherwise specified.

[a]Total bile acids after removing UDCA and UDCA conjugates. [b]Clinical events included adjudication-confirmed progression to cirrhosis, hepatic decompensation, liver transplantation, qualification for transplantation, or death.
**ALP,** alkaline phosphatase; **ALT**, alanine transaminase; **AST**, aspartate transferase; **ELF**, Enhanced Liver Fibrosis; **GGT**, γ-glutamyl transferase; **IBD**, inflammatory bowel disease; **LSM**, liver stiffness measurement; **Q**, quartile; **UDCA**, ursodeoxycholic Acid.

# Treatment With CILO was Not Associated With a Change in ANALI Score Versus Placebo

| ANALI score | CILO (n = 277) | | Placebo (n = 139) | |
|---|---|---|---|---|
| | n | Median (Q1, Q3) | n | Median (Q1, Q3) |
| **Baseline** | 262 | 2 (1, 4) | 126 | 2 (2, 4) |
| **Week 96** | 201 | 3 (2, 4) | 101 | 4 (2, 4) |
| **Change at week 96** | 194 | 1 (0, 2) | 91 | 1 (0, 2) |

**CILO**, cilofexor; **Q**, quartile.

# Summary

- At baseline, ANALI score was associated with noninvasive markers of liver fibrosis and levels of liver enzymes in patients with noncirrhotic PSC
- Higher baseline ANALI scores were associated with increased incidence of cholangitis events during the 96-week PRIMIS study duration
- The association between ANALI score and other PSC-related clinical events requires further exploration in future studies with longer follow-up
- ANALI score or components could become non-invasive biomarkers for usage in PSC trials

**PSC**, primary sclerosing cholangitis.

# Acknowledgements


- This study was funded by Gilead Sciences, Inc.
- We acknowledge patients and investigators in the PRIMIS study. We thank Xiaomin Lu for her contributions to the analysis of the data.
- Medical writing support was provided by Michael Molloy-Bland PhD of Oxford PharmaGenesis, Melbourne, Australia, and funded by Gilead Sciences, Inc.

# Backup slides

# At Baseline, IHBD Was Not Significantly Associated With Fibrosis Biomarkers or Liver Enzymes

| | IHBD = 0 (n = 61) | IHBD = 1 (n = 69) | IHBD = 2 (n = 258) | *P* value |
|---|---|---|---|---|
| **ELF score** | 9.1 (8.4, 9.6) | 9.2 (8.3, 10.1) | 9.1 (8.5, 9.7) | 0.88 |
| **LSM, kPa** | 6.3 (5.0, 9.2) | 7.0 (5.3, 8.6) | 7.2 (5.3, 9.1) | 0.26 |
| **ALT, IU/L** | 50 (26, 88) | 57 (27, 102) | 48 (26, 94) | 0.59 |
| **AST, IU/L** | 41 (25, 62) | 39 (26, 73) | 38 (25, 63) | 0.38 |
| **GGT, IU/L** | 132 (52, 337) | 194 (48, 537) | 145 (55, 327) | 0.70 |
| **ALP, IU/L** | 162 (102, 271) | 162 (101, 324) | 179 (108, 304) | 0.79 |
| **Total bile acids,[a] ng/mL** | 2314 (722, 3385) | 1665 (691, 4380) | 1852 (838, 5009) | 0.52 |
| **IBD, n (%)** | 36 (59.0) | 46 (66.7) | 187 (72.5) | 0.11 |
| **Fecal calprotectin, µg/g** | 52 (29, 220) | 72 (29, 206) | 93 (29, 304) | 0.40 |
| **Cholangitis, n (%)** | 1 (1.6) | 3 (4.3) | 17 (6.6) | 0.35 |
| **Clinical events,[b] n (%)** | 1 (1.6) | 1 (1.4) | 8 (3.1) | 0.90 |

Statistical comparisons were assessed using Kruskal–Wallis test, except for IBD (Pearson's Chi-square test), and cholangitis and clinical events (both Fisher's exact test owing to small patient numbers). Data shown are median (Q1, Q3) unless otherwise specified.

[a]Total bile acid after removing UDCA and UDCA conjugates. [b]Clinical events included adjudication-confirmed progression to cirrhosis, hepatic decompensation, liver transplantation, qualification for transplantation, or death.
**ALP,** alkaline phosphatase; **ALT**, alanine transaminase; **AST**, aspartate transferase; **ELF**, Enhanced Liver Fibrosis; **GGT**, γ-glutamyl transferase; **IBD**, inflammatory bowel disease; **IHBD**, intrahepatic bile duct; **LSM**, liver stiffness measurement; **Q**, quartile; **UDCA**, ursodeoxycholic Acid.

# Baseline Risk Factors for ANALI Score Increase to > 2

| | Odds ratio (95% CI) | *P* value |
|---|---|---|
| **UDCA, yes vs no** | 1.43 (0.77, 2.65) | 0.2519 |
| **Fibrosis stage (Ludwig), F3 vs F0–2** | 1.19 (0.59, 2.37) | 0.6261 |
| **IBD, yes vs no** | 1.38 (0.73, 2.61) | 0.3205 |
| **LSM, ≥ 9.6 vs < 9.6** | 0.83 (0.38, 1.80) | 0.6388 |
| **ELF score, ≥ 9.8 vs < 9.8** | 1.71 (0.85, 3.46) | 0.1347 |
| **ALP, > 1.5 x ULN vs ≤ 1.5 x ULN** | 1.22 (0.66, 2.27) | 0.5294 |

Odds ratios and *P* values derived from multivariable logistic regression analysis.

**ALP,** alkaline phosphatase; **CI**, confidence interval; **ELF**, Enhanced Liver Fibrosis; **IBD**, inflammatory bowel disease; **LSM**, liver stiffness measurement; **UDCA**, ursodeoxycholic acid.