Validation of the PREsTo machine learning algorithm for the prediction of disease progression in patients with primary sclerosing cholangitis (PSC)

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Background: PREsTo is a machine learning-based algorithm that accurately predicted the risk of hepatic decompensation in patients with non-advanced PSC. Our objective was to prospectively validate the PREsTo algorithm for the prediction of disease progression in a randomized trial of PSC patients.

Methods: We included 234 adults with large-duct PSC enrolled in a phase 2b, placebo-controlled trial of simtuzumab (SIM). Since SIM was ineffective in this 96-week study, treatment groups were combined for this analysis. The estimated risk of hepatic decompensation at 2 years was calculated according to the PREsTo algorithm using baseline (BL) age, alkaline phosphatase (ALP), AST, bilirubin, albumin, sodium, hemoglobin, platelets, and PSC duration. Liver fibrosis was staged according to the Ishak classification at BL, week 48, and week 96. Discrimination of PREsTo for hepatic decompensation, PSC-related clinical events (i.e. decompensation, ascending cholangitis, cholangiocarcinoma, transplantation), and progression to cirrhosis was determined using c-statistics. Model calibration was evaluated according to tertiles of predicted risk using the Hosmer and Lemeshow goodness-of-fit statistic.

Results: The median age was 45 years, 64% were male, 48% had UC, 62% were on UDCA, 51% had bridging fibrosis or cirrhosis, and the median (IQR) serum ALP and bilirubin at BL were 260 U/L (129-401) and 0.7 mg/dL (0.5-1.1), respectively. Over a median follow-up of 23.0 months (range, 2.8, 27.8), 10 subjects (4.3%) developed hepatic decompensation (ascites [n=6], encephalopathy [n=2], variceal hemorrhage [n=2]), 47 subjects (20%) developed a PSC-related clinical event (first events of ascending cholangitis [n=27], decompensation [n=6],
cholangiocarcinoma [n=3], and other [n=11]), and 36 of 209 (17%) non-cirrhotic subjects progressed to cirrhosis. PREsTo accurately predicted hepatic decompensation (c-statistic, 0.87 [95% CI 0.79-0.96]), but discrimination was lower for PSC-related clinical events (0.74 [95% CI 0.67-0.82]) and progression to cirrhosis (0.62 [95% CI 0.52-0.73]). Calibration of PREsTo for hepatic decompensation was good (observed vs expected events: low-risk: 0 vs 0.8; medium-risk: 1 vs 1.0; high-risk: 9 vs 8.4; p=0.36).

**Conclusions:** In this prospective clinical trial of patients with PSC, the PREsTo algorithm accurately predicted the risk of hepatic decompensation, but had reduced performance for other PSC-related complications including progression to cirrhosis.