Background: Alagille syndrome (ALGS) and Progressive familial intrahepatic cholestasis (PFIC) are rare, inherited cholestatic disorders with risk of end-stage liver disease requiring liver transplantation (LT). Diagnosis often requires liver biopsy for histological evaluation and fibrosis staging. Non-invasive biomarkers APRI and FIB-4 have been shown to be reliable surrogates of fibrosis in adult and pediatric liver disease. We investigate use of biomarkers to predict fibrosis severity and risk for LT in children with ALGS and PFIC.

Materials/Methods: This retrospective, multi-center cross-sectional study evaluated APRI, FIB-4, and conjugated bilirubin (CB) in predicting liver fibrosis severity and risk for LT in children with ALGS or PFIC who had ≥ 1 liver biopsy. Diagnoses were confirmed by genetics or strict clinical criteria. Liver fibrosis was staged (METAVIR) by a single, blinded pathologist. F0-2 was classified as “non-severe” and F3-4 as “severe.” APRI and FIB-4 were calculated and CB was collected from labs ±90 days of biopsy. Patient demographics and clinical characteristics were compared by Fisher’s exact test or Wilcoxon rank sum test. Logistic regression and area under receiver operating characteristic curves (AUC) were used to assess association of biomarkers with fibrosis severity and risk for LT.

Results: In 64 total patients, (40 ALGS, 24 PFIC; 67% male) the median biopsy age was 2.1 years (IQR 0.5, 6.1). 30% received a LT at a median age of 3.5 years (0.5, 6.1). To distinguish F3-4 vs F0-2 in ALGS, the AUC was 0.72 (p=0.01) for APRI, 0.68 (p=0.04) for FIB-4 and 0.69 (p=0.12) for CB. With a 50% increase in APRI, odds of F3-4 were 1.3-higher (p=0.02) in ALGS. To distinguish F3-4 vs F0-2 in PFIC, the AUC was 0.74 (p=0.04) for APRI, 0.65 (p=0.22) for FIB-4 and 0.26 for CB. In ALGS, APRI (AUC 0.87, p<0.01) and FIB-4 (AUC 0.84, p<0.01) were good predictors of LT. In ALGS, a 50% increase in APRI, FIB-4, and CB increased odds of LT by 1.55-fold (p=0.001), 1.41-fold (p<0.01), or 1.3-fold (p<0.01), respectively. In PFIC, only FIB-4 (AUC 0.80, p=0.002) demonstrated good prediction of LT.

Conclusions: This liver biopsy validated study suggests that APRI is a fair predictor of F3-4 fibrosis in both ALGS and PFIC, outperforming FIB-4 and CB as a non-invasive surrogate of fibrosis. APRI and FIB-4 are also good predictors of risk for LT in ALGS. CB appears to be unable to distinguish F3-4 or predict risk for LT in either ALGS or PFIC. In PFIC, only FIB-4 is a good predictor of risk for LT.