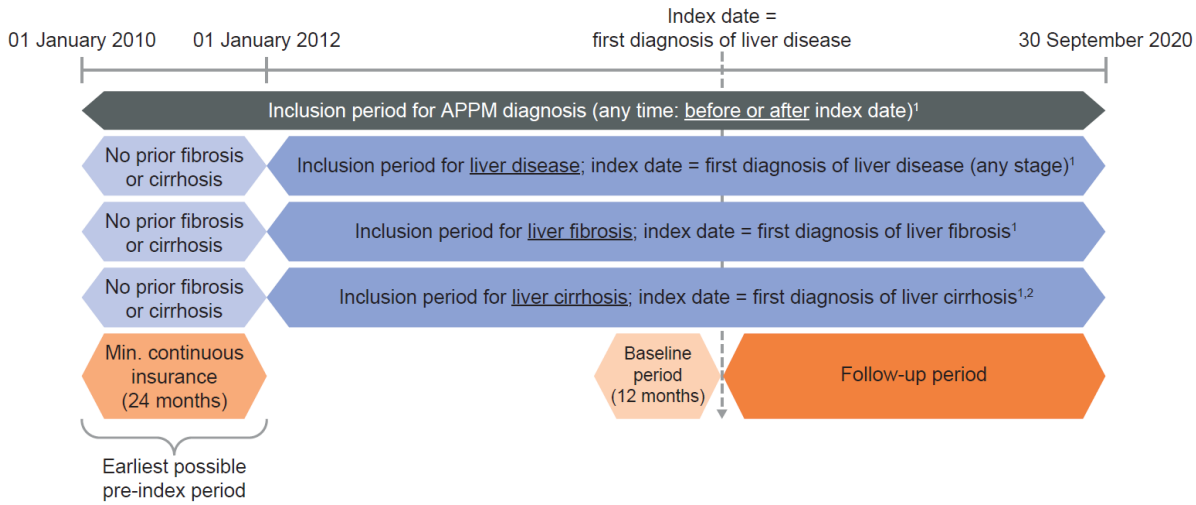
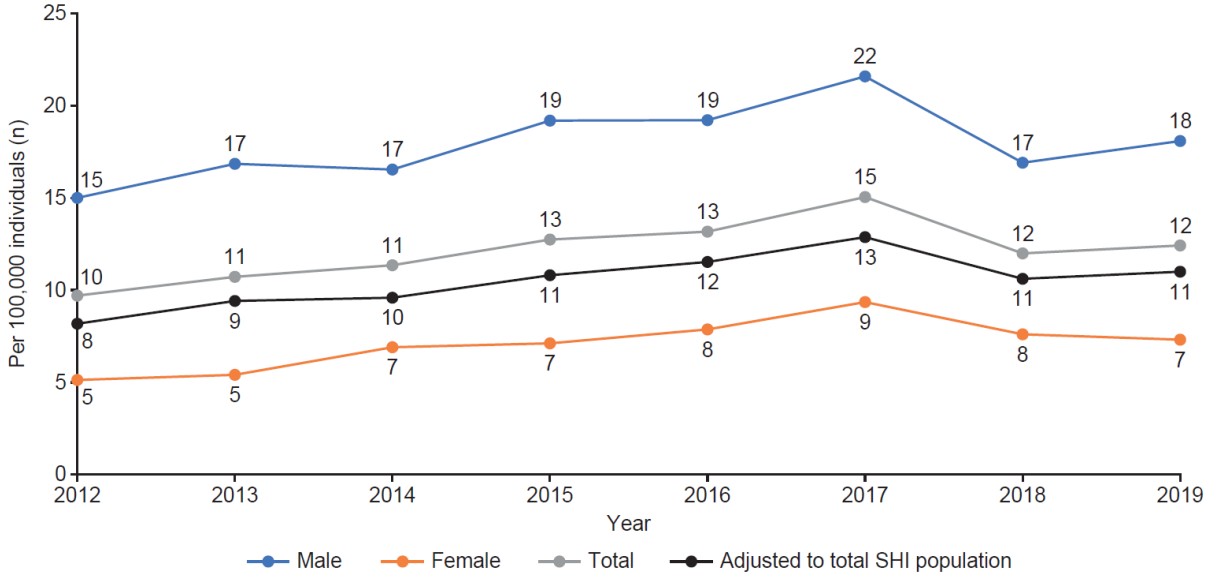
Supplementary material

Supplementary Figure 1 Study period and eligibility of patients with alterations in plasma protein metabolism and incident liver disease.



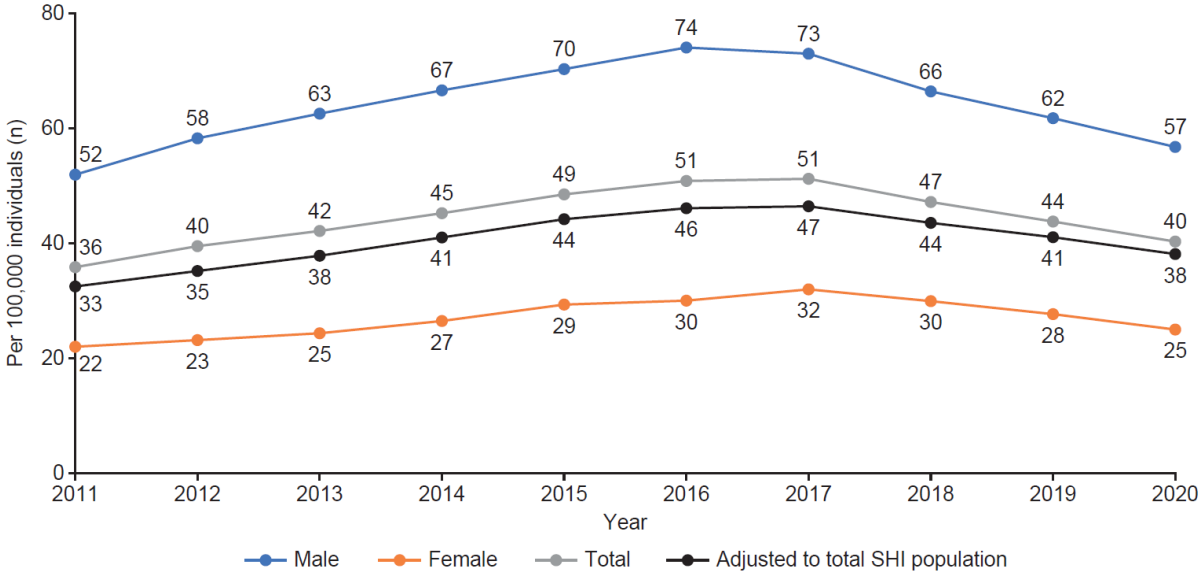
[1]One inpatient diagnosis or two confirmed outpatient diagnoses (within 1 year) with the relevant ICD-10-GM codes. ICD-10-GM codes for liver disease were divided into two groups, fibrotic (K74.0-2, K70.2) and cirrhotic (K74.3-7, K70.3, K71.7), while APPM was identified with the code E88.0. [2]Incident fibrotic patients who developed cirrhosis after 01 January 2012 (one inpatient or one confirmed outpatient diagnosis) were also included in the cirrhotic cohort, with the date of their first cirrhosis diagnosis being the new index date. APPM, alterations in plasma protein metabolism; ICD-10-GM, German Modification of the International Classification of Diseases – 10th Revision.

Supplementary Figure 2 Cumulative incidence of liver disease in patients with APPM in 2012–2019.



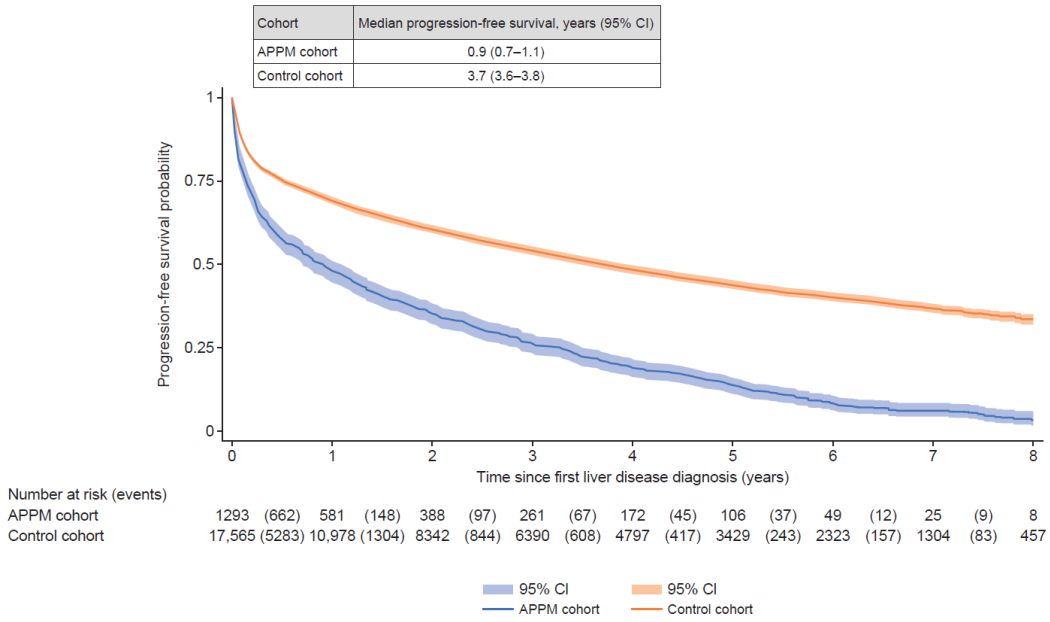
Data are rounded to the nearest integer. For calculation of the cumulative incidence of liver disease in patients with APPM, the numerator was the number of patients with APPM diagnosed at any point and with liver disease diagnosed during the year of the index date, but without any diagnosis (inpatient or outpatient) of liver disease within the previous 2 years (and with continuous insurance coverage during this period). The denominator was the number of patients alive at the beginning of the respective calendar year for whom no liver disease diagnosis was documented in the 24 months before the index date, and with continuous insurance over this period. Cumulative incidence was adjusted for age and sex differences compared with the German SHI population. APPM, alterations in plasma protein metabolism; SHI, statutory health insurance.

Supplementary Figure 3 Point prevalence of liver disease in patients with APPM in 2011–2020.



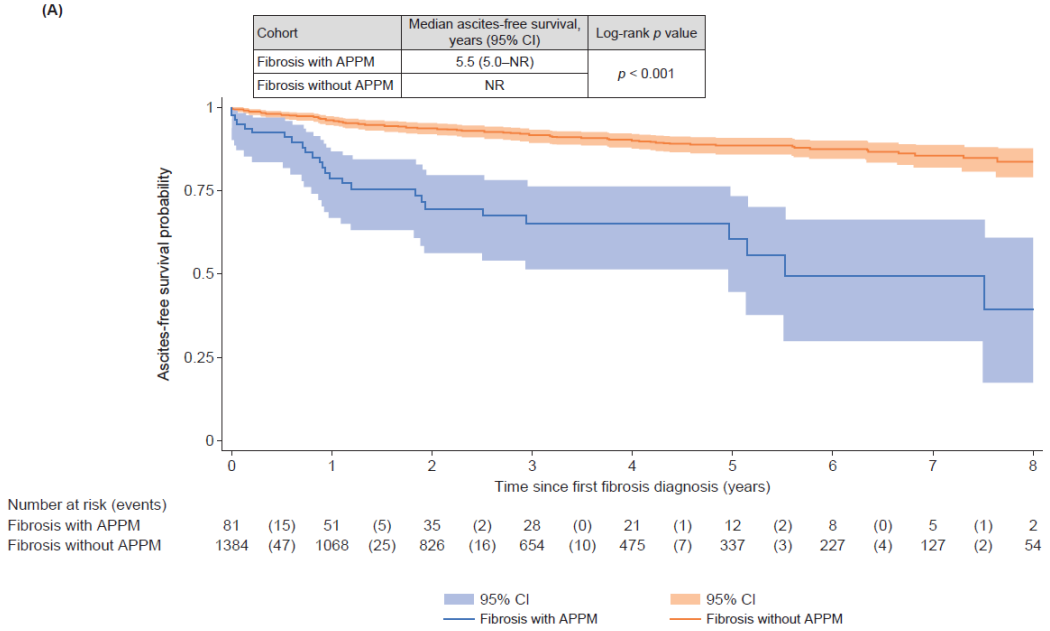
Data are rounded to the nearest integer. For calculation of the point prevalence of liver disease in patients with APPM, the denominator was the number of individuals insured by AOK PLUS on 01 January of the respective calendar year (2011–2020) and during the preceding 12 months. The numerator was the number of patients who were alive on the first day of each year, had evidence of confirmatory diagnosis/diagnoses of APPM (made in two different quarters within the same year) and a diagnosis of liver disease during the previous year, and with continuous insurance coverage with AOK PLUS during that year. Point prevalence was adjusted for age and sex differences compared with the German SHI population. APPM, alterations in plasma protein metabolism; SHI, statutory health insurance.

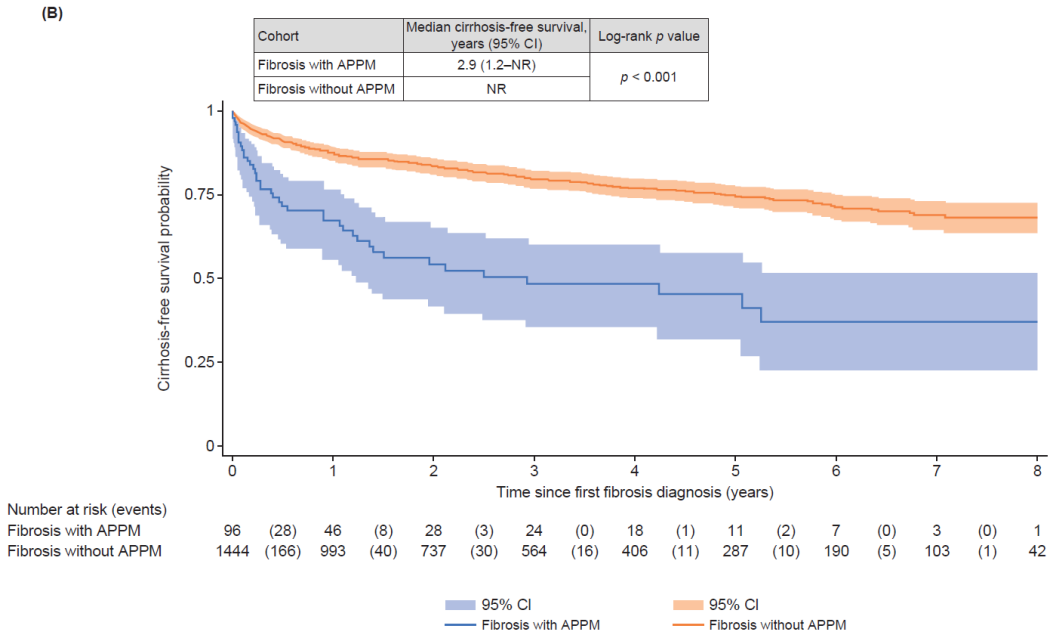
Supplementary Figure 4 Progression-free survival (composite endpoint).

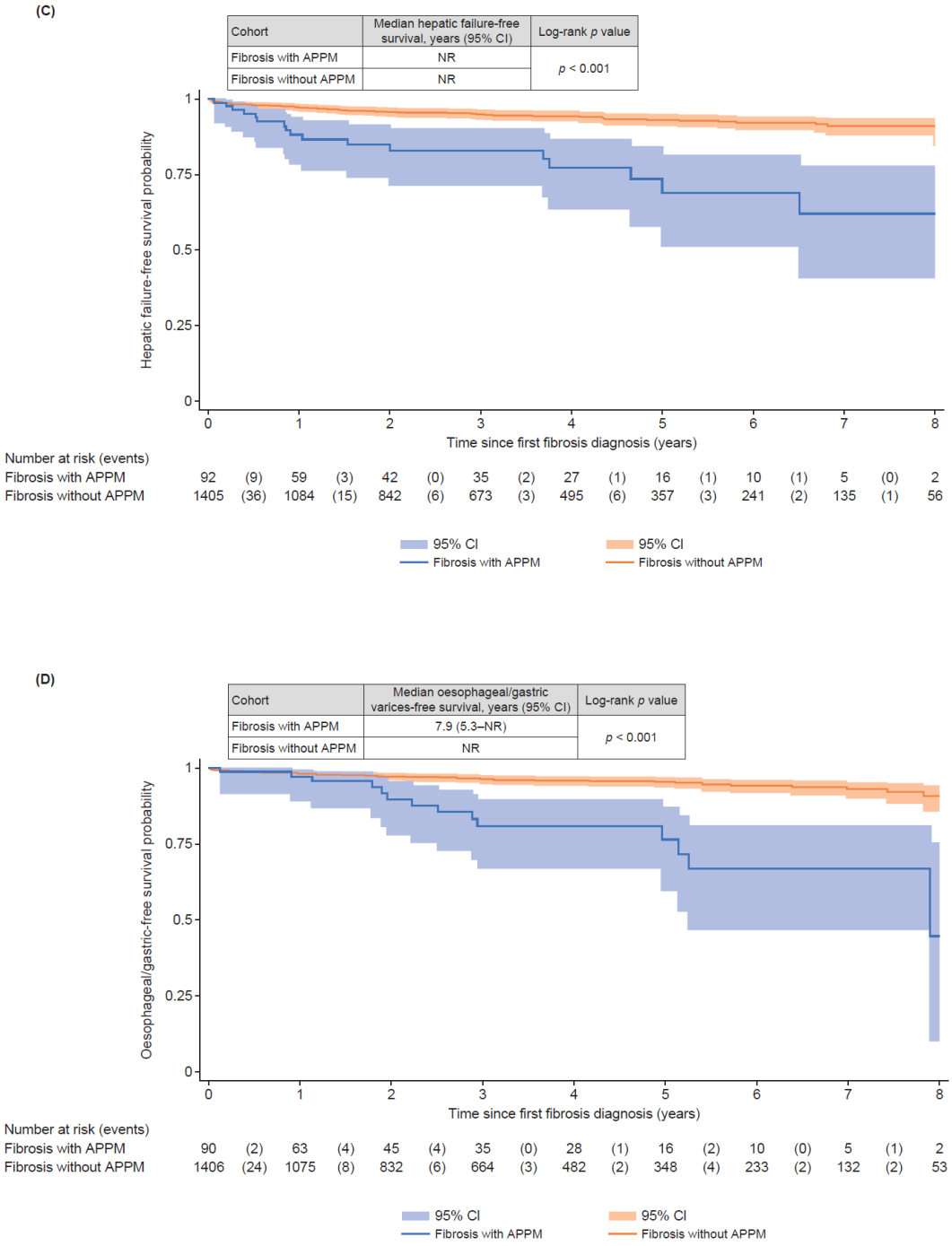


A composite endpoint of progression-free survival was defined as the time from index date until the first date with acute peritonitis, ascites, cirrhosis (only among patients with fibrosis), oesophageal/gastric varices, hepatocellular carcinoma, hepatic encephalopathy, hepatic failure, liver transplantation or all-cause death. AATD, alpha-1 antitrypsin deficiency; CI, confidence interval; LD, liver disease.

Supplementary Figure 5 Event-free survival following disease progression events in patients with fibrosis with and without APPM: (A) ascites; (B) cirrhosis; (C) hepatic failure; and (D) oesophageal and gastric varices.

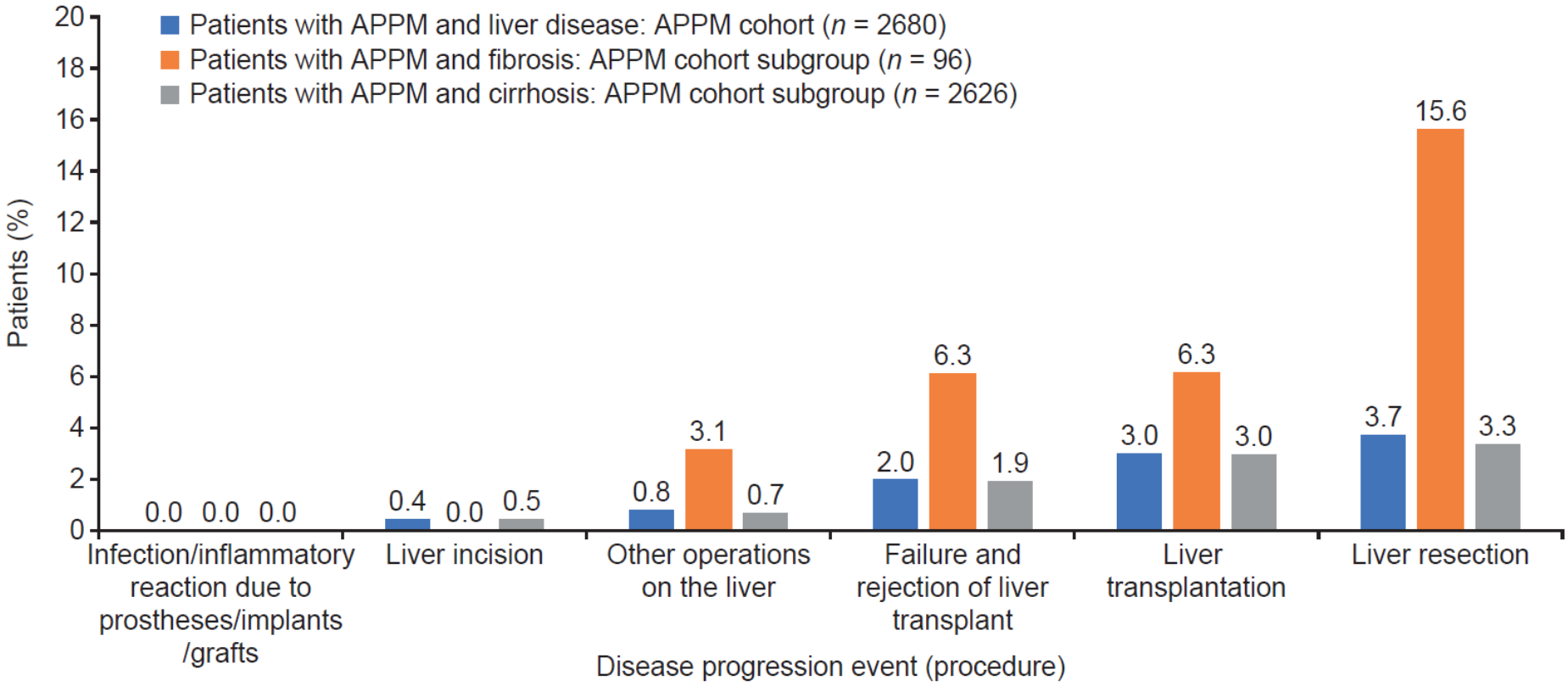






AATD, alpha-1 antitrypsin deficiency; CI, confidence interval; NR, not reached.

Supplementary Figure 6 Procedures and procedure-related events indicating disease progression.



Disease progression events that occurred after the index date until the end of the study. In patients with fibrosis in the control cohort, 93 patients (6.4%) had a liver resection and three patients (0.2%) had a liver transplantation indicating disease progression. In patients with cirrhosis in the control cohort, 488 patients (1.9%) had a liver resection and 31 patients (0.1%) had a liver transplantation indicating disease progression. APPM, alterations in plasma protein metabolism.