large populations of patients and controls, regardless of ABCB4 status. Our secondary aim was to estimate the frequency of the syndrome among patients with symptomatic cholelithiasis.
Method: This retrospective case-control study included all patients diagnosed with LPAC syndrome based on original criteria in 4 French centers (one referral center and 3 general hospitals). Patients who underwent cholecystectomy for classical gallstone disease in a general hospital served as controls. A multivariate logistic regression model adjusted on age, sex, body mass index, and metabolic syndrome was used to identify the variables independently associated with LPAC syndrome. A diagnostic score was developed and validated. Patients were compared according to ABCB4 mutation status. Frequency of LPAC syndrome was estimated based on the number of all patients cholecystectomized for gallstones during the same period.
Results: 512 adult patients (306 cases, 206 controls) were included. In addition to the 3 previously established criteria (age at first symptoms <40; recurrence of symptoms after cholecystectomy; ultrasound signs of intrahepatic microlithiasis), 2 new criteria were identified: (1) features suggestive of common bile duct lithiasis, (2) lack of cholecystitis evidence. The new score had a high diagnostic performance (c-statistic: 0.99). ABCB4 mutation was present in 43% of LPAC patients. These patients had an increased risk of intrahepatic cholestasis of pregnancy (ICP; 34% vs. 17%), chronic elevation of GGT (33% vs. 14%) and transaminases (16% vs. 8%), history suggestive of common bile duct lithiasis (80% vs. 68%), and personal or familial history of primary liver cancer (6% vs. 1%). One (1.5%) out of 68 controls who had an expert ultrasound focused on signs of intrahepatic microlithiasis showed typical features of LPAC syndrome. In line with this, the frequency of LPAC syndrome within all patients with symptomatic cholelithiasis varied from 0.5% to 1.9%.
Conclusion: Common bile duct stone in young patients with no prior history of cholecystectomy should suggest LPAC syndrome. LPAC patients with ABCB4 alteration seem more exposed to the risk of ICP, chronic cholestasis, and personal or familial primary liver cancer. LPAC syndrome represents about 1% of patients with symptomatic cholelithiasis.

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Role of alpha-1 antitrypsin genotypes in the progression of adult liver disease

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Background and Aims: Alpha-1 antitrypsin deficiency (A1AD) is an autosomal codominant disease associated with an increased risk of liver and lung disease in adults. The association between liver disease and homozygosity for the mutant Z allele (PiZZ) is well-established, however, the contribution of other genotypes to the pathogenesis of adult liver disease is unclear. We aimed to assess the prevalence of liver fibrosis in different A1AD genotypes, including rare variants.
Method: Multicenter cross-sectional case-control study, including adult A1AD patients treated in pneumology departments of four Portuguese academic and one non-academic centers. Data pertaining pulmonary function and imaging were retrospectively collected. Clinical, biochemical, and liver stiffness (LS) measured by transient elastography (TE, Fibroscan) data were prospectively collected at time of enrollment. Significant liver fibrosis was defined by LS values ≥7.0 kPa. Patients with concomitant liver diseases were excluded. Controls were recruited within a prospective epidemiological study in the general adult population.
Results: 142 cases and 200 controls were included. Our study comprised 47 PiZZ, as well as 76 PiZ heterozygotes (38 MZ, 34 SZ, 3 MheerlenZ, 1 ZQ0s), 10 PiS (5 SS, 5 MS), and 9 PiMmalton or PiMpalermo carriers. Cases and controls did not differ in terms of age, BMI, alcohol consumption, serum lipid levels, or CAP. Cases had significantly higher serum levels of ALT, AST and GGT ($p < 0.0001$) compared to controls. CAP values were higher in A1AD patients but the difference did not attain statistical significance ($p = 0.114$).
LS was 5.2 ± 1.5 kPa in controls and 6.0 ± 4.1 kPa in A1AD ($p = 0.046$) being highest in PiZZ (7.3 ± 5.3 kPa) and PiZ heterozygotes (5.7 ± 3.6 kPa). Liver fibrosis was detected in 20% (29/142) of patients. The genotype-specific prevalence was: PiZZ 34%(16/47), PiZ- 16%(12/76), while none of the PiS carriers had significant liver fibrosis. Among patients with rare A1AD variants, one PiMmalton/PiMmalton had significant liver fibrosis. Liver fibrosis was statistically significantly associated with lower alpha-1 antitrypsin ($p < 0.0001$) and higher total cholesterol ($p = 0.024$). Importantly, only 18% (26/142) of patients with liver fibrosis had abnormal liver tests.

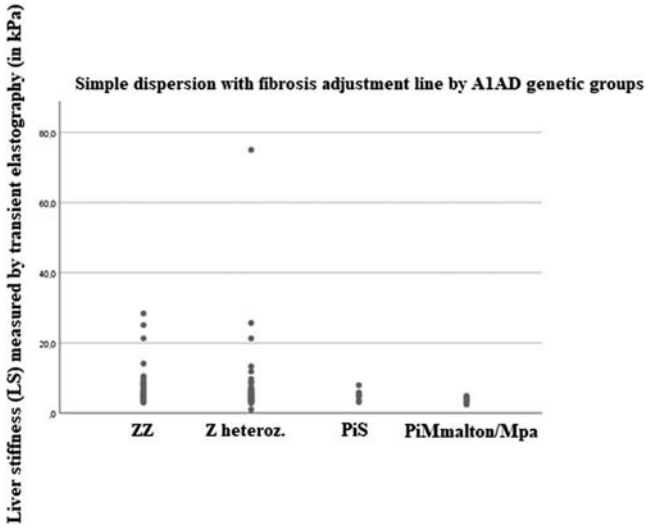

Figure 1: Liver fibrosis by alpha-1 antitrypsin deficiency genetic group.

Conclusion: Akin to PiZZ, PiZ heterozygoty is associated with liver fibrosis development. Moreover, our results suggest that rare A1AD variants may also promote liver fibrogenesis. Routine laboratory tests are not predictive of significant liver fibrosis, highlighting the need for non-invasive methods such as TE in patients with A1AD.