Supplementary material

Patients and methods

Laboratory tests

In sub-study I, laboratory tests were performed using a fasting blood sample obtained at the day of study inclusion. In addition to hepatitis A/B/C/E serology, we performed serologic tests for autoimmune hepatitis and primary biliary as well as primary sclerosing cholangitis. Moreover, patients were evaluated for other metabolic liver diseases (hemochromatosis [serum iron, transferrin, and ferritin levels, as well as transferrin saturation] and Wilson's disease [serum copper and ceruloplasmin levels]).

Short form (36) health survey and alcohol use disorders identification test

Health-related quality of life was assessed using the German translation of the SF-36v2 survey (Optum, Eden Prairie, MN, USA). This questionnaire has extensively been used in patients with pulmonary manifestation of A1AD, as well as chronic liver disease populations.[1-5] The SF-36 consists of 36 questions measuring eight health domains, providing psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. Norm-based scaling in reference to a general population with an average value of 50 points was applied. Values between 45 and 55 points denote normal HRQOL, while scores <45 and >55 points indicate worse and better HRQOL, respectively.

Hepatic venous pressure gradient measurement

The Vienna Hepatic Hemodynamic Lab at the Medical University of Vienna performed the hepatic venous pressure gradient (HVPG) measurements in patients included in sub-study II according to a standardized operating procedure [6]. HVPG measurements were performed in the absence of non-selective beta blockers and nitrates. Clinically significant portal hypertension (CSPH) was defined by HVPG values ≥10 mmHg.[7, 8]

SERPINA1 genotyping

Subjects included in sub-study I were genotyped by a reference laboratory. In patients with CSPH and liver donors (sub-study II), *SERPINA1 rs28929474* genotyping was performed using using a StepOnePlus Real-Time PCR System and a TaqMan SNP Genotyping Assay (Applied Biosystems, USA).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 24 (IBM, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA).

Continuous variables were reported as mean ±standard error of the mean or median (interquartile range), while categorical variables were reported as number of subjects with (proportion of subjects with) the certain characteristic.

Student's t test was used for group comparisons of continuous variables when applicable. Otherwise, Mann-Whitney U test was applied. Group comparisons of categorical variables were performed using Chi squared or Fisher's Exact test. Spearman's rank correlation analysis was used to investigate correlates of liver stiffness and CAP.

A *P* value ≤0.05 was considered statistically significant.

Results

Sub-study II

Patient characteristics

The median age of the subjects enrolled in sub-study II was 54.2(27.5) years. The mean body mass index (BMI) was 25.1 0.6 kg x m^{-2}. About one third (38.1%[16/42]) of the study participants were overweight (25-29.9 kg x m^{-2}), while 11.9%(5/42) were obese (≥30 kg x m^{-2}). Among patients treated by pulmonologists (Pi*ZZ/SZ), the median forced expiratory volume in 1 second (FEV_1) was 44(40) %. The proportion of patients on α1-antitrypsin augmentation therapy was (61.2%[19/31]), while 71%(22/31) and 25.8%(8/31) received bronchodilators and long-term oxygen treatment, respectively. Four patients (12.9%[4/31]) had a history of lung transplantation. Importantly, none of the subjects enrolled in sub-study I had a history of congestive heart failure or showed evidence of extrahepatic cholestasis, which could have interfered with liver stiffness measurements.[9] Additional patient characteristics are shown in Table 1.

Hepatitis A/B vaccination and hepatitis E seroprevalence

Only 26.2%(11/42) of subjects included in sub-study II were vaccinated against hepatitis A/B. Even in the subgroup of patients on α1-antitrypsin augmentation therapy, the vaccination rate was only 45%(9/20). In this subgroup of patients, the rate of hepatitis E antibody positivity was 25%(5/20).

Health-related quality of life

In the overall cohort, we observed a PCS of 38.9±2 points, indicating impaired physical health (Table 1). In contrast, MCS suggests better-than-average mental health (55.5[8.6] points). As expected, health-related quality of life was unaffected by the presence of liver fibrosis ≥F2.

References

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Supplementary table 1

	Liver stiffness, n=42		CAP, n=41	
	ρ	*P* value	ρ	*P* value
Age, years	0.089	0.573	0.339	0.03
BMI, kg x m^{-2}	0.276	0.077	0.449	0.003
Liver stiffness, kPa	-	-	0.304	0.053
CAP, dB x m^{-1}	0.304	0.053	-	-
Platelet count, G x L^{-1}	-0.38	0.013	-0.157	0.326
Bilirubin, mg x dL^{-1}	-0.019	0.907	-0.231	0.147
Albumin, g x L^{-1}	0.069	0.663	-0.299	0.057
Prothrombin time, %	-0.281	0.071	-0.029	0.856
AP, U x L^{-1}	0.102	0.518	-0.018	0.912
AST, U x L^{-1}	0.175	0.267	0.102	0.528
ALT, U x L^{-1}	0.144	0.363	0.126	0.432
GGT, U x L^{-1}	0.266	0.089	0.166	0.299
Triglycerides, mg x dL^{-1}	0.201	0.201	0.282	0.074
Cholesterol, mg x dL^{-1}	0.024	0.878	0.18	0.259
LDL, mg x dL^{-1}	0.081	0.611	0.001	0.997
HDL, mg x dL^{-1}	-0.324	0.036	0.029	0.859
HbA1c, %	-0.08	0.625	0.394	0.013
HOMA-IR, mg x µU x dL^{-1} x mL^{-1}	0.231	0.141	0.474	0.002
hsCRP, mg x L^{-1}	0.081	0.618	0.418	0.008
vWF antigen, %	0.032	0.842	0.451	0.003
α1-antitrypsin, mg x dL^{-1}	0.158	0.317	-0.081	0.616
SF-36 PCS, points	-0.245	0.144	-0.366	0.028
SF-36 MCS, points	0.175	0.3	0.098	0.568

AUDIT, points	0.047	0.769	-0.249	0.117

Supplementary table 1. Correlation between liver stiffness/controlled attenuation parameter (CAP) and epidemiologic and anthropometric characteristics, laboratory parameters, health-related quality of life, and alcohol use.

Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; AP, alkaline phosphatase; AST, aspartate transaminase; AST, alanine transaminase; GGT, gamma-glutamyltransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; vWF, von Willebrand factor; SF-36, short form (36) health survey; AUDIT, alcohol use disorders identification test