Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

The impact of transmembrane 6 superfamily 2 (TM6SF2) rs58542926 on liver-related events in patients with advanced chronic liver disease

Lorenz Balcar[a,b,1], Bernhard Scheiner[a,b,1], Markus Urheu[a], Patrick Weinberger[a], Rafael Paternostro[a,b], Benedikt Simbrunner[a,b], Georg Semmler[a,b], Claudia Willheim[a], Matthias Pinter[a], Peter Ferenci[a], Michael Trauner[a], Thomas Reiberger[a,b], Albert Friedrich Stättermayer[a,b,2,*], Mattias Mandorfer[a,b,2,*]

[a] Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria
[b] Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

ARTICLE INFO

Article history:
Received 27 September 2022
Accepted 11 February 2023
Available online xxx

Keywords:
Cirrhosis
Decompensation
Genetics
Liver fibrosis
Portal hypertension

ABSTRACT

Background & aims: Genetic factors such as the transmembrane 6 superfamily 2 (*TM6SF2*) *rs58542926* single nucleotide variant(SNV) modulate the susceptibility for (advanced) chronic liver disease ([A]CLD). However, the impact of this variant in patients who have already progressed to ACLD is unknown.
Methods: The association between *TM6SF2-rs58542926* genotype and liver-related events was evaluated in 938 ACLD patients undergoing hepatic venous pressure gradient (HVPG) measurement.
Results: Mean HVPG was 15±7 mmHg and mean UNOS MELD (2016) 11±5 points. Viral hepatitis (n = 495, 53%) was the most common cause of ACLD, followed by alcohol-related (ARLD; n = 342, 37%) and non-alcoholic fatty liver disease (NAFLD; n = 101, 11%).

While 754 (80%) patients harboured the *TM6SF2* wild-type (*C/C*), 174 (19%) and 10 (1%) patients had one or two *T*-alleles. At baseline, patients with at least one *TM6SF2 T*-allele had more pronounced portal hypertension (HVPG: 16±7 vs. 15±7 mmHg; p = 0.031), higher gamma-glutamyl transferase levels (123 [63-229] vs. 97 [55-174] UxL^{-1}; p = 0.002), and more commonly hepatocellular carcinoma (17% vs. 12%; p = 0.049).

Harbouring the *TM6SF2 T*-allele was associated with the composite endpoint hepatic decompensation/liver transplantation/liver-related death (SHR: 1.44 [95%CI: 1.14-1.83]; p = 0.003). This was confirmed in multivariable competing risk regression analyses that were adjusted for severity of portal hypertension and hepatic dysfunction at baseline.
Conclusion: The *TM6SF2* variant modulates liver disease progression beyond the development of ACLD, as it modifies the risks of hepatic decompensation and liver-related death, independently of baseline liver disease severity.

1. Introduction

Candidate gene and genome-wide association studies have revealed that genetic variants modulate the susceptibility for and progression of chronic liver diseases. Important examples include detrimental variants in *PNPLA3, TM6SF2, MBOAT7, GCKR*, and *SERPINA1*, as well as protective variants in *HSD7B13*, all of which seemed to be particularly relevant in the context of fatty liver disease [1–5].

The protein encoded by the *transmembrane 6 superfamily member 2* (*TM6SF2*) gene is located in the endoplasmic reticulum and Golgi apparatus and regulates hepatic lipid metabolism [6,7]. The malfunctioning protein resulting from the loss-of-function *rs58542926 C>T/E167K* variant leads to impaired very-low-density lipoprotein (VLDL) export, and thus, pathological storage of lipid droplets [6]. Harbouring the *TM6SF2 T*-allele – which is quite common in Europeans (allelic frequency 0.08) – does not only increase the risk of hepatocellular fat accumulation, but also promotes hep-

* Corresponding authors at: Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.
E-mail addresses: albertfriedrich.staettermayer@meduniwien.ac.at (A.F. Stättermayer), mattias.mandorfer@meduniwien.ac.at (M. Mandorfer).
[1] Authors shared first authorship.
[2] Authors shared corresponding/last authorship.

https://doi.org/10.1016/j.dld.2023.02.012
1590-8658/

atic inflammation, liver fibrosis [8], and hepatocellular carcinoma (HCC) development [9]. However, it was not associated with overall mortality [8]. This might be explained by the reduction of circulating lipids (cholesterol and triglycerides) caused by *TM6SF2 T*-allele, which in turn is associated with reduced cardiovascular events [10].

In general, most previous studies aiming at elucidating the effects of genetic variants on liver disease were cross-sectional and lacked detailed information on liver disease (especially portal hypertension) severity. Furthermore, there are no longitudinal studies investigating the role of *TM6SF2* variants on the course of advanced chronic liver disease (ACLD). Therefore, the aim of our study was to evaluate, if the *TM6SF2 rs58542926 C>T/E167K* variant impacts the development of liver-related events in a large, thoroughly characterized cohort of patients who have already progressed to ACLD.

2. Methods

2.1. Study design and patients

For this retrospective, single-centre cohort study, we considered ACLD patients undergoing hepatic venous pressure gradient (HVPG) measurement at the Vienna Hepatic Hemodynamic Lab. We only included patients, if the following criteria were fulfilled: (i) evidence of ACLD, as defined by liver stiffness measurement (LSM) ≥10 kPa and/or an HVPG ≥6 mmHg, (ii) viral hepatitis or alcohol-related (ARLD)/NAFLD as underlying aetiology, and (iii) availability of information on *TM6SF2* genotype. Exclusion criteria were as follows: History of liver transplantation, active extrahepatic malignancy, vascular liver diseases, or unavailable information on important laboratory parameters and/or clinical follow-up.

2.2. HVPG measurement

HVPG measurements were performed under local anaesthesia, as previously reported [11]. Briefly, a catheter introducer sheath was inserted into the right jugular vein and a large hepatic vein was cannulated via a balloon catheter. To obtain reliable measures, the free and the wedged hepatic venous pressures were measured at least three times and the mean was used for statistical analysis [12].

2.3. Genotyping

DNA was extracted using the QIAamp DNA Blood Mini Kit (QIAGEN) and stored at −20°C until genotyping for *TM6SF2 rs58542926 C>T* was performed by 7500 Fast Real-Time PCR System and a TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA).

2.4. Reporting of ethnicity

Ethnicity was determine based on geographic origin and reporting adhered to recently published guidelines [13].

2.5. Removal of the primary aetiological factor

The date of initiation of anti-hepatitis B treatment, sustained virological response in patients with hepatitis C infection, or reported sustained alcohol abstinence in active drinkers defined removal of the primary aetiological factor.

2.6. Definition of hepatic decompensation

Hepatic decompensation was defined by the presence/history of at least one decompensating event, i.e., ascites, variceal bleeding, or hepatic encephalopathy.

2.7. Statistical analysis

Details on statistical analyses can be found in the Supplementary materials.

2.8. Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (EK1526/2017). The requirement of written informed consent was waived by the ethics committee. However, all patients signed a written informed consent for genetic testing.

3. Results

3.1. Study population

Overall, 2550 patients underwent HVPG measurement within the study period (Fig. 1). After applying in- and exclusion criteria, 938 patients were finally included into our study. Mean age at HVPG measurement was 55±11 years and most patients were male (n = 684, 73%; Table 1). Viral hepatitis was the most common aetiology of liver disease (n = 495, 53%), followed by ARLD (n = 342, 37%) and NAFLD (n = 101, 11%). Regarding portal hypertension severity, mean HVPG was 15±7 mmHg and 62% of patients (n = 482) had varices, of whom 113 (12%) had a history of variceal bleeding. Mean UNOS MELD (2016) was 11±5, and mean CTP score was 6±2 points. Most patients were classified as CTP-A (n = 591, 63%), whereas 29% of patients were classified as CTP-B (n = 269) and 8% as CTP-C (n = 78). Four hundred and two patients (45%) had already experienced hepatic decompensation at study inclusion. Furthermore, 13% (n = 122) of patients had been diagnosed with HCC at baseline.

Seven hundred and fifty-four (80%) patients harboured the *TM6SF2* wild-type (*C/C*), while 174 (19%) and 10 (1%) patients had one and two *T*-alleles, respectively. Due to the low number of patients homozygous for the *T*-allele (only 1% of the study population), we decided to merge patients with at least one *T*-allele for all further analyses (Table 1). Accordingly, 20% of patients harboured at least one *T*-allele (n = 184).

The vast majority of included patients were of European descent (n = 856, 91%), followed by patients of Arabic (n = 66, 7%), Asian (n = 13, 1.4%), or African descent (n = 3, 0.3%).

3.2. Clinical events during follow-up

Patients were followed for a median of 70.8 (95%CI: 64.3-75.4) months. Fifty-two deaths (6%) were considered non-liver-related, and 310 patients (33%) achieved removal of the primary aetiological factor during follow-up (hepatitis B virus infection: n = 19, median time to date of initiation of antiviral therapy: 10.6 months [95%CI: 0-41.2]; hepatitis C virus infection: n = 251, median time to sustained virological response: 12.0 months [95%CI: 9.6-14.4]; ARLD: n = 40, median time to sustained alcohol abstinence: 5.9 months [95%CI: 4.1-7.7]). Overall, 53 patients (6%) underwent TIPS placement (median time to TIPS placement: 5.1 months [95%CI: 1.0-9.3]) and 69 patients (7%) developed HCC during follow-up (median time to HCC diagnosis: 41.2 months [95%CI: 32.5-49.9]). For the combined endpoint including hepatic decompensation, 252 patients (27%) experienced first/further hepatic decompensation. In total, fifty-eight patients were transplanted (6%) and 190 deaths (20%) were considered liver-related. This resulted in 340 first events for the combined endpoint with 354 competing events [i] and 205 events for the combined endpoint with 430 competing risks [ii].

Table 1
Comparison of patient characteristics according to the *transmembrane 6 superfamily 2* (*TM6SF2*) *rs58542926* genotype.

Patient characteristics	*TM6SF2* rs58542926				*TM6SF2* rs58542926		
	C/C n = 754 (80%)	T/C n = 174 (19%)	T/T n = 10 (1%)	p-value	C/C n = 754 (80%)	T/C or T/T n = 184 (20%)	p-value
Age, years, mean ± SD	54.6±11.1	56.8±11.8	59.7±11.0	**0.025**	54.6±11.1	57.0±11.8	**0.010**
Sex, n (%)							
Male	541 (72%)	135 (78%)	8 (80%)	0.260	541 (72%)	143 (78%)	0.102
Female	213 (28%)	39 (22%)	2 (20%)		213 (28%)	41 (22%)	
Etiology, n (%)							
ARLD	265 (35%)	71 (41%)	6 (60%)	0.061	265 (35%)	77 (42%)	**0.040**
NAFLD	76 (10%)	23 (13%)	2 (20%)		76 (10%)	25 (14%)	
Viral	413 (55%)	80 (46%)	2 (20%)		413 (55%)	82 (45%)	
HVPG, mmHg, mean ± SD	15±7	16±7	16±7	0.096	15±7	16±7	**0.031**
UNOS MELD (2016) score, point, mean ± SD	12±5	11±4	14±5	0.219	12±5	11±4	0.539
CTP score, mean ± SD	6±2	6±2	7±2	0.507	6±2	6±2	0.389
A, n (%)	475 (63%)	112 (64%)	4 (40%)	0.173	475 (63%)	116 (63%)	0.382
B, n (%)	212 (28%)	51 (29%)	6 (60%)		212 (28%)	57 (31%)	
C, n (%)	67 (9%)	11 (6%)	-		67 (9%)	11 (6%)	
Varices[1], n (%)	387 (62%)	88 (62%)	7 (70%)	0.879	387 (62%)	95 (63%)	0.967
History of variceal bleeding, n (%)	84 (11%)	28 (16%)	1 (10%)	0.191	84 (11%)	29 (16%)	0.084
Non-selective betablocker treatment exposure during follow-up							
No initiation/never	312 (41%)	72 (41%)	2 (20%)	0.185	312 (41%)	74 (40%)	0.263
Minority of time	86 (11%)	21 (12%)	1 (10%)		86 (11%)	22 (12%)	
Majority of time	106 (14%)	17 (10%)	-		106 (14%)	17 (9%)	
All of the time	250 (33%)	64 (37%)	7 (70%)		250 (33%)	71 (39%)	
Decompensated, n (%)	332 (44%)	81 (47%)	7 (70%)	0.227	332 (44%)	88 (48%)	0.353
HCC, n (%)	90 (12%)	30 (17%)	2 (20%)	0.139	90 (12%)	32 (17%)	**0.049**
Metabolic characteristics							
BMI, kg x m^{-2}, mean ± SD	26.8±5.1	27.1±5.5	27.9±6.9	0.582	26.8±5.1	27.2±5.6	0.350
Overweight[2], n (%)	442 (59%)	113 (65%)	7 (70%)	0.249	442 (59%)	120 (65%)	0.102
Obesity[3], n (%)	185 (25%)	42 (24%)	3 (30%)	0.916	185 (25%)	45 (25%)	0.982
Prediabetes[4], n (%)	152 (27%)	35 (27%)	1 (13%)	0.640	152 (27%)	36 (26%)	0.750
Diabetes[5], n (%)	172 (31%)	38 (29%)	4 (44%)	0.603	172 (31%)	42 (30%)	0.850
Arterial hypertension[6], n (%)	349 (46%)	89 (51%)	7 (70%)	0.182	349 (46%)	96 (52%)	0.152
Statin, n (%)	57 (8%)	16 (11%)	-	0.488	57 (8%)	16 (9%)	0.613
Hypertriglyceridemia[7], n (%)	71 (10%)	17 (11%)	-	0.555	71 (10%)	17 (10%)	0.982
Hypercholesterolemia[8], n (%)	69 (10%)	21 (13%)	-	0.253	69 (10%)	21 (12%)	0.320
HDL below threshold[9], n (%)	214 (33%)	50 (33%)	6 (60%)	0.200	214 (33%)	56 (35%)	0.681
Hepatic steatosis[10], n (%)	290 (45%)	75 (49%)	6 (86%)	0.074	290 (45%)	81 (50%)	0.217
Laboratory parameters							
Sodium, mmol x L^{-1}, mean ± SD	137.9±3.6	138.2±3.2	135.8±3.4	0.089	137.9±3.6	138.1±3.1	0.489
Creatinine, mg x dL^{-1}, median (IQR)	0.8 (0.7-0.9)	0.8 (0.7-1.0)	0.8 (0.7-1.2)	0.272	0.8 (0.7-0.9)	0.8 (0.7-1.0)	0.107
Bilirubin, mg x dL^{-1}, median (IQR)	1.0 (0.7-1.8)	1.1 (0.7-1.8)	1.0 (0.6-1.6)	0.810	1.0 (0.7-1.8)	1.0 (0.7-1.6)	0.520
Albumin, g x L^{-1}, mean ± SD	36.5±5.9	36.9±5.5	37.7±6.0	0.564	36.5±5.9	37.0±5.5	0.325
CRP, mg x L^{-1}, median (IQR)	0.3 (0.1-0.6)	0.3 (0.1-0.7)	0.5 (0.2-3.6)	0.321	0.3 (0.1-0.6)	0.3 (0.1-0.8)	0.343
INR, mean ± SD	1.3±0.3	1.3±0.3	1.5±0.3	0.232	1.3±0.3	1.3±0.3	0.739
AST, U x L^{-1}, median (IQR)	52 (36-82)	52 (35-80)	43 (30-60)	0.441	52 (36-82)	52 (35-79)	0.418
ALT, U x L^{-1}, median (IQR)	38 (24-71)	39 (24-65)	30 (19-50)	0.260	38 (24-71)	38 (24-63)	0.349
GGT, U x L^{-1}, median (IQR)	97 (55-174)	125 (63-229)	86 (58-163)	**0.006**	97 (55-174)	123 (63-229)	**0.002**
Triglycerides, mg x dL^{-1}, mean ± SD	98±54	94±47	87±32	0.608	98±54	94±46	0.356
Total cholesterol, mg x dL^{-1}, mean ± SD	148±43	148±49	109±43	**0.023**	148±43	145±49	0.603
HDL-C, mg x dL^{-1}, mean ± SD	44±17	44±18	31±16	0.059	44±17	43±18	0.893
LDL-C, mg x dL^{-1}, mean ± SD	63±45	58±49	41±31	0.140	63±45	57±48	0.100
VWF, %, median (IQR)[11]	287 (210-378)	304 (219-387)	288 (203-328)	0.566	287 (210-378)	304 (218-382)	0.398
VITRO, median (IQR)[11]	2.7 (1.5-4.3)	3.1 (1.9-5.1)	2.0 (1.2-3.7)	**0.046**	2.7 (1.5-4.3)	3.1 (1.9-4.9)	**0.047**
LSM, kPa, median (IQR)[12]	27.7 (16.9-48.8)	29.9 (20.2-55.3)	60.1 (24.8-75.0)	0.104	27.7 (16.9-48.8)	30.9 (20.2-60.1)	0.093

[1] Data available in 773 patients (82%)
[2] BMI ≥25 kg x m^{-2}
[3] BMI ≥30 kg x m^{-2}
[4] Fasting blood glucose 100-125mg x dL^{-1}; HbA1c 5.7-6.4%
[5] Fasting blood glucose >125mg x dL^{-1}, HbA1c ≥6.5%, or antidiabetic medication
[6] Blood pressure >140/90mmHg, or antihypertensive medication
[7] Triglycerides >150 mg x dL^{-1}
[8] Total cholesterol >200 mg x dL^{-1}
[9] <35mg x dL^{-1} for males and <39mg x dL^{-1} for females
[10] Biopsy-proven, controlled attenuation parameter >248dB x m^{-1}, or diagnosed by ultrasound
[11] Data available in 849 patients (91%)
[12] Data available in 658 patients (70%)Abbreviations: ARLD alcohol-related liver disease; ALT alanine-aminotransferase; AST aspartate-aminotransferase; CRP C-reactive protein; CTP Child-Turcotte-Pugh; GGT gamma-glutamyl transferase; HCC hepatocellular carcinoma; HDL-C high-density lipoprotein cholesterol; HVPG hepatic venous pressure gradient; INR international normalized ratio; LDL-C low-density lipoprotein cholesterol; LSM liver stiffnes measurement; NAFLD non-alcoholic fatty liver disease; UNOS MELD (2016) United Network for Organ Sharing model for end-stage liver disease (2016) score; VITRO VWF to platelet ratio; VWF von Willebrand factor antigen.

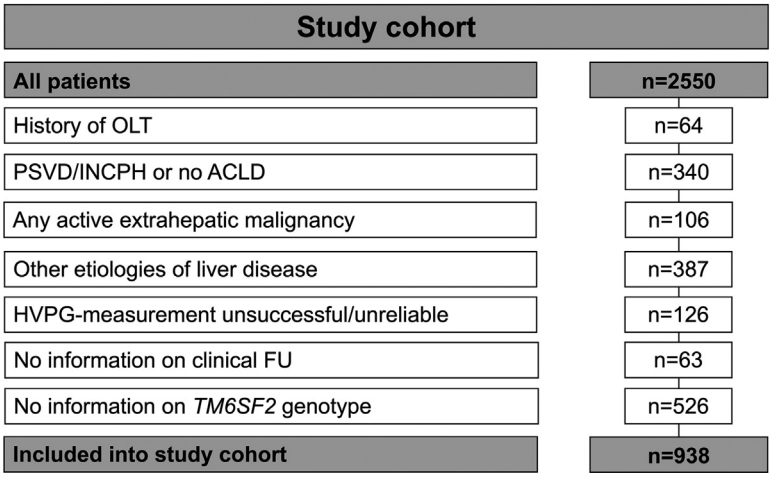

Fig. 1. Study flow-chart. *Abbreviations: ACLD advanced chronic liver disease; FU follow-up; HVPG hepatic venous pressure gradient; INCPH idiopathic non-cirrhotic portal hypertension; OLT orthotopic liver transplantation; PSVD porto-sinusoidal vascular disorder; TM6SF2 transmembrane 6 superfamily 2.*

3.3. Patient characteristics according to TM6SF2 genotypes

Patients harbouring at least one *TM6SF2 T*-allele were older (57.0±11.8 vs. 54.6±11.1 years; $p = 0.010$), had more commonly ARLD/NAFLD aetiology (56% vs. 45%; $p = 0.040$), more pronounced portal hypertension as indicated by higher HVPG (16±7 vs. 15±7 mmHg; $p = 0.031$), and accordingly, history of variceal bleeding was more common in *T*-allele carriers (16% vs. 11%; $p = 0.084$; Table 1). Interestingly, patients harbouring a *T*-allele had more commonly been diagnosed with HCC (17% vs. 12%; $p = 0.049$) and presented with higher median gamma-glutamyltransferase levels at study inclusion (123 [IQR: 63-229] vs. 97 [IQR: 55-174] U x L^{-1}; $p = 0.002$).

While we observed no statistically significant differences in serum lipid profile when comparing patients harbouring at least one *TM6SF2 T*-allele vs. non-carriers, total cholesterol was significantly lower in those with the *TM6SF2 TT* genotype (*TT*: 109±43 vs. *CT*: 148±49 vs. *CC*: 148±43 mg x dL^{-1}; $p = 0.023$).

3.4. Impact of the TM6SF2 T-allele on hepatic decompensation/requirement of liver-transplantation/liver-related death in competing risk analyses

In competing risk analysis, harbouring the *TM6SF2 T*-allele was associated with hepatic decompensation/requirement of liver transplantation/liver-related death (subdistribution hazard ratio [SHR]: 1.44 [95%CI: 1.14-1.83]; $p = 0.003$; Fig. 2). After adjusting for age, BMI, HVPG, and CTP stage (model 1) as well as age, BMI, HVPG, UNOS MELD (2016) score, and a history/presence of hepatic decompensation (model 2), associations remained statistically significant for models 1 (adjusted SHR [aSHR]: 1.40 [95%CI: 1.09-1.80]; $p = 0.008$) and 2 (aSHR: 1.35 [95%CI: 1.05-1.74]; $p = 0.019$; Table 2).

3.5. Impact of the TM6SF2 T-allele on requirement of liver transplantation/liver-related death in competing risk analysis

When combining requirement of liver transplantation/liver-related death into a composite endpoint, harbouring the *TM6SF2 T*-allele tended to increase the risks of the outcome of interest (SHR: 1.31 [95%CI: 0.96-1.79]; $p = 0.090$; Fig. 3). After adjusting for relevant covariables, carriage of the *TM6SF2 T*-allele was associated with an increased risk of liver transplantation/liver-related death on a trend-wise level (model 1: aSHR: 1.27 [95%CI: 0.92-1.75]; $p = 0.150$; model 2: aSHR: 1.25 [95%CI: 0.90-1.72]; $p = 0.180$; Table 3). Higher age, BMI, HVPG, CTP stage, and UNOS MELD (2016) score were associated with the endpoint of interest (Table 3).

3.6. Impact of the TM6SF2 T-allele in different aetiologies of liver disease

Interestingly, the *TM6SF2 T*-allele impacted outcomes in patients with viral hepatitis, while no impact in patients with fatty liver was observed (Supplementary materials). Cumulative incidence plots for the different disease aetiology subgroups are provided in the Supplementary materials.

4. Discussion

Longitudinal data evaluating the impact of genetic variants on the outcome of patients who have already progressed to ACLD are scarce. Although several chronic liver disease-modifying alleles have been identified [4,5,14-18], the implications of genetics in patients who have already progressed to ACLD are poorly defined. In the present retrospective longitudinal study, we found that harbouring a *TM6SF2 rs58542926 T*-allele increases the risk of liver-related events, even after accounting for severity of portal hypertension and hepatic dysfunction at baseline.

Not surprisingly, the *TM6SF2* risk variants were overrepresented in our cohort as compared to the general population (*T*-allele frequency: *TM6SF2*: 20% vs. 8%). This underlines the importance of this variant in regard to the susceptibility for and progression of chronic liver disease to ACLD in general as well as ARLD/NAFLD in particular, as fatty liver disease was significantly overrepresented among *T*-allele carriers. Mechanistically, this may be explained by the *TM6SF2* loss-of-function mutation and the accumulation of liver fat [2,8].

Interestingly, carriage of the *TM6SF2 T*-allele was associated with more pronounced portal hypertension at baseline, as indicated by higher HVPG. Since no experimental/clinical study so far has investigated the impact of the *TM6SF2 T*-allele on portal hypertension, we can only speculate about the reason for this association. Most mechanistic considerations are derived from mice models, in which the *TM6SF2* protein is expressed 10-fold higher in the small intestine vs. the liver, thereby limiting the translation of findings from mice to humans [7]. In humans, the *TM6SF2 T*-allele has been linked to more pronounced hepatic inflammation [19], which may increase intrahepatic resistance, thereby potentially aggravating portal hypertension [19]. In line with previous findings in regard to *PNPLA3* [20], recent reports suggest that *TM6SF2* genotype

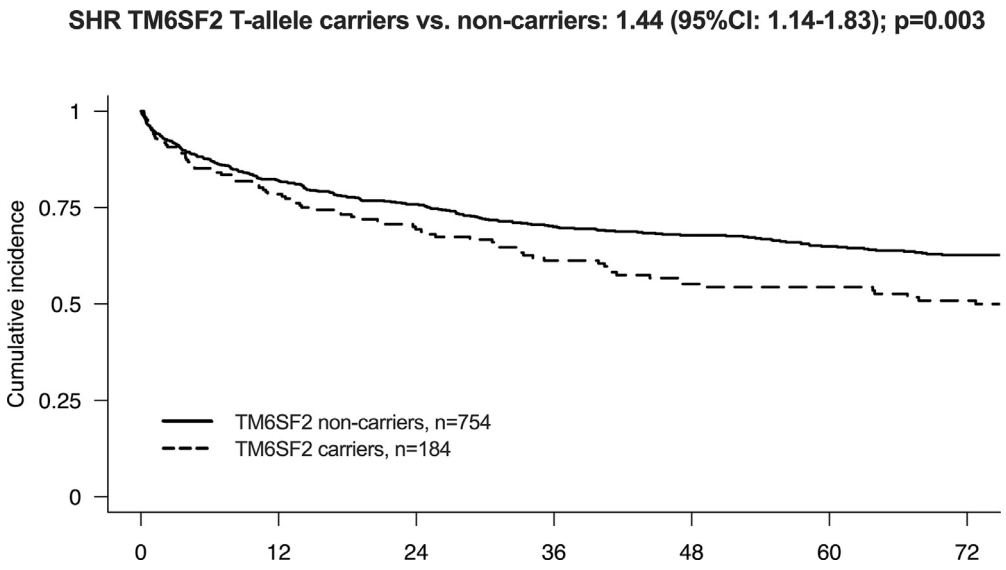

Fig. 2. Cumulative incidence plot of hepatic decompensation/requirement of liver transplantation/liver-related death stratified according to *TM6SF2* genotype.
Abbreviations: SHR subdistribution hazard ratio; TM6SF2 transmembrane 6 superfamily 2.

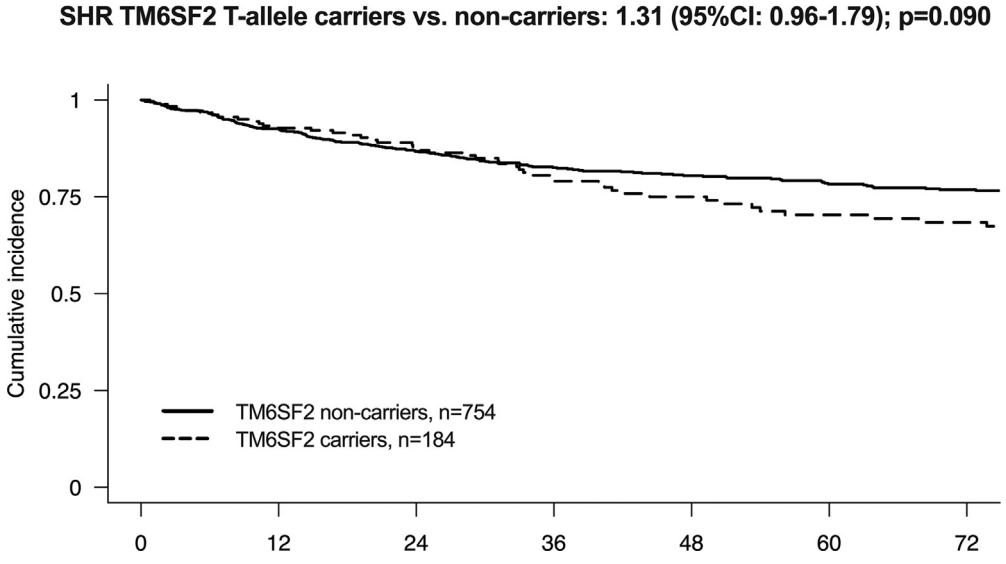

Fig. 3. Cumulative incidence plot of requirement of liver transplantation/liver-related death stratified according to *TM6SF2 genotype.*
Abbreviations: SHR subdistribution hazard ratio; TM6SF2 transmembrane 6 superfamily 2.

Table 2
Multivariable competing risk regression analyses for hepatic decompensation/requirement of liver transplantation/liver-related death including – among other parameters – CTP score (model 1) or history/presence of hepatic decompensation, and UNOS MELD (2016) score (model 2) with removal of the aetiological factor, non-liver-related death, TIPS placement, and HCC development as competing risks.

Patient characteristics	Model 1		Model 2	
	aSHR (95%CI)	*p*-value	aSHR (95%CI)	*p*-value
Age, year	1.02 (1.01-1.03)	**<0.001**	1.02 (1.01-1.03)	**<0.001**
BMI, per kg x m^{-2}	1.03 (1.01-1.05)	**0.003**	1.03 (1.01-1.05)	**0.003**
HVPG, mmHg	1.04 (1.02-1.06)	**<0.001**	1.04 (1.03-1.06)	**<0.001**
CTP stage A	1	-	-	-
CTP stage B	2.63 (2.03-3.42)	**<0.001**	-	-
CTP stage C	3.29 (2.19-4.96)	**<0.001**	-	-
UNOS MELD (2016) score, point	-	-	1.06 (1.03-1.09)	**<0.001**
History/presence of hepatic decompensation	-	-	1.62 (1.24-2.10)	**<0.001**
TM6SF2 T-allele	1.40 (1.09-1.80)	**0.008**	1.35 (1.05-1.74)	**0.019**

Abbreviations: aSHR adjusted subdistribution hazard ratio; BMI body mass index; CTP Child-Turcotte-Pugh score; HCC hepatocellular carcinoma; HVPG hepatic venous pressure gradient; UNOS MELD (2016) United Network for Organ Sharing model for end-stage liver disease (2016) score; TIPS transjugular intrahepatic portosystemic shunt; TM6SF2 transmembrane 6 superfamily 2.

Table 3
Multivariable competing risk regression analyses for requirement of liver transplantation/liver-related death including – among other parameters – CTP score (model 1) or history/presence of hepatic decompensation, and UNOS MELD (2016) score (model 2) with removal of the aetiological factor, non-liver-related death, TIPS placement, and HCC development as competing risks.

Patient characteristics	Model 1		Model 2	
	aSHR (95%CI)	*p*-value	aSHR (95%CI)	*p*-value
Age, year	1.03 (1.02-1.05)	<0.001	1.03 (1.02-1.05)	<0.001
BMI, per kg x m^{-2}	1.04 (1.01-1.06)	0.002	1.03 (1.01-1.06)	0.003
HVPG, mmHg	1.01 (0.99-1.04)	0.240	1.02 (0.99-1.04)	0.130
CTP stage A	1	-	-	-
CTP stage B	1.87 (1.32-2.67)	<0.001	-	-
CTP stage C	4.48 (2.81-7.13)	<0.001	-	-
UNOS MELD (2016) score, point	-	-	1.09 (1.05-1.12)	<0.001
History/presence of hepatic decompensation	-	-	1.02 (0.72-1.45)	0.900
TM6SF2 T-allele	1.27 (0.92-1.75)	0.150	1.25 (0.90-1.72)	0.180

Abbreviations: aSHR adjusted subdistribution hazard ratio; BMI body mass index; CTP Child-Turcotte-Pugh score; HCC hepatocellular carcinoma; HVPG hepatic venous pressure gradient; UNOS MELD (2016) United Network for Organ Sharing model for end-stage liver disease (2016) score; TIPS transjugular intrahepatic portosystemic shunt; TM6SF2 transmembrane 6 superfamily 2.

may impact hepatic stellate cell (HSC) activation [21], which would directly affect the hepatic vascular tone [19]. Furthermore, hepatic lipid accumulation/lipotoxicity in *TM6SF2 T*-allele carriers [2,8] may promote hepatocyte ballooning, thereby reducing sinusoidal space and increasing intrahepatic resistance [22]. As an alternative explanation, higher HVPG in patients harbouring the *TM6SF2 T*-allele may simply indicate more advanced liver disease. The latter may be attributed to between-genotype differences in aetiology, with a slight overrepresentation of NAFLD but also ARLD patients – who often present late, i.e., after the development of hepatic decompensated – among carriers. Notably, NAFLD also seems to be accompanied by additional presinusoidal increases in intrahepatic resistance [23], which may explain the discrepancies in the correlation between HVPG and hepatic decompensation in NAFLD patients, as compared to viral hepatitis [22]. Accordingly, it may be hypothesized that HVPG even underestimates the true increase in portal pressure in *TM6SF2 T*-allele carriers, which on the hand, would explain an increased risk of clinical events, but may also promote fibrosis progression via mechanosensing pathways, thereby contributing to clinical disease progression [24]. Carriage of the *TM6SF2 TT* genotype was associated with increased serum cholesterol levels at baseline, which is well in line with the variant's effect on hepatic lipid metabolism and previous data on the serum lipid profile in patients with less advanced disease [10]. Nevertheless, this finding has to be interpreted with caution, as patients harbouring this genotype tended to have more sever liver disease, which may have impacted the circulating lipid profile [25].

Importantly, our findings remained unaffected when (i) exchanging HVPG with non-invasive prognostic indicators (i.e., von Willebrand factor antigen [VWF], VWF to platelet ratio [VITRO], or liver stiffness measurement [LSM] by vibration-controlled transient elastography) or (ii) combining HVPG and VWF This supports the concept that genetics may extend the prognostic value of biomarkers that reflect the stage of liver disease in patients with ACLD, although findings in the general population suggest that the gain in prognostic information is limited [26].

Our centre has adopted the recommendations of the national Billroth I-III consensus statements [27–29], and thus, wide-spread (i.e., including primary prophylaxis for small varices) NSBB treatment was the standard of care at our centre throughout the study period. Accordingly, 552 patients of the whole study population were receiving NSBB therapy, which may be seen as an advantage of our study, as it is reflective of today's (i.e., after Baveno VII [30]) clinical practice, thereby increasing the generalisability of our findings. Importantly, NSBB exposure during follow-up did not differ between *TM6SF2* genotypes/risk-allele carriers vs. non-carriers, and thus, is unlikely to have impacted our main finding. Notably, the utilisation of HVPG-response assessment according to [31] and the rates of HVPG-response to NSBB therapy were comparable across carriers and non-carriers (data available in $n = 362$ patients [39%]; 55% in carriers vs. 56% in non-carriers; $p = 0.820$). Thus, the latter is unlikely to have affected our findings.

When considering non-liver-related death and aetiological cure as competing events, harbouring the *TM6SF2 T*-allele significantly increased the risks for developing the two evaluated composite endpoints. In general, these findings were confirmed after adjustment for liver disease and portal hypertension severity at inclusion, although some analyses yielded trends rather than statistically significant results. While harbouring the *TM6SF2 T*-allele statistically significantly increased the risks (by approximately 30%) for the first composite endpoint including hepatic decompensation, requirement of liver transplantation, and liver-related death in model 1, the effect of the *TM6SF2 T*-allele only attained borderline significance in the other model. For the composite endpoint comprising liver transplantation and liver-related death, only trends towards an increased risk (by approximately 30%) in *TM6SF2 T*-allele carriers were observed, which may be explained by limited statistical power, as the aSHR were very similar to the other composite endpoint. To put these findings into perspective, harbouring the less common *PNPLA3 rs738409 G/G* genotype (prevalence of only 7%, as compared to 20% *TM6SF2 T*-allele carriers) was associated with a 42%-increased risk for liver-related death in a previous analysis of an overlapping population of patients with ACLD due to viral hepatitis/fatty liver disease [32]. Accordingly, the magnitude of the *TM6SF2*-mediated effect was only slightly lower vs. *PNPLA3*, while affecting a considerably larger patient population. Importantly, we considered removal of primary etiologic factors (as defined by Baveno VII [33]) as competing risks, as it profoundly changes hepatic function and the severity of portal hypertension, and thus, the risk of events, in particular first hepatic decompensation [19]. Accordingly, removal of the primary etiologic factor denotes a paragon of a competing risk that modifies the probability of the event of interest. Moreover, findings in HCV-infected ACLD patients achieving sustained virologic response question the relevance of SNV for disease regression [34].

Of note, the mean UNOS MELD (2016) of our study population was low (i.e., 12 points) indicating that the vast majority of patients were not on the waiting list for liver transplantation. Thus, the requirement of liver transplantation denotes an adverse liver-related outcome in this patient population, which is why we in-

cluded the requirement of liver transplantation into the composite endpoints, rather than analysing liver transplantation as a competing event.

Cross-sectional studies indicate that the *TM6SF2 T*-allele may promote liver fibrosis in patients with hepatitis C. In three studies conducted in Italian chronic hepatitis C cohorts, the *TM6SF2 T*-allele was an independent risk factor of steatosis [35,36], and advanced fibrosis/cirrhosis (OR of ~1.8-2.2) [36]. In line, carriage of the *TM6SF2 T*-allele was linked to significant fibrosis in viral hepatitis patients recruited in Australia and China, with a slightly lower OR (1.39), as compared to NAFLD (OR of 1.62) [37]. However, there was also a study from Petta et al. [38] reporting that the *TM6SF2 T*-allele was not associated with the severity of hepatic steatosis or liver fibrosis in a large (n = 694) cohort of patients with hepatitis C virus infection [38]. Of note, our study had a very different focus, as all included patients had already developed ACLD. Interestingly, the impact of the *TM6SF2 T*-allele among patients with viral hepatitis was considerably stronger (SHR of ~1.8), as compared to the overall study population (SHR of ~1.3) and the fatty liver disease subgroup, in which no meaningful effect was observed. This contrasts our previous findings on the *PNPLA3 rs738409 G/G*-genotype, which modified the course of ACLD due to fatty liver disease but did not impact liver-related mortality in NAFLD patients. The previous smaller study [32] was performed in a partly overlapping and therefore likely comparable patient cohort. While both polymorphisms impact on hepatic lipid metabolism and show a similar pattern of associations in less advanced patient cohorts, their pathophysiological relevance in patients with ACLD has not been thoroughly investigated. Thus, the available data does not provide a compelling explanation for the etiology-specific differences, which may be an important area for further research. In this regard, we would like to emphasize that observations on indirect endpoints (e.g., liver fibrosis) in less advanced patient cohorts should not be extrapolated to ACLD patients. This is also highlighted by a recent study from our centre evaluating the impact of the presumably protective *HSD17B13 rs72613567 TA*-allele in patients who had already developed ACLD [39], which observed no significant differences in liver-related outcomes between carriers and non-carriers [40].

In the light of important advances in the field of gene therapies in other indications as well as promising data on RNA interference-based therapeutics in patients with alpha-1 antitrypsin-related liver disease (*SERPINA1 rs28929474, Pi*ZZ*) in whom liver fibrosis regression was achieved [41], the drug-ability of further SNV requires evaluation. This is particularly important in ACLD patients, as they are at significant risk for developing hepatic decompensation and death, indicating the urgent need for disease-modifying therapies [42]. However, while the loss-of-function *TM6SF2* mutation investigated in our study leads to liver fat accumulation, an upregulation of this gene may cause dyslipidaemia, and thus, increase cardiovascular risk. Moreover, preclinical data suggests that an upregulation of the *TM6SF2* wild-type may even lead to a paradoxical worsening of liver disease [43].

The main limitation of our study is its retrospective design. However, patients were thoroughly characterized at the time of HVPG measurement. Since this was a retrospective data analysis, we cannot exclude that some hepatic decompensation events have been missed. However, we have thoroughly reviewed electronic health records of the Vienna hospital association and nationwide electronic health records. Moreover, we have also performed searches of the liver transplant database of our institution (i.e., the only transplant centre in eastern Austria) and examined the nation-wide death registry. Since complete information on (reason of) death is guaranteed by the latter measure, we included liver-related death in all composite endpoints to ensure the ascertainment of the most severe disease courses. Of note, lack of adjustment for portal hypertension severity may be an important limitation of previous studies investigating the impact of genetic variants on the course of ACLD, as patients harbouring the respective risk/protective genotypes (i.e., *PNPLA3* [32], *TM6SF2* in the present study, or *HSD17B13* [39]) had more/less pronounced portal hypertension at baseline and portal hypertension is a main driver of liver-related events [44]. Accordingly, previous studies without information on baseline portal hypertension severity [32,45] may have not sufficiently accounted for the baseline condition of the patients, and thus, overestimated the impact of genetic variants on the risk of future events. This is in line with the above-mentioned concept that genetic variants may only offer slight improvements in risk prediction, after accounting for disease stage (i.e., FIB-4). In the context of our study, this potential limitation was overcome by accounting for HVPG, the most accurate surrogate of portal hypertension severity with profound prognostic implications [46]. However, we cannot rule-out selection bias since we included patients at the time of HVPG measurement. Hemodynamic evaluation of our patients are performed on a routinely basis as a standard tool for risk stratification and treatment monitoring purposes, and thus, we are convinced that our study population is not highly selected [12]. Above, we have pointed out the importance of interethnic differences in the interpretation of study results for genetic variants in different patient cohorts and ethnicities. Therefore, we want to emphasize that our study may only be applying for subjects of European descent, as they represent the vast majority of included patients. Finally, we did not include a validation cohort, as we are not aware of another adequately sized cohort connecting data on HVPG and genetics.

In conclusion, ACLD patients harbouring the *TM6SF2 T*-allele are at higher risk of developing liver-related events, however, this effect seemed to be restricted to those with viral hepatitis. Our findings extend previous knowledge, as they indicate that the *TM6SF2 T*-allele does not only modulate the risk of ACLD development, but also the further disease course.

Conflict of interest

The authors have nothing to disclose regarding the work under consideration for publication.

Conflicts of interests outside the submitted work:

L.B., M.U., P.W., R.P., G.S., C.W., and A.F.S. have nothing to disclose.

B.Sc. received travel support from AbbVie, Ipsen, and Gilead.

B.Si. received travel support from AbbVie and Gilead.

M.P. served as a speaker and/or consultant and/or advisory board member for Bayer, Bristol-Myers Squibb, Eisai, Ipsen, Lilly, MSD, and Roche, and received travel support from Bayer and Bristol-Myers Squibb.

P.F. served as a speaker and/or consultant and/or advisory board member for AbbVie, Gilead, MYR Pharmaceuticals, and Vivaraxx and received grants/research support from Gilead.

M.T. served as a speaker and/or consultant and/or advisory board member for Albireo, BiomX, Falk, Boehringer Ingelheim, Bristol-Myers Squibb, Falk, Genfit, Gilead, Intercept, Janssen, MSD, Novartis, Phenex, Pliant, Regulus, and Shire, and received travel support from AbbVie, Falk, Gilead, and Intercept as well as grants/research support from Albireo, Alnylam, Cymabay, Falk, Gilead, Intercept, MSD, Takeda, and UltraGenyx. He is also co-inventor of patents on the medical use of 24-norursodeoxycholic acid.

T.R. served as a speaker and/or consultant and/or advisory board member for AbbVie, Bayer, Boehringer Ingelheim, Gilead, Intercept, MSD, Siemens, and W. L. Gore & Associates and received grants/research support from AbbVie, Boehringer Ingelheim, Gilead, Intercept, MSD, Myr Pharmaceuticals, Pliant, Philips, Siemens, and

W. L. Gore & Associates as well as travel support from AbbVie, Boehringer Ingelheim, Gilead and Roche.

M.M. served as a speaker and/or consultant and/or advisory board member for AbbVie, Collective Acumen, Gilead, and W. L. Gore & Associates and received travel support from AbbVie, Gilead, and Takeda.

CRediT authorship contribution statement

Lorenz Balcar: Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Bernhard Scheiner:** Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Markus Urheu:** Data curation, Writing – review & editing. **Patrick Weinberger:** Data curation, Writing – review & editing. **Rafael Paternostro:** Data curation, Writing – review & editing. **Benedikt Simbrunner:** Writing – review & editing. **Georg Semmler:** Writing – review & editing. **Claudia Willheim:** Data curation, Writing – review & editing. **Matthias Pinter:** Writing – review & editing. **Peter Ferenci:** Writing – review & editing. **Michael Trauner:** Writing – review & editing. **Thomas Reiberger:** Data curation, Writing – review & editing. **Albert Friedrich Stättermayer:** Data curation, Writing – original draft, Writing – review & editing. **Mattias Mandorfer:** Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Financial support

No specific financial support was received for this study.

Data statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.02.012.

References

[1] Buch S, Stickel F, Trépo E, Way M, Herrmann A, Nischalke HD, et al. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. Nat Genet 2015;47(12):1443–8.
[2] Trépo E, Valenti L. Update on NAFLD genetics: from new variants to the clinic. J Hepatol 2020;72(6):1196–209.
[3] Holmen OL, Zhang H, Fan Y, Hovelson DH, Schmidt EM, Zhou W, et al. Systematic evaluation of coding variation identifies a candidate causal variant in TM6SF2 influencing total cholesterol and myocardial infarction risk. Nat Genet 2014;46(4):345–51.
[4] Bianco C, Casirati E, Malvestiti F, Valenti L. Genetic predisposition similarities between NASH and ASH: identification of new therapeutic targets. JHEP Rep 2021;3(3):100284.
[5] Strnad P, Buch S, Hamesch K, Fischer J, Rosendahl J, Schmelz R, et al. Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis. Gut 2019;68(6):1099–107.
[6] Kozlitina J, Smagris E, Stender S, Nordestgaard BG, Zhou HH, Tybjærg-Hansen A, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2014;46(4):352–6.
[7] Luo F, Oldoni F, Das A. TM6SF2: a novel genetic player in nonalcoholic fatty liver and cardiovascular disease. Hepatol Commun 2022;6(3):448–60.
[8] Liu YL, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JB, et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nat Commun 2014;5:4309.
[9] Pelusi S, Baselli G, Pietrelli A, Dongiovanni P, Donati B, McCain MV, et al. Rare pathogenic variants predispose to hepatocellular carcinoma in nonalcoholic fatty liver disease. Sci Rep 2019;9(1):3682.
[10] Dongiovanni P, Petta S, Maglio C, Fracanzani AL, Pipitone R, Mozzi E, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. Hepatology 2015;61(2):506–14.
[11] Ferlitsch A, Bota S, Paternostro R, Reiberger T, Mandorfer M, Heinisch B, et al. Evaluation of a new balloon occlusion catheter specifically designed for measurement of hepatic venous pressure gradient. Liver Int 2015;35(9):2115–20.
[12] Reiberger T, Schwabl P, Trauner M, Peck-Radosavljevic M, Mandorfer M. Measurement of the hepatic venous pressure gradient and transjugular liver biopsy. JoVE 2020(160):e58819.
[13] Flanagin A, Frey T, Christiansen SL. Updated guidance on the reporting of race and ethnicity in medical and science journals. Jama 2021;326(7):621–7.
[14] Bianco C, Jamialahmadi O, Pelusi S, Baselli G, Dongiovanni P, Zanoni I, et al. Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. J Hepatol 2020.
[15] De Vincentis A, Tavaglione F, Jamialahmadi O, Picardi A, Antonelli Incalzi R, Valenti L, et al. A polygenic risk score to refine risk stratification and prediction for severe liver disease by clinical fibrosis scores. Clin Gastroenterol Hepatol 2022;20(3):658–73.
[16] Paternostro R, Staufer K, Traussnigg S, Stättermayer AF, Halilbasic E, Keritam O, et al. Combined effects of PNPLA3, TM6SF2 and HSD17B13 variants on severity of biopsy-proven non-alcoholic fatty liver disease. Hepatol Int 2021;15(4):922–33.
[17] Whitfield JB, Schwantes-An TH, Darlay R, Aithal GP, Atkinson SR, Bataller R, et al. A genetic risk score and diabetes predict development of alcohol-related cirrhosis in drinkers. J Hepatol 2022;76(2):275–82.
[18] Gellert-Kristensen H, Richardson TG, Davey Smith G, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. Hepatology 2020;72(3):845–56.
[19] Gracia-Sancho J, Marrone G, Fernández-Iglesias A. Hepatic microcirculation and mechanisms of portal hypertension. Nat Rev Gastroenterol Hepatol 2019;16(4):221–34.
[20] Bruschi FV, Claudel T, Tardelli M, Caligiuri A, Stulnig TM, Marra F, et al. The PNPLA3 I148M variant modulates the fibrogenic phenotype of human hepatic stellate cells. Hepatology 2017;65(6):1875–90.
[21] Liu S, Murakami E, Nakahara T, Ohya K, Teraoka Y, Makokha GN, et al. In vitro analysis of hepatic stellate cell activation influenced by transmembrane 6 superfamily 2 polymorphism. Mol Med Rep 2021;23(1).
[22] Bassegoda O, Olivas P, Turco L, Mandorfer M, Serra-Burriel M, Tellez L, et al. Decompensation in advanced nonalcoholic fatty liver disease may occur at lower hepatic venous pressure gradient levels than in patients with viral disease. Clin Gastroenterol Hepatol 2021.
[23] Ferrusquía-Acosta J, Bassegoda O, Turco L, Reverter E, Pellone M, Bianchini M, et al. Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis. J Hepatol 2021;74(4):811–818.
[24] Baffy G, Bosch J. Overlooked subclinical portal hypertension in non-cirrhotic NAFLD: is it real and how to measure it? J Hepatol 2022;76(2):458–63.
[25] Unger LW, Forstner B, Schneglberger S, Muckenhuber M, Eigenbauer E, Scheiner B, et al. Patterns and prevalence of dyslipidemia in patients with different etiologies of chronic liver disease. Wien Klin Wochenschr 2019;131(17-18):395–403.
[26] Innes H, Morling JR, Buch S, Hamill V, Stickel F, Guha IN. Performance of routine risk scores for predicting cirrhosis-related morbidity in the community. J Hepatol 2022;77(2):365–76.
[27] Peck-Radosavljevic M, Trauner M, Schreiber F. Austrian consensus on the definition and treatment of portal hypertension and its complications. Endoscopy 2005;37(7):667–73.
[28] Peck-Radosavljevic M, Angermayr B, Datz C, Ferlitsch A, Ferlitsch M, Fuhrmann V, et al. Austrian consensus on the definition and treatment of portal hypertension and its complications (Billroth II). Wien Klin Wochenschr 2013;125(7-8):200–19.
[29] Reiberger T, Puspok A, Schoder M, Baumann-Durchschein F, Bucsics T, Datz C, et al. Austrian consensus guidelines on the management and treatment of portal hypertension (Billroth III). Wiener klinische Wochenschrift 2017;129(Suppl 3):135–58.
[30] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C. Baveno VII - renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–74.
[31] Reiberger T, Bucsics T, Paternostro R, Pfisterer N, Riedl F, Mandorfer M. Small esophageal varices in patients with cirrhosis—should we treat them? Current Hepatology Reports 2018;17(4):301–15.
[32] Mandorfer M, Scheiner B, Stättermayer AF, Schwabl P, Paternostro R, Bauer D, et al. Impact of patatin-like phospholipase domain containing 3 rs738409 G/G genotype on hepatic decompensation and mortality in patients with portal hypertension. Aliment Pharmacol Ther 2018;48(4):451–9.
[33] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII - renewing consensus in portal hypertension: report of the Baveno VII Consensus Workshop: personalized care in portal hypertension. J Hepatol
[34] Semmler G, Binter T, Kozbial K, Schwabl P, Chromy D, Bauer D, et al. Influence of genetic variants on disease regression and outcomes in HCV-related advanced chronic liver disease after SVR. J Pers Med 2021;11(4).
[35] Coppola N, Rosa Z, Cirillo G, Stanzione M, Macera M, Boemio A, et al. TM6SF2 E167K variant is associated with severe steatosis in chronic hepatitis C, regardless of PNPLA3 polymorphism. Liver Int 2015;35(8):1959–63.
[36] Milano M, Aghemo A, Mancina RM, Fischer J, Dongiovanni P, De Nicola S,

et al. Transmembrane 6 superfamily member 2 gene E167K variant impacts on steatosis and liver damage in chronic hepatitis C patients. Hepatology 2015;62(1):111–17.
[37] Eslam M, Mangia A, Berg T, Chan HL, Irving WL, Dore GJ, et al. Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes. Hepatology 2016;64(1):34–46.
[38] Petta S, Maida M, Grimaudo S, Pipitone RM, Macaluso FS, Cabibi D, et al. TM6SF2 rs58542926 is not associated with steatosis and fibrosis in large cohort of patients with genotype 1 chronic hepatitis C. Liver Int 2016;36(2):198–204.
[39] Scheiner B, Stättermayer AF, Schwabl P, Bucsics T, Paternostro R, Bauer D, et al. Impact of HSD17B13 rs72613567 genotype on hepatic decompensation and mortality in patients with portal hypertension. Liver Int 2020;40(2):393–404.
[40] Abul-Husn NS, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. New Engl J Med 2018;378(12):1096–106.
[41] Strnad P, Mandorfer M, Choudhury G, Griffiths W, Trautwein C, Loomba R, et al. LP10: aro-aat reduces Z-AAT protein in PiZZ patients and leads to improvements in clinically relevant liver biomarkers. Hepatology 2021; 74(S1).
[42] D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39(10):1180–93.
[43] Romeo S, Sanyal A, Valenti L. Leveraging human genetics to identify potential new treatments for fatty liver disease. Cell Metab 2020;31(1):35–45.
[44] Mandorfer M, Simbrunner B. Prevention of first decompensation in advanced chronic liver disease. Clin Liver Dis 2021;25(2):291–310.
[45] Scheiner B, Mandorfer M, Schwabl P, Payer BA, Bucsics T, Bota S, et al. The Impact of PNPLA3 rs738409 SNP on liver fibrosis progression, portal hypertension and hepatic steatosis in HIV/HCV coinfection. PLoS One 2015;10(11):e0143429.
[46] Mandorfer M, Hernández-Gea V, García-Pagán JC, Reiberger T. Noninvasive diagnostics for portal hypertension: a comprehensive review. Semin Liver Dis 2020;40(3):240–55.