

## SUPPLEMENT

**Supplementary Table-1**

|                                       | PNPLA3<br>C/C<br>n=623 | PNPLA3<br>C/G or G/G<br>n=634 | P                | SERPINA1<br>M/M or M/S<br>n=1190 | SERPINA1<br>M/Z or Z/Z<br>n=67 | P            |
|---------------------------------------|------------------------|-------------------------------|------------------|----------------------------------|--------------------------------|--------------|
| Age, years                            | 52.8±15.4              | 52.6±15.0                     | 0.877            | 52.6±15.1                        | 54.1±15.8                      | 0.441        |
| Male sex,                             | 377 (60.5%)            | 382 (60.3%)                   | 0.925            | 730 (61.3%)                      | 29 (43.3%)                     | <b>0.003</b> |
| BMI, kg/m <sup>2</sup>                | 26.2±4.8               | 27.5±5.2                      | 0.053            | 27.2±5.0                         | 26.3±5.4                       | 0.134        |
| Bilirubin, mg/dL                      | 0.6 (0.4-0.9)          | 0.6 (0.4-0.9)                 | 0.164            | 0.6 (0.4-0.9)                    | 0.7 (0.4-1.0)                  | 0.307        |
| Albumin, g/dL                         | 45.0±4.1               | 45.2±4.0                      | 0.491            | 45.1±4.0                         | 45.5±4.6                       | 0.385        |
| INR                                   | 1.2 (1.2-1.2)          | 1.2 (1.2-1.2)                 | 0.120            | 1.2 (1.2-1.2)                    | 1.2 (1.2-1.2)                  | 0.146        |
| Creatinine, mg/dL                     | 0.9 (0.8-1.0)          | 0.9 (0.8-1.0)                 | 0.916            | 0.9 (0.8-1.0)                    | 0.9 (0.8-1.0)                  | 0.252        |
| Na, mmol/L                            | 139.7±2.4              | 139.6±2.7                     | 0.537            | 139.7±2.5                        | 139.1±2.7                      | 0.077        |
| Platelets, x10 <sup>9</sup> /L        | 239.5 (203.0-282.0)    | 235.0 (188.0-285.0)           | 0.176            | 238.0 (195.0-283.0)              | 220.0 (188.0-286.0)            | 0.441        |
| White-cell count, x10 <sup>9</sup> /L | 6.3 (5.3-7.6)          | 6.4 (5.3-7.8)                 | 0.792            | 6.4 (5.3-7.7)                    | 6.0 (5.1-7.8)                  | 0.246        |
| CRP, mg/dL                            | 0.2 (0.1-0.4)          | 0.2 (0.1-0.5)                 | 0.062            | 0.2 (0.1-0.5)                    | 0.2 (0.1-0.6)                  | 0.635        |
| AP, U/L                               | 76.0 (61.0-95.5)       | 75.0 (60.0-97.0)              | 0.980            | 75.5 (61.0-96.0)                 | 75.0 (53.0-101.0)              | 0.249        |
| AP/ULN                                | 0.73 (0.59-0.92)       | 0.72 (0.58-0.93)              | 0.980            | 0.73 (0.59-0.92)                 | 0.72 (0.51-0.97)               | 0.249        |
| AST, U/L                              | 31.0 (24.0-43.0)       | 35.0 (26.0-52.8)              | <b>&lt;0.001</b> | 34.0 (26.0-48.0)                 | 33.0 (26.0-44.3)               | 0.614        |
| AST/ULN                               | 0.83 (0.65-1.10)       | 0.93 (0.71-1.37)              | <b>&lt;0.001</b> | 0.88 (0.68-1.23)                 | 0.85 (0.70-1.23)               | 0.895        |
| ALT, U/L                              | 38.0 (25.0-59.0)       | 44.0 (28.0-72.0)              | <b>0.001</b>     | 41.0 (27.0-65.0)                 | 36.0 (24.0-55.0)               | 0.096        |
| ALT/ULN                               | 0.86 (0.60-1.31)       | 1.00 (0.66-1.61)              | <b>0.001</b>     | 0.94 (0.63-1.46)                 | 0.82 (0.64-1.22)               | 0.351        |
| GGT, U/L                              | 70.0 (31.5-147.5)      | 71.5 (34.0-169.3)             | 0.626            | 72.0 (33.0-159.8)                | 62.0 (30.0-134.0)              | 0.218        |
| GGT/ULN                               | 0.50 (0.01-1.93)       | 0.60 (0.01-1.85)              | 0.388            | 0.58 (0.01-1.95)                 | 0.01 (0.01-1.10)               | <b>0.009</b> |
| Cholinesterase, U/L                   | 8.3 (7.0-9.5)          | 8.2 (6.7-9.4)                 | 0.241            | 8.3 (6.8-9.5)                    | 7.5 (6.2-8.5)                  | <b>0.003</b> |

**Supplementary Table-1.** Patient and disease characteristics compared among carriers and non-carriers of the *PNPLA3* G-allele and *SERPINA1* Z-allele. The ULN was defined as follows: AP ≥ 104 U/L; AST ≥ 40 U/L for men/≥ 35 U/L for women; ALT ≥ 50 U/L for men/≥ 35 for women, GGT ≥ 60 for men/≥ 40 for women.

Abbreviations:

ALT alanine transferase  
 AST aspartate aminotransferase  
 CRP C-reactive protein  
 GGT gamma-glutamyl transferase  
 ULN upper limit of normal

**Supplementary Table-2**

| <i>Genotypes</i>                                      | <b>LSM, kPa</b> | <b>CAP, dB/m</b>    | <b>CPS</b>     | <b>MELD</b> | <b>Fib-4</b>  |
|-------------------------------------------------------|-----------------|---------------------|----------------|-------------|---------------|
| <b>PNPLA3 C/C</b><br><b>n=623</b>                     | 5.8 (4.5-8.0)   | 275.5 (224.0-324.3) | <b>5.2±0.6</b> | 9.4±2.1     | 1.1 (0.7-1.7) |
| <b>PNPLA3</b><br><b>G/C or G/G</b><br><b>n=634</b>    | 6.1 (4.6-11.2)  | 285.0 (236.0-330.3) | 5.2±0.7        | 9.6±2.4     | 1.2 (0.8-2.0) |
| <b>P</b>                                              | <b>0.002</b>    | 0.083               | 0.131          | 0.331       | <b>0.036</b>  |
| <b>SERPINA1</b><br><b>M/M or M/S</b><br><b>n=1190</b> | 5.9 (4.5-9.1)   | 281.0 (233.0-328.0) | 5.2±0.6        | 9.5±2.3     | 1.1 (0.8-1.8) |
| <b>SERPINA1</b><br><b>M/Z or Z/Z</b><br><b>n=67</b>   | 6.0 (4.4-11.0)  | 251.0 (202.5-312.0) | 5.3±0.9        | 9.5±2.2     | 1.2 (0.7-1.8) |
| <b>P</b>                                              | 0.979           | <b>0.016</b>        | 0.235          | 0.975       | 0.773         |
| <b>No risk allele</b><br><b>n=588</b>                 | 5.8 (4.4-8.0)   | 279.0 (226.0-326.0) | 5.2±0.6        | 9.4±2.1     | 1.1 (0.7-1.7) |
| <b>One risk allele</b><br><b>n=637</b>                | 6.1 (4.6-11.1)  | 283.0 (235.0-329.0) | 5.2±0.7        | 9.6±2.4     | 1.2 (0.8-2.0) |
| <b>Two risk</b><br><b>alleles</b><br><b>n=32</b>      | 6.4 (4.2-13.1)  | 279.0 (217.5-333.3) | 5.4±1.1        | 9.3±2.0     | 1.1 (0.7-1.7) |
| <b>P</b>                                              | <b>0.008</b>    | 0.516               | 0.100          | 0.397       | 0.062         |

**Supplementary Table-2.** Comparison of liver stiffness measurement (LSM), controlled attenuation parameter (CAP), Child-Pugh-score (CPS), MELD score and Fib-4 score among patients with and without the respective risk alleles.

Abbreviations:

CAP controlled attenuation parameter

CPS Child-Pugh score

IQR interquartile range

LSM liver stiffness measurement

**Supplementary Table-3**

| <i>Genotypes</i>                                      | <b>HCC</b>     | <b>ACLD</b>      | <b>dACLD</b>   | <b>CSPH</b>      | <i>P</i> |        |       |       |
|-------------------------------------------------------|----------------|------------------|----------------|------------------|----------|--------|-------|-------|
| <b>PNPLA3 C/C</b><br><b>n=623</b>                     | n=5<br>(0.8%)  | n=119<br>(19.1%) | n=27<br>(4.3%) | n=71<br>(11.4%)  | 0.063    | <0.001 | 0.012 | 0.001 |
| <b>PNPLA3 G/C</b><br><b>or G/G</b><br><b>n=634</b>    | n=13<br>(2.1%) | n=190<br>(30.0%) | n=49<br>(7.7%) | n=114<br>(18.0%) |          |        |       |       |
| <b>SERPINA1</b><br><b>M/M or M/S</b><br><b>n=1190</b> | n=16<br>(1.3%) | n=289<br>(24.3%) | n=70<br>(5.9%) | n=171<br>(14.4%) | 0.249    | 0.303  | 0.289 | 0.142 |
| <b>SERPINA1</b><br><b>M/Z or Z/Z</b><br><b>n=67</b>   | n=2<br>(3.0%)  | n=20<br>(29.9%)  | n=6<br>(9.0%)  | n=14<br>(20.9%)  |          |        |       |       |

**Supplementary Table-3.** Comparison of prevalence of hepatocellular carcinoma (HCC), advanced chronic liver disease (ACLD), decompensated ACLD (dACLD), and clinically significant portal hypertension (CSPH) in patients with and without the respective risk allele.

Abbreviations:

ACLD advanced chronic liver disease

dACLD decompensated ACLD

CSPH clinically significant portal hypertension

HCC hepatocellular carcinoma

**Supplementary Table-4**

|                                          | LSM, kPa         | CAP, dB/m           | CPS     | MELD     | Fib-4         |
|------------------------------------------|------------------|---------------------|---------|----------|---------------|
| <i>ACLD</i>                              |                  |                     |         |          |               |
| <b>PNPLA3<br/>C/C<br/>n=119</b>          | 16.3 (11.6-29.7) | 305.0 (262.0-342.5) | 5.6±1.0 | 10.4±3.1 | 2.3 (1.3-4.1) |
| <b>PNPLA3<br/>G/C or G/G<br/>n=190</b>   | 18.5 (12.0-35.3) | 306.0 (261.3-350.8) | 5.6±1.1 | 10.3±3.0 | 2.6 (1.5-3.9) |
| <b>P</b>                                 | 0.060            | 0.784               | 0.944   | 0.922    | 0.582         |
| <i>CSPH</i>                              |                  |                     |         |          |               |
| <b>PNPLA3<br/>C/C<br/>n=71</b>           | 25.7 (16.3-39.6) | 293.0 (243.5-329.0) | 5.9±1.2 | 11.2±3.6 | 2.8 (1.4-5.1) |
| <b>PNPLA3<br/>G/C or G/G<br/>n=114</b>   | 32.5 (21.7-53.9) | 295.0 (249.3-342.0) | 5.8±1.3 | 10.9±3.4 | 3.0 (1.8-4.7) |
| <b>P</b>                                 | <b>0.017</b>     | 0.573               | 0.814   | 0.530    | 0.628         |
| <i>ACLD</i>                              |                  |                     |         |          |               |
| <b>SERPINA1<br/>M/M or M/S<br/>n=289</b> | 17.0 (11.8-34.3) | 306.0 (264.0-351.0) | 5.6±1.1 | 10.4±3.1 | 2.5 (1.5-4.0) |
| <b>SERPINA1<br/>M/Z or Z/Z<br/>n=20</b>  | 22.7 (11.2-36.5) | 274.0 (229.0-333.0) | 5.7±1.4 | 9.8±2.4  | 3.3 (1.6-5.1) |
| <b>P</b>                                 | 0.736            | 0.063               | 0.743   | 0.401    | 0.354         |
| <i>CSPH</i>                              |                  |                     |         |          |               |
| <b>SERPINA1<br/>M/M or M/S<br/>n=171</b> | 29.6 (20.9-48.0) | 295.5 (250.0-333.3) | 5.9±1.2 | 11.1±3.5 | 2.9 (1.6-4.8) |
| <b>SERPINA1<br/>M/Z or Z/Z<br/>n=14</b>  | 32.0 (19.0-43.3) | 260.0 (229.0-341.0) | 5.9±1.6 | 10.3±2.7 | 3.4 (1.7-5.2) |
| <b>P</b>                                 | 0.985            | 0.460               | 0.994   | 0.454    | 0.681         |

**Supplementary Table-4.** Comparison of liver stiffness measurement (LSM), controlled attenuation parameter (CAP), Child-Pugh-score (CPS), MELD score and Fib-4 score among patients with and without the respective risk alleles when only considering patients with ACLD or CSPH.

Abbreviations:

ACLD advanced chronic liver disease

CAP controlled attenuation parameter

CPS Child-Pugh score

CSPH clinically significant portal hypertension

LSM liver stiffness measurement

**Supplementary Table-5**

| <b>A</b>               | <b>LSM, kPa</b>                        | <b>ACLD</b>                            | <b>CSPH</b>                            |
|------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Age, year              | 0.112 (0.080-0.143)<br><i>P</i> <0.001 | 1.061 (1.046-1.076)<br><i>P</i> <0.001 | 1.060 (1.041-1.078)<br><i>P</i> <0.001 |
| BMI, kg/m <sup>2</sup> | 0.445 (0.347-0.542)<br><i>P</i> <0.001 | 1.181 (1.138-1.226)<br><i>P</i> <0.001 | 1.125 (1.077-1.175)<br><i>P</i> <0.001 |
| PNPLA3 G-allele        | 1.324 (0.353-2.294)<br><i>P</i> =0.008 | 2.029 (1.405-2.929)<br><i>P</i> <0.001 | 1.843 (1.162-2.926)<br><i>P</i> =0.009 |

| <b>B</b>               | <b>LSM, kPa</b>                         | <b>ACLD</b>                            | <b>CSPH</b>                            |
|------------------------|-----------------------------------------|----------------------------------------|----------------------------------------|
| Age, year              | 0.109 (0.078-0.141)<br><i>P</i> <0.001  | 1.059 (1.044-1.073)<br><i>P</i> <0.001 | 1.058 (1.040-1.077)<br><i>P</i> <0.001 |
| BMI, kg/m <sup>2</sup> | 0.459 (0.361-0.556)<br><i>P</i> <0.001  | 1.184 (1.141-1.229)<br><i>P</i> <0.001 | 1.129 (1.082-1.179)<br><i>P</i> <0.001 |
| SERPINA1 Z-allele      | 1.899 (-0.180-3.977)<br><i>P</i> =0.073 | 1.478 (0.710-3.075)<br><i>P</i> =0.296 | 1.924 (0.859-4.311)<br><i>P</i> =0.112 |

| <b>C</b>               | <b>LSM, kPa</b>                         | <b>ACLD</b>                            | <b>CSPH</b>                            |
|------------------------|-----------------------------------------|----------------------------------------|----------------------------------------|
| Age, year              | 0.111 (0.079-0.142)<br><i>P</i> <0.001  | 1.061 (1.046-1.076)<br><i>P</i> <0.001 | 1.059 (1.040-1.078)<br><i>P</i> <0.001 |
| BMI, kg/m <sup>2</sup> | 0.450 (0.352-0.547)<br><i>P</i> <0.001  | 1.182 (1.138-1.227)<br><i>P</i> <0.001 | 1.125 (1.078-1.175)<br><i>P</i> <0.001 |
| PNPLA3 G-allele        | 1.318 (0.349-2.287)<br><i>P</i> =0.008  | 2.039 (1.411-2.946)<br><i>P</i> <0.001 | 1.858 (1.169-2.953)<br><i>P</i> =0.009 |
| SERPINA1 Z-allele      | 1.880 (-0.192-3.952)<br><i>P</i> =0.075 | 1.529 (0.730-3.201)<br><i>P</i> =0.260 | 1.974 (0.875-4.452)<br><i>P</i> =0.101 |

| <b>D</b>               | <b>ACLD</b>                             | <b>CSPH</b>                             |
|------------------------|-----------------------------------------|-----------------------------------------|
| Age, year              | 1.060 (1.046-1.075)<br><i>P</i> <0.001  | 1.059 (1.041-1.078)<br><i>P</i> <0.001  |
| BMI, kg/m <sup>2</sup> | 1.183 (1.139-1.228)<br><i>P</i> <0.001  | 1.126 (1.078-1.176)<br><i>P</i> <0.001  |
| No risk allele         | Reference                               | Reference                               |
| One risk allele        | 1.871 (1.286-2.722)<br><i>P</i> =0.001  | 1.769 (1.098-2.852)<br><i>P</i> =0.019  |
| Two risk alleles       | 4.212 (1.558-11.385)<br><i>P</i> =0.005 | 4.278 (1.453-12.596)<br><i>P</i> =0.008 |

**Supplementary Table-5.** Linear and logistic regression analyses investigating the association of individual risk alleles with liver stiffness measurement (LSM), presence of advanced chronic liver disease (ACLD) and clinically significant portal hypertension (CSPH) in patients with non-alcoholic fatty liver disease (n=1048) only: (A) for PNPLA3 and covariables, (B) for SERPINA1 and covariables and (C) in a combined regression model for both PNPLA3 and SERPINA1. (D) Logistic regression

model comparing patients with no risk allele (reference) to those with any and two risk alleles. Covariates were: Age (per year) and BMI (per kg/m<sup>2</sup>).

Abbreviations:

ACLD advanced chronic liver disease

BMI body mass index

CSPH clinically significant portal hypertension

LSM liver stiffness measurement

**Supplementary Table-6**

| <b>A</b>                     | <b>LSM, kPa</b>                                 | <b>ACLD</b>                                    | <b>CSPH</b>                            |
|------------------------------|-------------------------------------------------|------------------------------------------------|----------------------------------------|
| <b>Age, year</b>             | 0.126 (-0.126-0.377)<br><i>P</i> =0.326         | 1.051 (1.023-1.081)<br><i>P</i> < <b>0.001</b> | 1.015 (0.991-1.040)<br><i>P</i> =0.215 |
| <b>BMI, kg/m<sup>2</sup></b> | -0.073 (-0.656-0.509)<br><i>P</i> =0.804        | 0.993 (0.936-1.054)<br><i>P</i> =0.826         | 0.966 (0.912-1.022)<br><i>P</i> =0.223 |
| <b>PNPLA3 G-allele</b>       | 9.912 (3.931-15.893)<br><i>P</i> = <b>0.001</b> | 1.854 (1.016-3.383)<br><i>P</i> = <b>0.044</b> | 1.468 (0.833-2.588)<br><i>P</i> =0.184 |

  

| <b>B</b>                     | <b>LSM, kPa</b>                          | <b>ACLD</b>                                    | <b>CSPH</b>                             |
|------------------------------|------------------------------------------|------------------------------------------------|-----------------------------------------|
| <b>Age, year</b>             | 0.134 (-0.124-0.391)<br><i>P</i> =0.308  | 1.050 (1.021-1.079)<br><i>P</i> = <b>0.001</b> | 1.015 (0.991-1.039)<br><i>P</i> =0.234  |
| <b>BMI, kg/m<sup>2</sup></b> | -0.057 (-0.654-0.540)<br><i>P</i> =0.851 | 0.995 (0.938-1.054)<br><i>P</i> =0.858         | 0.966 (0.912-1.022)<br><i>P</i> =0.231  |
| <b>SERPINA1 Z-allele</b>     | 7.929 (-8.747-24.604)<br><i>P</i> =0.350 | NE                                             | 3.113 (0.585-16.560)<br><i>P</i> =0.183 |

  

| <b>C</b>                     | <b>LSM, kPa</b>                                  | <b>ACLD</b>                                    | <b>CSPH</b>                             |
|------------------------------|--------------------------------------------------|------------------------------------------------|-----------------------------------------|
| <b>Age, year</b>             | 0.113 (-0.138-0.365)<br><i>P</i> =0.376          | 1.050 (1.021-1.079)<br><i>P</i> = <b>0.001</b> | 1.014 (0.990-1.039)<br><i>P</i> =0.259  |
| <b>BMI, kg/m<sup>2</sup></b> | -0.075 (-0.656-0.507)<br><i>P</i> =0.800         | 0.995 (0.937-1.056)<br><i>P</i> =0.857         | 0.965 (0.912-1.021)<br><i>P</i> =0.220  |
| <b>PNPLA3 G-allele</b>       | 10.312 (4.311-16.314)<br><i>P</i> = <b>0.001</b> | 1.997 (1.086-3.673)<br><i>P</i> = <b>0.026</b> | 1.544 (0.870-2.742)<br><i>P</i> =0.138  |
| <b>SERPINA1 Z-allele</b>     | 10.768 (-5.565-27.101)<br><i>P</i> =0.195        | NE                                             | 3.546 (0.655-19.185)<br><i>P</i> =0.142 |

  

| <b>D</b>                     | <b>ACLD</b>                                    | <b>CSPH</b>                            |
|------------------------------|------------------------------------------------|----------------------------------------|
| <b>Age, yr</b>               | 1.050 (1.022-1.080)<br><i>P</i> = <b>0.001</b> | 1.014 (0.990-1.039)<br><i>P</i> =0.251 |
| <b>BMI, kg/m<sup>2</sup></b> | 0.993 (0.936-1.054)<br><i>P</i> =0.829         | 0.965 (0.912-1.021)<br><i>P</i> =0.218 |
| <b>No risk allele</b>        | Reference                                      | Reference                              |
| <b>One risk allele</b>       | 2.125 (1.159-3.897)<br><i>P</i> = <b>0.015</b> | 1.515 (0.853-2.690)<br><i>P</i> =0.157 |
| <b>Two risk alleles</b>      | NE                                             | NE                                     |

**Supplementary Table-6.** Linear and logistic regression analyses investigating the association of individual risk alleles with liver stiffness measurement (LSM), presence of advanced chronic liver disease (ACLD) and clinically significant portal hypertension (CSPH) in patients with alcoholic liver disease (n=209) only: **(A)** for PNPLA3 and covariables, **(B)** for SERPINA1 and covariables and **(C)** in a combined regression model for both PNPLA3 and SERPINA1. **(D)** Logistic regression model comparing patients with no risk allele (reference) to those with any and two risk

alleles. Covariates were: Age (per year), BMI (per kg/m<sup>2</sup>), active or past alcohol abuse (women  $\geq$  2 drinks per day, men  $\geq$  3 drinks per day).

Abbreviations:

ACLD advanced chronic liver disease

BMI body mass index

CSPH clinically significant portal hypertension

LSM liver stiffness measurement

NE not evaluable



Supplementary Table-7

| A                             | LSM, kPa                               | ACLD                                   | CSPH                                   |
|-------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Age, year                     | 0.157 (0.112-0.202)<br><i>P</i> <0.001 | 1.057 (1.045-1.068)<br><i>P</i> <0.001 | 1.046 (1.033-1.060)<br><i>P</i> <0.001 |
| BMI, kg/m <sup>2</sup>        | 0.294 (0.159-0.429)<br><i>P</i> <0.001 | 1.104 (1.072-1.137)<br><i>P</i> <0.001 | 1.041 (1.007-1.077)<br><i>P</i> =0.017 |
| Alcohol consumption, drinks/d | 1.336 (1.044-1.628)<br><i>P</i> <0.001 | 1.206 (1.139-1.276)<br><i>P</i> <0.001 | 1.199 (1.130-1.273)<br><i>P</i> <0.001 |
| PNPLA3 G-allele               | 3.124 (1.774-4.474)<br><i>P</i> <0.001 | 1.977 (1.477-2.644)<br><i>P</i> <0.001 | 1.742 (1.241-2.444)<br><i>P</i> =0.001 |

| B                             | LSM, kPa                                | ACLD                                   | CSPH                                   |
|-------------------------------|-----------------------------------------|----------------------------------------|----------------------------------------|
| Age, year                     | 0.155 (0.110-0.200)<br><i>P</i> <0.001  | 1.055 (1.043-1.066)<br><i>P</i> <0.001 | 1.046 (1.033-1.059)<br><i>P</i> <0.001 |
| BMI, kg/m <sup>2</sup>        | 0.316 (0.180-0.452)<br><i>P</i> <0.001  | 1.106 (1.074-1.139)<br><i>P</i> <0.001 | 1.045 (1.011-1.080)<br><i>P</i> =0.009 |
| Alcohol consumption, drinks/d | 1.351 (1.056-1.646)<br><i>P</i> <0.001  | 1.205 (1.139-1.274)<br><i>P</i> <0.001 | 1.202 (1.133-1.276)<br><i>P</i> <0.001 |
| SERPINA1 Z-allele             | 2.038 (-0.968-5.044)<br><i>P</i> =0.184 | 1.515 (0.828-2.772)<br><i>P</i> =0.178 | 1.764 (0.924-3.370)<br><i>P</i> =0.085 |

| C                             | LSM, kPa                                | ACLD                                   | CSPH                                   |
|-------------------------------|-----------------------------------------|----------------------------------------|----------------------------------------|
| Age, year                     | 0.156 (0.111-0.201)<br><i>P</i> <0.001  | 1.056 (1.045-1.068)<br><i>P</i> <0.001 | 1.046 (1.033-1.059)<br><i>P</i> <0.001 |
| BMI, kg/m <sup>2</sup>        | 0.298 (0.163-0.433)<br><i>P</i> <0.001  | 1.105 (1.073-1.138)<br><i>P</i> <0.001 | 1.042 (1.008-1.077)<br><i>P</i> =0.015 |
| Alcohol consumption, drinks/d | 1.345 (1.053-1.638)<br><i>P</i> <0.001  | 1.209 (1.142-1.279)<br><i>P</i> <0.001 | 1.204 (1.134-1.279)<br><i>P</i> <0.001 |
| PNPLA3 G-allele               | 3.132 (1.783-4.482)<br><i>P</i> <0.001  | 1.988 (1.485-2.890)<br><i>P</i> <0.001 | 1.757 (1.251-2.468)<br><i>P</i> =0.001 |
| SERPINA1 Z-allele             | 2.102 (-0.881-5.084)<br><i>P</i> =0.167 | 1.572 (0.855-2.890)<br><i>P</i> =0.145 | 1.822 (0.952-3.487)<br><i>P</i> =0.070 |

| D                             | ACLD                                   | CSPH                                   |
|-------------------------------|----------------------------------------|----------------------------------------|
| Age, year                     | 1.056 (1.045-1.068)<br><i>P</i> <0.001 | 1.046 (1.033-1.059)<br><i>P</i> <0.001 |
| BMI, kg/m <sup>2</sup>        | 1.105 (1.073-1.138)<br><i>P</i> <0.001 | 1.042 (1.008-1.077)<br><i>P</i> =0.015 |
| Alcohol consumption, drinks/d | 1.209 (1.143-1.280)<br><i>P</i> <0.001 | 1.204 (1.134-1.279)<br><i>P</i> <0.001 |
| No risk allele                | Reference                              | Reference                              |
| One risk allele               | 1.957 (1.454-2.634)<br><i>P</i> <0.001 | 1.733 (1.223-2.456)<br><i>P</i> =0.002 |
| Two risk alleles              | 3.173 (1.344-7.491)<br><i>P</i> =0.008 | 3.407 (1.395-8.319)<br><i>P</i> =0.007 |

**Supplementary Table-7.** Multivariable linear and logistic regression analyses investigating the association of individual risk alleles with liver stiffness measurement (LSM), presence of advanced chronic liver disease (ACLD) and clinically significant portal hypertension (CSPH): **(A)** for PNPLA3 and covariables, **(B)** for SERPINA1 and covariables and **(C)** in a combined regression model for both PNPLA3 and SERPINA1. **(D)** Logistic regression model comparing patients with no risk allele (reference) to those with any and two risk alleles. Covariables were: Age (per year), BMI (per kg/m<sup>2</sup>), alcohol consumption (per drink per day).

Abbreviations:

ACLD advanced chronic liver disease

BMI body mass index

CSPH clinically significant portal hypertension

LSM liver stiffness measurement

Supplementary Table-8

| <b>A</b>                 | <b>LSM kPa</b>                            | <b>ACLD</b>                             | <b>CSPH</b>                             |
|--------------------------|-------------------------------------------|-----------------------------------------|-----------------------------------------|
| Age, year                | 0.087 (0.044-0.130)<br><i>P</i> <0.001    | 1.048 (1.036-1.061)<br><i>P</i> <0.001  | 1.036 (1.022-1.051)<br><i>P</i> <0.001  |
| BMI, kg/m <sup>2</sup>   | 0.273 (0.147-0.400)<br><i>P</i> <0.001    | 1.111 (1.076-1.147)<br><i>P</i> <0.001  | 1.041 (1.004-1.078)<br><i>P</i> =0.028  |
| Alcohol abuse            | 13.397 (11.773-15.022)<br><i>P</i> <0.001 | 8.522 (5.976-12.153)<br><i>P</i> <0.001 | 8.064 (5.565-11.686)<br><i>P</i> <0.001 |
| Type 2 diabetes mellitus | 5.801 (3.790-7.813)<br><i>P</i> <0.001    | 3.265 (2.162-4.931)<br><i>P</i> <0.001  | 2.954 (1.875-4.655)<br><i>P</i> <0.001  |
| PNPLA3 G-allele          | 2.610 (1.353-3.867)<br><i>P</i> <0.001    | 1.943 (1.420-2.659)<br><i>P</i> <0.001  | 1.655 (1.154-2.373)<br><i>P</i> =0.006  |

| <b>B</b>                 | <b>LSM kPa</b>                            | <b>ACLD</b>                             | <b>CSPH</b>                             |
|--------------------------|-------------------------------------------|-----------------------------------------|-----------------------------------------|
| Age, year                | 0.083 (0.040-0.127)<br><i>P</i> <0.001    | 1.046 (1.034-1.059)<br><i>P</i> <0.001  | 1.035 (1.021-1.049)<br><i>P</i> <0.001  |
| BMI, kg/m <sup>2</sup>   | 0.293 (0.166-0.421)<br><i>P</i> <0.001    | 1.113 (1.079-1.150)<br><i>P</i> <0.001  | 1.043 (1.007-1.081)<br><i>P</i> =0.018  |
| Alcohol abuse            | 13.634 (12.000-15.267)<br><i>P</i> <0.001 | 8.683 (6.103-12.354)<br><i>P</i> <0.001 | 8.463 (5.828-12.290)<br><i>P</i> <0.001 |
| Type 2 diabetes mellitus | 5.913 (3.892-7.934)<br><i>P</i> <0.001    | 3.332 (2.214-5.015)<br><i>P</i> <0.001  | 3.028 (1.921-4.774)<br><i>P</i> <0.001  |
| SERPINA1 Z-allele        | 2.581 (-0.208-5.370)<br><i>P</i> =0.070   | 1.791 (0.934-3.434)<br><i>P</i> =0.079  | 2.181 (1.082-4.394)<br><i>P</i> =0.029  |

| <b>C</b>                 | <b>LSM kPa</b>                            | <b>ACLD</b>                             | <b>CSPH</b>                             |
|--------------------------|-------------------------------------------|-----------------------------------------|-----------------------------------------|
| Age, year                | 0.086 (0.043-0.129)<br><i>P</i> <0.001    | 1.048 (1.035-1.061)<br><i>P</i> <0.001  | 1.036 (1.021-1.050)<br><i>P</i> <0.001  |
| BMI, kg/m <sup>2</sup>   | 0.279 (0.152-0.406)<br><i>P</i> <0.001    | 1.112 (1.076-1.148)<br><i>P</i> <0.001  | 1.041 (1.005-1.079)<br><i>P</i> =0.025  |
| Alcohol abuse            | 13.476 (11.851-15.101)<br><i>P</i> <0.001 | 8.721 (6.104-12.459)<br><i>P</i> <0.001 | 8.391 (5.765-12.212)<br><i>P</i> <0.001 |
| Type 2 diabetes mellitus | 5.801 (3.791-7.810)<br><i>P</i> <0.001    | 3.283 (2.170-4.966)<br><i>P</i> <0.001  | 2.982 (1.888-4.711)<br><i>P</i> <0.001  |
| PNPLA3 G-allele          | 2.618 (1.363-3.874)<br><i>P</i> <0.001    | 1.960 (1.431-2.684)<br><i>P</i> <0.001  | 1.678 (1.169-2.410)<br><i>P</i> =0.005  |
| SERPINA1 Z-allele        | 2.623 (-0.149-5.394)<br><i>P</i> =0.064   | 1.865 (0.968-3.596)<br><i>P</i> =0.063  | 2.255 (1.120-4.544)<br><i>P</i> =0.023  |

| <b>D</b>                 | <b>ACLD</b>                             | <b>CSPH</b>                             |
|--------------------------|-----------------------------------------|-----------------------------------------|
| Age, year                | 1.048 (1.035-1.061)<br><i>P</i> <0.001  | 1.036 (1.022-1.050)<br><i>P</i> <0.001  |
| BMI, kg/m <sup>2</sup>   | 1.112 (1.077-1.148)<br><i>P</i> <0.001  | 1.041 (1.005-1.079)<br><i>P</i> =0.025  |
| Alcohol abuse            | 8.735 (6.115-12.476)<br><i>P</i> <0.001 | 8.385 (5.764-12.199)<br><i>P</i> <0.001 |
| Type 2 diabetes mellitus | 3.285 (2.172-4.969)<br><i>P</i> <0.001  | 2.971 (1.881-4.693)<br><i>P</i> <0.001  |

|                         |                                        |                                         |
|-------------------------|----------------------------------------|-----------------------------------------|
| <b>No risk allele</b>   | Reference                              | Reference                               |
| <b>One risk allele</b>  | 1.941 (1.409-2.674)<br><i>P</i> <0.001 | 1.658 (1.145-2.402)<br><i>P</i> =0.007  |
| <b>Two risk alleles</b> | 3.791 (1.496-9.606)<br><i>P</i> =0.005 | 4.252 (1.620-11.162)<br><i>P</i> =0.003 |

**Supplementary Table-8.** Multivariable linear and logistic regression analyses investigating the association of individual risk alleles with liver stiffness measurement (LSM), presence of advanced chronic liver disease (ACLD) and clinically significant portal hypertension (CSPH): (A) for PNPLA3 and covariables, (B) for SERPINA1 and covariables and (C) in a combined multivariable regression model for both PNPLA3 and SERPINA1. (D) Multivariable logistic regression model comparing patients with no risk allele (reference) to those with any and two risk alleles. Covariables were: Age (per year), BMI (per kg/m<sup>2</sup>), active or past alcohol abuse (women ≥ 2 drinks per day, men ≥ 3 drinks per day), type 2 diabetes mellitus.

Abbreviations:

ACLD advanced chronic liver disease  
BMI body mass index  
CSPH clinically significant portal hypertension  
LSM liver stiffness measurement