**Supplementary Material**

**Supplementary Figure**

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**Supplementary Figure 1.** Receiver operator characteristic (ROC) curve of Lp(a) for predicting carotid atherosclerosis in different MAFLD subtypes with and without advanced fibrosis defined by liver stiffness.

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**Supplementary Figure 2.** The flow chart of enrollment and specific tests.

**Supplementary Table**

**Supplementary Table 1. Comparison of MAFLD patients with and without advanced fibrosis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **NFS****≤-1.836****n=967** | **NFS****>-1.836****n=379** | ***p* value\*** | **LSM<6.3kPa****n=321** | **LSM≥6.3kPa****n=173** | ***p* value†** |
| **Age (years), mean±SD** | 42.9±12.4 | 58.8±11.2 | <0.001 | 39.8±12.2 | 44.2±12.4 | <0.001 |
| **Male, n(%)** | 662(68.5) | 220(58.1) | <0.001 | 235(73.2) | 128(73.7) | 0.7989 |
| **Hypertension, n(%)** | 178(18.4) | 180(47.5) | <0.001 | 22(6.9) | 29(16.5) | <0.001 |
| **Diabetes, n(%)** | 31(3.2) | 142(37.5) | <0.001 | 16(5.0) | 26(14.9) | <0.001 |
| **Current smoker, n(%)** | 167(17.3) | 86(22.7) | 0.051 | 46(14.3) | 26(15.2) | 0.814 |
| **BMI, kg/m2** | 25.7±3.2 | 27.5±4.2 | <0.001 | 26.0±3.4 | 27.9±4.0 | <0.001 |
| **Waist-to-hip ratio** | 0.89±0.05 | 0.91±0.05 | <0.001 | 0.89±0.04 | 0.91±0.05 | <0.001 |
| **SBP, mmHg** | 131±15 | 135±21 | <0.001 | 129±16 | 135±16 | 0.001 |
| **DBP, mmHg** | 84±13 | 81±14 | 0.003 | 84±14 | 88±14 | 0.002 |
| **Liver and metabolism marker, mean±SD** |  |  |  |  |  |  |
| ALT (U/L)† | 51±44 | 53±49 | <0.001 | 49±45 | 66±54 | <0.001 |
| AST (U/L)† | 34±26 | 36±57 | 0.344 | 34±30 | 52±47 | <0.001 |
| GGT(U/L)† | 59±82 | 56±74 | 0.412 | 53±73 | 83±98 | <0.001 |
| ALB(g/L) | 45.6±15.4 | 41.5±3.7 | <0.001 | 46.1±1.5 | 42.9±3.4 | <0.001 |
| Uric acid (μmol/L) | 406±106 | 394±98 | 0.017 | 409±109 | 424±101 | 0.102 |
| FBG (mmol/L) | 5.1±1.2 | 6.5±3.7 | <0.001 | 5.0±1.2 | 5.5±1.4 | 0.001 |
| FINS (mmol/L)† | 11.2±7.5 | 12.2±9.9 | 0.135 | 10.6±7.5 | 13.5±7.9 | <0.001 |
| HOMA-IR† | 2.5±1.8 | 3.1±1.7 | <0.001 | 2.5±1.7 | 3.3±2.3 | <0.001 |
| **Lipid profiles, mean±SD** |  |  |  |  |  |  |
| Total cholesterol (mmol/L) | 5.2±1.3 | 5.2±3.0 | 0.644 | 5.1±1.1 | 5.3±1.5 | 0.022 |
| Triglyceride (mmol/L) | 1.94±1.26 | 2.11±1.87 | 0.068 | 1.67±1.20 | 1.82±1.09 | 0.100 |
| HDL-c (mmol/L) | 1.20±0.43 | 1.14±0.32 | <0.001 | 1.16±0.26 | 1.18±0.34 | 0.783 |
| LDL-c (mmol/L) | 3.17±0.92 | 3.32±0.81 | 0.001 | 3.24±0.73 | 3.41±0.86 | 0.009 |
| ApoA1 (g/L) | 1.28±0.22 | 1.30±0.27 | 0.247 | 1.26±0.29 | 1.25±0.24 | 0.675 |
| ApoB (g/L) | 0.97±0.30 | 1.00±0.29 | 0.020 | 0.94±0.25 | 1.00±0.42 | 0.014 |
| ApoE (mg/L) | 49±21 | 48±21 | 0.137 | 45±16 | 46±16 | 0.085 |
| Lp(a) (mg/L)† | 194±290 | 191±127 | 0.061 | 171±199 | 157±203 | 0.071 |
| PLT (109/L) | 261±53 | 210±46 | <0.001 | 255±54 | 242±64 | 0.001 |
| **CIMT≥1.0mm, n(%)** | 262(27.1) | 219(57.7) | <0.001 | 54(16.8) | 45(25.8) | 0.004 |

**\**p* value was comparison of MAFLD patients with NFS≤-1.836 and NFS>-1.836**

**†*p* value was comparison of MAFLD patients with LSM<6.3kPa and LSM≥6.3kPa**

**Supplementary table 2. Associations of quantiles of Lp(a) with carotid atherosclerosis in both MAFLD and non MAFLD patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Quantile of Lp(a) | All cases | Non MAFLD | MAFLD  | MAFLD with advanced fibrosis\* |
| Model 1 | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| Q1 | Reference |  | Reference |  | Reference |  | Reference |  |
| Q2 | 1.38(1.11-1.74)  | 0.001  | 1.68(1.26-2.25) | <0.001 | 1.34(1.02-1.88) | 0.044 | 1.53(0.65-6.42) | 0.512  |
| Q3 | 1.84(1.48-2.25)  | <0.001  | 1.97(1.48-2.62) | <0.001 | 2.09(1.43-3.21) | <0.001 | 0.83(0.21-4.45) | 0.452  |
| Q4 | 2.50(2.03-3.06)  | <0.001  | 3.41(2.59-4.49) | <0.001 | 1.90(1.35-2.54) | <0.001 | 0.62(0.21-3.45) | 0.381  |
| P for trend | <0.001  | 　 | <0.001 |  | <0.001 |  | 0.482  |  |
| Model 2 |  | 　 |  |  |  |  |  |  |
| Q1 | Reference |  | Reference |  | Reference |  | Reference |  |
| Q2 | 1.13(0.87-1.41)  | 0.310  | 1.43(1.05-1.97) | 0.026 | 1.03(0.74-1.55) | 0.805 | 1.15(0.39-4.72) | 0.199  |
| Q3 | 1.44(1.14-1.80)  | 0.001  | 1.70(1.25-2.31) | 0.001 | 1.50(1.02-2.01) | 0.031 | 1.34(0.86-3.31) | 0.801  |
| Q4 | 2.20(1.73-2.72)  | <0.001  | 3.42(2.53-4.63) | <0.001 | 1.33(0.94-1.93) | 0.102 | 0.43(0.91-3.96) | 0.442 |
| P for trend | <0.001  | 　 | <0.001 |  | 0.071 |  | 0.421 |  |
| Model 3 | 　 | 　 |  |  |  |  |  |  |
| Q1 | Reference |  | Reference |  | Reference |  | Reference |  |
| Q2 | 1.12(0.87-1.43)  | 0.363  | 1.45(1.05-1.99) | 0.024 | 0.98(0.69-1.54) | 0.856 | 1.68(0.42-5.12) | 0.110  |
| Q3 | 1.40(1.13-1.75)  | 0.003  | 1.74(1.28-2.38) | <0.001 | 1.36(0.98-2.01) | 0.073 | 1.82(0.82-2.72) | 0.653  |
| Q4 | 2.12(1.70-2.69)  | <0.001  | 3.49(2.57-4.75) | <0.001 | 1.20(0.88-1.80) | 0.212 | 0.56(0.39-1.41) | 0.712  |
| P for trend | <0.001 |  | <0.001 |  | 0.214 |  | 0.412 |  |
| Model 4 |  |  |  |  |  |  |  |  |
| Q1 | Reference |  | Reference |  | Reference |  | Reference |  |
| Q2 | 1.11(0.85-1.43)  | 0.419 | 1.41(1.02-1.96) | 0.039 | 0.96(0.67-1.39) | 0.687 | 1.67(0.48-3.92) | 0.623 |
| Q3 | 1.40(1.09-1.78)  | 0.004  | 1.73(1.25-2.39) | 0.001 | 1.32(0.89-1.92) | 0.144 | 1.61(0.68-3.34) | 0.312 |
| Q4 | 2.02(1.59-2.55)  | <0.001  | 3.37(2.45-4.63) | <0.001 | 1.11(0.80-1.75) | 0.537 | 1.89(0.52-3.62) | 0.431 |
| P for trend | <0.001  | 　 | <0.001 |  | 0.263 |  | 0.482 |  |

\*Advanced fibrosis was defined as LSM≥9kPa

Model 1 was the crude model

Model 2 was adjusted for age and gender

Model 3 was adjusted for factors of Model 2 and BMI, history of type-2 diabetes and smoking

Model 4 was adjusted for factors of Model 3 and ALT, Uric acid, HOMA-IR, total cholesterol, TG, HDL-c and ApoB/ApoA ratio.

|  |  |  |
| --- | --- | --- |
| Quantile of Lp(a) | Crude model | Muti-variable adjusted model† |
| OR(95% CI) | *p* value | OR(95% CI) | *p* value |
| Q1 | Reference |  | Reference |  |
| Q2 | 0.75(0.45-1.36) | 0.421 | 0.39(0.10-1.04) | 0.075 |
| Q3 | 0.64(0.24-1.75) | 0.543 | 0.43(0.11-1.60) | 0.207 |
| Q4 | 0.43(0.28-1.10) | 0.084 | 0.23(0.10-1.02) | 0.058 |
| *p* for trend | 0.144 | 0.077 |
| *p* interaction‡ | 0.022 | 0.045 |

Supplementary Table 3. Multi-variable adjusted logistic regression for the association between carotid atherosclerosis misdiagnosed by Lp(a) regression model and quartile of serum Lp(a) level.

†Adjusting variable including age, sex, BMI, smoking history, ALT, uric acid, HOMA-IR, total cholesterol, triglycerides, HDL-c and ApoB/ApoA ratio.

‡*p* interaction represents the significance of the coefficient of the interaction term of hepatic fibrosis degree measured by liver stiffness and quartile of Lp(a).

Supplementary Table 4. Sensitivity, specificity, NPV and PPV for cut-offs predicting carotid atherosclerosis.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Sensitivity****(%)** | **Specitivity****(%)** | **PPV****(%)** | **NPV****(%)** | **Lp(a) Cut-off,**  **mg/L** |
| Non MAFLD | 76.9 | 70.1 | 42.6 | 91.2 | 284 |
| MAFLD with NFS≤-1.836 | 74.0 | 69.1 | 45.5 | 88.7 | 213 |
| MAFLD with NFS>-1.836 | 62.3 | 68.5 | 73.4 | 55.2 | 189 |
| MAFLD with LSM<6.3kPa | 77.2 | 73.3 | 36.8 | 92.0 | 253 |
| MAFLD with LSM≥6.3kPa and <9.0kPa | 97.4 | 63.0 | 54.8 | 98.6 | 214 |
| MAFLD with LSM≥9.0kPa  | 76.3 | 52.3 | 53.9 | 80.1 | 169 |

**Abbreviation:** MAFLD, metabolic associated fatty liver disease; Lp(a), lipoprotein (a); NFS, NAFLD fibrosis score; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value.

Supplementary table 5. The association of carotid atherosclerosis with Lp(a) in different MAFLD subgroup

|  |  |
| --- | --- |
| Quantile of Lp(a) | MAFLD subgroup |
| Overweight/obesity　 | Lean/normal weight　 | Type-2 diabetes　 |
| Model 1 | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| Q1 | Reference |  | Reference |  | Reference |  |
| Q2 | 1.16(0.80-1.68) | 0.399  | 2.54(0.94-6.88) | 0.067  | 1.17(0.48-2.88) | 0.726  |
| Q3 | 1.63(1.12-2.36) | 0.011  | 3.3(1.98-7.89) | 0.000  | 1.75(0.76-4.04) | 0.191  |
| Q4 | 1.62(1.13-2.30) | 0.008  | 2.81(1.1-7.16) | 0.030  | 1.92(0.82-4.47) | 0.133  |
| P for trend | 0.017  |  | <0.001  |  | 0.361  |  |
| Model 2 |  |  |  |  |  |  |
| Q1 | Reference |  | Reference |  | Reference |  |
| Q2 | 1.04(0.70-1.56) | 0.875  | 1.31(0.43-4.01) | 0.640  | 0.86(0.32-2.29) | 0.764  |
| Q3 | 1.09(0.71-1.67) | 0.690  | 4.20(1.60-7.06) | 0.004  | 1.60(0.66-3.91) | 0.299  |
| Q4 | 1.28(0.86-1.90) | 0.201  | 1.34(0.47-3.85) | 0.587  | 1.46(0.59-3.59) | 0.414  |
| P for trend | 0.579  |  | 0.010  |  | 0.458  |  |
| Model 3 |  |  |  |  |  |  |
| Q1 | Reference |  | Reference |  | Reference |  |
| Q2 | 1.18(0.67-2.05) | 0.589  | 1.56(0.22-6.23) | 0.658  | 0.86(0.32-2.31) | 0.762  |
| Q3 | 1.19(0.67-2.12) | 0.551  | 1.67(0.71-3.68) | 0.119  | 1.47(0.59-3.61) | 0.406  |
| Q4 | 1.47(0.87-2.55) | 0.162  | 0.88(0.15-5.08) | 0.885  | 1.31(0.52-3.28) | 0.570  |
| P for trend | 0.565  |  | 0.239  |  | 0.638  |  |
| Model 4 |  |  |  |  |  |  |
| Q1 | Reference |  | Reference |  | Reference |  |
| Q2 | 1.28(0.60-2.83) | 0.527  | 1.75(0.07-4.68) | 0.736  | 4.42(0.65-30.19) | 0.130  |
| Q3 | 0.98(0.38-2.52) | 0.973  | 1.32(0.19-8.64) | 0.413  | 3.22(0.54-19.02) | 0.197  |
| Q4 | 1.02(0.42-2.47) | 0.976  | 0.87(0.51-6.36) | 0.343  | 1.29(0.24-7.03) | 0.768  |
| P for trend | 0.909  |  | 0.376  |  | 0.350  |  |

Model 1 was the crude model

Model 2 was adjusted for age and gender

Model 3 was adjusted for factors of Model 2 and BMI, history of type-2 diabetes and smoking

Model 4 was adjusted for factors of Model 3 and ALT, Uric acid, HOMA-IR, total cholesterol, TG, HDL-c and ApoB/ApoA ratio.

Supplementary Table 6. Sensitivity, specificity, NPV and PPV for cut-offs predicting carotid atherosclerosis of different MAFLD subgroup

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **MAFLD subtypes** | **Sensitivity****(%)** | **Specitivity****(%)** | **PPV****(%)** | **NPV****(%)** |
| Overweight/obesity with LSM<6.3kPa | 66.05 | 84.05 | 13.6 | 31.2 |
| Overweight/obesity with LSM≥6.3kPa | 59.10 | 78.04 | 12.1 | 30.1 |
| Lean/normal weight with LSM <6.3kPa | 100.00 | 66.67 | 23.8 | 0 |
| Lean/normal weight with LSM ≥6.3kPa | 72.5 | 79.4 | 26.5 | 29.1 |
| Type-2 diabetes with LSM <6.3kPa | 71.3 | 72.2 | 27.6 | 29.0 |
| Type-2 diabetes with LSM ≥6.3kPa | 68.9 | 72.3 | 25.6 | 30.1 |

**Abbreviation:** MAFLD, metabolic associated fatty liver disease; Lp(a), lipoprotein (a); LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value.