

Title page

Comparison between MAFLD and NAFLD definitions for identifying patients at higher risk of chronic kidney disease

Short title: MAFLD and risk of CKD

Authors' name

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Abbreviations

ACR = albumin to creatinine ratio, ANOVA = analysis of variance, BMI = body mass
index, BUN = blood urea nitrogen, CI = confidence interval, DBP = diastolic blood
pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein
cholesterol, LDL-C = low-density lipoprotein cholesterol, NAFLD = non-alcoholic

fatty liver disease, non-MD-NAFLD = non-metabolic dysfunction-associated
NAFLD, Scr = serum creatinine, SBP = systolic blood pressure, SD = standard
derivation, TC = total cholesterol, TG = triglyceride, HOMA-IR = homeostasis model
assessment of insulin resistance, eGFR = estimated glomerular filtration rate,
MAFLD = metabolic dysfunction-associated fatty liver disease, NFS = NAFLD
fibrosis score, FIB-4 = fibrosis 4, T2DM = type 2 diabetes mellitus

Abstract

Background/aims: Whereas nonalcoholic fatty liver disease (NAFLD) is a multisystem disease, the association between metabolic dysfunction-associated fatty liver disease (MAFLD) and extra-hepatic diseases is not known. The aim of this cross-sectional study was to compare the prevalence of chronic kidney disease (CKD) in patients with either MAFLD or NAFLD, and then to examine the association between the presence and severity of MAFLD and CKD and abnormal albuminuria.

Methods: A total of 12,571 individuals with complete biochemical and liver ultrasonography data from the Third National Health and Nutrition Examination Survey (1988-1994) were included in the analysis. Multivariable logistic regression analyses were performed to test the independence of associations between MAFLD or MAFLD severity as the key exposures and CKD (defined as either CKD stage ≥ 1 or stage ≥ 3) or abnormal albuminuria (urinary albumin-to-creatinine ratio ≥ 3 mg/mmol) as the outcomes.

Results: The prevalence of MAFLD and NAFLD was 30.2% (n=3,794) and 36.2% (n=4,552), respectively. MAFLD individuals had a lower eGFR (74.96 ± 18.21 vs. 76.46 ± 18.24 mL/min/1.73 m², $P < 0.001$) and a greater prevalence of CKD (29.60% vs. 26.56%, $P < 0.05$) than NAFLD individuals. Similarly, there was a higher prevalence CKD in MAFLD than in non-metabolic dysfunction-associated NAFLD ($P < 0.05$). Notably, after adjustment for sex, age, ethnicity, alcohol intake and

diabetes, the severity of MAFLD (i.e. NAFLD fibrosis score ≥ 0.676) was associated with 1.34-fold higher risk of prevalent CKD ($P < 0.05$).

Conclusions: MAFLD identifies patients with CKD better than NAFLD. MAFLD and MAFLD with increased liver fibrosis score are strongly and independently associated with CKD and abnormal albuminuria.

Keywords: metabolic dysfunction-associated fatty liver disease, non-alcoholic fatty liver disease, chronic kidney disease

1. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are two worldwide public health problems because of their increasing prevalence, affecting up to nearly 30% and 15% of the general adult population, respectively [1, 2]. Recently, it has been reported that NAFLD is a risk factor for the development of incident CKD [3, 4], and the severity of NAFLD can further increase the risk of CKD, regardless of the coexisting metabolic diseases, such as obesity, hypertension, type 2 diabetes mellitus (T2DM) or metabolic syndrome [5, 6].

The current definition of NAFLD requires the exclusion of significant alcohol consumption and other secondary causes of chronic liver disease [7]. However, the fatty liver disease we understand today not only focuses on patients with or without excessive alcohol consumption, but is also potentially a disease driver in patients with other forms of chronic liver disease. To better understand fatty liver disease, an international panel of experts from 22 countries has recently taken the initiative to propose a new name and definition for NAFLD in adult individuals, i.e., metabolic dysfunction-associated fatty liver disease (MAFLD) [8]. The newly proposed diagnostic criteria for MAFLD are based on the evidence of hepatic steatosis, and the coexistence of overweight/obesity or T2DM; or in lean/normal weight subjects, the presence of hepatic steatosis and the coexistence of two other risk factors related to metabolic dysregulation [8]. Additionally, MAFLD can be diagnosed regardless of daily alcohol consumption and other concomitant liver diseases. Therefore, MAFLD has been proposed as a more appropriate term to describe the liver disease associated

with underlying metabolic dysfunction [9-12].

Recently, the definition of MAFLD has been tested and validated in the third National Health and Nutrition Examination Surveys (NHANES-III 1988-1994) database, and it was confirmed that MAFLD was a more practical and accurate definition for identifying patients with fatty liver at high risk of liver disease progression compared to NAFLD [13]. Thus, MAFLD comprises a new set of diagnostic criteria, which is different from, but may in due course replace, NAFLD [14]. Whereas it is becoming established that NAFLD is a 'multisystem' disease [15], the relationship between MAFLD and extra-hepatic diseases is currently not known. To date, whether the renaming of NAFLD to MAFLD can better identify patients at higher risk of having CKD (i.e., an important NAFLD-related extra-hepatic complication) is uncertain.

Therefore, using the NHANES-III database, we aimed to compare the prevalence of CKD in patients diagnosed by either MAFLD or NAFLD definitions; and then to examine the association between the presence and severity of MAFLD (assessed by non-invasive liver fibrosis scores) and risk of both prevalent CKD and abnormal albuminuria.

2. MATERIALS AND METHODS

2.1 Study design

Our analysis is based upon cross-sectional data from the NHANES database 1988-1994, which is a nationally representative survey, frequently used for the study on NAFLD [16, 17]. This database consists of more than 10,000 individuals who had periodic surveys conducted by the National center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention of the United States. All participants' related data were gathered by well-trained examiners, including demographic variables, biochemical parameters, liver ultrasonography, and nutritional status (including daily alcohol intake for every participant). We extracted demographic/clinical data and laboratory parameters from the original NHANES-III (1988-1994) database that is now a publicly accessible database. The NHANES III protocols were approved by the institutional review board of NCHS and then all participants signed informed consent forms (1984-1994). An exemption from signing the consent forms was provided by the ethics committee for the subsequent use of the publicly available database [18].

2.2 Data collection

In total, 14,797 individuals aged 20-74 years, who underwent liver ultrasound examinations were initially identified from the database. Subsequently, as summarized in **supplementary Figure 1**, those who were positive for serum hepatitis markers, or had missing important clinical and laboratory data for the outcome of

interest were excluded from the analysis. As a consequence, 12,571 individuals were included in the final analysis.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Diabetes mellitus was defined by a fasting plasma glucose level ≥ 7.0 mmol/L or hemoglobin A1c $\geq 6.5\%$ or prescribed hypoglycemic medications.

Hypertension was defined as systolic blood pressure (SBP) ≥ 130 mmHg and diastolic blood pressure (DBP) ≥ 85 mmHg or prescribed antihypertensive medications.

Homeostasis model assessment-estimated insulin resistance (HOMA-IR score) was calculated using fasting glucose and insulin measurements as follows: [fasting insulin (mU/mL) \times fasting glucose (mmol/L)/22.5].

2.3 Diagnostic criteria of NAFLD and MAFLD

NAFLD was defined by evidence of hepatic steatosis on ultrasound and the exclusion of significant alcohol consumption (defined as ≥ 21 drinks/weeks for men and 14 drinks/weeks for women, respectively) and other competing causes for hepatic steatosis (e.g. viral hepatitis and others).

MAFLD was defined by evidence of hepatic steatosis on ultrasound in addition to one of the following three criteria, namely overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation [8]. The presence of metabolic dysregulation among lean/normal weight individuals with hepatic steatosis who did not have T2DM

was defined as the presence of two or more of the following metabolic risk abnormalities: 1) waist circumference ≥ 102 cm in men and 88 cm in women, 2) blood pressure $\geq 130/85$ mmHg or specific drug treatment, 3) serum triglycerides (TG) ≥ 1.70 mmol/L or specific drug treatment, 4) high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L for men and < 1.3 mmol/L for women, 5) prediabetes (i.e., fasting glucose levels 5.6 to 6.9 mmol/L, or 2-hour post-load glucose levels 7.8 to 11.0 mmol/L or HbA1c 5.7% to 6.4%), 6) a HOMA-IR score ≥ 2.5 , and 7) a plasma C-reactive protein level > 2 mg/L.

Patients with non-metabolic dysfunction-associated NAFLD (referred as non-MD-NAFLD group) were defined as those patients with NAFLD who did not meet the definition of MAFLD; in another words, this group of patients had hepatic steatosis without coexisting overweight/obesity, T2DM or metabolic dysregulation (as defined above) [13].

The assessment of liver fibrosis was estimated non-invasively by using NAFLD fibrosis score (NFS) and fibrosis 4 (FIB-4) score. The NFS was calculated as: $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{impaired fasting glucose/diabetes (yes =1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet count (} \times 10^9/\text{L)} - 0.66 \times \text{albumin (g/dl)}$. The Fibrosis-4 (FIB-4) score was calculated according to the following formula: $\text{age} \times \text{AST (IU/L)} / [\text{platelet count (} \times 10^9/\text{L)} \times \text{ALT (IU/L)}^{0.5}]$. The lower cutoff and the upper cutoff for NFS were -1.455 and 0.676, and

for FIB-4 were 1.3 and 2.67, respectively. A score below the lower cutoff was used to exclude advanced fibrosis, while a score above the upper cutoff was indicative of advanced fibrosis [19].

2.4 Assessment of chronic kidney disease

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR [20]. The CKD-EPI equation is as follows: $eGFR = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. Stages of CKD were defined according to the KDIGO guidelines: stage 1, urinary albumin-to-creatinine ratio (ACR) ≥ 3 mg/mmol with eGFR ≥ 90 ml/min/1.73 m²; stage 2, ACR ≥ 3 mg/mmol with eGFR of 60-89 ml/min/1.73 m²; stage 3, eGFR of 30-59 ml/min/1.73 m² (with or without ACR ≥ 3 mg/mmol); stage 4, eGFR of 15-29 ml/min/1.73 m²; and stage 5, eGFR of <15 ml/min/1.73 m².

2.5 Statistical analysis

Statistical analyses were conducted using SPSS version 22.0 (SPSS, Chicago, IL). Continuous variables were expressed as means \pm standard deviation (SD), and categorical variables were presented as counts or percentages (%). The clinical and biochemical characteristics of the study population were compared using the one-way analysis of variance (ANOVA) for continuous variables and the χ^2 -test for categorical

variables. Multivariable logistic regression analyses were performed to test the independence of associations of NAFLD and MAFLD definitions with CKD (defined as either CKD stage ≥ 1 or CKD stage ≥ 3) and abnormal albuminuria after adjusting for known confounding variables (age, sex, ethnicity, alcohol intake and pre-existing diabetes); the data are expressed as odds ratio (OR) and 95% confidence interval (CI). Furthermore, the intra- and inter-rater reliability estimates were calculated by the Cohen's kappa coefficient. All tests were 2-sided and a *P* value of <0.05 (two-tailed) was considered statistically significant.

3. RESULTS

3.1 Baseline characteristics of participants

In the whole cohort of NHANES III participants with completed liver ultrasonography and laboratory data, a total of 3,794 (30.2%) individuals had MAFLD, whereas 4,552 (36.2%) individuals had NAFLD. As shown in **Table 1**, compared to the non-MAFLD group, patients with MAFLD were more likely to be men, older, and to have significantly lower eGFR, a more atherogenic lipid profile, and higher values of BMI, HbA1c, fasting glucose, serum liver enzymes, liver fibrosis scores (NFS and FIB-4) and urinary ACR levels. They also had a higher prevalence of T2DM and hypertension compared to those belonging to the non-MAFLD group. Upon further investigation, similar differences were also observed between subjects with NAFLD and those without NAFLD. Interestingly, we found that the concordance between MAFLD and NAFLD definitions for identifying subjects with fatty liver disease was good (Cohen's κ coefficient = 0.85, 95%CI 0.84-0.86, $P < 0.001$).

3.2 MAFLD and decreased kidney function

A comparison of kidney function parameters and stages of CKD between patients with MAFLD and those with NAFLD is illustrated in **Table 2**. Compared to the NAFLD or non-MD-NAFLD groups, the MAFLD population was more likely to be men, older and had significantly lower eGFR and a greater prevalence of both CKD and abnormal albuminuria. In particular, the MAFLD population had the lowest mean value of eGFR (74.96 ± 18.21 mL/min/1.73 m²) and the highest prevalence of

abnormal albuminuria (14.02%) compared to the NAFLD and non-MD-NAFLD groups. MAFLD patients without alcohol intake had higher eGFR values compared to their counterparts with alcohol intake, whilst there was no significant difference in the prevalence of CKD between these two patient groups. Compared to MAFLD patients without coexisting T2DM, those with MAFLD and T2DM had significantly lower eGFR values, and higher prevalence of both CKD and abnormal albuminuria. A good intra-rater agreement for CKD (Cohen's κ coefficient = 0.97, 95%CI 0.96-0.98, $P < 0.001$) and for abnormal albuminuria ($\kappa = 0.73$, 95%CI 0.70-0.76, $P < 0.001$) was found between NAFLD and MAFLD.

3.3 MAFLD severity and risk of prevalent CKD

As shown in **Figure 1** and **Table 3**, the severity of kidney dysfunction and the prevalence of CKD stage ≥ 1 increased progressively across the severity of MAFLD. Similar data were obtained regardless of whether MAFLD severity was assessed by either NFS or FIB-4 scores. To further understand the association between MAFLD and kidney damage, we performed univariable and multivariable logistic regression analyses stratified by MAFLD severity. For instance, as shown in **Table 3**, in univariable regression analysis, after stratifying MAFLD patients by increasing levels of NFS, the unadjusted-ORs for prevalent CKD stage ≥ 1 were 0.83 (95%CI 0.72-0.94), 2.55 (2.27-2.86) and 5.38 (4.36-6.66) respectively, whereas for prevalent CKD stage ≥ 3 were 0.56 (95%CI 0.47-0.67), 2.43 (2.14-2.75) and 5.33 (4.31-6.59), respectively. After adjustment for age, sex, ethnicity and alcohol intake, the ORs for

prevalent of CKD stage ≥ 1 remained statistically significant (all $P < 0.05$). Conversely, for prevalent of CKD stage ≥ 3 , the significant association was observed only in MAFLD with NFS ≥ 0.676 (OR 1.49 [1.18-1.88], $P < 0.05$). Similarly, there was a significant graded association between the severity of MAFLD and abnormal albuminuria. Notably, after adjustment for age, sex, ethnicity, alcohol intake and pre-existing diabetes, the ORs for prevalent of CKD stage ≥ 1 remained still statistically significant (all $P < 0.05$). The ORs in the MAFLD population, stratified by FIB-4, mostly exhibited the same trends as those observed after stratification for NFS (data not shown). Collectively, these data clearly suggest that MAFLD with increased liver fibrosis scores are strongly associated with greater risk of having CKD and abnormal albuminuria.

4. DISCUSSION

The novel results of this cross-sectional analysis from the NHANES-III 1998-94 database suggest that MAFLD identifies patients with CKD better than NAFLD, and both MAFLD and MAFLD with increased liver fibrosis scores are both strongly and independently associated with CKD and abnormal albuminuria. To our knowledge, this is the first community-based study to compare the association of MAFLD and NAFLD definitions with CKD (defined either CKD stage ≥ 1 or CKD stage ≥ 3) or abnormal albuminuria, and to investigate the association between the severity MAFLD (by non-invasive fibrosis scores) and CKD or abnormal albuminuria in a nationally representative cohort of individuals from the USA.

Recently, Lin et al. [13] have compared the characteristics of MAFLD and NAFLD in this same NHANES-III database and showed that patients with MAFLD were more likely to have multiple metabolic comorbidities (e.g., obesity, hypertension and diabetes), higher HOMA-IR values and more cases with advanced liver fibrosis (as detected by non-invasive fibrosis scores, such as NFS and FIB-4) compared to those with NAFLD. These findings suggest that the MAFLD definition is more accurate than the NAFLD definition for identifying those subjects with fatty liver who are at high risk of liver disease progression.

Our results confirm and extend the findings by Lin et al [13], besides we also found that patients with MAFLD were more likely to have lower levels of eGFR, as well as a higher prevalence of both CKD and abnormal albuminuria than those with NAFLD.

Collectively, therefore, the evidence from these two studies using the NHANES-III database clearly suggest that the MAFLD definition is more accurate than the NAFLD definition for identifying not only those subjects with fatty liver who are at high risk of having advanced liver disease but also those at higher risk of having CKD.

In this study, we found that patients with MAFLD with coexisting T2DM had a higher prevalence of both abnormal albuminuria and CKD than their counterparts without diabetes. With regard to this, the results of our study appear to be at variance with those of a recent meta-analysis of 19 studies (17 cross-sectional studies and two cohort studies) showing an increased risk of albuminuria only among NAFLD patients without diabetes, but not among those with T2DM [21]. A possible explanation to such disparity could be that all included studies in the meta-analysis were derived from Asian and European cohorts with varying population characteristics as compared to our study. However, further large cohort studies are certainly needed to better clarify this issue. In this study, we did not find any significant difference in the prevalence of CKD and abnormal albuminuria between MAFLD patients with and without alcohol consumption. In addition, and most importantly, we also found that the coexistence of MAFLD with increased liver fibrosis scores (such as increased NFS or FIB-4 scores) was strongly associated with an increased likelihood of having CKD and abnormal albuminuria, even after adjusting for age, sex, ethnicity, daily alcohol intake and pre-existing T2DM.

Recently, it was proposed by an international panel of experts that there should be a name change from NAFLD to MAFLD [22]. However, the diagnostic criteria for NAFLD and MAFLD are different and, therefore, before there is any name change it is important to establish that there is equivalence (or at least good concordance) between both conditions, not only for liver-related complications of this fatty liver disease, but also for the extra-hepatic complications of NAFLD, such as CKD.

Growing evidence indicates that NAFLD is strongly associated with an increased prevalence and incidence of CKD [23-25]. Our previous study has also indicated that the prevalence of CKD was higher in NAFLD patients with liver fibrosis than those without liver fibrosis (22.14% vs 4.82%, $P < 0.05$) [4]. Similarly, Park H *et al* found that NAFLD was associated with an increased risk of incident CKD (hazard ratio 1.41, 95%CI 1.36-1.46), and this association remained statistically significant (hazard ratio 1.58, 95%CI 1.52-1.66) even after adjusting for established renal risk factors and time-varying covariates [26].

Interestingly, as reported above, the results of the present study suggest that the MAFLD definition may be more accurate than the NAFLD definition for identifying those patients with hepatic steatosis who are at higher risk of having CKD. In addition, the prevalence of CKD and abnormal albuminuria did not significantly differ between MAFLD patients with alcohol intake and those without alcohol intake, suggesting that alcohol intake does not adversely affect the risk of kidney injury in

this group of patients. Finally, patients diagnosed with non-MD-NAFLD appeared to be “healthier” than subjects with MAFLD or NAFLD. In fact, patients with non-MD-NAFLD had the highest eGFR levels, and the lowest prevalence of both albuminuria and CKD. Overall, these findings support the value of MAFLD criteria in overcoming the high heterogeneity of patient population that was identified by the previous NAFLD, “exclusion” definition. While the MAFLD criteria would help to identify a more homogeneous group of patients. Since by definition in patients with MAFLD there is a coexistence of multiple metabolic conditions (especially T2DM and overweight/obesity) that are strong risk factors risk of CKD, it is clinically important to control and manage the underlying metabolic dysfunction associated with MAFLD to prevent or reduce the risk of CKD [27-29].

The major strength of this study is that, to our knowledge, this is the first comparative examination of the association between MAFLD and NAFLD definitions and risk of prevalent CKD in a community-based cohort of individuals. However, our study has also some important limitations. First, the cross-sectional design of this nationally representative cohort of subjects from the United States does not allow the establishment of temporality and causality of the observed associations between presence and severity of MAFLD and CKD. Second, there may have been a selection bias, since a number of subjects were excluded from the study due to the imposed exclusion criteria. Third, a standard oral glucose tolerance test (OGTT) for the diagnosis of diabetes was lacking in the NHANES III database. Fourth, the cohort

population is derived from the NHANES 1988-1994 database and the clinical characteristics of this population might be different from more contemporary populations. However, NHANES-III is a large unbiased community-based database with extensive liver ultrasound examinations and laboratory data and the time gap may not markedly affect the evaluation and validation of diagnostic criteria for NAFLD and MAFLD in the United States. However, although the study sample is representative of the United States population, these results might not be generalizable to other study settings, samples, or populations. Although liver biopsy is the gold-standard for diagnosing and staging NAFLD/MAFLD, it is not possible to perform liver biopsies in a community-based study such as this, and therefore non-invasive methods are widely used to diagnose hepatic steatosis and the severity of liver disease by using ultrasonography combined with non-invasive biomarkers of advanced fibrosis (such as NFS or FIB-4 scores). Specifically, NFS has been the most extensively studied and validated score, both in the general population and in patient cohorts with NAFLD in order to triage patients at risk of advanced liver fibrosis [30].

In conclusion, we found that there was a higher prevalence of CKD in subjects with MAFLD than in those with NAFLD from the NHANES III 1988-94 database, suggesting that MAFLD can identify patients with CKD better than NAFLD.

Moreover, MAFLD with increased advanced fibrosis scores is strongly associated with higher risk of prevalent CKD and abnormal albuminuria. Future prospective cohort studies are needed to examine the risk of developing CKD in patients with

MAFLD, compared with those with NAFLD.

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Conflict of interest statement

None.

Authors' contributions

Authors contributions: Dan-Qin Sun and Ming-Hua Zheng designed the study and prepared the figures. Yan Jin and Ting-Yao Wang analyzed the data. Wei-Jie Yuan and Hao-Yang Zhang performed statistical analyses. Kenneth I. Zheng, Rafael S Rios,

Giovanni Targher and Christopher D Byrne contributed to writing and proof reading the manuscript. Dan-Qin Sun reviewed the results, interpreted data, and draft the manuscript. All authors contributed to the manuscript for important intellectual content and approved the submission.

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Table legends

Table 1. Comparison of baseline characteristics in subjects with and without MAFLD and in those with and without NAFLD.

Table 2. Comparison of renal function parameters and CKD stages between different groups of subjects with MAFLD or NAFLD.

Note:

* $P < 0.05$ for MAFLD vs. NAFLD;

$P < 0.05$ for NAFLD vs. Non-MD-NAFLD;

& $P < 0.05$ for MAFLD vs. Non-MD-NAFLD;

\$ $P < 0.05$ for comparison among the NAFLD, MAFLD and Non-MD-NAFLD.

Table 3. Associations of NAFLD and MAFLD with CKD (defined as either CKD stage ≥ 1 or CKD stage ≥ 3) and abnormal albuminuria (defined as ACR ≥ 3 mg/mmol) as well as associations of MAFLD severity (stratified by NFS score) with CKD and abnormal albuminuria.

Supplementary table 1. Association of NAFLD or MAFLD with CKD stratified by diabetes mellitus.

Figure legends

Figure 1. Comparison of eGFR values (panel A), prevalence of CKD (stages 1-5; panel B) and presence of abnormal albuminuria (panel C) between subjects without MAFLD and those with MAFLD stratified by NAFLD fibrosis score (NFS).

Note:

* $P < 0.05$ for No MAFLD vs. $NFS < -1.455$;

$P < 0.05$ for No MAFLD vs. $-1.455 \leq NFS < 0.676$;

\$ $P < 0.05$ for No MAFLD vs. $NFS \geq 0.676$;

** $P < 0.05$ for $NFS < -1.455$ vs. $-1.455 \leq NFS < 0.676$;

$P < 0.05$ for $NFS < -1.455$ vs. $NFS \geq 0.676$;

*** $P < 0.05$ for $-1.455 \leq NFS < 0.676$ vs. $NFS \geq 0.676$.

Supplementary figure 1. Flow-chart for the subjects' selection.