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ORIGINAL RESEARCH—CLINICAL

Use of Machine Learning to Predict Onset of NAFLD in an All-Comers Cohort—Development and Validation in 2 Large Asian Cohorts

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BACKGROUND AND AIMS: Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases. There are no universally accepted models that accurately predict time to onset of NAFLD. Machine learning (ML) models may allow prediction of such time-to-event (ie, survival) outcomes. This study aims to develop and independently validate ML-derived models to allow personalized prediction of time to onset of NAFLD in individuals who have no NAFLD at baseline. **METHODS:** The development dataset comprised 25,599 individuals from a South Korean NAFLD registry. A random 70:30 split divided it into training and internal validation sets. ML survival models (random survival forest, extra survival trees) were fitted, with time to NAFLD diagnosis in months as the target variable and routine anthropometric and laboratory parameters as predictors. The independent validation dataset comprised 16,173 individuals from a Chinese open dataset. Models were evaluated using the concordance index (c-index) and Brier score on both the internal and independent validation sets. **RESULTS:** The datasets (development vs independent validation) had 1,331,107 vs 543,874 person months of follow-up, NAFLD incidence of 25.7% (6584 individuals) vs 14.4% (2322 individuals), and median time to NAFLD onset of 60 (interquartile range 38–75) vs 24 (interquartile range 13–37) months, respectively. The ML models achieved a good c-index of >0.7 in the validation cohort—random survival forest 0.751 (95% confidence interval 0.742–0.759), extra survival trees 0.752 (95% confidence interval 0.744–0.762). **CONCLUSION:** ML models can predict time-to-onset of NAFLD based on routine patient data. They can be used by clinicians to deliver personalized predictions to patients, which may facilitate patient counseling and clinical decision making on interval imaging timing.

Keywords: NAFLD; Machine Learning; Artificial Intelligence; Survival Modeling; Time to Event; Random Survival Forest

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases, with an estimated prevalence of 25% worldwide.[1] It is characterized by fatty infiltration of the liver. Risk factors include obesity, diabetes, hyperlipidemia, and metabolic syndrome. It can be complicated by liver injury (ie, nonalcoholic steatohepatitis), liver fibrosis and cirrhosis, and is an increasingly common cause of hepatocellular carcinoma.[2] Although NAFLD is highly associated with obesity, it can also occur and cause complications in individuals without obesity.[3,4]

There are multiple risk models for NAFLD using demographic, anthropometric, and laboratory parameters as predictors.[5,6] Some have also employed machine learning techniques.[7,8] However, due to their study design, there are limitations to clinical utility of these risk models. Methods to predict prevalent NAFLD, such as cross-sectional analysis (ie, predicting the presence of NAFLD at the point which the predictive factors are collected), do not allow prediction of future NAFLD.[9] Methods to predict incident NAFLD, such as case-control analyses, are often formulated as binary (ie, yes-or-no) predictions of whether NAFLD develops within a fixed time period,[10] which is insufficiently granular to guide decisions for timing of imaging or management. A more clinically relevant method would be a survival (ie, time-to-event) analysis, to predict the time of onset of

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Abbreviations used in this paper: **ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; C-index, Concordance index; Cr, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; GLB, globulin; HDL-c, high-density lipoprotein cholesterol; IBS, Integrated Brier Score; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; ML, machine learning; NAFLD, nonalcoholic fatty liver disease; RSF, random survival forest; SBP, systolic blood pressure; SHAP, SHapley Additive exPlanations; Tbil, total bilirubin; TC, total cholesterol; TG, triglycerides; TP, total protein; UA, uric acid; XST, extra survival trees.**

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NAFLD after an individual's parameters are measured. This would allow personalized decision making on when to time a follow-up visit or imaging.

Machine learning (ML) is a modeling approach that may improve clinical prediction models, and has been applied in cross-sectional studies of NAFLD.[7,8] The main advantage of ML methods is that they generally do not require linear relationships between predictive parameters and the outcome, unlike classical regression-based methods (eg, Cox proportional hazards model). However, we have not identified any studies in the literature that have applied ML to survival modeling for time to onset of NAFLD.

Hence, our main objective was to develop survival models to predict time to onset of NAFLD, using ML models trained on readily available demographic, anthropometric, and laboratory parameters as predictors. Two independent cohorts were used—a cohort of South Korean patients for development of the algorithm, and an open data cohort of Chinese patients for independent validation. These were cohorts of individuals undergoing routine laboratory screening for metabolic diseases who had no NAFLD at baseline, and were serially followed up for development of NAFLD. Our outcome of interest was the predictive performance of the ML models for time to onset of NAFLD.

Methods

Development Cohort Details

The development cohort was derived from a retrospective, population-based cohort study conducted at the Seoul National University Hospital Gangnam Center (H-PEACE cohort).[11] The full H-PEACE cohort contained a total of 91,336 individuals. For this dataset, we used data from a subset comprising 25,599 individuals without fatty liver on baseline ultrasonography, who had undergone at least yearly ultrasonography during a 5-year follow-up period. Individuals with a history of viral hepatitis were excluded.

Validation Cohort Details

The validation cohort was extracted from a prior study by Sun et al[12,13] in the Dryad Digital Repository (http://www.datadryad.org/). This longitudinal study consisted of 16,173 individuals without NAFLD at baseline who presented for annual health screening at the Wenzhou Medical Center of Wenzhou People's Hospital from January 2010 to December 2014, who did not have NAFLD at baseline. The dataset excluded individuals with significant alcohol usage (>140 g/wk for men and >70 g/wk for women); on antihypertensive, antidiabetic, or antilipid therapy; or with a history of viral hepatitis, autoimmune hepatitis or other known causes of chronic liver disease. Individuals with a body mass index (BMI) of $\geq$25 kg/m^2 or a low-density lipoprotein cholesterol (LDL-c) of >3.12 mmol/L were excluded by the dataset authors.

Variables of Interest

Both datasets contained similar variables. Predictive variables included demographics (eg, age, sex), anthropometric variables (ie, BMI, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP)), and laboratory tests (ie, fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), LDL-c, blood urea nitrogen, creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, total protein, albumin, and globulins (GLBs)).

Outcome variables were the diagnosis of NAFLD and the follow-up time. NAFLD was excluded at baseline by liver ultrasound examination, and diagnosed by a finding of liver steatosis on serial liver ultrasonography during follow-up. The eventual time to diagnosis of NAFLD was denoted in months from the initial recording of baseline parameters.

Statistical Methods

Analysis was conducted using Python 3.8, using the Anaconda 3 distribution. Base python functions as well as the *pandas*, *numpy*, *scikitlearn*, and *scikitlearn-pandas* packages were used for data manipulation, and to report overall summary statistics of the cohort. Continuous variables were summarized by their mean and standard deviation, with the exception of time to NAFLD diagnosis, which was summarized by median and interquartile range as it was non-normally distributed. Categorical variables were summarized by counts and percentages.

For continuous variables with clinically important cut-off points, these were also binned and summarized as categorical variables for better appreciation of the study population. The continuous variables that were binned were the BMI (using the Asian cut-offs[14] of 18.5–22.9 kg/m^2 for normal weight and 23–27.5 kg/m^2 for overweight), the fasting plasma glucose (>7.0 mmol/L denoting fasting hyperglycemia), and the blood pressure (either SBP >140 mmHg or DBP >90 mmHg denoting hypertension).

We included all the available predictive variables except BMI, GLB, and LDL-c. This was because the information given by the BMI is already represented by including height and weight as predictive variables, and the information given by GLB is represented by the total protein and albumin. LDL-c is usually calculated from the total cholesterol, HDL-c, and triglycerides, rather than by direct measurement. We noted that some of the other predictive variables were highly correlated—alanine aminotransferase and aspartate aminotransferase (R2 = 0.73); SBP, and DBP (R2 = 0.79); height and weight (R2 = 0.74), and sex with height (R2 = 0.73), and weight (R2 = 0.72). However, as these predictive variables are clinically distinct, we opted to include all of them into our predictive models. The full correlation plot is included in Appendix 1.

The development cohort was randomly split into a training and internal validation set in a 70:30 ratio, with equal proportions of NAFLD in both sets. Individuals who did not develop NAFLD during the period of follow up were deemed to have been censored. Continuous predictors were normalized before entry into ML models.

The ML models used were the random survival forest (RSF) and extra survival trees model, using the *sklearn-survival* package.[15] RSF and extra survival trees are both tree-based ML methods, where an ensemble of multiple tree-based learners is used to generate a final prediction.

The overall study flow is detailed in Figure 1.

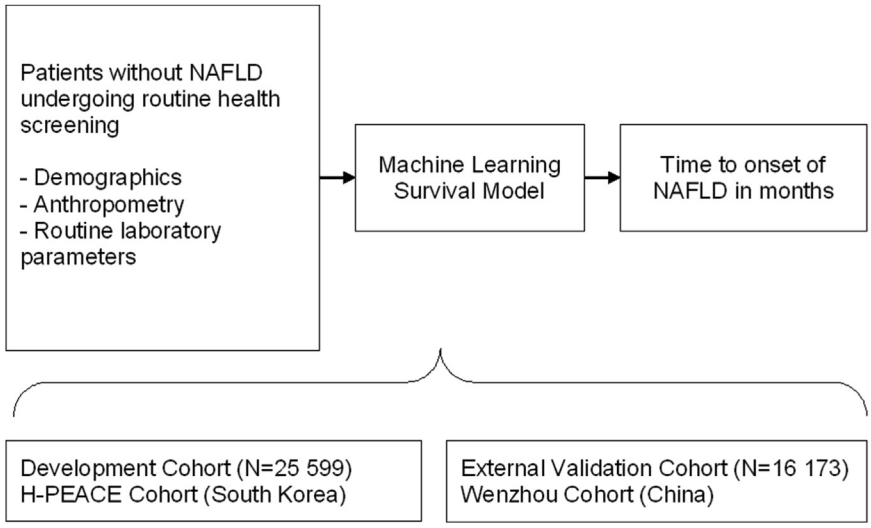

Figure 1. Overall study flow.

Evaluation was done using the concordance index (c-index) and integrated Brier score (IBS) methods. These scores are commonly used for evaluation of survival models. The c-index is the most common metric used in survival analysis and is a measure of how well a model predicts the ordering of event times. c = 0.5 is the average c-index of a random model, whereas c = 1 denotes a perfect ranking of death times. The IBS is an overall calculation of the model accuracy at all available times, and is calculated by integrating the Brier score (the average squared distances between the observed survival status and the predicted survival probability) over the time period examined. The benchmark for models with useful accuracy is a Brier score <0.25. Confidence limits were estimated by 100 iterations of bootstrapping on the validation sets.

We also inspected the important features of the models to ensure that they were consistent with clinical understanding. For ML models, feature importance was determined by using the SHapley Additive exPlanations (SHAP) method[16] on the internal and independent validation sets. The SHAP method is an established means of interpreting complex models by additive feature importance measures, allowing ranking of variables by the amount of contribution they make to the model's prediction.

Relevant Patient Consent and Ethical Approvals

For the development cohort, consent waiver was granted for use of deidentified patient data. No additional patient consent was required for the validation cohort as it is a publicly available dataset. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Results

Baseline Characteristics and Risk Factors of NAFLD

Of the initial 25,599 individuals in the development set, 51 had a follow-up time of <1 month and were excluded from the analysis. The development cohort used for analysis thus included 25,548 individuals, who completed 1,331,107 person-months of follow-up. The overall incidence of NAFLD was 25.7% (6584 individuals) in the development cohort, and the median time to NAFLD onset was 52 months.

All individuals from the independent validation cohort were included, comprising a total of 543,874 person-months of follow-up. The overall incidence of NAFLD was 14.4% (2322 individuals) in the entire cohort, and the median time to NAFLD onset was 33 months.

The baseline characteristics for the overall development cohort and independent validation cohort are summarized in Table 1.

Model Performance

The c-index and IBS for each model are reported in Table 2. All models had an acceptable IBS of < 0.25. The ML models had excellent performance, with the RSF attaining a c-index of >0.75 on both the internal validation and the independent validation sets.

Important Variables of the RSF Model

We further inspected the important variables of the RSF Model, which was the top performing ML model. The SHAP values were calculated on both the internal validation and independent validation sets. They are depicted in Figure 2, and are ranked by their importance in descending order of SHAP value magnitude (a greater magnitude indicates a greater importance). Overall, the important variables were consistent between the internal and independent validation sets.

Discussion

General Discussion

To our knowledge, this is the first study conducted in large cohorts that uses ML to predict time to onset of NAFLD in individuals who are initially NAFLD-free, using only routine data (demographic, anthropometric, and laboratory) collected during metabolic health screening. The ML models delivered accurate predictions of time-to-onset of NAFLD. A high c-index

Table 1. Summary Statistics for Overall Cohort, Training and Internal Validation Sets, and Independent Validation Cohort

	Development cohort	Independent validation cohort
Variables	N = 25,548	N = 16,173
NAFLD, n (%)	6507.0 (25.47%)	2322.0 (14.36%)
Months to NAFLD, median (IQR)	52.1 (30.19)	33.63 (13.77)
Age (y), mean (SD)	45.13 (10.72)	43.23 (14.96)
Male, n (%)	10,963.0 (42.91%)	8483.0 (52.45%)
BMI ≥23, n (%)	9508.0 (37.22%)	4074.0 (25.19%)
Height (m), mean (SD)	1.64 (0.08)	1.65 (0.08)
Weight (kg), mean (SD)	60.25 (10.36)	58.08 (8.55)
SBP (mmHg), mean (SD)	113.52 (14.74)	120.73 (16.71)
SBP >140 mmHg, n(%)	1102.0 (4.31%)	1774.0 (10.97%)
DBP (mmHg), mean (SD)	73.34 (11.57)	72.81 (10.35)
DBP >140 mmHg, n(%)	1949.0 (7.63%)	833.0 (5.15%)
FPG (mmol/L), mean (SD)	5.14 (0.57)	5.14 (0.78)
FPG >7 mmol/L, n(%)	181.0 (0.71%)	365.0 (2.26%)
ALT (IU/mL), mean (SD)	20.02 (17.86)	20.06 (16.48)
AST (IU/mL), mean (SD)	21.68 (12.24)	23.04 (9.53)
TP (g/L), mean (SD)	71.55 (4.09)	73.89 (4.19)
ALB (g/L), mean (SD)	43.77 (2.54)	44.4 (2.71)
ALP (IU/mL), mean (SD)	57.11 (16.84)	72.35 (23.22)
GGT (IU/mL), mean (SD)	26.05 (26.24)	30.13 (31.29)
TBil (μmol/L), mean (SD)	18.11 (7.38)	12.12 (4.95)
BUN (mmol/L), mean (SD)	4.71 (1.25)	4.57 (1.37)
Cr (mmol/L), mean (SD)	83.3 (16.88)	78.48 (25.68)
UA (μmol/L), mean (SD)	301.55 (78.93)	279.81 (85.92)
HDL-c (mmol/L), mean (SD)	1.5 (0.34)	1.46 (0.36)
LDL-c (mmol/L), mean (SD)	3.02 (0.77)	2.26 (0.46)
TC (mmol/L), mean (SD)	4.94 (0.83)	4.62 (0.74)
TG (mmol/L), mean (SD)	1.02 (0.56)	1.3 (0.92)

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; FPG, fasting plasma glucose; IQR, interquartile range; SD, standard deviation; TBil, total bilirubin; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid.

of >0.75 on both internal and independent validations sets was attained by the RSF model. This new knowledge is important in the clinical management of individuals undergoing routine screening for metabolic diseases, and adds an additional dimension where risk of incident NAFLD developing can also be calculated. The output for each individual patient, which is a survival curve (examples provided in Figure 3) can be used to guide timing of further screening investigations and for patient counseling.

Important predictors of the RSFs model included weight, HDL-c and creatinine, which is consistent with published literature showing the association of anthropometric, lipid,[17] and renal parameters[18] on the incidence of NAFLD. Also consistent with published literature from cross-sectional studies were less important predictors, such as GGT[19,20] and uric acid.[21] There is recent research demonstrating the utility of GGT in predicting future onset of NAFLD[22] as well. However, the exact nature of such effects

Table 2. C-Index and IBS Results in Training, Internal Validation, and Independent Validation Sets

Model	Metric	Training set	Internal validation	Independent validation
Random survival forest	c-index	0.859 (0.854–0.864)	0.709 (0.697–0.722)	0.751 (0.742–0.759)
	IBS	0.047 (0.045–0.049)	0.055 (0.052–0.058)	0.083 (0.08–0.086)
Extra survival trees	c-index	0.735 (0.728–0.744)	0.681 (0.669–0.699)	0.752 (0.744–0.762)
	IBS	0.056 (0.054–0.059)	0.058 (0.054–0.061)	0.087 (0.083–0.09)

C-index, concordance index.

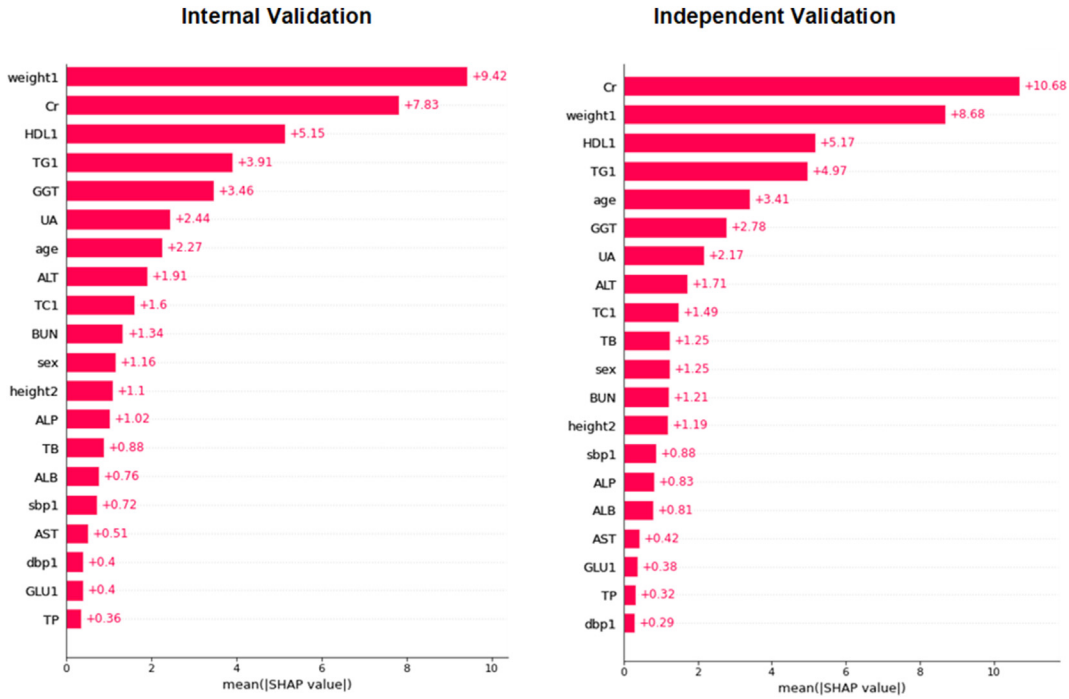

Figure 2. Important variables of the RSF model.

cannot easily be determined from ML models, and no equivalent of hazard ratios exists for further interpretation.

Study Strengths

This is the first study to our knowledge which performs survival modeling to predict time to NAFLD onset, and the first to employ ML prediction techniques. It was conducted in 2 large cohorts with serial liver ultrasonography. This allowed it to correctly address the clinical problem of predicting time to NAFLD onset, using only routine demographic, anthropometric, and laboratory test data from metabolic health screening.

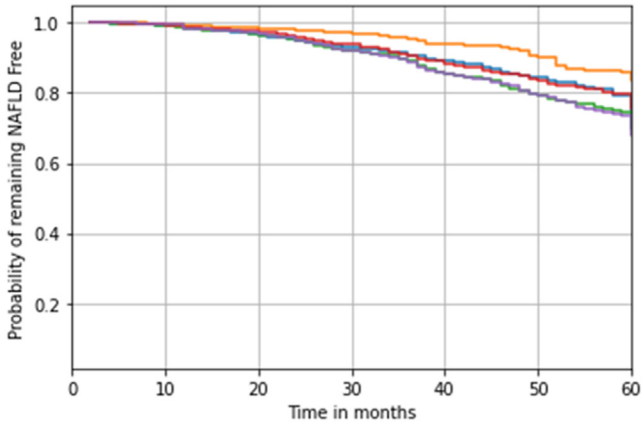

Figure 3. Examples of individual survival curves generated by the RSF model for 5 cases.

We are aware of work by Wang et al[23] that has attempted a continuously valued prediction of future NAFLD onset in nonobese individuals, making use of the same dataset by Sun et al.[12,13] We note that the eventual method used was a nomogram based on a classical Cox proportional hazards model that had a high reported c-index of 0.82. However, the study aggregated the survival times to the timescale of years. On the other hand, the ML models in our study were designed to output a continuously valued survival prediction in the timescale of months, which is more granular and potentially more clinically actionable. Even with a more challenging problem formulation (using a more granular outcome), our ML model had a comparable c-index of 0.75.

At present, the management of individuals identified to have NAFLD focuses on lifestyle change and control of underlying metabolic risk factors. The immediate relevance of our models lies in educating individuals about their personalized risk profile and potentially driving behavior change. As therapies for NAFLD emerge, this model may assist clinicians in identifying such individuals.

Study Limitations

Our study has some important limitations. First, NAFLD was diagnosed based on the demonstration of liver steatosis on liver ultrasonography whereas the gold standard of NAFLD determination is liver biopsy. However, serial liver biopsies for the histopathological diagnosis of NAFLD are not a viable option in clinical practice in view of its risks as an invasive procedure, and this is likely the best available approach from an observational data standpoint.

Second, when NAFLD is diagnosed via periodic ultrasound, the disease may develop in the inter-investigation period, causing a rightward bias for the time of event. However, there are no consensus guidelines on the optimal periodicity of screening ultrasonography to diagnose NAFLD. In addition, it is difficult to achieve very frequent screening intervals in clinical practice.

Third, both cohorts were derived from health screening populations, which may make them vulnerable to selection biases (eg, bias towards individuals with a higher socioeconomic status). While both development and independent validation cohorts were large, they were from single centers serving predominantly urban Asian populations. As these are retrospective population level cohorts, differences in local epidemiology and screening practices may account for the observed differences in baseline risk factors between the 2 cohorts. The external validation cohort excluded individuals with BMI >25 and individuals on antihypertensive, antidiabetic, and antilipid therapy. Future validation work in more general cohorts would be helpful. This difference may also account for the apparently better performance of the model in the external validation cohort, as the laboratory values used are not modified by concomitant medical therapy.

Future Work

Validation of our findings in multiethnic cohorts, as well as in other centers including individuals of all racial and economic profiles, will further confirm the generalizability of our models. Inclusion of other parameters, such as physical activity levels, or other laboratory parameters like HbA1c, may also help in improving the predictive power of the models. Finally, as ML techniques develop in survival analysis, we can consider other deep learning based survival models for future work.

Conclusion

We developed and independently validated accurate ML prediction models for time to onset of NAFLD using routine demographic, anthropometric, and laboratory test data. These models can be used to generate individualized survival curves of time to NAFLD that can guide further investigation and counseling of specific patients.

Supplementary Materials

Material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.gastha.2024.06.007.

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Authors' Contributions:
Daniel Yan Zheng Lim: Data collection, Analysis, Writing – first draft. Goh Eun Chung: Data collection. Won Kim: Data collection. Pei Hua Cher: Analysis. Ramasamy Chockalingam Jnr: Analysis. Chee Kiat Tan: Writing – first draft. All authors commented on subsequent versions of the manuscript, read and approved the final manuscript, and contributed to the study conception and design.

Conflicts of Interest:
The authors disclose no conflicts.

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Ethical Statement:
This study is IRB exempt in view of the use of unidentifiable data.

Data Transparency Statement:
Data from the Wenzhou NAFLD cohort are freely accessible online via the references stated in our text. Data from the H-PEACE cohort require approval for access.

Reporting Guidelines:
RECORD checklist.