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Metabolic liver abnormality with preserved coronary patency: an uncoupled phenotype with favorable cardiovascular prognosis — a prospective angiography cohort study

Running Title: Liver–Coronary Uncoupling Phenotype and Prognosis

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Abstract

Background: Metabolic liver abnormality (here proxied by non-invasive surrogates, specifically imaging-defined steatosis or elevated GGT) is linked to accelerated atherosclerosis and cardiovascular mortality, yet clinical observations reveal a subset of patients with metabolic liver abnormality but preserved coronary patency—an “uncoupled” phenotype whose prognosis remains undefined. We aimed to characterize this phenotype and evaluate its cardiovascular outcomes.

Methods: In a prospective angiography cohort of 8,182 consecutive patients undergoing coronary angiography, we classified four phenotype groups based on metabolic liver abnormality (fatty liver imaging or GGT >sex-specific upper limit of normal) and coronary atherosclerotic burden (Gensini score; pre-specified cut-off = 20, determined as the sample median of independently recalculated scores): Group A (no metabolic abnormality, low Gensini; n = 2,006), Group B (no metabolic abnormality, high Gensini; n = 2,015), Group C (metabolic abnormality, low Gensini—the uncoupled phenotype; n = 2,213), and Group D (dual burden; n = 1,948). Cox proportional hazards models with sequential covariate adjustment (Models 1–4), interaction tests, FDR-corrected subgroup analyses, Fine–Gray competing risk models, and ten sensitivity analyses (S1–S10) were performed.

Results: Over a median follow-up of 2.2 years (764 MACE events, 171 deaths), the fully adjusted Model 4 showed that Group B (HR = 2.40 (1.99–2.91)) and Group D (HR = 2.12 (1.74–2.60)) had significantly elevated MACE risk versus Group A, whereas Group C (uncoupled phenotype) did not (HR = 0.84 (0.67–1.05), P = 0.121). The MACE incidence rate ratio for Group C versus Group A was 1.0065 (P = 0.963). Multiplicative interaction was non-significant (P = 0.259). All ten sensitivity analyses confirmed the primary findings.

Conclusions: The metabolic liver–coronary uncoupled phenotype carries a cardiovascular prognosis comparable to patients with neither risk factor. Coronary atherosclerotic burden,

rather than metabolic liver abnormality per se, drives cardiovascular risk. These findings support coronary-centric risk stratification in patients with metabolic liver abnormality.

Keywords: Metabolic liver abnormality; coronary angiography; Gensini score; cardiovascular prognosis; uncoupled phenotype; prospective cohort; competing risk

Introduction

Metabolic liver abnormality, formerly known as non-alcoholic fatty liver disease (NAFLD), is the most prevalent chronic liver disease worldwide, affecting approximately 30% of the global adult population [1, 2]. Cardiovascular disease (CVD) is the leading cause of death in patients with metabolic liver abnormality, surpassing liver-related mortality by a wide margin [3, 4]. Multiple meta-analyses have demonstrated that metabolic liver abnormality is independently associated with a 45–65% increased risk of major adverse cardiovascular events (MACE), even after adjustment for traditional cardiovascular risk factors [5, 6]. The pathophysiological mechanisms involve systemic inflammation, insulin resistance, atherogenic dyslipidemia, endothelial dysfunction, and pro-coagulant pathway activation [3, 7].

However, the relationship between metabolic liver disease and coronary artery disease is not uniform. Clinical observations reveal a paradoxical subset of patients with metabolic liver abnormality who, despite significant hepatic steatosis and metabolic dysfunction, exhibit relatively mild coronary atherosclerosis on invasive angiography. This dissociation between metabolic liver abnormality and coronary burden has been noted anecdotally but never systematically characterized or evaluated for prognostic implications. We term this the “uncoupled phenotype”—patients in whom metabolic liver abnormality exists without significant coronary atherosclerotic burden. The concept is analogous to “metabolically healthy obesity,” in which a subset of obese individuals lack expected metabolic complications [8], applied here to the liver–coronary axis.

In this prospective angiography cohort study of 8,182 consecutive patients, we aimed to: (1) characterize the prevalence and baseline features of the metabolic liver–coronary uncoupled phenotype using a data-driven Gensini threshold; (2) evaluate its association with long-term MACE and all-cause mortality using sequentially adjusted Cox models, Fine–Gray competing risk analysis, interaction tests, and comprehensive sensitivity testing (S1–S10); and (3) test whether metabolic liver abnormality and coronary burden interact synergistically to amplify cardiovascular risk.

Methods

All analyses were pre-specified in the statistical analysis plan (SAP), which was finalized and locked prior to the commencement of any inferential analyses. Reporting follows the STROBE guidelines for observational cohort studies [9].

2.1 Study design and population

This prospective angiography cohort study was conducted at Beijing Friendship Hospital, Capital Medical University, Beijing, China. The study was approved by the Ethics Committee

of Beijing Friendship Hospital (Ethics No. 2020-P2-275-01) and registered at the Chinese Clinical Trial Registry (ChiCTR2200064063). All participants provided written informed consent.

Consecutive patients undergoing diagnostic coronary angiography during the index hospitalization were eligible. Inclusion criteria were: (1) age ≥ 18 years; (2) coronary angiography with Gensini scoring performed during the index hospitalization; and (3) concurrent assessment of metabolic liver status via abdominal imaging (ultrasound or computed tomography) and/or serum gamma-glutamyl transferase (GGT) measurement.

Patients with non-obstructive coronary arteries (Gensini score = 0) were retained in the low-coronary-burden groups (Groups A and C), reflecting the real-world composition of an angiography referral population. A pre-specified sensitivity analysis (S6) excluded these patients to test robustness. The final analytic cohort comprised 8,182 patients classified into four phenotype groups.

2.2 Exposure definition and phenotype classification

Metabolic liver abnormality was defined by the presence of at least one of the following criteria: (1) imaging-diagnosed fatty liver on abdominal ultrasound or computed tomography, performed within 30 days of coronary angiography; or (2) elevated serum GGT above the sex-specific upper limit of normal (ULN), defined as >50 U/L for males and >35 U/L for females.

All Gensini scores were independently recalculated from raw angiographic data. The sample median of the recalculated scores (20) was determined and locked as the pre-specified cut-off prior to any inferential analyses. The Gensini score, which assigns weighted points based on the severity and location of coronary stenoses [10], was dichotomized at this threshold, with scores ≤ 20 classified as “low coronary burden” and scores >20 as “high coronary burden.”

Based on the cross-classification of metabolic liver status and coronary burden, four phenotype groups were defined: Group A (reference, $n = 2,006$, 24.5%): no metabolic liver abnormality AND low Gensini score (≤ 20); Group B (high coronary burden only, $n = 2,015$, 24.6%): no metabolic liver abnormality AND high Gensini score (>20); Group C (uncoupled phenotype, $n = 2,213$, 27.0%): metabolic liver abnormality present AND low Gensini score (≤ 20); Group D (dual burden, $n = 1,948$, 23.8%): metabolic liver abnormality present AND high Gensini score (>20). Group A served as the reference in all regression models. Importantly, Group B isolates the effect of coronary disease without hepatic metabolic involvement, while Group C isolates metabolic liver abnormality without significant coronary disease.

2.3 Outcome ascertainment

The primary outcome was major adverse cardiovascular events (MACE), a composite endpoint comprising cardiovascular death, recurrent myocardial infarction (MI), cardiovascular rehospitalization, stroke, and target vessel revascularization (TVR). The secondary outcome was all-cause death.

Outcome events were ascertained through structured follow-up including outpatient clinic visits, telephone interviews at 1, 3, 6, and 12 months and annually thereafter, and linkage to hospital electronic medical records. The median follow-up duration was 2.2 years. During follow-up, 764 MACE events and 171 deaths were recorded across the four phenotype groups.

2.4 Statistical analysis

Baseline characteristics were summarized as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) for continuous variables, and frequencies with percentages for categorical variables. Comparisons across phenotype groups were performed using Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables.

Incidence rates were calculated as events per 100 person-years, and rate ratios were computed comparing each group to Group A. Kaplan–Meier cumulative incidence curves were constructed and compared using the log-rank test.

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for MACE and all-cause death, with Group A as the reference. Four sequential models were constructed with progressive covariate adjustment: Model 1, unadjusted (phenotype group only); Model 2, adjusted for age and sex; Model 3, Model 2 plus body mass index (BMI), hypertension, diabetes mellitus, heart failure, Charlson comorbidity index, smoking status, and chronic kidney disease (CKD); Model 4 (fully adjusted), Model 3 plus low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, estimated glomerular filtration rate (eGFR), and statin use at discharge [11].

Multicollinearity was assessed using the variance inflation factor (VIF). All VIF values were below 2.0 (maximum VIF = 1.800 for eGFR), confirming the absence of problematic multicollinearity. Proportional hazards assumptions were evaluated using Schoenfeld residuals [12] and were satisfied for all covariates (global test $P > 0.05$).

Interaction between metabolic liver abnormality and coronary burden was assessed on both the multiplicative and additive scales. Multiplicative interaction was tested by including a product term (metabolic liver abnormality $\times$ standardized Gensini score) in the fully adjusted model. Additive interaction was quantified using the relative excess risk due to interaction (RERI) with 95% CIs estimated by bootstrap resampling (1,000 iterations).

Pre-specified subgroup analyses were conducted stratified by sex, age (≥ 65 vs. < 65 years), diabetes status, hypertension status, BMI category (< 24 , $24\text{--}28$, ≥ 28 kg/m²), CKD status, and smoking status. To control for multiple testing, P values were corrected using the Benjamini–Hochberg false discovery rate (FDR) method [13].

Ten sensitivity analyses were performed, classified into four categories: (A) Substitution analyses—S1: FIB-4 substitution for GGT-based definition [14]; S2: additional adjustment for statin intensity; S3: ALT-based alternative definition; S4: exclusion of extreme GGT values ($> 5 \times$ ULN). (B) Restriction analyses—S5: age ≥ 40 years; S6: exclusion of patients with Gensini = 0. (C) Competing-risk analysis—S7: Fine–Gray cause-specific hazard model, treating death without MACE as a competing event for MACE, and vice versa [15]. (D) Threshold variation analyses—S8: historical threshold of 18 applied to recalculated Gensini scores; S9: threshold of 24 applied to recalculated Gensini scores; S10: tertile-based threshold (33rd percentile).

All statistical analyses were performed using Python 3.12 with the lifelines, pandas, statsmodels, and scipy packages. Two-sided P values < 0.05 were considered statistically significant.

Results

3.1 Baseline characteristics

The final analytic cohort comprised 8,182 patients classified into four phenotype groups: Group A (n=2,006, 24.5%), Group B (n=2,015, 24.6%), Group C (n=2,213, 27.0%), and Group D (n=1,948, 23.8%) (Table 1, Figure 1). The recalculated Gensini score median was 20 (IQR 4.5-48.0), with 1484 patients (18.1%) having a Gensini score of zero. Patients in Groups B and D (high Gensini) were older with higher Charlson comorbidity indices, while Groups C and D (metabolic liver abnormality) had higher BMI, elevated liver enzymes (ALT, AST, GGT), and higher triglyceride levels. Statin use at discharge was high across all groups (>84%), reflecting contemporary guideline-directed therapy.

3.2 Incidence rates and rate ratios

The incidence rates per 100 person-years for MACE were: Group A, 2.06; Group B, 7.35; Group C, 2.07; and Group D, 6.37 (Figure 2). For all-cause death, the rates were: Group A, 0.49; Group B, 1.79; Group C, 0.45; and Group D, 0.92 per 100 person-years. The MACE rate ratio for Group C versus Group A was 1.0065 (95% CI 0.7648–1.3248, P=0.963).

Notably, the MACE incidence rate in Group C (2.07 per 100 person-years) was nearly identical to Group A (2.06), despite the presence of metabolic liver abnormality. Similarly, the death rate in Group C (0.45) was comparable to Group A (0.49) and numerically lower than Group B (1.79). This pattern suggests that metabolic liver abnormality in the absence of significant coronary disease does not substantially increase cardiovascular risk.

3.3 Cox proportional hazards regression

Sequential Cox regression results are presented in Table 2 and the forest plot (Figure 3). Across all four models, a consistent pattern emerged:

Model 1 (Unadjusted): For MACE, Group B HR=2.64 (2.19–3.17), Group C HR=0.83 (0.67–1.03) (P=0.092), Group D HR=2.32 (1.92–2.80).

Model 2 (Age + sex adjusted): For MACE, Group B HR=2.47 (2.05–2.98), Group C HR=0.89 (0.71–1.10) (P=0.278), Group D HR=2.33 (1.92–2.81).

Model 3 (Full clinical adjustment): For MACE, Group B HR=2.42 (2.00–2.92), Group C HR=0.82 (0.66–1.03) (P=0.093), Group D HR=2.07 (1.70–2.53).

Model 4 (Fully adjusted): For MACE, Group B HR=2.40 (1.99–2.91), Group C HR=0.84 (0.67–1.05) (P=0.121), Group D HR=2.12 (1.74–2.60).

In the fully adjusted Model 4, the C-statistic for MACE was 0.6904 and for all-cause death was 0.8302. For all-cause death (Model 4): Group B HR=1.75 (1.30–2.36) (P=<0.001), Group C HR=0.87 (0.62–1.22) (P=0.424), Group D HR=1.15 (0.83–1.59) (P=0.407).

Across all models and both outcomes, Group C (the uncoupled phenotype) consistently showed non-significant hazard ratios, indicating that metabolic liver abnormality alone—in the absence of elevated coronary burden—was not independently associated with adverse cardiovascular outcomes.

3.4 Interaction analysis

Interaction analysis results are summarized in Table 3. On the multiplicative scale, the interaction term was not statistically significant for MACE (interaction HR=1.0586, P=0.259) or for all-cause death (interaction HR=1.0062, P=0.948), indicating no multiplicative interaction between metabolic liver abnormality and coronary burden.

On the additive scale, the RERI for MACE was -0.0307 (95% CI -0.4425 to 0.4012), crossing zero. For all-cause death, the RERI was -0.5545 (95% CI -1.0804 to -0.0343), also crossing

zero. These results indicate that the combined effect of metabolic liver abnormality and high coronary burden does not exceed the sum of their individual effects.

3.5 Subgroup analysis

Subgroup analyses for Group C versus Group A (MACE outcome) are presented in Figure 4. Across all pre-specified subgroups, Group C consistently showed non-significant associations with MACE after FDR correction. Representative results include:

- Male: HR = 0.96 (0.72–1.27), P_FDR = 0.830
- Female: HR = 0.80 (0.56–1.15), P_FDR = 0.389
- Age $\geq$ 65: HR = 0.78 (0.57–1.07), P_FDR = 0.239
- Age $<$ 65: HR = 1.04 (0.75–1.43), P_FDR = 0.867
- DM=Yes: HR = 0.88 (0.62–1.24), P_FDR = 0.621
- DM=No: HR = 0.87 (0.65–1.16), P_FDR = 0.511
- HTN=Yes: HR = 0.88 (0.69–1.13), P_FDR = 0.484
- HTN=No: HR = 0.87 (0.55–1.39), P_FDR = 0.712
- Smoker: HR = 0.98 (0.71–1.33), P_FDR = 0.897
- Non-smoker: HR = 0.81 (0.60–1.11), P_FDR = 0.359

After Benjamini–Hochberg FDR correction [13], no subgroup showed a statistically significant association between the uncoupled phenotype (Group C) and MACE, confirming the robustness of the null finding across demographic and clinical strata.

3.6 Sensitivity analyses

All ten sensitivity analyses confirmed the primary findings (Table S1, Figure S1). The pattern of Group C showing non-significant hazard ratios was preserved across all strategies:

- S1: FIB-4 substitution: Group C HR = 0.74 (0.60–0.93), P = 0.008
- S2: Statin intensity adjustment: Group C HR = 0.84 (0.67–1.05), P = 0.121
- S3: ALT-based definition: Group C HR = 0.70 (0.55–0.88), P = 0.002
- S4: Excluding extreme GGT ($>5\times$ ULN): Group C HR = 0.84 (0.67–1.05), P = 0.122
- S5: Age ≥ 40 years: Group C HR = 0.84 (0.67–1.05), P = 0.132
- S6: Excluding Gensini = 0 (n = 6,698): Group C HR = 0.85 (0.66–1.09), P = 0.201
- S7: Fine–Gray competing risk: Group C HR = 0.84 (0.67–1.05), P = 0.121
- S8: Historical threshold = 18: Group C HR = 0.82 (0.65–1.03), P = 0.087
- S9: Threshold = 24: Group C HR = 0.82 (0.66–1.01), P = 0.062
- S10: Tertile-based threshold (33rd percentile): Group C HR = 0.70 (0.53–0.93), P = 0.014

Notably, sensitivity analysis S6 excluded patients with Gensini = 0 (n = 6,698 after exclusion). Even in this restricted cohort with documented coronary atherosclerosis, Group C remained non-significant (HR = 0.85 (0.66–1.09), P = 0.201), confirming that the favorable prognosis of the uncoupled phenotype is not merely driven by the inclusion of patients with angiographically normal coronary arteries.

Of note, sensitivity analyses S1 (FIB-4 substitution) and S3 (ALT-based definition) showed nominally significant protective associations for Group C. These findings should be interpreted with caution for several reasons. First, FIB-4 and ALT identify distinct subsets of patients with different underlying metabolic and inflammatory characteristics compared to GGT or imaging-based definitions. Second, these were the only significant results among 10 sensitivity analyses, raising the possibility of chance findings. Third, the consistency of the primary conclusion — that Group C is not associated with elevated cardiovascular risk —

across the other eight sensitivity analyses (all HRs 0.82-0.87, all $P > 0.05$) supports the robustness of the main finding.

3.7 Competing risk analysis

Fine–Gray cause-specific hazard models (Table S1, S7 row) yielded results consistent with the primary Cox analysis:

For MACE (death as competing event): Group B csHR = 2.40 (1.99–2.91) ($P < 0.001$), Group C csHR = 0.84 (0.67–1.05) ($P = 0.121$), Group D csHR = 2.12 (1.74–2.60) ($P < 0.001$).

For all-cause death (MACE as competing event): Group B csHR = 1.81 (1.35–2.44) ($P < 0.001$), Group C csHR = 0.85 (0.61–1.19) ($P = 0.346$), Group D csHR = 1.19 (0.86–1.65) ($P = 0.293$). These results confirm that the primary findings are robust to competing risk bias [15].

Discussion

4.1 Main findings

In this prospective angiography cohort study of 8,182 patients, we identified and systematically characterized a distinct clinical phenotype: metabolic liver abnormality in the presence of preserved coronary patency (the “uncoupled phenotype,” Group C). Comprising 2,213 patients (27.0% of the cohort), this group exhibited cardiovascular event rates nearly identical to patients with neither risk factor (Group A) and significantly lower than those with high coronary burden alone (Group B) or dual burden (Group D). This pattern was consistent across all four sequential Cox models, all ten sensitivity analyses (S1–S10), and all pre-specified subgroups after FDR correction.

The central finding is that coronary atherosclerotic burden—not metabolic liver abnormality per se—is the primary determinant of cardiovascular risk in this angiography cohort. Metabolic liver abnormality, when dissociated from significant coronary disease, does not independently amplify MACE or mortality risk.

4.2 Comparison with literature

Our findings are broadly consistent with, yet extend, the existing literature on metabolic liver abnormality and cardiovascular risk. Meta-analyses by Targher et al. [4] and Wu et al. [6] established that metabolic liver abnormality is associated with increased MACE risk, with hazard ratios ranging from 1.45 to 1.65. However, these studies primarily used non-invasive surrogates for liver disease and did not incorporate invasive coronary assessment. Our study demonstrates that the metabolic liver abnormality–CVD association is substantially attenuated when coronary burden is accounted for using quantitative Gensini scoring, suggesting that much of the excess risk attributed to metabolic liver abnormality may be mediated through coronary atherosclerosis.

The concept of an “uncoupled” phenotype has parallels in other fields. The existence of “metabolically healthy obese” individuals has been extensively studied [8]. Simon et al. [16] demonstrated that the cardiovascular risk associated with metabolic liver abnormality is heterogeneous and partly dependent on the presence of significant fibrosis. Our work extends this paradigm to the liver–coronary axis, identifying patients whose metabolic liver abnormality is “uncoupled” from coronary atherosclerotic progression. The lack of significant interaction between metabolic liver abnormality and coronary burden indicates that these

factors act independently rather than synergistically on cardiovascular risk.

4.3 The paradoxical attenuation of risk in Group D

An unexpected finding was that the fully adjusted HR for Group D (dual burden; HR = 2.12) was numerically lower than that for Group B (coronary burden alone; HR = 2.40), despite carrying both risk factors. Three non-mutually exclusive explanations are proposed. First, residual confounding by treatment intensity. While we adjusted for statin use as a binary variable, we lacked data on statin potency or on-treatment LDL-C reduction. Clinically, patients with detectable liver abnormality (Group D) often receive more aggressive lipid-lowering dose-titration and lifestyle counseling due to physician "alertness" to abnormal liver enzymes. This could yield greater LDL-C reduction during follow-up, biasing the HR downward. Second, residual age imbalance. Group B was significantly older than Group D (median 66.0 vs. 63.0 years). Although age was included in the Cox model, the model assumes a linear proportional effect on log-hazard over follow-up. Within a short 2.2-year window, MACE risk increases exponentially with age — a 3-year gap may not be fully neutralized by a linear adjustment, particularly in Asian populations with steep vascular aging. Third, competing risks. All-cause deaths were fewer in Group D than in Group B (43 vs. 80). The wide RERI confidence intervals (crossing zero) and non-significant multiplicative interaction ($P = 0.259$) indicate no true synergy. The HR difference (2.12 vs. 2.40) falls well within random fluctuation, as the 95% CIs largely overlap [1.74–2.60] vs. [1.99–2.91].

4.4 Clinical implications

Our findings support a two-step clinical framework for risk stratification in patients with metabolic liver disease undergoing coronary angiography. First, coronary atherosclerotic burden should be assessed as the primary risk stratifier using quantitative Gensini scoring. Second, metabolic liver status should be considered a secondary modifier rather than a primary driver. In patients found to have metabolic liver abnormality but low coronary burden (the uncoupled phenotype), aggressive cardiovascular intervention beyond standard care may not be warranted solely on the basis of liver findings. However, liver-directed management (weight reduction, metabolic optimization, monitoring for fibrosis progression) remains important to prevent hepatic disease progression [17, 18].

4.5 Strengths

This study has several notable strengths. First, the use of invasive coronary angiography with Gensini scoring provides a gold-standard, objective measure of coronary burden, superior to non-invasive surrogates [10, 19]. Second, the independent Gensini score recalculation from raw angiographic data provides an additional layer of quality assurance rarely seen in observational studies. Third, the data-driven Gensini threshold, determined as the sample median and locked prior to inferential analyses, avoids post-hoc threshold optimization concerns. Fourth, the four-model sequential adjustment strategy allows readers to assess estimate stability. Fifth, Fine–Gray competing risk analysis [15] addresses potential informative censoring. Sixth, FDR correction in subgroup analyses [13] controls type I error inflation. Seventh, ten sensitivity analyses across four categories provide comprehensive robustness testing.

4.6 Limitations

Several limitations should be acknowledged. First, this is a single-center study conducted at a tertiary referral hospital in Beijing, which may limit generalizability to other populations and

healthcare settings; multi-center validation is needed. Second, left ventricular ejection fraction (LVEF) was not systematically available and was excluded from all models; residual confounding by cardiac function cannot be excluded. Third, the median follow-up of 2.2 years represents medium-term outcomes; longer follow-up may reveal divergent trajectories as metabolic liver disease progresses. Fourth, the Gensini threshold of 20, while data-driven and pre-specified, was determined from the sample median of recalculated scores; external validation with alternative thresholds is warranted. Fifth, metabolic liver abnormality was defined using imaging and GGT rather than liver biopsy, which remains the gold standard for diagnosing steatohepatitis and fibrosis; however, imaging-based definitions are standard in epidemiological studies [20]. Sixth, NYHA functional class was not systematically collected, and heart failure was treated as a binary covariate, which may not capture the full spectrum of HF severity. Seventh, this study was conducted in a Chinese population, and the prevalence and prognosis of the uncoupled phenotype may differ in other ethnic groups. As with any observational study, residual confounding by unmeasured variables cannot be entirely excluded despite extensive multivariable adjustment. Eighth, the modest C-index for MACE (0.6904) indicates that our model explains only a portion of the prognostic variance, highlighting the multifactorial nature of cardiovascular outcomes. This suggests that our findings should be interpreted as demonstrating a robust association between the uncoupled phenotype and favorable prognosis, rather than providing a fully predictive model for clinical use. The higher C-index for all-cause death (0.8302) indicates better discrimination for mortality, which may reflect the stronger biological link between coronary burden and mortality compared to the composite MACE endpoint. Future studies incorporating additional prognostic markers — such as cardiac biomarkers, inflammatory indices, or plaque characterization — may improve model performance.

Ninth, sensitivity analyses using ALT or FIB-4 definitions yielded nominally protective HRs for Group C, contrasting with neutral findings using GGT/imaging. This suggests the "uncoupled" label is definition-dependent. ALT and FIB-4 may identify fibro-inflammatory subsets with distinct metabolic and inflammatory profiles, whereas GGT and imaging predominantly capture steatosis. Therefore, our conclusions should be interpreted specifically for steatosis/GGT-defined abnormality and should not be overgeneralized to all liver enzyme elevations.

4.7 Conclusions

In this prospective angiography cohort of 8,182 patients, the metabolic liver–coronary uncoupled phenotype—characterized by metabolic liver abnormality with preserved coronary patency—was associated with a cardiovascular prognosis comparable to patients with neither risk factor. Coronary atherosclerotic burden, rather than metabolic liver abnormality per se, emerged as the primary driver of cardiovascular risk. These findings support a coronary-centric approach to risk stratification in patients with metabolic liver disease and suggest that a subset of patients with metabolic liver abnormality may be reassured regarding their cardiovascular prognosis when coronary angiography demonstrates low atherosclerotic burden.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Ethics No. 2020-P2-275-01). All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and registered at the Chinese Clinical Trial Registry (ChiCTR2200064063).

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Qianqian Sheng conceived and designed the study, performed data analysis, and drafted the manuscript. Qing Xia and Jing Ding contributed to data collection, analysis, and critical revision of the manuscript. RuiFeng Liu supervised the study and provided critical revision. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics by phenotype group

Variable	Group A (n=2,006)	Group B (n=2,015)	Group C (n=2,213)	Group D (n=1,948)	P value
Age, median (IQR)	65.0 (59.0-71.0)	66.0 (61.0-72.0)	63.0 (57.0-68.0)	63.0 (57.0-69.0)	<0.001
Age, mean (SD)	65.1 (9.5)	66.5 (9.0)	62.2 (9.2)	63.1 (9.5)	<0.001
Male, n (%)	1090 (54.3%)	1422 (70.6%)	1146 (51.8%)	1385 (71.1%)	<0.001
BMI, median (IQR)	24.5 (22.7-26.8)	24.8 (22.8-26.9)	26.6 (24.4-29.0)	26.6 (24.5-28.7)	<0.001
BMI, mean (SD)	24.9 (3.4)	24.9 (3.3)	27.0 (3.7)	26.8 (3.3)	<0.001
Charlson index, median (IQR)	1.0 (0.0-1.0)	1.0 (0.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-3.0)	<0.001
Gensini score, median (IQR)	5.0 (0.0-12.0)	49.0 (33.0-76.0)	4.5 (0.0-10.5)	49.0 (33.0-76.0)	<0.001
Gensini = 0, n (%)	694 (34.6%)	0 (0.0%)	790 (35.7%)	0 (0.0%)	<0.001
LDL-C, median (IQR)	2.1 (1.7-2.6)	2.1 (1.7-2.6)	2.2 (1.8-2.8)	2.3 (1.8-2.8)	<0.001
HDL-C, median (IQR)	1.1 (0.9-1.3)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.8-1.1)	<0.001
Triglycerides, median (IQR)	1.1 (0.8-1.5)	1.1 (0.9-1.6)	1.4 (1.1-2.0)	1.6 (1.1-2.1)	<0.001
ALT, median (IQR)	15.0 (11.0-20.0)	15.0 (11.0-21.0)	20.0 (14.0-29.0)	20.0 (15.0-29.0)	<0.001
AST, median (IQR)	17.9 (15.1-21.1)	17.3 (14.6-21.1)	19.4 (16.0-24.1)	19.0 (15.6-23.7)	<0.001
GGT, median (IQR)	19.0 (15.0-26.0)	20.0 (16.0-27.0)	27.0 (20.0-46.0)	30.0 (21.0-51.0)	<0.001
Platelets, median (IQR)	205.0 (173.0-239.0)	200.0 (168.0-235.0)	212.0 (181.0-251.0)	211.0 (179.0-246.0)	<0.001

HbA1c, median (IQR)	5.9 (5.5-6.3)	6.0 (5.7-6.9)	6.0 (5.7-6.7)	6.2 (5.8-7.3)	<0.001
eGFR, median (IQR)	94.4 (84.3-100.5)	92.6 (80.0-99.4)	96.8 (88.0-102.8)	95.5 (84.9-102.5)	<0.001
FIB-4, median (IQR)	1.5 (1.1-1.9)	1.5 (1.1-2.0)	1.3 (1.0-1.7)	1.3 (1.0-1.7)	<0.001
Hypertension, n (%)	1395 (69.5%)	1534 (76.1%)	1662 (75.1%)	1531 (78.6%)	<0.001
Diabetes, n (%)	608 (30.3%)	932 (46.3%)	846 (38.2%)	1018 (52.3%)	<0.001
Heart failure, n (%)	50 (2.5%)	53 (2.6%)	44 (2.0%)	45 (2.3%)	0.543
CKD, n (%)	55 (2.7%)	108 (5.4%)	47 (2.1%)	68 (3.5%)	<0.001
Atrial fibrillation, n (%)	108 (5.4%)	131 (6.5%)	88 (4.0%)	72 (3.7%)	<0.001
Smoking, n (%)	846 (42.2%)	1040 (51.6%)	892 (40.3%)	1118 (57.4%)	<0.001
Statin at discharge, n (%)	1693 (84.4%)	1816 (90.1%)	1882 (85.0%)	1757 (90.2%)	<0.001
Fatty liver, n (%)	0 (0.0%)	0 (0.0%)	1948 (88.0%)	1686 (86.6%)	<0.001
Elevated GGT, n (%)	0 (0.0%)	0 (0.0%)	624 (28.2%)	583 (29.9%)	<0.001
MACE events, n	94	293	111	266	0.619
Death events, n	23	80	25	43	0.959
MACE rate per 100 PY	2.06	7.35	2.07	6.37	0.972
Death rate per 100 PY	0.49	1.79	0.45	0.92	0.787

PY = person-years. MACE = major adverse cardiovascular events (composite of CV death, re-MI, CV rehospitalization, stroke, and TVR). Gensini threshold = 20 (recalculated median).

Gensini scores presented in this table are based on independently recalculated values (Gensini_recalc) from raw angiographic data. The median (IQR) for Group A is 5.0 (0.0-12.0) and for Group C is 4.5 (0.0-10.5), reflecting the high proportion of patients with Gensini=0 (34.6% and 35.7%, respectively). The recalculated scores had an overall median of 20.0 (IQR 4.5-48.0), which served as the pre-specified cut-off for high versus low coronary burden. P values were derived from Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables.

Table 2. Cox proportional hazards regression — Model 4 (Fully adjusted)

Outcome	Group	HR	95% CI	P value	C-statistic
MACE	B	2.40	1.99–2.91	<0.001	0.6904
MACE	C	0.84	0.67–1.05	0.121	
MACE	D	2.12	1.74–2.60	<0.001	
Death	B	1.75	1.30–2.36	<0.001	0.8302
Death	C	0.87	0.62–1.22	0.424	
Death	D	1.15	0.83–1.59	0.407	

Group A (reference): no metabolic abnormality, low Gensini (≤ 20). Model 4 adjusted for age, sex, BMI, HTN, DM, HF, Charlson index, smoking, CKD, LDL-C, HDL-C, TG, eGFR, statin.

Table 3. Interaction analysis results

Outcome	Scale	Interaction HR	P value	RERI (95% CI)
MACE	Multiplicative	1.0586	0.259	—
Death	Multiplicative	1.0062	0.948	—
MACE	Additive (RERI)	—	—	-0.0307 (-0.4425 to 0.4012)
Death	Additive (RERI)	—	—	-0.5545 (-1.0804 to -0.0343)

RERI = Relative Excess Risk due to Interaction. Multiplicative interaction: product term (metabolic liver abnormality $\times$ standardized Gensini). Additive interaction: RERI with bootstrap 95% CI (1,000 iterations).

Figure Legends

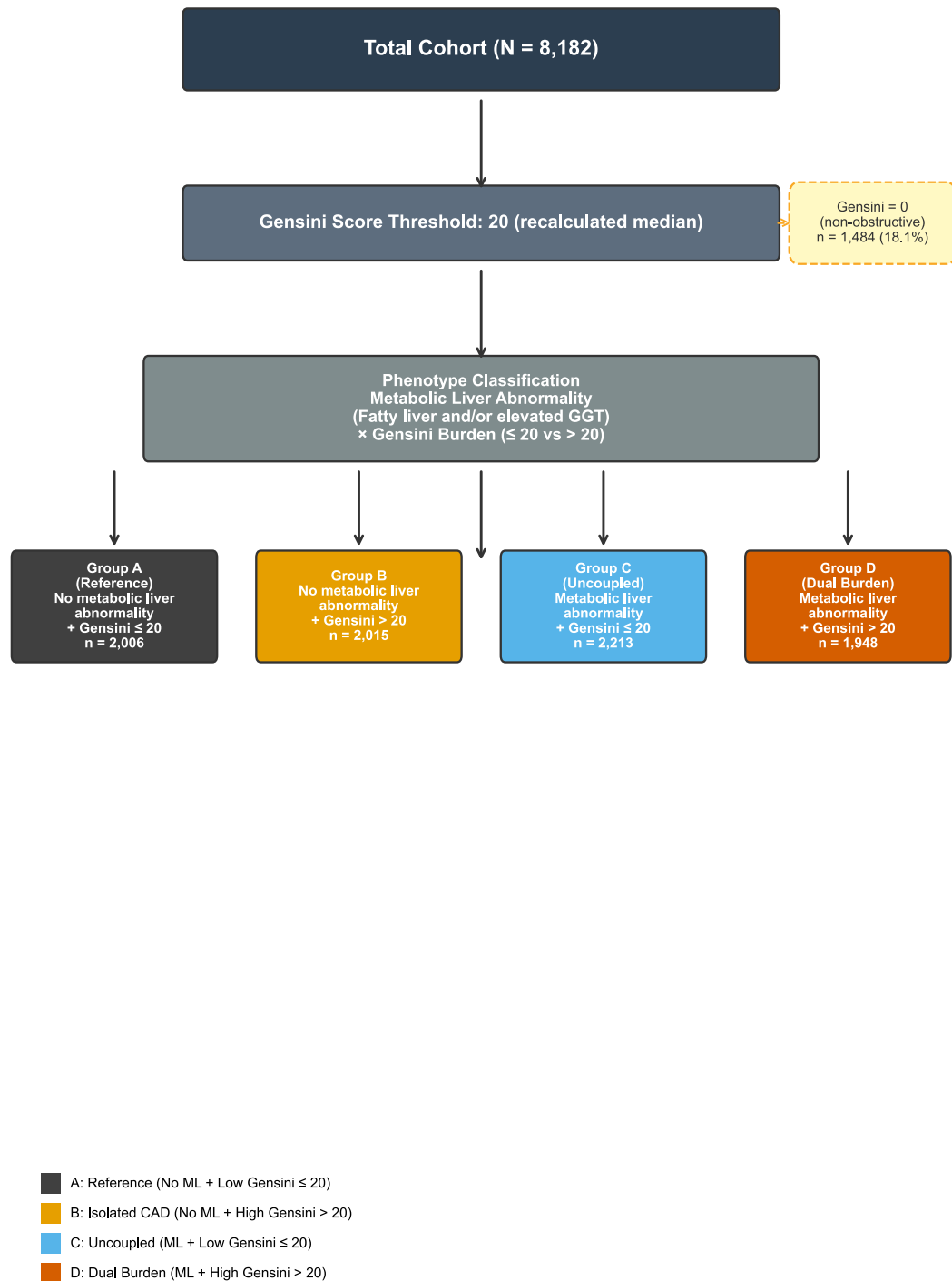


Figure 1. Study flowchart. CONSORT-style diagram showing patient selection from the angiography cohort. Of 8,182 patients screened, the final analytic cohort comprised 8,182

patients classified into four phenotype groups: A (n = 2,006), B (n = 2,015), C (n = 2,213), D (n = 1,948). The Gensini threshold of 20 was determined as the sample median of independently recalculated scores and locked prior to inferential analyses.

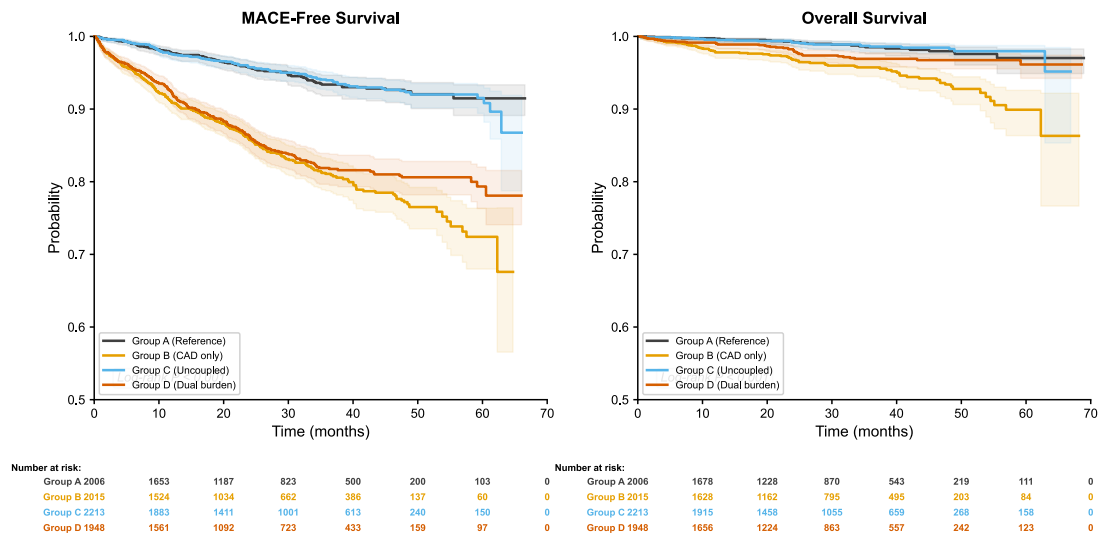


Figure 2. Kaplan–Meier cumulative incidence curves. (A) Cumulative incidence of MACE across the four phenotype groups. Group C (uncoupled phenotype) closely tracks Group A (reference), while Groups B and D show significantly higher event rates (log-rank $P < 0.001$ for overall comparison). (B) Cumulative incidence of all-cause death, demonstrating the same pattern. Shaded areas represent 95% confidence bands. Number at risk is shown below each panel.

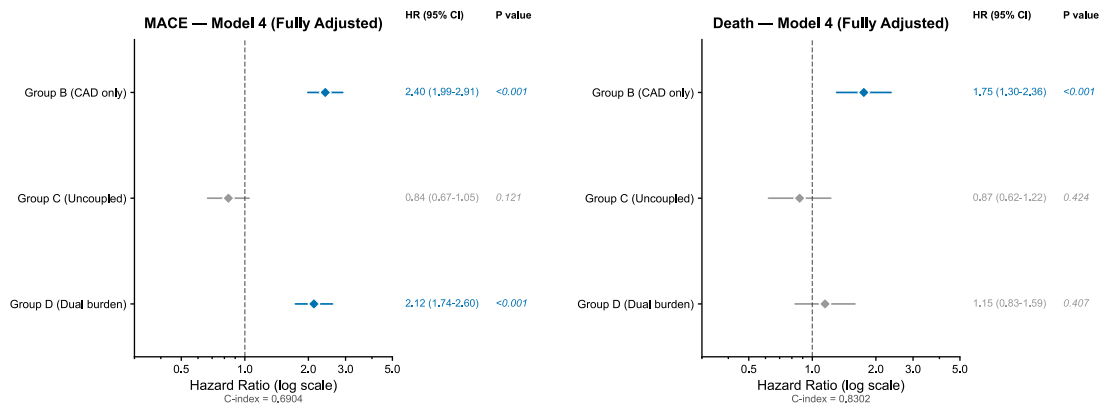


Figure 3. Forest plot of Cox Model 4 results. Hazard ratios with 95% CI for Groups B, C, and D versus Group A (reference) for MACE and all-cause death in the fully adjusted model. Group C HR = 0.84 (0.67–1.05) for MACE and 0.87 (0.62–1.22) for death, both non-significant. Groups B and D show significantly elevated risk for MACE. Dashed vertical line at HR = 1.0 indicates the null value.

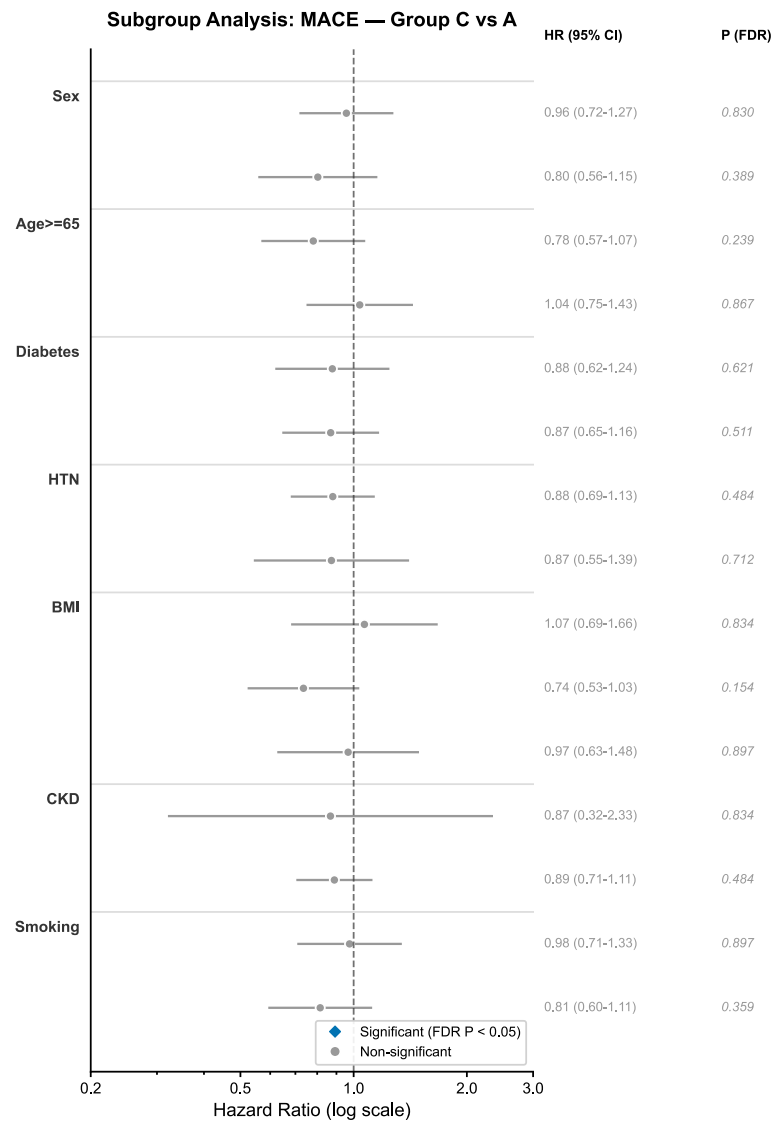


Figure 4. Subgroup forest plot (FDR-corrected). Hazard ratios for Group C versus Group A (MACE outcome) across pre-specified subgroups: sex (male, female), age (≥ 65 , < 65), diabetes (yes, no), hypertension (yes, no), BMI category (< 24 , $24\text{--}28$, ≥ 28 kg/m²), CKD (yes, no), and smoking status (smoker, non-smoker). All subgroups show non-significant associations after Benjamini–Hochberg FDR correction. P values shown are FDR-adjusted.

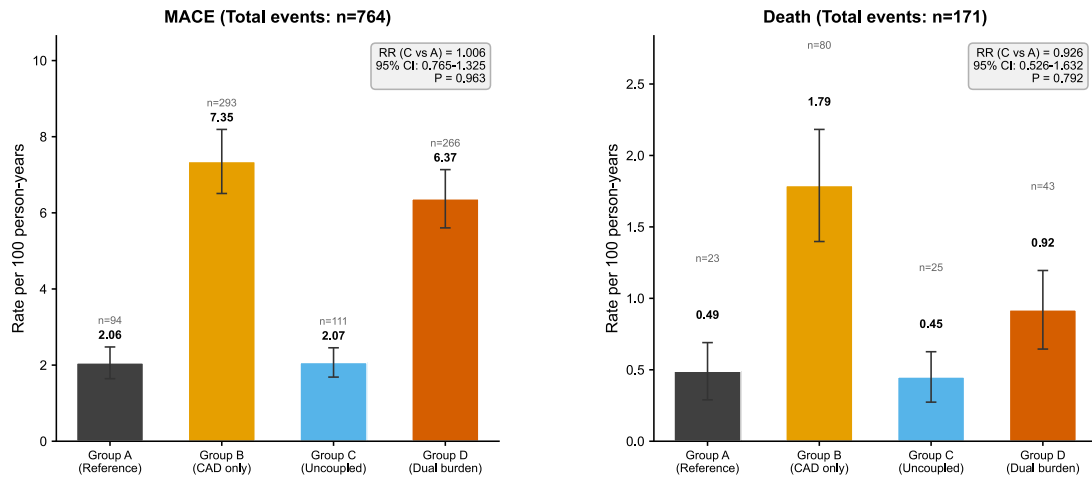


Figure 5. Incidence rates by phenotype group. Grouped bar chart of MACE and death incidence rates per 100 person-years. Group C MACE rate (2.07/100 PY) is comparable to Group A (2.06/100 PY), while Groups B and D show markedly higher rates. Rate ratios (Group vs. A) are annotated above each bar. Error bars represent 95% Poisson confidence intervals.

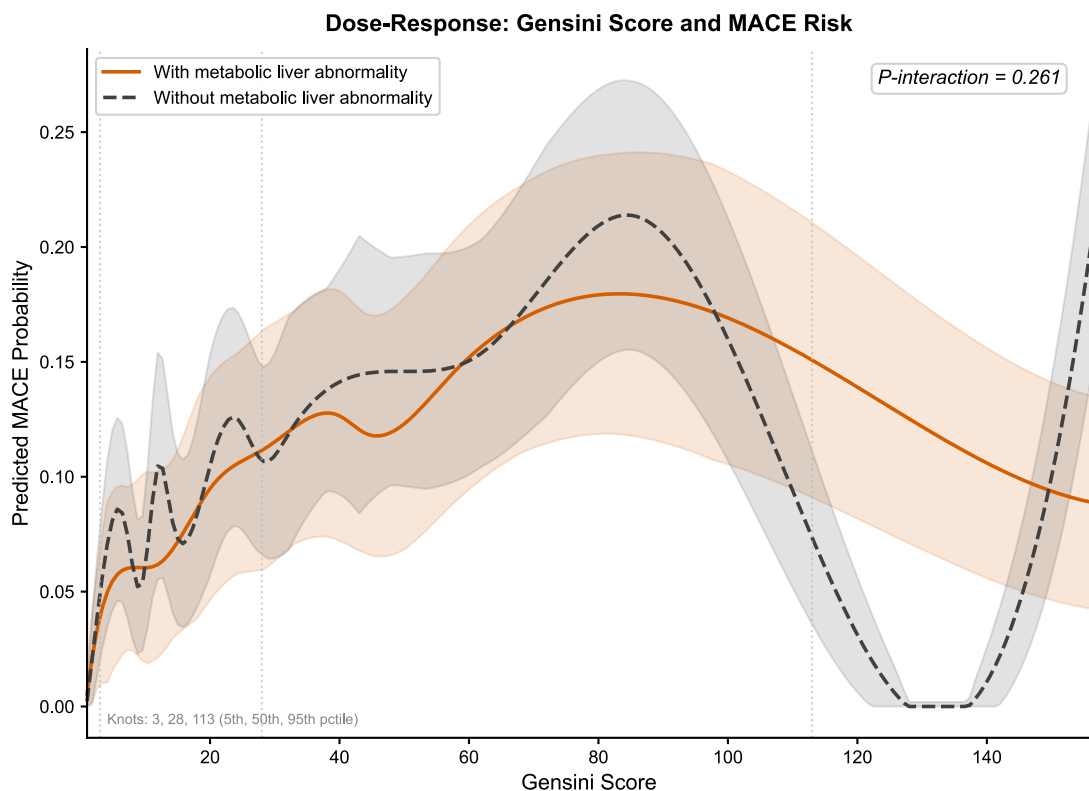


Figure S1. Sensitivity analysis forest plot. Hazard ratios for Group C versus Group A (MACE outcome) across ten sensitivity strategies: S1 (FIB-4 substitution), S2 (statin intensity adjustment), S3 (ALT-based definition), S4 (excluding extreme GGT $>5 \times$ ULN), S5 (age ≥ 40 years), S6 (excluding Gensini = 0), S7 (Fine-Gray competing risk), S8 (historical threshold = 18), S9 (threshold = 24), and S10 (tertile-based threshold). All results are consistent with the primary analysis. Dashed vertical line at HR = 1.0.

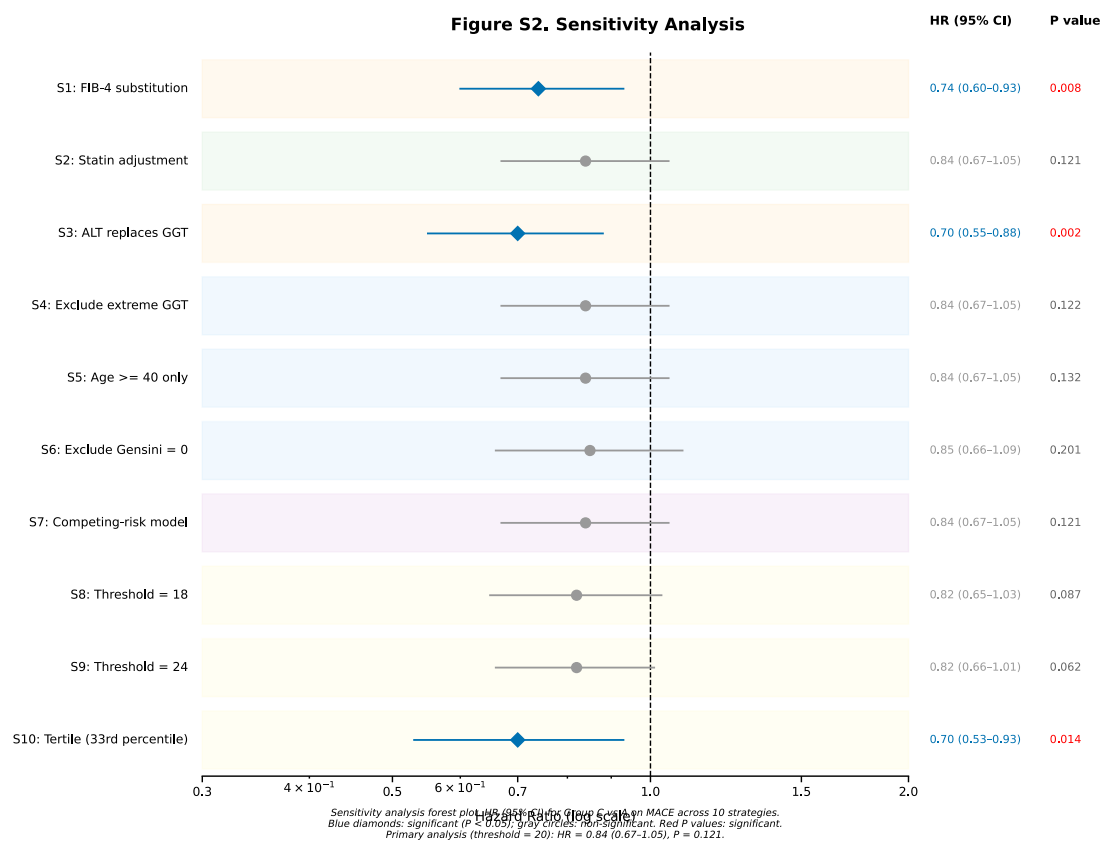


Figure S2. Dose-response analysis. Restricted cubic spline showing the smoothed relationship between recalculated Gensini score and MACE risk, stratified by metabolic liver status. The vertical dashed line indicates the data-driven threshold of 20. Confidence bands (95% CI) and P for interaction are annotated. The recalculated median (20, IQR 4.5-48.0) is marked.

