Clinical Characteristics and Cardiovascular Disease Risk in Patients with Type 2 Diabetes at Different Risks of Liver Fibrosis: A Postprint Study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated fatty liver disease (MAFLD) exert mutual influence, and their coexistence further increases the risk of adverse outcomes including cardiovascular disease (CVD) and liver fibrosis. Therefore, MAFLD screening and liver fibrosis risk stratification are necessary in T2DM patients, particularly those with multiple cardiometabolic risk factors.

Objective: To investigate the clinical characteristics and CVD risk among T2DM patients with varying degrees of liver fibrosis risk.

Methods: A total of 1425 T2DM patients hospitalized in the Department of Endocrinology at Nanjing Drum Tower Hospital between July 2020 and June 2023 were retrospectively enrolled. All patients underwent transient elastography examination using FibroTouch. According to the 2023 American Diabetes Association (ADA) Standards of Care in Diabetes, patients were stratified into three groups based on the Fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM): low liver fibrosis risk group (n=1235), intermediate liver fibrosis risk group (n=110), and high liver fibrosis risk group (n=80). Clinical characteristics were compared across groups, and the 10-year CVD risk was assessed using the Framingham Risk Score (FRS). Additionally, patients were further classified into four subgroups based on CVD risk stratification: low cardiac and low hepatic risk group (n=214), high cardiac and low hepatic risk group (n=1021), high cardiac and high hepatic risk group (n=178), and low cardiac and high hepatic risk group (n=12). Clinical characteristics were compared among the first three T2DM patient subgroups.

Results: Among the 1425 T2DM patients, 5.6% were classified as having high liver fibrosis risk. The high liver fibrosis risk group exhibited higher levels of age,

alanine aminotransferase (ALT), direct bilirubin (DBIL), glycated hemoglobin (HbA1c), ultrasound attenuation parameter (UAP), liver stiffness measurement (LSM), Fibrosis-4 index (FIB-4), prevalence of reduced muscle mass, diabetic peripheral neuropathy, and lipid-lowering therapy compared to the low liver fibrosis risk group, whereas platelet count (PLT), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and skeletal muscle index (SMI) were lower. Aspartate aminotransferase (AST) and diabetic retinopathy were higher in the high liver fibrosis risk group compared to both the low and intermediate liver fibrosis risk groups ($P<0.05$). Stratification analysis revealed that T2DM patients with age >60 years, HbA1c >9%, abnormal liver enzymes, and concomitant reduced muscle mass had higher liver fibrosis risk ($P<0.05$). The prevalence of high CVD risk increased progressively with escalating liver fibrosis risk (^{2} trend=35.900, $P<0.001$). Patients in the high cardiac and high hepatic risk group demonstrated higher age, AST, DBIL, UAP, LSM, FIB-4, FRS, prevalence of diabetic peripheral neuropathy, and lipid-lowering therapy, along with lower PLT compared to both the low cardiac and low hepatic risk group and the high cardiac and low hepatic risk group ($P<0.05$).

Conclusion: T2DM patients constitute a high-risk population for liver fibrosis and CVD. Advanced age, poor glycemic control, multiple diabetes complications, abnormal liver enzymes, increased hepatic lipid deposition, or reduced muscle mass augment the risk of CVD and liver fibrosis. Enhanced early monitoring and preventive management should be implemented for these high-risk patients.

Full Text

Clinical Characteristics and Cardiovascular Disease Risk in Type 2 Diabetes Populations with Different Liver Fibrosis Risks

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Abstract

Background Type 2 diabetes mellitus (T2DM) and metabolism-associated fatty liver disease (MAFLD) interact reciprocally, and their coexistence further increases the risk of adverse outcomes such as cardiovascular disease

(CVD) and liver fibrosis. Therefore, MAFLD screening and liver fibrosis risk stratification are necessary in patients with T2DM, particularly those with multiple cardiometabolic risk factors. **Objective** To investigate the clinical characteristics and CVD risk in T2DM patients with varying degrees of liver fibrosis risk. **Methods** A total of 1,425 T2DM patients admitted to the Department of Endocrinology at Nanjing Drum Tower Hospital between July 2020 and June 2023 were retrospectively enrolled. All patients underwent liver transient elastography (FibroTouch) examination. Following the 2023 American Diabetes Association (ADA) Standards of Medical Care in Diabetes, patients were classified into three groups based on the Fibrosis-4 Index (FIB4) and liver stiffness measurement (LSM): low-risk (n=1,235), intermediate-risk (n=110), and high-risk (n=80) for liver fibrosis. Clinical characteristics were compared among groups, and 10-year CVD risk was assessed using the Framingham Risk Score (FRS). Furthermore, patients were re-stratified into four groups based on combined liver fibrosis and CVD risk: low-cardiovascular/low-hepatic risk (n=214), high-cardiovascular/low-hepatic risk (n=1,021), high-cardiovascular/high-hepatic risk (n=178), and low-cardiovascular/high-hepatic risk (n=12). Clinical characteristics were compared among the first three groups. **Results** Among the 1,425 T2DM patients, 5.6% were classified as high-risk for liver fibrosis. The high-risk group exhibited higher age, alanine aminotransferase (ALT), direct bilirubin (DBIL), glycated hemoglobin (HbA1c), ultrasound attenuation parameter (UAP), LSM, FIB4, muscle mass loss, diabetic peripheral neuropathy, and lipid-lowering therapy compared to the low-risk group, while platelet count (PLT), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and skeletal muscle mass index (SMI) were lower. Aspartate aminotransferase (AST) and diabetic retinopathy were higher in the high-risk group compared to both low- and intermediate-risk groups ($P<0.05$). Stratified analysis revealed that T2DM patients aged >60 years, with HbA1c >9%, abnormal liver enzymes, or combined muscle mass loss had higher liver fibrosis risk ($P<0.05$). The prevalence of high CVD risk increased progressively with liver fibrosis risk (^{2} trend=35.900, $P<0.001$). The high-cardiovascular/high-hepatic risk group showed higher age, AST, DBIL, UAP, LSM, FIB4, FRS, diabetic peripheral neuropathy, and lipid-lowering therapy, and lower PLT compared to the low-cardiovascular/low-hepatic and high-cardiovascular/low-hepatic risk groups ($P<0.05$). **Conclusion** T2DM patients are at high risk for both liver fibrosis and CVD. Advanced age, poor glycemic control, multiple diabetic complications, abnormal liver enzymes, increased hepatic lipid deposition, and decreased muscle mass collectively increase CVD and liver fibrosis risk. Enhanced early monitoring and preventive management are warranted for this high-risk population.

Keywords: Diabetes mellitus, type 2; Hepatic fibrosis; Cardiovascular diseases; Metabolic associated fatty liver disease; Cardiovascular risk

Introduction

Type 2 diabetes mellitus (T2DM) and metabolism-associated fatty liver disease (MAFLD) are closely interrelated. Epidemiological data indicate that approximately 60-70% of T2DM patients have concurrent MAFLD. Compared to non-diabetic individuals, T2DM patients with MAFLD face a 2-3 fold increased risk of hepatic decompensation and hepatocellular carcinoma. Moreover, MAFLD further elevates cardiovascular disease (CVD) risk in T2DM patients, and the coexistence of MAFLD, CVD, and T2DM accelerates adverse cardiorenal events and mortality. The 2023 American Diabetes Association (ADA) Standards of Medical Care in Diabetes, for the first time, recommended that all T2DM patients, particularly those with multiple cardiometabolic risk factors, undergo MAFLD screening and liver fibrosis risk stratification using the Fibrosis-4 Index (FIB4) combined with transient elastography. Therefore, analyzing the clinical characteristics and CVD risk in T2DM populations with different liver fibrosis risks is essential to provide evidence for early screening and refined management of liver fibrosis and CVD risk in T2DM patients with MAFLD.

1.1 Study Subjects

A total of 2,587 T2DM patients hospitalized in the Department of Endocrinology at Nanjing Drum Tower Hospital between July 2020 and June 2023 who underwent FibroTouch examination were retrospectively enrolled. Inclusion criteria were: (1) T2DM diagnosis according to the Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2020 Edition); and (2) age $ $18 years. Exclusion criteria included: (1) viral hepatitis, alcoholic liver disease (defined as excessive alcohol consumption >280 g/week for men or >140 g/week for women), autoimmune liver disease, primary biliary cirrhosis, or other liver diseases; (2) pregnancy; (3) acute diabetic complications such as diabetic ketoacidosis; (4) thyroid dysfunction; and (5) malignancies. This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital Affiliated to Nanjing University of Chinese Medicine (approval number: 2022-444-02), with a waiver of informed consent.

1.2 Data Collection and Definitions

1.2.1 General Clinical Data: Retrospectively collected clinical data included age, sex, disease duration, newly diagnosed diabetes status, smoking history, alcohol consumption history, hypertension, muscle mass loss, diabetic retinopathy, diabetic nephropathy, diabetic peripheral neuropathy, medication history (antihypertensive and lipid-lowering drugs), body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), fasting blood glucose (FBG), fasting C-peptide, glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count (PLT), total bilirubin (TBIL), and direct bilirubin (DBIL).

1.2.2 Definitions and Criteria: (1) Newly diagnosed T2DM: No prior history of diabetes and diagnosis within 12 months. (2) Smoking history: Defined according to WHO (1984) recommendations as smoking >1 cigarette/day for $ 1$year.(3)$Alcoholconsumption : Weeklydrinkingatleastoncefora continuousorcumulativeperiodof1year;to$ $280g/weekformenand < 140g/weekforwomen.(4)Hypertension : Priordiagnosisorcurrentuseofantihyperte$ 140/90$mmHg(1mmHg = 0.133kPa).(5)Musclemassloss : SMI <$ $7kg/m\hat{}\{2\}$ for men and <5.7 kg/m^2 for women. (6) Diabetic complications: Diabetic retinopathy was diagnosed based on fundus photography; diabetic peripheral neuropathy based on ankle reflex, vibration, pressure, temperature, pinprick sensation, and nerve conduction studies; diabetic nephropathy based on persistently elevated urinary albumin-to-creatinine ratio (UACR) and/or decreased estimated glomerular filtration rate (eGFR) after excluding other chronic kidney diseases. (7) Medication history: Antihypertensive therapy included ACE inhibitors, ARBs, calcium channel blockers, diuretics, and beta-blockers; lipid-lowering therapy included statins, fibrates, or other lipid-lowering agents.

1.2.3 Transient Elastography: Liver steatosis and fibrosis were assessed using FibroTouch (Hisky, China). The instrument recommends appropriate probes based on real-time assessment of skin-to-capsule distance. Patients were placed in a supine position with the right arm fully abducted, and the right liver lobe was scanned through intercostal spaces. At least 10 measurements were performed at the same point using one probe, with the median value taken as the result. Measurements were considered reliable if the interquartile range was less than one-third of the median and the success rate was $ $60%, with all examinations performed by the same trained physician. At least three different measurement sites were selected for each patient, and the average was taken as the final value, yielding both the ultrasound attenuation parameter (UAP) and liver stiffness measurement (LSM). Results were expressed in dB/m for UAP and kPa for LSM. Hepatic steatosis was defined as UAP $ $244 dB/m.

1.2.4 Body Composition Analysis: A Korean Biospace Inbody 770 body composition analyzer was used to measure visceral fat area (VFA) and skeletal muscle mass index (SMI) via bioelectrical impedance analysis (BIA).

1.2.5 Calculations: The homeostasis model assessment of insulin resistance (HOMA2-IR) was calculated using the online calculator (https://www2.dtu.ox.ac.uk/homacalculator). FIB4 was calculated as: age (years) × AST (U/L) / [PLT ($×10$\hat{}\{9\}$/L) × √ALT (U/L)].

1.3 Risk Stratification

1.3.1 Liver Fibrosis Risk Stratification: According to the 2022 American Association for the Study of Liver Diseases (AASLD) criteria for diabetic populations (with diagnostic thresholds converted between FibroTouch and FibroScan based on the Chinese consensus on liver fibrosis diagnosis and treatment), patients were divided into: low-risk (FIB4<1.30 or FIB4=1.30-2.67 with LSM<8

kPa), intermediate-risk (FIB4=1.30-2.67 with LSM=8-11 kPa), and high-risk (FIB4>2.67 or FIB4=1.30-2.67 with LSM>11 kPa) groups.

1.3.2 Ten-Year Atherosclerotic Cardiovascular Disease (ASCVD) Risk: Calculated using the Framingham Risk Score (FRS). FRS <10% indicated low risk, 10-20% intermediate risk, and >20% or prior CVD events (including angina, myocardial infarction, sudden death, stroke, and transient ischemic attack) indicated high risk.

1.3.3 Combined Risk Stratification: Based on liver fibrosis and CVD risk, patients were further classified into four groups [Figure 1: see original paper]: (1) Low-cardiovascular/low-hepatic risk: low liver fibrosis risk and low ASCVD risk; (2) High-cardiovascular/low-hepatic risk: low liver fibrosis risk but high ASCVD risk; (3) Low-cardiovascular/high-hepatic risk: intermediate/high liver fibrosis risk but low ASCVD risk; (4) High-cardiovascular/high-hepatic risk: intermediate/high liver fibrosis risk and high ASCVD risk.

1.4 Statistical Analysis

SPSS 27.0 software was used for statistical analysis. Categorical data were expressed as frequencies and percentages, with between-group comparisons using ^{2} tests. Normality was assessed using the Kolmogorov-Smirnov test, and homogeneity of variance using Levene's test. Normally distributed continuous data were expressed as mean ± standard deviation and compared using one-way ANOVA. Non-normally distributed data were expressed as median (Q1, Q3) and compared using Kruskal-Wallis H test with post-hoc Dunn-Bonferroni correction. P<0.05 was considered statistically significant.

Results

2.1 Clinical Characteristics of T2DM Patients Across Liver Fibrosis Risk Groups

A total of 1,425 T2DM patients were included (950 men [66.7%] and 475 women [33.3%]), with a mean age of 50$±$11 years. Patients were stratified into three groups: low-risk (n=1,235, 86.7%), intermediate-risk (n=110, 7.7%), and high-risk (n=80, 5.6%) for liver fibrosis. Significant differences were observed among groups in sex, age, DBP, ALT, AST, PLT, DBIL, LDL-C, TC, HbA1c, UAP, LSM, FIB4, FRS, SMI, muscle mass loss, diabetic retinopathy, diabetic peripheral neuropathy, and lipid-lowering therapy (P<0.05). No significant differences were found in BMI, SBP, TBIL, HDL-C, TG, fasting C-peptide, FBG, HOMA2-IR, VFA, disease duration, newly diagnosed diabetes, smoking, alcohol consumption, hypertension, diabetic nephropathy, or antihypertensive therapy (P>0.05).

Specifically, the high-risk group exhibited higher age, ALT, DBIL, HbA1c, UAP, LSM, FIB4, muscle mass loss, diabetic peripheral neuropathy, and lipid-lowering therapy, but lower PLT, LDL-C, TC, and SMI compared to the low-risk group.

AST and diabetic retinopathy were higher in the high-risk group compared to both low- and intermediate-risk groups (all P<0.05) .

Subgroup analyses based on age, HbA1c, BMI, liver enzyme status (abnormal defined as ALT and/or AST >30 U/L), and muscle mass loss revealed that T2DM patients aged >60 years, with HbA1c >9%, abnormal liver enzymes, or muscle mass loss had significantly higher liver fibrosis risk (P<0.05) .

2.2 CVD Risk Prevalence Across Liver Fibrosis Risk Groups

The prevalence of low, intermediate, and high CVD risk in the overall T2DM population was 22.4%, 33.7%, and 43.9%, respectively. Among low liver fibrosis risk patients, CVD low, intermediate, and high-risk prevalence was 24.8% (306/1,235), 33.8% (417/1,235), and 41.4% (512/1,235), respectively. In the intermediate liver fibrosis risk group, these rates were 8.2% (9/110), 33.6% (37/110), and 58.2% (64/110), respectively. In the high liver fibrosis risk group, they were 3.8% (3/80), 32.5% (26/80), and 63.7% (51/80), respectively. The prevalence of high CVD risk increased progressively with liver fibrosis risk (^{2} trend=35.900, P<0.001) [Figure 2: see original paper].

2.3 Clinical Characteristics After Combined Liver Fibrosis and CVD Risk Stratification

When stratified by combined risk, the high-cardiovascular/low-hepatic risk group was largest (n=1,021, 71.6%), while the low-cardiovascular/high-hepatic risk group was smallest (n=12, 0.8%) and excluded from statistical analysis due to insufficient sample size. Significant differences among the remaining three groups were observed in sex, age, DBP, SBP, AST, PLT, DBIL, LDL-C, TC, TG, HbA1c, UAP, LSM, FIB4, FRS, hypertension, muscle mass loss, diabetic nephropathy, diabetic peripheral neuropathy, and lipid-lowering therapy (P<0.05). No significant differences were found in BMI, ALT, TBIL, HDL-C, fasting C-peptide, FBG, HOMA2-IR, VFA, disease duration, newly diagnosed diabetes, diabetic retinopathy, or antihypertensive therapy (P>0.05) .

The high-cardiovascular/high-hepatic risk group had higher age, AST, DBIL, UAP, LSM, FIB4, FRS, diabetic peripheral neuropathy, and lipid-lowering therapy, and lower PLT compared to both the low-cardiovascular/low-hepatic and high-cardiovascular/low-hepatic risk groups (P<0.05). The high-cardiovascular/low-hepatic risk group had higher proportions of men, DBP, LDL-C, and TC compared to the other two groups (P<0.05).

Discussion

T2DM and MAFLD share insulin resistance as a common pathophysiological basis. T2DM is a risk factor for poor liver fibrosis outcomes. Previous studies indicate that at least one-sixth of T2DM patients have moderate to severe liver

fibrosis, which contributes to cirrhosis and mortality in this population. The 2023 ADA Standards of Medical Care in Diabetes, for the first time, recommended systematic MAFLD screening and liver fibrosis risk stratification using FIB4 combined with transient elastography for all T2DM patients. However, few studies have applied this recommended sequential screening approach, leaving the clinical characteristics of T2DM patients across different liver fibrosis risk categories unclear. Previous studies using FIB4 and transient elastography reported a prevalence of clinically significant fibrosis ($\geq$F2) in T2DM patients ranging from 7.5% to 18.9%. Our retrospective analysis found that 13.3% of hospitalized T2DM patients had intermediate or high liver fibrosis risk, consistent with prior research.

Our findings demonstrate that T2DM patients aged >60 years, with HbA1c >9%, abnormal liver enzymes, or muscle mass loss have higher liver fibrosis risk. Previous research has shown that glycemic control is closely associated with liver fibrosis progression. In our study, HbA1c levels were significantly higher in the intermediate and high liver fibrosis risk groups, and stratified analysis revealed that patients with HbA1c >9% had 2.5 times higher prevalence of high liver fibrosis risk compared to those with HbA1c <7.0% (8.3% vs. 3.3%), highlighting the importance of intensive glycemic control to reduce fibrosis risk. Additionally, AST levels were significantly higher in the high-risk group, though 3.2% of patients with normal liver enzymes still had high liver fibrosis risk, supporting ADA guideline recommendations for fibrosis screening even in patients with normal liver enzymes.

Notably, SMI values were significantly lower in intermediate and high liver fibrosis risk groups, with muscle mass loss being 1.6 times more prevalent in these patients (12.2% vs. 20.7%). Numerous studies have identified muscle mass loss as a significant risk factor for liver fibrosis. In MAFLD patients, sarcopenia increases the risk of progression to metabolic dysfunction-associated steatotic liver disease (MASH) and significant fibrosis by 2.5-fold. A large cohort study of 20,069 patients demonstrated that sarcopenia significantly increased MAFLD prevalence, and reduced skeletal muscle mass promoted MAFLD and fibrosis progression. These findings suggest that targeted dietary and exercise interventions to preserve muscle mass in diabetic populations may be valuable for reducing liver fibrosis risk.

Diabetes substantially increases CVD risk, which represents the leading cause of death in T2DM. CVD is also a common extrahepatic complication of fatty liver disease, with liver fibrosis severity being an independent risk factor for CVD development. Current management of metabolic diseases, including fatty liver disease and T2DM, focuses on controlling risk factors to reduce cardiovascular events. Our results showed that 77.6% of enrolled patients had intermediate or high CVD risk, with prevalence increasing significantly alongside liver fibrosis risk, reaching 63.7% in the high liver fibrosis risk group. This underscores the importance of early screening and management of high liver fibrosis risk in T2DM patients to improve both hepatic and cardiovascular outcomes.

To further characterize patients with different combinations of liver fibrosis and CVD risk, we performed a four-group stratification. The low-cardiovascular/high-hepatic risk group was smallest, suggesting that T2DM patients with high liver fibrosis risk typically also have elevated CVD risk. The high-cardiovascular/high-hepatic risk group was older with higher AST and UAP levels. Both high-risk groups had higher HbA1c than the low-cardiovascular/low-hepatic risk group, while the high-cardiovascular/high-hepatic risk group had lower SMI and higher prevalence of muscle mass loss. These findings indicate that T2DM patients who are older, have elevated AST, poor glycemic control, and reduced SMI require intensified screening and early intervention for both cardiac and hepatic risks. Additionally, the high-cardiovascular/high-hepatic risk group had the highest prevalence of diabetic peripheral neuropathy, emphasizing the need for early identification and intervention to prevent other complications.

The 2023 American Heart Association (AHA) introduced the concept of Cardiovascular-Kidney-Metabolic (CKM) syndrome, describing a systemic condition resulting from interactions among obesity, diabetes, chronic kidney disease, and CVD. This framework highlights the close relationship between cardiovascular, renal, and metabolic diseases and emphasizes comprehensive management through weight reduction, blood pressure control, lipid modification, and glycemic control. High-risk CKM patients should be screened for T2DM and MAFLD every 1-2 years. Our findings similarly demonstrate that T2DM patients with concurrent high CVD and liver fibrosis risk have poorer metabolic control and higher complication rates. While fatty liver disease is currently screened as an important risk factor in CKM management, whether the liver should be considered a primary target organ alongside the heart and kidneys in metabolic diseases warrants further investigation. Future early screening and intervention strategies for T2DM may need to conceptualize cardiovascular-liver-renal health as an integrated CKM entity, enabling multidisciplinary, comprehensive prevention and management strategies for more effective chronic disease control.

Summary and Outlook

This retrospective analysis demonstrates that T2DM patients are at high risk for both liver fibrosis and CVD, with 13.3% having intermediate or high liver fibrosis risk and 77.6% having intermediate or high CVD risk. Advanced age, poor glycemic control, multiple diabetic complications, abnormal liver enzymes, increased hepatic lipid deposition, and decreased muscle mass collectively elevate CVD and liver fibrosis risk. Using guideline-recommended sequential screening, we identified early metabolic liver disease-induced fibrosis in diabetic patients and, for the first time, stratified patients by combined CVD and liver fibrosis risk to characterize different risk profiles, providing prognostic information for future CVD and cirrhosis risk.

Study limitations include the single-center, hospitalized patient cohort, which

may introduce selection bias, and the cross-sectional design lacking cardiovascular endpoint events such as cardiovascular death or sudden cardiac death. Future studies should incorporate more comprehensive clinical outcome measures to reflect long-term prognosis. Additionally, the 2023 AHA's CKM syndrome concept emphasizes the interconnectedness of metabolic diseases, suggesting that future T2DM management may require integrated cardiovascular-liver-renal assessment and multidisciplinary prevention strategies.

Author Contributions: NIE Yuanyuan collected, organized, and analyzed clinical data and drafted the manuscript; FANG Da created figures and assisted with statistical analysis; XU Hao assisted with manuscript revision; YANG Donghui performed FibroTouch examinations; BI Yan reviewed and edited the manuscript; GU Tianwei conceived the study, designed the research protocol, finalized the manuscript content, and takes responsibility for the work.

Conflict of Interest: The authors declare no conflict of interest.

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