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Original Article

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Association between low-normal thyroid function and advanced liver fibrosis in metabolic dysfunction-associated fatty liver disease patients: a retrospective cohort study

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Abstract

Background: Recent studies have found that thyroid function may be associated with the occurrence and development of advanced liver fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD). However, the majority of such research has consisted of cross-sectional studies. This retrospective cohort study aimed to investigate the effect of low-normal thyroid function on advanced liver fibrosis in MAFLD patients over a 5-year period.

Methods: This retrospective cohort study enrolled 825 outpatients and inpatients with MAFLD who attended the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between January 2011 and December 2018. Based on plasma thyroid hormone and thyroid-stimulating hormone levels, these patients were divided into two groups, namely a low-normal thyroid function group and a strict-normal thyroid function group. The fibrosis-4 score was used to assess advanced liver fibrosis. A chi-square test was conducted to compare the occurrence of advanced fibrosis between the groups.

Results: Among the 825 MAFLD patients, 117 and 708 were defined as having low-normal thyroid function and strict-normal thyroid function, respectively. Follow-up data were available for 767 patients (93.0%) during a 5-year period. Eight (7.5%) MAFLD patients with low-normal thyroid function and 26 (3.9%) with strict-normal thyroid function developed advanced liver fibrosis and the cumulative incidence was not significantly different ($P = 0.163$). Stratification analysis showed that the lean MAFLD patients (body mass index $\leq 23\,kg/m^2$) with low-normal thyroid function had a higher risk of advanced liver fibrosis than the lean MAFLD patients with strict-normal thyroid function ($P < 0.05$).

Conclusion: Low-normal thyroid function is associated with advanced liver fibrosis among lean MAFLD patients.

Keywords: fatty liver; hepatic fibrosis; liver metabolism; thyroid function

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a common chronic liver disease. In MAFLD, fat accumulates in the liver (known as hepatic steatosis) in association with one or more of the following conditions: being overweight/obese, having type 2 diabetes mellitus, and showing evidence of metabolic dysregulation [1]. In contrast with the formerly diagnosed non-alcoholic fatty liver disease, MAFLD does not exclude a fatty liver resulting from alcohol intake and focuses on the homogeneity of patients with hepatic steatosis due to various causes.

As a newly proposed terminology, there are few reliable data about the prevalence of MAFLD. A meta-analysis showed that the pooled prevalence of MAFLD was 39.22% at a global scale [2]. The serious long-term complications of MAFLD are liver fibrosis and cirrhosis. Liver fibrosis is considered an inevitable early histopathological stage that may develop into more severe and irreversible stages, such as cirrhosis and hepatocellular carcinoma [3]. Patients who met the criteria for MAFLD were more likely to have advanced fibrosis [4, 5]. There is thus an urgent need to investigate the factors that contribute to the progression of MAFLD into advanced fibrosis.

Thyroid hormones and thyroid-stimulating hormone (TSH) are critical hormones in the human body that regulate a wide array of biological functions, including metabolism and development [6]. The metabolism of carbohydrates and cholesterol may be affected directly or indirectly by thyroid function, leading to

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further MAFLD progression. Some clinical studies have suggested that thyroid function may affect MAFLD progression to advanced liver fibrosis negatively [7–9]. In addition, clinical observations have revealed that even low-normal thyroid function may negatively affect health, similarly to the case of overt hypothyroidism and subclinical hypothyroidism [10–12]. However, the majority of recent studies have been cross-sectional studies that were unable to determine the causal association between low-normal thyroid function and long-term MAFLD progression. Therefore, the present study aimed to investigate the association between low-normal thyroid function and advanced liver fibrosis in MAFLD patients in a 5-year follow-up study.

Methods

Study population

This was a retrospective cohort study using patient electronic medical records. Files of adult outpatients and inpatients with MAFLD treated in the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between January 2011 and December 2018 were reviewed. The inclusion criteria of MAFLD diagnosis referred to an international expert consensus statement published in 2020 [1]. The inclusion criteria were hepatic steatosis of ≥5% of hepatocytes detected by using either imaging techniques or liver histology in addition to one of three criteria, namely being overweight/obese, having type 2 diabetes mellitus, or having at least two of the following metabolic risk abnormalities: (i) waist circumference of ≥90 cm in males and ≥80 cm in females; (ii) systolic blood pressure of ≥130 mmHg and diastolic blood pressure of ≥85 mmHg or diagnosed hypertension; (iii) triglyceride level of ≥150 mg/dL (≥1.70 mmol/L); (iv) high-density lipoprotein cholesterol of <40 mg/dL (<1.0 mmol/L) for males and <50 mg/dL (<1.3 mmol/L) for females; (v) prediabetes (fasting blood glucose level of 5.6–6.9 mmol/L, or 2-hour glucose levels of 7.8–11.0 mmol/L or glycated hemoglobin level of 5.7%–6.4%); (vi) homeostasis model assessment of insulin resistance score (HOMA-IR) of ≥2.5; and (vii) C-reactive protein level of >2 mg/L. As fasting serum insulin was not measured for the majority of the patients, HOMA-IR was not considered as a criterion for metabolic dysfunction in the present study.

A total of 1,243 adult MAFLD patients with complete baseline records were enrolled. Patients with baseline liver-related adverse events ($n = 6$) and Child–Pugh B or C ($n = 16$) were excluded. Liver-related adverse events included hepatic fibrosis/cirrhosis, ascites, gastroesophageal varices/bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, liver transplantation, hepatocellular cancer, hepatopulmonary syndrome, and liver failure. To avoid the direct effects of drugs on the results of thyroid function tests, patients receiving thyroid medications at baseline were excluded ($n = 105$). Thyroid function medications included methimazole tablets, propylthiouracil tablets, propranolol hydrochloride tablets, metoprolol tartrate tablets, and levothyroxine sodium tablets. Patients who were pregnant at baseline were also excluded ($n = 2$). As the present study focused on the effects of low-normal thyroid function compared with strict-normal function, patients with thyroid function outside the reference range (0.4–4.5 μIU/mL for TSH, 2.43–6.01 pmol/L for FT_3, and 9.01–19.05 pmol/L for FT_4) ($n = 289$) were excluded. Ultimately, a total of 825 MAFLD patients were included in the study. The 825 patients were divided into a low-normal thyroid function group and a strict-normal thyroid function group according to the results of thyroid function tests at baseline, namely free thyroxine, free triiodothyronine, and TSH plasma levels.

The study was conducted in strict accordance with the Declaration of Helsinki, approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, and registered under permit number [2019] 02–600-01. Informed consent was waived by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University due to the retrospective nature of the study.

Data collection

Clinical information compiled from electronic medical records was used to assess the associations between low-normal thyroid function and advanced liver fibrosis. Data on demographic characteristics and clinical examination were collected at baseline. Clinical examination results were collected at inpatient or outpatient visits annually after enrollment as follow-up data. Among the patients with more than one examination during the follow-up year, only the result closest to the time of imaging examination or the first result in the year was collected and analysed.

Outcome and factors

The primary outcome in this study was advanced liver fibrosis, defined as the high probability of advanced fibrosis according to the fibrosis-4 (FIB-4) score. The FIB-4 score was calculated according to the values of age, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) using the published formula: FIB-4 score = (age [years] × AST [U/L])/(platelets [10^9/L] × ALT [U/L]$^{1/2}$) [13]. In this study, we defined advanced fibrosis as a FIB-4 score of >3.25, referring to the related literature [14].

Low-normal thyroid function was defined as a TSH level of 2.5–4.5 μIU/mL and euthyroid FT_3 and FT_4 levels (2.43–6.01 pmol/L for FT_3 and 9.01–19.05 pmol/L for FT_4). Strict-normal thyroid function was defined as a TSH level of 0.4–2.5 μIU/mL and euthyroid FT_3 and FT_4 levels [10].

The body mass index (BMI) was calculated as body weight (kg)/body height^2 (m^2). Heavy drinking was defined as ethanol consumption of >280 g/week for males and >140 g/week for females. As all patients were Chinese (Asian), the Asian-specific BMI criteria were adopted for further stratified analyses. Metabolic syndrome was defined according to published criteria [15].

Statistical analysis

Continuous variables conforming to a normal distribution are expressed as the mean ± standard deviation, whereas non-normally distributed continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are expressed as counts and percentages. The normally distributed variables were compared using Student's *t*-test, whereas the non-normally distributed variables were compared using the Kruskal–Wallis test. Categorical variables, such as the number of cases and proportions were analysed using the chi-square test. Log-rank tests were used to compare the Kaplan–Meier curves between groups. All statistical analyses were performed using R software (version 4.1.0), with *P*-values of <0.05 considered statistically significant.

Results

Patient characteristics at baseline

Among the 825 MAFLD patients, 117 had low-normal thyroid function and 708 had strict-normal thyroid function. A total of 461 (55.9%) were male and the median age was 55.0 years. In the low-normal group, the ALT and AST levels were higher, the proportion of men was lower, and the proportion of patients with metabolic syndrome was higher than those in the strict-normal

Table 1. Baseline characteristics of the MAFLD patients based on thyroid function

Characteristic	Total ($N = 825$)	Strict-normal thyroid function group ($n = 708$)	Low-normal thyroid function group ($n = 117$)	*P*-value
Age, years, median (IQR)	55.0 (44.0, 64.0)	55.0 (45.0, 64.0)	54.0 (42.0, 65.0)	0.408
Male, *n* (%)	461 (55.9)	409 (57.8)	52 (44.4)	**0.010**
BMI, kg/m^2, median (IQR)	25.7 (23.8, 28.0)	25.7 (23.8, 27.9)	26.0 (23.7, 28.5)	0.306
T2DM, *n* (%)	467 (56.6)	410 (57.9)	57 (48.7)	0.079
Hypertension, *n* (%)	474 (57.5)	399 (56.4)	75 (64.1)	0.142
Heavy drinking, *n* (%)	30 (3.6)	29 (4.1)	1 (0.9)	0.142
CHB, *n* (%)	51 (6.2)	43 (6.1)	8 (6.8)	0.912
MetS, *n* (%)	610 (74.0)	514 (72.6)	96 (82.1)	**0.041**
CHOL, mg/dL, median (IQR)	4.9 (4.1, 5.7)	4.9 (4.1, 5.7)	4.9 (2.1, 5.7)	0.943
HDL-C, mg/dL, median (IQR)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	0.570
TG, mg/dL, median (IQR)	1.6 (1.2, 2.4)	1.6 (1.2, 2.4)	1.7 (1.3, 2.5)	0.285
LDL-C, mg/dL, median (IQR)	3.1 (2.4, 3.7)	3.1 (2.4, 3.7)	3.2 (2.3, 3.9)	0.607
ALT, U/L, median (IQR)	24 (17, 36)	23.0 (17, 35)	27.0 (18, 41)	**0.029**
AST, U/L, median (IQR)	20 (17, 27)	20.0 (17, 26)	23.0 (18, 31)	**<0.001**
Platelet,10^9/L, median (IQR)	234 (192, 275)	233.5 (191, 274)	238 (198, 282)	0.381
TBIL, μmol/L, median (IQR)	10.2 (7.4, 13.2)	10.4 (7.4, 13.4)	9.5 (7.6, 11.9)	0.122
FT3, pmol/L, median (IQR)	4.5 (4.0, 4.9)	4.5 (4.0, 4.9)	4.5 (3.8, 5.0)	0.323
FT4, pmol/L, median (IQR)	14.9 (13.1, 16.7)	14.9 (13.1, 16.7)	15.2 (12.9, 16.7)	0.650
TSH, μIU/mL, median (IQR)	1.5 (1.0, 2.1)	1.3 (1.0, 1.8)	3.1 (2.8, 3.6)	**<0.001**

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CHB = chronic hepatitis B, CHOL = total cholesterol, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, MAFLD = metabolic dysfunction-associated fatty liver disease, MetS = metabolic syndrome, T2DM = type 2 diabetes mellitus, TBIL = total bilirubin, TG = triglyceride, TSH = thyroid-stimulating hormone.

Table 2. Cumulative incidence of advanced fibrosis in the MAFLD patients

Group	1-year			3-year			5-year		
	Advanced fibrosis (FIB-4 > 3.25)	Non-advanced fibrosis (FIB-4 ≤ 3.25)	*P*	Advanced fibrosis (FIB-4 > 3.25)	Non-advanced fibrosis (FIB-4 ≤ 3.25)	*P*	Advanced fibrosis (FIB-4 > 3.25)	Non-advanced fibrosis (FIB-4 ≤ 3.25)	*P*
Total, *n* (%)	8 (1.0)	759 (99.0)		30 (3.9)	737 (96.1)		34 (4.4)	733 (95.6)	
Strict-normal, *n* (%)	6 (0.9)	654 (99.1)	0.694	22 (3.3)	638 (96.7)	0.075	26 (3.9)	634 (96.1)	0.163
Low-normal, *n* (%)	2 (1.9)	105 (98.1)		8 (7.5)	99 (92.5)		8 (7.5)	99 (92.5)	

FIB-4 = the fibrosis-4 score, MAFLD = metabolic dysfunction-associated fatty liver disease.

group ($P < 0.05$). Other characteristics were similar between the two groups ($P > 0.05$). Further details are shown in Table 1.

Liver fibrosis incidence during the 5-year follow-up

Follow-up data were available for 767 (93.0%) of the MAFLD patients during the 5-year follow-up period. Among these MAFLD patients, 8 (1.0%) developed advanced fibrosis within 1 year of follow-up, 30 (3.9%) developed advanced fibrosis within 3 years of follow-up, and 34 (4.4%) developed advanced fibrosis within 5 years of follow-up. The cumulative incidence of advanced fibrosis within 5 years was 7.5% for MAFLD patients with low-normal thyroid function and 3.9% for those with strict-normal thyroid function. The low-normal thyroid function group had a higher cumulative incidence of advanced fibrosis within 1, 3, and 5 years than the strict-normal thyroid function group, but this difference was not significant (Table 2). Kaplan–Meier curves of survival in patients with no advanced liver fibrosis are presented in Figure 1.

Stratified analyses were performed by sex, age (<65 years vs ≥65 years) and BMI (<23 kg/m^2 vs >23 kg/m^2). The cumulative incidence of advanced fibrosis in each subgroup and the results of the chi-square tests are presented in Table 3. Kaplan–Meier curves and the log-rank test results are presented in Figure 2. Among the MAFLD patients with a BMI of <23 kg/m^2, the low-normal thyroid function group had a significantly higher cumulative incidence of advanced liver fibrosis than the strict-normal thyroid function group within 3 years ($P = 0.048$) and 5 years ($P = 0.048$).

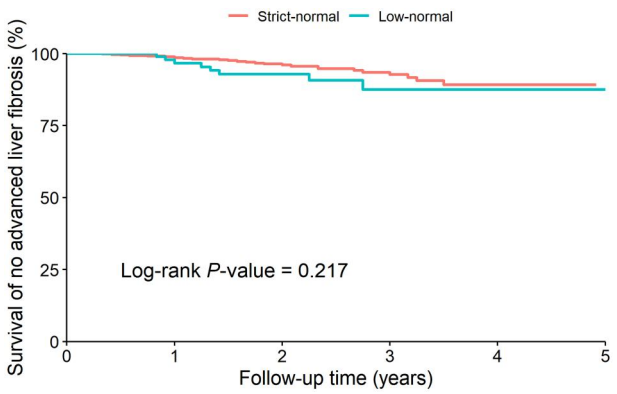

Figure 1. Kaplan–Meier curves between groups. The Kaplan–Meier curves show no significant difference in the survival of no advanced fibrosis between MAFLD patients with low-normal thyroid function and those with strict-normal thyroid function.

Discussion

Previous studies have examined the relationship between thyroid function and fatty liver disease [7, 8]. In a cross-sectional study

Table 3. Cumulative incidence of advanced fibrosis in the MAFLD patients with different characteristics

Factor	1-year			3-year			5-year		
	Advanced fibrosis (FIB-4 > 3.25)	Non-advanced fibrosis (FIB-4 ≤ 3.25)	P	Advanced fibrosis (FIB-4 > 3.25)	Non-advanced fibrosis (FIB-4 ≤ 3.25)	P	Advanced fibrosis (FIB-4 > 3.25)	Non-advanced fibrosis (FIB-4 ≤ 3.25)	P
BMI < 23 kg/m^2, *n* (%)									
Strict-normal	1 (0.9)	115 (99.1)	0.654	6 (5.2)	110 (94.8)	**0.048**	6 (5.2)	110 (94.8)	**0.048**
Low-normal	1 (5.3)	18 (94.7)		4 (21.1)	15 (78.9)		4 (21.1)	15 (78.9)	
BMI ≥ 23 kg/m^2, *n* (%)									
Strict-normal	5 (0.9)	539 (99.1)	1.000	16 (2.9)	528 (97.1)	0.639	20 (3.7)	524 (96.3)	0.924
Low-normal	1 (1.1)	87 (98.9)		4 (4.6)	84 (94.4)		4 (4.6)	84 (95.4)	
Male, *n* (%)									
Strict-normal	2 (0.5)	373 (99.5)	0.087	10 (2.7)	365 (97.3)	0.086	12 (3.2)	363 (96.8)	0.154
Low-normal	2 (4.4)	44 (95.6)		4 (8.7)	42 (91.3)		4 (8.7)	42 (91.3)	
Female, *n* (%)									
Strict-normal	4 (1.4)	281 (98.6)	0.787	12 (4.2)	273 (95.8)	0.648	14 (4.9)	271 (95.1)	0.836
Low-normal	0 (0.0)	61 (100.0)		4 (6.6)	57 (93.4)		4 (6.6)	57 (93.4)	
Age < 65 years, *n* (%)									
Strict-normal	3 (0.6)	489 (99.4)	0.280	11 (2.2)	481 (97.8)	0.083	12 (2.4)	480 (97.6)	0.113
Low-normal	2 (2.6)	75 (97.4)		5 (6.5)	72 (93.5)		5 (6.5)	72 (93.5)	
Age ≥ 65 years, *n* (%)									
Strict-normal	3 (1.8)	165 (98.2)	1.000	11 (6.5)	157 (93.5)	0.770	14 (8.3)	154 (91.7)	1.000
Low-normal	0 (0.0)	30 (100.0)		3 (10.0)	27 (90.0)		3 (10.0)	27 (90.0)	

conducted in the USA, Kim *et al.* [16] found that low-normal thyroid function was associated with advanced liver fibrosis in adults. A similar population-based study in Spain also found a link between low-normal thyroid function and advanced liver fibrosis [17]. Moreover, a meta-analysis showed that only patients with overt hypothyroidism or subclinical hypothyroidism had a significantly positive association with liver fibrosis risk [18]. Our 5-year longitudinal study showed that patients with low-normal thyroid function had a higher risk of advanced liver fibrosis than the patients with strict-normal thyroid function among the MAFLD patients with a BMI of <23 kg/m^2.

The gold standard in fibrosis diagnosis is liver biopsy, which is invasive and inappropriate as a screening tool for mild patients. Several non-invasive methods have been developed to identify individuals at high risk of liver fibrosis [19, 20]. Among them, the FIB-4 score is objectively based on biochemical indicators, namely alanine aminotransferase (ALT), aspartate aminotransferase (AST), age, and platelets. Studies have shown FIB-4 to be an accurate, simple, and cost-effective method of assessing advanced liver fibrosis [21]. This study thus used the FIB-4 score to investigate the progression of MAFLD and risk factors for advanced fibrosis in MAFLD patients during their 5-year follow-up.

The underlying mechanism linking low-normal thyroid function to an elevated risk of advanced liver fibrosis in MAFLD patients is elucidated as follows. TSH plays a crucial role in regulating lipid metabolism, including hepatic lipogenesis [6]. Higher levels of TSH may upregulate the 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (*HMGCR*) expression and the activity of HMGCR, which may promote the uptake of fatty acids in hepatocytes and cholesterol biosynthesis in the liver [22, 23]. In addition, TSH activates SREBP1c, which may increase lipogenesis in hepatocytes via the cAMP/PKA/PPARα signaling pathway, which is associated with adenosine monophosphate activated kinase protein (AMPK) in hepatic cells [24]. The above pathways amplify endoplasmic reticulum stress, oxidative stress, and inflammasome activation in the liver, which might activate hepatic stellate cells. Activated hepatic stellate cells can transform into myofibroblasts [25] and produce extracellular matrix, which directly leads to hepatic fibrosis [26–30].

In this study, the increased risk of advanced liver fibrosis due to low-normal thyroid function was not significant in all of the MAFLD patients, but rather only in lean MAFLD patients. The possible mechanisms are as follows. First, fat accumulation in lean MAFLD patients can progress to a state of inflammation accompanied by tissue damage. This contributes to the formation of specific lipotoxic lipids that promote cell injury and lead to severe stress responses and inflammatory reactions in the viscera including the liver. Thus, promoting hepatic stellate cell activation and fibrogenesis are activated [31–33]. Second, previous study has also suggested that patients with different BMIs have different genetic susceptibilities and alterations in gut microbiota, which may contribute to the different effects of existing low-normal thyroid function on MAFLD progression [34]. Further studies are needed to explore the mechanisms underlying the associations between low thyroid function and the risk of advanced fibrosis among MAFLD patients with different BMIs.

The findings of this study may help clinicians to assess the progression risk in lean MAFLD patients. The present study also used the definitions of low-normal thyroid function and strict-normal thyroid function aiming to classify patients with different characteristics. We aimed to help clinicians identify early inapparent changes in thyroid function to predict fibrosis progression in MAFLD patients.

The present study has some limitations. First, as the study was retrospective and based on clinical records, our data collection was limited in terms of knowing the patients' lifestyles and detailed medication use. Second, the present study was based on real-world clinical data from different departments, which may have included unrecorded confounding factors. Third, thyroid antibodies, anti-thyroid peroxidase, and anti-thyroglobulin antibodies were not measured, so the effect of thyroid autoimmunity on the association between thyroid function and the progression of MAFLD was uncertain. Fourth, MAFLD patients who were receiving thyroid medications at baseline were excluded from the study, as the degree and direction of the effect of thyroid medications on the levels of thyroid hormones and TSH are complex and mostly undetermined. Therefore, the outcomes of those patients were not followed up and the exact effect of thyroid medications was not assessed. Finally, owing to the small sample

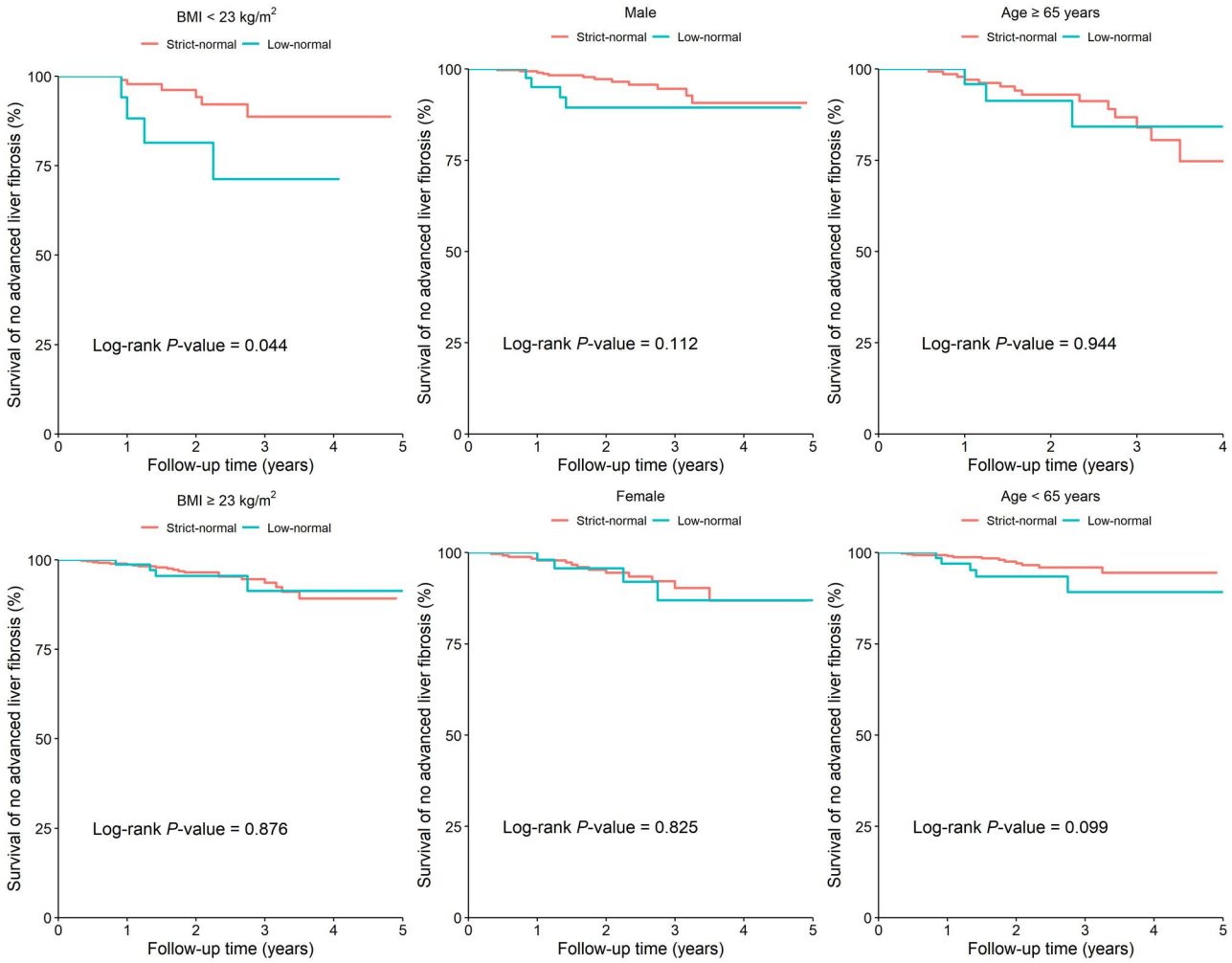

Figure 2. Kaplan–Meier curves at different stratifications. Statistically significant difference is shown between patients with low-normal thyroid function and those with strict-normal thyroid function among MAFLD patients with different BMIs. No significant difference between the two groups regarding sex stratifications and age stratifications. The Kaplan–Meier curves were plotted based on the actual and the longest follow-up time of each patient.

size, more nuanced stratified analyses were not possible, resulting in the imprecise estimation of effect sizes and the less accurate characterization of rapid progressors.

Conclusions

The progression of MAFLD in lean patients may be affected by early inapparent changes in thyroid function. Therefore, it is recommended that clinicians should pay more attention to the thyroid function in lean MAFLD patients. Our findings may help clinicians to identify MAFLD patients with specific characteristics who may progress rapidly and require more targeted and personalized interventions.

Authors' Contributions

Z.L. and X.W. conceived, designed, and realized the study, performed statistical analyses of the data, and drafted the manuscript. Z.C., X.W., and W.C. provided useful input for the analyses and helped to edit the manuscript. All authors have read and approved the final version of the manuscript. Z.L. and X.W. contributed equally to this article.

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Conflict of Interest

None declared.

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