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Prevalence and risk factors of metabolic fatty liver disease during 2014-2018 from three cities of Liaoning province

Running title: Prevalence of MAFLD in Liaoning, China

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ABSTRACT

Objectives: To investigate the incidence and disease characteristics of metabolic fatty liver disease (MAFLD) in physical examination populations in Liaoning (China).

Design: Retrospective study

Setting: Single center.

Participants: Adults who underwent routine health examination at Xikang Medical Center in Liaoning Province (Shenyang, Dandong, and Dalian) between 01/2014 and 12/2018.

Interventions: Not applicable.

Primary And Secondary Outcome Measures: Not applicable.

Results: Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28%. The total prevalence of MAFLD in Shenyang, Dandong, and Dalian in the past five years is 35.8%, 40.41%, and 31.7%, respectively. Men had a prevalence of 46.12%, which is higher than in women (21.80%). The percentage of MAFLD in BMI <23 and ≥23 kg/m^2 is 6.49 % and 53.23%, respectively. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all P<0.001). In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all P<0.001).

Conclusions: The prevalence of MAFLD in Liaoning is related to sex, cities with

different economic statuses, BMI, and multiple metabolic indicators.

Key words: metabolic fatty liver disease; prevalence; risk factors; body mass index; lean.

Strengths and limitations of this study

1. Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD.
2. Men had a prevalence of 46.12%, which is higher than in women (21.80%).
3. The prevalence of MAFLD in Liaoning is related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators.
4. This cross-sectional study cannot provide any causal relationship between MAFLD and the associated factors.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is defined as the presence of ≥5% of hepatic steatosis (HS) (1, 2). Recently, it was recommended to rename NAFLD as metabolic (dysfunction) associated fatty liver disease (MAFLD), which might increase the awareness of the disease and decrease its stigma (3, 4). NAFLD is associated with chronic diseases like insulin resistance and/or type 2 diabetes (T2DM), dyslipidemia, hypertriglyceridemia, and hypertension (5-8). The reported prevalence of MAFLD is reported to be 24%-45%, with an estimated prevalence of 76% in patients with T2DM (9). For non-obese patients, MAFLD is associated with elevated triglyceride (TG) levels, increased waist circumference, and insulin resistance (10).

Chinese individuals have substantially higher risks of MAFLD, even at much lower BMI levels, compared with the US population (11). Factors like waist circumference, T2DM, increased TG, low high - density lipoprotein (HDL)-cholesterol, and metabolic syndrome are known to be predictive factors for MAFLD in adults, and the metabolic syndrome is considered as a strong predictive factor (12, 13). MAFLD is also associated with dyslipidemia characterized by high TG, high low-density lipoprotein (LDL), and low HDL-cholesterol levels (14). Determining the risk factors associated with a worse prognosis is essential for improving the therapeutic strategies.

Since the 21st century, the prevalence of MAFLD in China has increased

significantly to reach about one in three mainland Chinese residents (12). A recent meta-analysis showed that the incidence of MAFLD is higher in northern China (35.78%) and lower in northwestern China (21.52%) (15). Among the provinces in northern China, Heilongjiang has the highest incidence, with up to 50.48% (15). Nevertheless, the results might be biased due to the small number of studies, yet MAFLD incidence in northern China is significantly higher than that in the southern provinces. In addition, the risk of MAFLD-related mortality has also increased significantly, mainly due to diseases associated with liver fibrosis (16). MAFLD has become an important health issue affecting the Chinese population, increasing the socioeconomic burden (11, 12, 15). Therefore, Chinese medical professionals and stakeholders urgently need to carry out early scientific prevention and control of MAFLD. Multiple studies have shown that MAFLD is a heterogeneous entity and that its development is related to sex, age, race, mild-to-moderate alcohol consumption, dietary intake, lifestyle, obesity, metabolism, genetic variation, and education (11, 12, 15, 16). With uneven economic development and diverse lifestyles among the different provinces, the epidemiology of MAFLD in China has marked regional differences. By understanding the epidemiology of MAFLD in Liaoning Province, we can conduct targeted education and clinical research for precise prevention and control of MAFLD.

There have been no data from large-scale epidemiological investigations of MAFLD in Liaoning province in northern China in the past ten years. Therefore, this

retrospective study aims to investigate the incidence and disease characteristics of MAFLD in physical examination populations in Liaoning. The study uses physical examination data of residents collected from 2014 to 2018 in three cities with different economic levels in Liaoning (Shenyang, Dandong, and Dalian).

METHODS

Study subjects

This is a retrospective study of adults who underwent routine health examination at Xikang Medical Center in Liaoning Province (which has clinics in Shenyang, Dandong, and Dalian) between January 2014 and December 2018. The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital of China Medical University ([2020]2020-257-2). The ethics committee waived the requirement for informed consent because of the retrospective nature of the study.

The three cities are from different parts of the province (North, South, and East (Figure 1), and they have different economic levels. Shenyang, situated in North Liaoning Province, is a highly developed inland city, while Dalian in South Liaoning is a developed coastal city. Dandong, in the east of Liaoning Province, is a poorly developed city bordering North Korea.

The inclusion criteria are 1) >18 years of age; 2) have been living in Shenyang, Dalian, or Dandong for at least 5 years; 3) participate in the annual physical

examination; and 4) no missing data (as listed in Table 1). The exclusion criteria are 1) liver cirrhosis; 2) liver cancer; 3) any liver ultrasound lesions; or 4) no ultrasound examination. For individuals with more than one examination during the study period, only the first examination is included in this study.

The selected patients are divided into the MAFLD group and the non-MAFLD group based on ultrasound features (17). All study subjects are classified as lean (BMI <23 kg/m^2) or overweight-obese (BMI ≥23 kg/m^2), according to the standards recommended by the World Health Organization for Asians (18).

Physical examination

All physical examinations included in this study are part of the routine examination. Blood pressure measurements, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), are taken twice after the participants have been sitting, in a calm state, for at least 5 min, using an electronic sphygmomanometer (HEM-7200, OMRON Healthcare, Kyoto, Japan). Height and weight are measured in the morning on an empty stomach, and body mass index (BMI) is as kg/m^2.

Laboratory examination

All physical blood tests included in this study are part of the routine examination. Anterior cubital vein blood is drawn in the fasting state (at least 8 h). A midcourse morning urine specimen is also taken. Routine blood panel, liver function, kidney

function, serum uric acid (SUA), fasting blood glucose (FBG), blood lipids, and routine urine analysis are assessed using a 7600 autoanalyzer (Hitachi, Tokyo, Japan).

Color Doppler ultrasound of the liver and gallbladder

A liver ultrasound is part of the routine examination. It is performed by two experienced ultrasound radiologists with at least 5 years of experience and using an IU 22 system (Philips, Best, The Netherlands). An individual is diagnosed with MAFLD when the ultrasound examination shows that the liver has fatty liver changes (hyperechogenicity due to increased acoustic interface caused by the intracellular accumulation of lipid vesicles, blurring of vascular margins, increased liver size, and increased acoustic attenuation (10, 17)) and after excluding other causes of liver fatty disease (such as excessive alcohol consumption) (17).

Statistical analysis

R 3.5.3 and R Commander 2.5-3 were used for statistical analysis. The categorical data are expressed as n (%) and were analyzed using the chi-square test. The continuous variables conforming to the normal distribution (according to the Kolmogorov-Smirnov test) are expressed as means ± standard deviations and were analyzed using Student's t-test. Non-normally distributed continuous variables are presented as medians (interquartile range (IQR)) and were analyzed using the Mann-Whitney U-test. The factors associated with MAFLD were identified using

univariable analyses. Variables with P-values <0.05 were included in a multivariable logistic regression model. P-values <0.05 were considered statistically significant.

RESULTS

Characteristics of the subjects

A total of 284,129 subjects were examined during the study period, and 204,394 met the inclusion criteria. Table 1 presents the characteristics of the subjects. The mean age is 39.6±13.6 years. The numbers of men and women are 111,782 and 92,612, respectively. The mean age of the men is 38.8±13.7 years, and that of women is 40.5±13.3 years. Shenyang includes 78,329 subjects, who were 39.3±12.7 years of age. The clinic in Dandong did not perform routine health examinations in 2014. Dandong includes 42,039 subjects, who were 47.8±14.1 years. Finally, Dalian has 84,026 subjects; they were 36.3±12.7 years.

MAFLD in the healthy population

Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28% (Table 1). The prevalence of MAFLD increases with the age groups (P<0.001), is higher in males than in females (P<0.001), is higher in overweight/obese subjects than in lean ones (P<0.001), and is higher in Dandong, followed by Shenyang and Dalian (P<0.001) (Table 1). The prevalence of MAFLD in Shenyang, Dandong, and Dalian in the past five years was 36.83%, 40.42%, and

31.78%, respectively.

MAFLD over time

The total prevalence of MAFLD from 2014 to 2018 is 30.01%, 30.11%, 33.22%, 34.58%, and 32.19%, respectively. The prevalence of MALFD over the 5 years mainly increased in the 30-39 groups (P=0.006), and both in males (P=0.029) and in females (P=0.035) (Table 2). The prevalence of MAFLD in Shenyang in the past 5 years was basically consistent with the general trend in Liaoning. The MAFLD prevalence in Dandong showed a significant increase annually in the past 4 years. The MAFLD prevalence in Dalian increased substantially in 2016, but it declined annually in 2017 and 2018 (Figure 2). The prevalence rate in men and women in the past five years is basically consistent with the general trend of MAFLD in Liaoning (Figure 3). As age increases, MAFLD prevalence in Liaoning increases.

Biomarkers and MAFLD

Table 3 presents the biomarkers in all subjects and according to lean/overweight-obese. Compared with the non-MAFLD group, the subjects with MAFLD have higher SBP, DBP, FBG, TG, TC, LDL-C, ALT, AST, ALP, GGT, BUN, Scr, and SUA, higher frequencies of UPRO and GBp, lower HDL-C, HCT, and MCV, and lower frequency of UOB (all P<0.001). The same tendencies are observed in lean subjects, except that there is no difference in UPRO (P=0.86).

Factors associated with MAFLD

Table 4 presents the univariable and multivariable analyses of the factors associated with MAFLD. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all P<0.001), while UOB (P=0.47) and GBp (P=0.21) are not. In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all P<0.001), while SBP (P=0.51), ALT (P=0.27), BUN (P=0.16), UPRO (P=0.57), UOB (P=0.06), and GBp (P=0.06) are not.

DISCUSSION

The present study shows that the prevalence of MAFLD in Shenyang, Dandong, and Dalian varied and that higher BMI and age play significant roles in the development of the disease. In addition, biomarkers like DBP, FBG, TG, LDL-C, ALT, GGT, BUN, SUA, HCT, UPRO, GBs, and GBp are independently and positively correlated with the prevalence of MAFLD, whereas HDL-C and MCV are negatively correlated. Therefore, the prevalence of MAFLD in Liaoning is related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators.

The increasing trend in the prevalence of MAFLD follows the level of industrialization and urbanization. At present, China is the fastest-growing major

economy in the world and displays the problems associated with a westernized diet, sedentary lifestyle, and population aging, which are associated with MAFLD. Studies have shown that the increase in the total annual MAFLD prevalence in China is consistent with the improvement in the per capita GDP (19). An increase in morbidity in various regions of mainland China is related to the increase in per capita GDP, but the area with the highest per capita GDP (≥$13,000) does not exhibit an increased incidence of MAFLD (20). According to the National Bureau of Statistics of China, the per capita GDP of Liaoning Province has been ranking first in Northeast China in the past five years, but it is still in the lower-middle level nationally. This study shows that the prevalence of MAFLD in Liaoning (35.1%) is slightly higher than the overall prevalence of MAFLD in China (29.2%) (12). This study selected two economically developed cites (Dalian and Shenyang) and one city with moderate development (Dandong). The prevalence of MAFLD in these three cities is inversely proportional to the level of urban economic development. The prevalence of MAFLD in Dalian is lower than that in Shenyang. A reason might be that Dalian is a coastal city, with dietary habits different from that of inland cities.

Differences in age are also involved. The prevalence of MAFLD in the 20-29 years group is 17.9%, while the prevalence in the >60 years group is 45.6%, which is in alignment with previous studies that show that age plays a crucial factor in MAFLD (11, 12, 15).

This study found that the overall prevalence of MAFLD in men is higher than

that in women, which is basically consistent with the findings in other regions in China (21). The prevalence of MAFLD in middle-aged men is highest and peaks at 40-49 years of age (50.27%). This high prevalence might be related to high stress, irregular work and rest, and decreased metabolism among middle-aged men. The prevalence of MAFLD in women over 50 years of age is significantly higher, which relates to the age range of menopause.

Obesity is closely related to metabolic-related diseases such as MAFLD. This study confirmed that BMI ≥23 kg/m^2 is an independent risk factor for MAFLD in Liaoning. Therefore, for overweight and obese people, it is necessary to improve diet and exercise management, even with the help of drugs or surgery if needed. It has been reported that the global prevalence of lean-MAFLD is 5%-26% (22). In the study, the prevalence of lean-MAFLD is 10.75%, which is similar to previous results (23).

In this study, both lean-MAFLD and non-lean-MAFLD were closely related to metabolic indicators. Those metabolic indicators are also associated with T2DM, metabolic syndrome, obesity, and liver diseases, as supported by previous studies (11, 12, 15, 21-23). In addition to obesity, the variation in the prevalence of MAFLD follows the epidemic trends of T2DM and MetS. The prevalence of MAFLD in hyperlipidemia and T2DM patients is higher, reaching 27%-92% and 28%-70%, respectively. Patients with MAFLD also often have hyperlipidemia, hypertension, T2DM, and metabolic syndrome (24). In this study, logistic regression analysis found

that DBP, TG, LDL-C, FBG, and SUA were independent risk factors for MAFLD, but HDL-C is independently associated with MAFLD. Therefore, paying attention to hyperlipidemia, hypertension, and T2DM should have important effects on the prevention and treatment of MAFLD. Regarding the correlation between SUA and MAFLD, SUA elevation is one of the risk factors for MAFLD (25).

Although it was not examined in this study, genetic susceptibility is involved in MAFLD. Polymorphisms in PNPLA3 (26), SREBF-2 (27), CETP (27, 28), and APOC3 (29) have been found to be associated with lean-MAFLD. In addition to genetic polymorphisms, lean-MAFLD people have increased bile acid and FXR activity due to metabolic abnormalities and changes in intestinal microbial composition (30, 31). Those factors should be examined in future studies.

This study has limitations. Even if the examinations were performed at the same clinical company, they were performed at three different physical locations and over 5 years. Biases due to the different locations and changes in practice over time cannot be excluded. In addition, ultrasound is operator-dependent, and a bias in the diagnosis of MAFLD cannot be excluded. Finally, this was a cross-sectional study that cannot provide any causal relationship between MAFLD and the associated factors.

In conclusion, the prevalence of MAFLD in Liaoning is related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators. Longitudinal studies are necessary to determine the factors associated with the development of MAFLD.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical statement: The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital of China Medical University ([2020]2020-257-2). The ethics committee waived the requirement for informed consent because of the retrospective nature of the study.

Author contributions

(I) Conception and design: LG, XHZ, YLL

(II) Administrative support: JS, DL, YLL

(III) Provision of study materials or patients: LG, XJ, NNW

(IV) Collection and assembly of data: HYT, XW, ZLZ

(V) Data analysis and interpretation: HF, JL

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.

2. Stal P. Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge with prognostic significance. World J Gastroenterol. 2015;21:11077-87.

3. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020;158:1999-2014 e1.

4. Fouad Y, Waked I, Bollipo S, et al. What's in a name? Renaming 'NAFLD' to 'MAFLD'. Liver Int. 2020;40:1254-61.

5. Pai RK. NAFLD Histology: a Critical Review and Comparison of Scoring Systems. Curr Hepatol Rep. 2019;18:473-81.

6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274-85.

7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012;142:1592-609.

8. Non-Alcoholic Fatty Liver Disease: Assessment and Management. National

Institute for Health and Care Excellence: Guidance. London2016.

9. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313:2263-73.

10. Shen FF, Lu LG. Advances in noninvasive methods for diagnosing nonalcoholic fatty liver disease. J Dig Dis. 2016;17:565-71.

11. Zhou J, Zhou F, Wang W, et al. Epidemiological Features of NAFLD From 1999 to 2018 in China. Hepatology. 2020;71:1851-64.

12. Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis. Hepatology. 2019;70:1119-33.

13. Caballeria L, Auladell MA, Toran P, et al. Risk factors associated with non-alcoholic fatty liver disease in subjects from primary care units. A case-control study. BMC Gastroenterol. 2008;8:44.

14. Hartmann P, Schnabl B. Risk factors for progression of and treatment options for NAFLD in children. Clin Liver Dis (Hoboken). 2018;11:11-5.

15. Wu Y, Zheng Q, Zou B, et al. The epidemiology of NAFLD in Mainland China with analysis by adjusted gross regional domestic product: a meta-analysis. Hepatol Int. 2020;14:259-69.

16. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;65:1557-65.

17. Mahale AR, Prabhu SD, Nachiappan M, et al. Clinical relevance of reporting fatty liver on ultrasound in asymptomatic patients during routine health checkups. J Int Med Res. 2018;46:4447-54.

18. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157-63.

19. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of nonalcoholic fatty liver disease. Med Res Rev. 2019;39:328-48.

20. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol. 2017;67:862-73.

21. Zhu JZ, Zhou QY, Wang YM, et al. Prevalence of fatty liver disease and the economy in China: A systematic review. World J Gastroenterol. 2015;21:5695-706.

22. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. Clin Nutr. 2019;38:975-81.

23. Shi Y, Wang Q, Sun Y, et al. The Prevalence of Lean/Nonobese Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2020;54:378-87.

24. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis. 2019;20:163-73.

25. Ma Z, Xu C, Kang X, et al. Changing trajectories of serum uric acid and risk of non-alcoholic fatty liver disease: a prospective cohort study. J Transl Med. 2020;18:133.

26. Musso G, Cassader M, Bo S, et al. Sterol regulatory element-binding factor 2 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and lipoprotein and glucose dysmetabolism. Diabetes. 2013;62:1109-20.

27. Adams LA, Marsh JA, Ayonrinde OT, et al. Cholesteryl ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity. J Gastroenterol Hepatol. 2012;27:1520-7.

28. Petersen KF, Dufour S, Hariri A, et al. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N Engl J Med. 2010;362:1082-9.

29. Li C, Guo P, Okekunle AP, et al. Lean non-alcoholic fatty liver disease patients had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and overtime work as obese non-alcoholic fatty liver disease patients. J Gastroenterol Hepatol. 2019;34:256-62.

30. Safari Z, Gerard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cell Mol Life Sci. 2019;76:1541-58.

31. Suk KT, Kim DJ. Gut microbiota: novel therapeutic target for nonalcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol. 2019;13:193-204.

Table 1. Characteristics of the patients with non-MAFLD and MAFLD

Subgroups	Age (years), Mean±**SD**	All N=204,394	Non-MAFLD n=132,638	MAFLD n=71,756	Prevalence (%)	P
Age						<0.001
20-29		22,822	18,728	4094	17.94	
30-39		80,227	54,671	25,556	31.85	
40-49		44,464	27,913	16,551	37.22	
50-59		30,861	17,173	13,688	44.35	
≥60		26,020	14,153	11,867		
Sex						<0.001
Male	38.8±13.7	111,782	60,222	51,560	46.13	
Female	40.5±13.3	92,612	72,416	20,196	21.81	
BMI (kg/m^2)						<0.001
<23		79,271	74,124	5147	6.49	
≥23		125,123	58,514	66,609	53.23	
City						<0.0

					01
Shenyang	39.3±12.7	78,329	50,265	28,064	36.83
Dandong	47.8±14.1	42,039	25,048	16,991	40.42
Dalian	36.3±12.7	84,026	57,325	26,701	31.78
Overall	39.6±13.6	204,394	132,638	71,756	35.11

MAFLD: metabolic-associated fatty liver disease; BMI: body mass index.

Table 2. Changes in the prevalence of MAFLD over time (2014-2018)

Subgroups	Year, %					P
	2014	2015	2016	2017	2018	
Age (years)						
20-29	16.43	17.20	17.30	18.82	18.18	0.081
30-39	29.24	28.60	31.05	33.37	34.33	0.006
40-49	35.65	34.50	35.40	39.04	38.69	0.200
50-59	46.32	39.40	41.67	46.96	45.44	0.636
≥60	44.83	40.65	45.34	48.39	46.50	0.234
Sex						
Male	42.60	42.63	44.36	48.12	48.45	0.029
Female	14.85	19.33	21.49	24.63	22.67	0.035
BMI (kg/m^2)						
<23	5.08	5.35	6.68	7.36	6.80	0.058
≥23	54.93	50.37	52.15	55.08	53.76	0.510
City						
Shenyang	34.89	34.80	34.27	37.36	36.92	0.182
Dandong	-	30.06	34.29	42.66	44.17	0.039
Dalian	26.36	29.00	33.20	32.36	32.98	0.048
Overall	30.01	30.11	33.22	34.58	32.19	<0.001

BMI: body mass index.

Table 3. Comparison of the metabolic tests between non-MAFLD and MAFLD

Variables	Overall		P	Lean (BMI<23)		P	Overweight (BMI >=23)		P
	Non-MAFLD	MAFLD		Non-MAFLD	MAFLD		Non-MAFLD	MAFLD	
SBP, mmHg	118±18	129±19	<0.001	114±16	122±19	<0.001	123±18	129±19	<0.001
DBP, mmHg	70±11	77±13	<0.001	67±10	73±12	<0.001	72±12	77±13	<0.001
FBG, mmol/L	5.15±1.30	5.82±1.63	<0.001	5.04±1.22	5.63±1.65	<0.001	5.3±1.38	5.83±1.63	<0.001
TG, mmol/L	1.07±0.85	2.12±1.73	<0.001	0.91±0.64	1.79±1.46	<0.001	1.28±1.01	2.14±1.75	<0.001
TC, mmol/L	4.41±1.43	4.96±1.34	<0.001	4.29±1.41	4.94±1.36	<0.001	4.55±1.43	4.97±1.34	<0.001
LDL-C, mmol/L	1.99±1.34	2.42±1.43	<0.001	1.9±1.28	2.46±1.38	<0.001	2.09±1.40	2.42±1.43	<0.001
HDL-C, mmol/L	1.01±0.71	0.9±0.60	<0.001	1.06±0.73	0.99±0.64	<0.001	0.93±0.67	0.9±0.60	<0.001
ALT, U/L	19.37±17.28	36.58±27.98	<0.001	17.09±14.34	27.89±21.40	<0.001	22.19±19.98	37.2±28.29	<0.001
AST, U/L	19.59±11.18	25.85±13.56	<0.001	18.76±10.03	23.55±13.08	<0.001	20.62±12.38	26.02±13.57	<0.001
ALP, U/L	7.01±22.44	9.62±25.91	<0.001	5.51±20.85	8.48±24.35	<0.001	8.98±24.13	9.7±26.02	<0.001

GGT, U/L	18.42±24.10	39.36±42.82	<0.001	15.54±20.76	31.41±48.78	<0.001	21.99±27.27	37.71±42.34	<0.001
BUN, mmol/L	4.32±1.97	4.8±1.80	<0.001	4.17±1.90	4.65±1.77	<0.001	4.51±2.04	4.81±1.80	<0.001
Scr, μmol/L	58.57±26.43	66.63±24.76	<0.001	56.12±25.14	62.05±22.61	<0.001	61.62±27.66	66.96±24.88	<0.001
SUA, μmol/L	283.17±125.06	369.05±135.06	<0.001	263.87±116.14	330.07±123.40	<0.001	307.09±131.43	371.84±135.42	<0.001
HCT, %	21.57±21.35	20.32±22.42	<0.001	21.95±20.97	20.36±21.90	<0.001	21.1±21.80	20.32±22.46	<0.001
MCV, fl	47.2±44.74	41.66±44.42	<0.001	48.78±44.68	42.74±44.70	<0.001	45.23±44.74	41.58±44.40	<0.001
UPRO, n (%)	6.70%	9.20%	<0.001	6.30%	6.20%	0.86	7.30%	9.40%	<0.001
UOB, n (%)	11.10%	8.80%	<0.001	11.20%	9.40%	0.00	10.80%	8.80%	<0.001
GBp, n (%)	7.40%	8.90%	<0.001	6.20%	8.60%	<0.001	8.90%	9.70%	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood;

GBp: gallbladder polyps.

Table 4. Multivariable analyses of the factors associated with MAFLD

Variables	Univariable logistical regression			Multivariable logistical regression			
	OR	OR (95% CI)	P	OR	OR (95% CI)		P
MAFLD							
BMI (kg/m^2)							
<23	0.057	0.056	0.060	<0.001	0.125	0.119	0.130	<0.001
≥23							
SBP, mmHg	1.033	1.033	1.034	<0.001	1.003	1.003	1.005	<0.001
DBP, mmHg	1.053	1.052	1.054	<0.001	1.014	1.012	1.016	<0.001
FBG, mmol/L	1.541	1.520	1.559	<0.001	1.122	1.104	1.131	<0.001
TG, mmol/L	2.899	2.854	2.953	<0.001	1.651	1.627	1.691	<0.001
TC, mmol/L	1.378	1.365	1.392	<0.001	0.879	0.866	0.893	<0.001
LDL-C, mmol/L	1.267	1.255	1.277	<0.001	1.231	1.216	1.259	<0.001

HDL-C, mmol/L	0.799	0.785	0.813	<0.001	0.717	0.690	0.740	<0.001
ALT, U/L	1.040	1.038	1.040	<0.001	1.036	1.035	1.038	<0.001
AST, U/L	1.055	1.054	1.057	<0.001	0.979	0.977	0.981	<0.001
ALP, U/L	1.004	1.004	1.005	<0.001	0.998	0.998	1.000	<0.001
GGT, U/L	1.025	1.025	1.026	<0.001	1.002	1.002	1.002	<0.001
BUN, mmol/L	1.145	1.139	1.154	<0.001	1.019	1.007	1.032	<0.001
Scr, μmol/L	1.014	1.013	1.014	<0.001	0.995	0.994	0.996	<0.001
SUA, μmol/L	1.005	1.005	1.006	<0.001	1.003	1.002	1.003	<0.001
HCT, %	0.998	0.997	0.998	<0.001	1.006	1.003	1.008	<0.001
MCV, fl	0.997	0.997	0.997	<0.001	0.994	0.993	0.995	<0.001
UPRO, n (%)	1.407	1.342	1.462	<0.001	1.112	1.069	1.198	<0.001
UOB, n (%)	0.762	0.749	0.811	<0.001	1.000	0.933	1.033	0.47
GBp, n (%)	1.233	1.176	1.280	<0.001	1.026	0.981	1.090	0.21

Lean (BMI<23), MAFLD

SBP, mmHg	1.027	1.025	1.029	<0.001	1.999	0.995	1.002	0.51
DBP, mmHg	1.046	1.042	1.048	<0.001	1.018	1.012	1.024	<0.001
FBG, mmol/L	1.393	1.346	1.424	<0.001	1.098	1.064	1.133	<0.001
TG, mmol/L	2.771	2.642	2.891	<0.001	1.878	1.781	1.968	<0.001
TC, mmol/L	1.498	1.465	1.565	<0.001	0.891	0.860	0.941	<0.001
LDL-C, mmol/L	1.455	1.393	1.485	<0.001	1.372	1.301	1.430	<0.001
HDL-C, mmol/L	1.890	0.831	0.920	<0.001	0.695	0.631	0.741	<0.001
ALT, U/L	1.028	1.026	1.030	<0.001	1.025	1.024	1.030	0.27
AST, U/L	1.028	1.026	1.030	<0.001	0.971	0.969	0.980	<0.001
ALP, U/L	1.006	1.004	1.007	<0.001	1.000	0.998	1.001	<0.001
GGT, U/L	1.016	1.016	1.018	<0.001	1.001	1.001	1.004	<0.001
BUN, mmol/L	1.150	1.133	1.182	<0.001	1.022	0.990	1.059	0.16

Scr, μmol/L	1.010	1.008	1.012	<0.001	0.898	0.987	0.993	<0.001
SUA, μmol/L	1.005	1.005	1.006	<0.001	1.004	1.004	1.004	<0.001
HCT, %	0.996	0.995	0.998	<0.001	1.016	1.005	1.023	<0.001
MCV, fl	0.997	0.996	0.998	<0.001	0.993	0.986	0.995	<0.001
UPRO, n (%)	1.000	0.841	1.149	<0.001	0.995	0.795	1.130	0.57
UOB, n (%)	0.802	0.716	0.926	<0.001	0.947	0.757	1.004	0.06
GBp, n (%)	1.444	1.242	1.629	<0.001	1.221	0.992	1.337	0.06

MAFLD: metabolic associated fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood; GBp: gallbladder polyps.

FIGURE LEHENDS

Figure 1. The location of the three study cities in Liaoning Province.

Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018). ***P<0.001.

Figure 1. The location of the three study cities in Liaoning Province.

80x71mm (300 x 300 DPI)

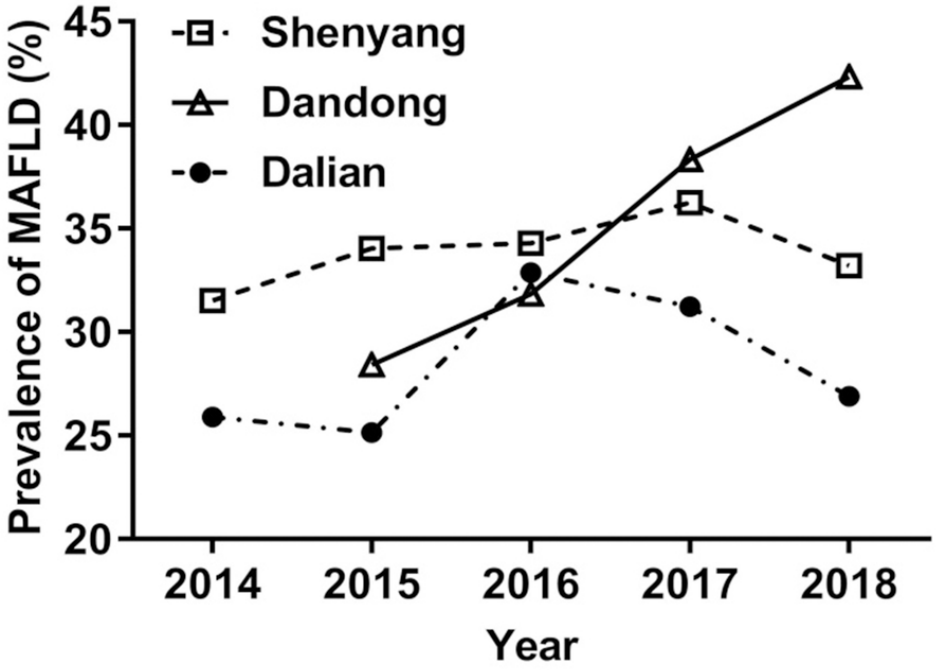

Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

80x61mm (300 x 300 DPI)

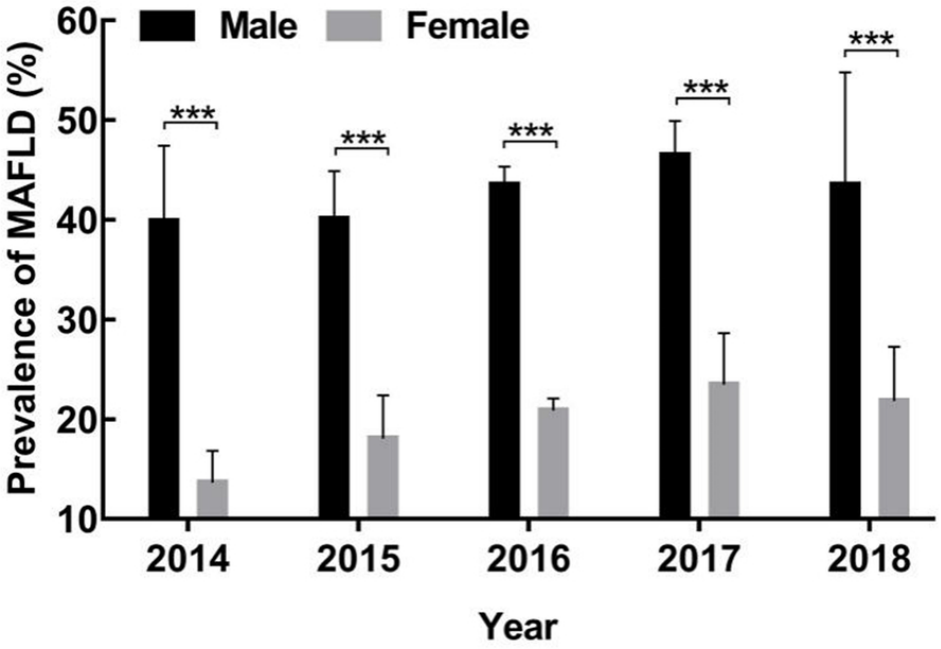

Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018).
***P<0.001.

79x55mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ***Case-control study***—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) ***Cohort study***—For matched studies, give matching criteria and number of exposed and unexposed ***Case-control study***—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) ***Cohort study***—If applicable, explain how loss to follow-up was addressed ***Case-control study***—If applicable, explain how matching of cases and controls was addressed ***Cross-sectional study***—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) ***Cohort study***—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	***Cohort study***—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Prevalence and risk factors of metabolic fatty liver disease during 2014-2018 from three cities of Liaoning province: An epidemiological survey

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Prevalence and risk factors of metabolic fatty liver disease during 2014-2018 from three cities of Liaoning province: An epidemiological survey

Running title: Prevalence of MAFLD in Liaoning, China

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical statement: The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital of China Medical University ([2020]2020-257-2). The ethics committee waived the requirement for informed consent because of the retrospective nature of the study.

Author contributions

(I) Conception and design: LG, XHZ, YLL

(II) Administrative support: JS, DL, YLL

(III) Provision of study materials or patients: LG, XJ, NNW

(IV) Collection and assembly of data: HYT, XW, ZLZ

(V) Data analysis and interpretation: HF, JL

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

ABSTRACT

Objectives: To investigate the incidence and disease characteristics of metabolic fatty liver disease (MAFLD) in physical examination populations in Liaoning (China).

Design: Retrospective study

Setting: Single center.

Participants: Adults who underwent routine health examination at Xikang Medical Center in Liaoning Province (Shenyang, Dandong, and Dalian) between 01/2014 and 12/2018.

Interventions: Not applicable.

Primary And Secondary Outcome Measures: Not applicable.

Results: Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28%. The total prevalence of MAFLD in Shenyang, Dandong, and Dalian in the past five years is 35.8%, 40.41%, and 31.7%, respectively. Men had a prevalence of 46.12%, which is higher than in women (21.80%). The percentage of MAFLD in BMI <23 and ≥23 kg/m^2 is 6.49 % and 53.23%, respectively. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all P<0.001). In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all P<0.001).

Conclusions: The prevalence of MAFLD in Liaoning is related to sex, cities with

different economic statuses, BMI, and multiple metabolic indicators.

Key words: metabolic fatty liver disease; prevalence; risk factors; body mass index; lean.

Strengths and limitations of this study

1. The study is a large-scale epidemiological survey.

2. It is one of the first epidemiological articles after NAFLD renamed as MAFLD.

3. The study provides time trends from three cities in China of varying economic development.

4. The data of MAFLD with T2DM is lacking in the study.

5. Although most of the metabolic risk factors have been discussed in the study, it is still not comprehensive enough.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is defined as the presence of ≥5% of hepatic steatosis (HS) (1, 2). Recently, it was recommended to rename NAFLD as metabolic (dysfunction) associated fatty liver disease (MAFLD), which might increase the awareness of the disease and decrease its stigma (3, 4). NAFLD is associated with chronic diseases like insulin resistance and/or type 2 diabetes (T2DM), dyslipidemia, hypertriglyceridemia, and hypertension (5-8). The reported prevalence of MAFLD is reported to be 24%-45%, with an estimated prevalence of 76% in patients with T2DM (9). For non-obese patients, MAFLD is associated with elevated triglyceride (TG) levels, increased waist circumference, and insulin resistance (10).

Chinese individuals have substantially higher risks of MAFLD, even at much lower BMI levels, compared with the US population (11). Factors like waist circumference, T2DM, increased TG, low high - density lipoprotein (HDL)-cholesterol, and metabolic syndrome are known to be predictive factors for MAFLD in adults, and the metabolic syndrome is considered as a strong predictive factor (12, 13). MAFLD is also associated with dyslipidemia characterized by high TG, high low-density lipoprotein (LDL), and low HDL-cholesterol levels (14). Determining the risk factors associated with a worse prognosis is essential for improving the therapeutic strategies.

Since the 21st century, the prevalence of MAFLD in China has increased significantly to reach about one in three mainland Chinese residents (12). A recent meta-analysis showed that the incidence of MAFLD is higher in northern China (35.78%) and lower in northwestern China (21.52%) (15). Among the provinces in northern China, Heilongjiang has the highest incidence, with up to 50.48% (15). Nevertheless, the results might be biased due to the small number of studies, yet MAFLD incidence in northern China is significantly higher than that in the southern provinces. In addition, the risk of MAFLD-related mortality has also increased significantly, mainly due to diseases associated with liver fibrosis (16). MAFLD has become an important health issue affecting the Chinese population, increasing the socioeconomic burden (11, 12, 15). Therefore, Chinese medical professionals and stakeholders urgently need to carry out early scientific prevention and control of MAFLD. Multiple studies have shown that MAFLD is a heterogeneous entity and that its development is related to sex, age, race, mild-to-moderate alcohol consumption, dietary intake, lifestyle, obesity, metabolism, genetic variation, and education (11, 12, 15, 16). With uneven economic development and diverse lifestyles among the different provinces, the epidemiology of MAFLD in China has marked regional differences. By understanding the epidemiology of MAFLD in Liaoning Province, we can conduct targeted education and clinical research for precise prevention and control of MAFLD.

There have been no data from large-scale epidemiological investigations of

MAFLD in Liaoning province in northern China in the past ten years. Therefore, this retrospective study aims to investigate the incidence and disease characteristics of MAFLD in physical examination populations in Liaoning. The study uses physical examination data of residents collected from 2014 to 2018 in three cities with different economic levels in Liaoning (Shenyang, Dandong, and Dalian).

METHODS

Study subjects

This is a retrospective study of adults who underwent routine health examination at Xikang Medical Center in Liaoning Province (which has clinics in Shenyang, Dandong, and Dalian) between January 2014 and December 2018. The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital of China Medical University ([2020]2020-257-2). The ethics committee waived the requirement for informed consent because of the retrospective nature of the study.

The three cities are from different parts of the province (North, South, and East (Figure 1), and they have different economic levels. Shenyang, situated in North Liaoning Province, is a highly developed inland city, while Dalian in South Liaoning is a developed coastal city. Dandong, in the east of Liaoning Province, is a poorly developed city bordering North Korea.

The inclusion criteria are 1) >18 years of age; 2) have been living in Shenyang,

Dalian, or Dandong for at least 5 years; 3) participate in the annual physical examination; and 4) no missing data (as listed in Table 1). The exclusion criteria are 1) liver cirrhosis; 2) liver cancer; 3) any liver ultrasound lesions; or 4) no ultrasound examination. For individuals with more than one examination during the study period, only the first examination is included in this study.

The selected patients are divided into MAFLD group and non-MAFLD group based on the ultrasound evidence of hepatic steatosis in addition to one of the following two criteria, namely overweight/obesity (BMI ≥23 kg/m^2， according to the standards recommended by the World Health Organization for Asians (18)) or BMI <23 kg/m^2 with at least two evidence of metabolic dysregulation, such as Blood pressure ≥130/85 mmHg, TG≥1.70 mmol/L, HDL-cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women, or prediabetes (fasting blood glucose levels 5.6 to 6.9 mmol/L) (19). Unfortunately, patients with presence of T2DM who received medical intervention were not included in this study, due to serious incomplete records of medical history.

Patient and Public Involvement

No patient involved

Physical examination

All physical examinations included in this study are part of the routine examination. Blood pressure measurements, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), are taken twice after the participants have been

sitting, in a calm state, for at least 5 min, using an electronic sphygmomanometer (HEM-7200, OMRON Healthcare, Kyoto, Japan). Height and weight are measured in the morning on an empty stomach, and body mass index (BMI) is as kg/m^2.

Laboratory examination

All physical blood tests included in this study are part of the routine examination. Anterior cubital vein blood is drawn in the fasting state (at least 8 h). A midcourse morning urine specimen is also taken. Routine blood panel, liver function, kidney function, serum uric acid (SUA), fasting blood glucose (FBG), blood lipids, and routine urine analysis are assessed using a 7600 autoanalyzer (Hitachi, Tokyo, Japan).

Color Doppler ultrasound of the liver and gallbladder

A liver ultrasound is part of the routine examination. It is performed by two experienced ultrasound radiologists with at least 5 years of experience and using an IU 22 system (Philips, Best, The Netherlands). An individual is diagnosed with hepatic steatosis when the ultrasound examination shows that the liver has fatty liver changes (hyperechogenicity due to increased acoustic interface caused by the intracellular accumulation of lipid vesicles, blurring of vascular margins, increased liver size, and increased acoustic attenuation (10, 17)) .

Statistical analysis

R 3.5.3 and R Commander 2.5-3 were used for statistical analysis. The categorical data are expressed as n (%) and were analyzed using the chi-square test. The continuous variables conforming to the normal distribution (according to the Kolmogorov-Smirnov test) are expressed as means ± standard deviations and were analyzed using Student's t-test. Non-normally distributed continuous variables are presented as medians (interquartile range (IQR)) and were analyzed using the Mann-Whitney U-test. The factors associated with MAFLD were identified using univariable analyses. Variables with P-values <0.05 were included in a multivariable logistic regression model. P-values <0.05 were considered statistically significant.

RESULTS

Characteristics of the subjects

A total of 284,129 subjects were examined during the study period, and 204,394 met the inclusion criteria. Table 1 presents the characteristics of the subjects. The mean age is 39.6±13.6 years. The numbers of men and women are 111,782 and 92,612, respectively. The mean age of the men is 38.8±13.7 years, and that of women is 40.5±13.3 years. Shenyang includes 78,329 subjects, who were 39.3±12.7 years of age. The clinic in Dandong did not perform routine health examinations in 2014. Dandong includes 42,039 subjects, who were 47.8±14.1 years. Finally, Dalian has 84,026 subjects; they were 36.3±12.7 years.

MAFLD in the healthy population

Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28% (Table 1). The prevalence of MAFLD increases with the age groups (P<0.001), is higher in males than in females (P<0.001), is higher in overweight/obese subjects than in lean ones (P<0.001), and is higher in Dandong, followed by Shenyang and Dalian (P<0.001) (Table 1). The prevalence of MAFLD in Shenyang, Dandong, and Dalian in the past five years was 36.83%, 40.42%, and 31.78%, respectively.

MAFLD over time

The total prevalence of MAFLD from 2014 to 2018 is 30.01%, 30.11%, 33.22%, 34.58%, and 32.19%, respectively. The prevalence of MALFD over the 5 years mainly increased in the 30-39 groups (P=0.006), and both in males (P=0.029) and in females (P=0.035) (Table 2). The prevalence of MAFLD in Shenyang in the past 5 years was basically consistent with the general trend in Liaoning. The MAFLD prevalence in Dandong showed a significant increase annually in the past 4 years. The MAFLD prevalence in Dalian increased substantially in 2016, but it declined annually in 2017 and 2018 (Figure 2). The prevalence rate in men and women in the past five years is basically consistent with the general trend of MAFLD in Liaoning (Figure 3). As age increases, MAFLD prevalence in Liaoning increases.

Biomarkers and MAFLD

Table 3 presents the biomarkers in all subjects and according to lean/overweight-obese. Compared with the non-MAFLD group, the subjects with MAFLD have higher SBP, DBP, FBG, TG, TC, LDL-C, ALT, AST, ALP, GGT, BUN, Scr, and SUA, higher frequencies of UPRO and GBp, lower HDL-C, HCT, and MCV, and lower frequency of UOB (all P<0.001). The same tendencies are observed in lean subjects, except that there is no difference in UPRO (P=0.86).

Factors associated with MAFLD

Table 4 presents the univariable and multivariable analyses of the factors associated with MAFLD. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all P<0.001), while UOB (P=0.47) and GBp (P=0.21) are not. In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all P<0.001), while SBP (P=0.51), ALT (P=0.27), BUN (P=0.16), UPRO (P=0.57), UOB (P=0.06), and GBp (P=0.06) are not.

DISCUSSION

The present study shows that the prevalence of MAFLD in Shenyang, Dandong, and Dalian varied and that higher BMI and age play significant roles in the

development of the disease. In addition, biomarkers like DBP, FBG, TG, LDL-C, ALT, GGT, BUN, SUA, HCT, UPRO, GBs, and GBp are independently and positively correlated with the prevalence of MAFLD, whereas HDL-C and MCV are negatively correlated. Therefore, the prevalence of MAFLD in Liaoning is related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators.

The increasing trend in the prevalence of MAFLD follows the level of industrialization and urbanization. At present, China is the fastest-growing major economy in the world and displays the problems associated with a westernized diet, sedentary lifestyle, and population aging, which are associated with MAFLD. Studies have shown that the increase in the total annual MAFLD prevalence in China is consistent with the improvement in the per capita GDP (20). An increase in morbidity in various regions of mainland China is related to the increase in per capita GDP, but the area with the highest per capita GDP (≥$13,000) does not exhibit an increased incidence of MAFLD (21). According to the National Bureau of Statistics of China, the per capita GDP of Liaoning Province has been ranking first in Northeast China in the past five years, but it is still in the lower-middle level nationally. This study shows that the prevalence of MAFLD in Liaoning (35.1%) is slightly higher than the overall prevalence of MAFLD in China (29.2%) (12). This study selected two economically developed cites (Dalian and Shenyang) and one city with moderate development (Dandong). The prevalence of MAFLD in these three cities is inversely proportional to the level of urban economic development. The prevalence of MAFLD in Dalian is

lower than that in Shenyang. A reason might be that Dalian is a coastal city, with dietary habits different from that of inland cities.

Differences in age are also involved. The prevalence of MAFLD in the 20-29 years group is 17.9%, while the prevalence in the >60 years group is 45.6%, which is in alignment with previous studies that show that age plays a crucial factor in MAFLD (11, 12, 15).

This study found that the overall prevalence of MAFLD in men is higher than that in women, which is basically consistent with the findings in other regions in China (22). The prevalence of MAFLD in middle-aged men is highest and peaks at 40-49 years of age (50.27%). This high prevalence might be related to high stress, irregular work and rest, and decreased metabolism among middle-aged men. The prevalence of MAFLD in women over 50 years of age is significantly higher, which relates to the age range of menopause.

Obesity is closely related to metabolic-related diseases such as MAFLD. This study confirmed that BMI ≥23 kg/m^2 is an independent risk factor for MAFLD in Liaoning. Therefore, for overweight and obese people, it is necessary to improve diet and exercise management, even with the help of drugs or surgery if needed. It has been reported that the global prevalence of lean-MAFLD is 5%-26% (23). In the study, the prevalence of lean-MAFLD is 10.75%, which is similar to previous results (24).

In this study, both lean-MAFLD and non-lean-MAFLD were closely related to

metabolic indicators. Those metabolic indicators are also associated with T2DM, metabolic syndrome, obesity, and liver diseases, as supported by previous studies (11, 12, 15, 22-24). In addition to obesity, the variation in the prevalence of MAFLD follows the epidemic trends of T2DM and MetS. The prevalence of MAFLD in hyperlipidemia and T2DM patients is higher, reaching 27%-92% and 28%-70%, respectively. Patients with MAFLD also often have hyperlipidemia, hypertension, T2DM, and metabolic syndrome (25). In this study, logistic regression analysis found that DBP, TG, LDL-C, FBG, and SUA were independent risk factors for MAFLD, but HDL-C is independently associated with MAFLD. Therefore, paying attention to hyperlipidemia, hypertension, and T2DM should have important effects on the prevention and treatment of MAFLD. Regarding the correlation between SUA and MAFLD, SUA elevation is one of the risk factors for MAFLD (26).

Although it was not examined in this study, genetic susceptibility is involved in MAFLD. Polymorphisms in PNPLA3 (27), SREBF-2 (28), CETP (28, 29), and APOC3 (30) have been found to be associated with lean-MAFLD. In addition to genetic polymorphisms, lean-MAFLD people have increased bile acid and FXR activity due to metabolic abnormalities and changes in intestinal microbial composition (31, 32). Those factors should be examined in future studies.

This study has limitations. Even if the examinations were performed at the same clinical company, they were performed at three different physical locations and over 5 years. Biases due to the different locations and changes in practice over time cannot

be excluded. In addition, ultrasound is operator-dependent, and a bias in the diagnosis of MAFLD cannot be excluded. Finally, this was a cross-sectional study that cannot provide any causal relationship between MAFLD and the associated factors.

In conclusion, the prevalence of MAFLD in Liaoning is related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators. Longitudinal studies are necessary to determine the factors associated with the development of MAFLD.

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.

2. Stal P. Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge with prognostic significance. World J Gastroenterol. 2015;21:11077-87.

3. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020;158:1999-2014 e1.

4. Fouad Y, Waked I, Bollipo S, et al. What's in a name? Renaming 'NAFLD' to 'MAFLD'. Liver Int. 2020;40:1254-61.

5. Pai RK. NAFLD Histology: a Critical Review and Comparison of Scoring Systems. Curr Hepatol Rep. 2019;18:473-81.

6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274-85.

7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012;142:1592-609.

8. Non-Alcoholic Fatty Liver Disease: Assessment and Management. National Institute for Health and Care Excellence: Guidance. London2016.

9. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313:2263-73.

10. Shen FF, Lu LG. Advances in noninvasive methods for diagnosing nonalcoholic fatty liver disease. J Dig Dis. 2016;17:565-71.

11. Zhou J, Zhou F, Wang W, et al. Epidemiological Features of NAFLD From 1999 to 2018 in China. Hepatology. 2020;71:1851-64.

12. Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis. Hepatology. 2019;70:1119-33.

13. Caballeria L, Auladell MA, Toran P, et al. Risk factors associated with non-alcoholic fatty liver disease in subjects from primary care units. A case-control study. BMC Gastroenterol. 2008;8:44.

14. Hartmann P, Schnabl B. Risk factors for progression of and treatment options for NAFLD in children. Clin Liver Dis (Hoboken). 2018;11:11-5.

15. Wu Y, Zheng Q, Zou B, et al. The epidemiology of NAFLD in Mainland China with analysis by adjusted gross regional domestic product: a meta-analysis. Hepatol Int. 2020;14:259-69.

16. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;65:1557-65.

17. Mahale AR, Prabhu SD, Nachiappan M, et al. Clinical relevance of reporting fatty liver on ultrasound in asymptomatic patients during routine health checkups. J Int Med Res. 2018;46:4447-54.

18. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157-63.

19. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic associated fatty liver disease: an international expert consensus statement. Journal of Hepatology. 2020;73(1):202-209.

20. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of nonalcoholic fatty liver disease. Med Res Rev. 2019;39:328-48.

21. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol. 2017;67:862-73.

22. Zhu JZ, Zhou QY, Wang YM, et al. Prevalence of fatty liver disease and the economy in China: A systematic review. World J Gastroenterol. 2015;21:5695-706.

23. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. Clin Nutr. 2019;38:975-81.

24. Shi Y, Wang Q, Sun Y, et al. The Prevalence of Lean/Nonobese Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2020;54:378-87.

25. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis. 2019;20:163-73.

26. Ma Z, Xu C, Kang X, et al. Changing trajectories of serum uric acid and risk of non-alcoholic fatty liver disease: a prospective cohort study. J Transl Med. 2020;18:133.

27. Musso G, Cassader M, Bo S, et al. Sterol regulatory element-binding factor 2 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and lipoprotein and glucose dysmetabolism. Diabetes. 2013;62:1109-20.

28. Adams LA, Marsh JA, Ayonrinde OT, et al. Cholesteryl ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity. J Gastroenterol Hepatol. 2012;27:1520-7.

29. Petersen KF, Dufour S, Hariri A, et al. Apolipoprotein C3 gene variants in

nonalcoholic fatty liver disease. N Engl J Med. 2010;362:1082-9.

30. Li C, Guo P, Okekunle AP, et al. Lean non-alcoholic fatty liver disease patients had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and overtime work as obese non-alcoholic fatty liver disease patients. J Gastroenterol Hepatol. 2019;34:256-62.

31. Safari Z, Gerard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cell Mol Life Sci. 2019;76:1541-58.

32. Suk KT, Kim DJ. Gut microbiota: novel therapeutic target for nonalcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol. 2019;13:193-204.

Table 1. Characteristics of the patients with non-MAFLD and MAFLD

Subgroups	Age (years), Mean±**SD**	All N=204,394	Non-MAFLD n=132,638	MAFLD n=71,756	Prevalence (%)	P
Age						<0.001
20-29		22,822	18,728	4094	17.94	
30-39		80,227	54,671	25,556	31.85	
40-49		44,464	27,913	16,551	37.22	
50-59		30,861	17,173	13,688	44.35	
≥60		26,020	14,153	11,867		
Sex						<0.001
Male	38.8±13.7	111,782	60,222	51,560	46.13	
Female	40.5±13.3	92,612	72,416	20,196	21.81	
BMI (kg/m^2)						<0.001
<23		79,271	74,124	5147	6.49	
≥23		125,123	58,514	66,609	53.23	
City						<0.0

					01
Shenyang	39.3±12.7	78,329	50,265	28,064	36.83
Dandong	47.8±14.1	42,039	25,048	16,991	40.42
Dalian	36.3±12.7	84,026	57,325	26,701	31.78
Overall	39.6±13.6	204,394	132,638	71,756	35.11

MAFLD: metabolic-associated fatty liver disease; BMI: body mass index.

Table 2. Changes in the prevalence of MAFLD over time (2014-2018)

Subgroups	Year, %					P
	2014	2015	2016	2017	2018	
Age (years)						
20-29	16.43	17.20	17.30	18.82	18.18	0.081
30-39	29.24	28.60	31.05	33.37	34.33	0.006
40-49	35.65	34.50	35.40	39.04	38.69	0.200
50-59	46.32	39.40	41.67	46.96	45.44	0.636
≥60	44.83	40.65	45.34	48.39	46.50	0.234
Sex						
Male	42.60	42.63	44.36	48.12	48.45	0.029
Female	14.85	19.33	21.49	24.63	22.67	0.035
BMI (kg/m^2)						
<23	5.08	5.35	6.68	7.36	6.80	0.058
≥23	54.93	50.37	52.15	55.08	53.76	0.510
City						
Shenyang	34.89	34.80	34.27	37.36	36.92	0.182
Dandong	-	30.06	34.29	42.66	44.17	0.039
Dalian	26.36	29.00	33.20	32.36	32.98	0.048
Overall	30.01	30.11	33.22	34.58	32.19	<0.001

BMI: body mass index.

Table 3. Comparison of the metabolic tests between non-MAFLD and MAFLD

Variables	Overall		P	Lean (BMI<23)		P	Overweight (BMI >=23)		P
	Non-MAFLD	MAFLD		Non-MAFLD	MAFLD		Non-MAFLD	MAFLD	
SBP, mmHg	118±18	129±19	<0.001	114±16	122±19	<0.001	123±18	129±19	<0.001
DBP, mmHg	70±11	77±13	<0.001	67±10	73±12	<0.001	72±12	77±13	<0.001
FBG, mmol/L	5.15±1.30	5.82±1.63	<0.001	5.04±1.22	5.63±1.65	<0.001	5.3±1.38	5.83±1.63	<0.001
TG, mmol/L	1.07±0.85	2.12±1.73	<0.001	0.91±0.64	1.79±1.46	<0.001	1.28±1.01	2.14±1.75	<0.001
TC, mmol/L	4.41±1.43	4.96±1.34	<0.001	4.29±1.41	4.94±1.36	<0.001	4.55±1.43	4.97±1.34	<0.001
LDL-C, mmol/L	1.99±1.34	2.42±1.43	<0.001	1.9±1.28	2.46±1.38	<0.001	2.09±1.40	2.42±1.43	<0.001
HDL-C, mmol/L	1.01±0.71	0.9±0.60	<0.001	1.06±0.73	0.99±0.64	<0.001	0.93±0.67	0.9±0.60	<0.001
ALT, U/L	19.37±17.28	36.58±27.98	<0.001	17.09±14.34	27.89±21.40	<0.001	22.19±19.98	37.2±28.29	<0.001
AST, U/L	19.59±11.18	25.85±13.56	<0.001	18.76±10.03	23.55±13.08	<0.001	20.62±12.38	26.02±13.57	<0.001
ALP, U/L	7.01±22.44	9.62±25.91	<0.001	5.51±20.85	8.48±24.35	<0.001	8.98±24.13	9.7±26.02	<0.001

GGT, U/L	18.42±24.10	39.36±42.82	<0.001	15.54±20.76	31.41±48.78	<0.001	21.99±27.27	37.71±42.34	<0.001
BUN, mmol/L	4.32±1.97	4.8±1.80	<0.001	4.17±1.90	4.65±1.77	<0.001	4.51±2.04	4.81±1.80	<0.001
Scr, μmol/L	58.57±26.43	66.63±24.76	<0.001	56.12±25.14	62.05±22.61	<0.001	61.62±27.66	66.96±24.88	<0.001
SUA, μmol/L	283.17±125.06	369.05±135.06	<0.001	263.87±116.14	330.07±123.40	<0.001	307.09±131.43	371.84±135.42	<0.001
HCT, %	21.57±21.35	20.32±22.42	<0.001	21.95±20.97	20.36±21.90	<0.001	21.1±21.80	20.32±22.46	<0.001
MCV, fl	47.2±44.74	41.66±44.42	<0.001	48.78±44.68	42.74±44.70	<0.001	45.23±44.74	41.58±44.40	<0.001
UPRO, n (%)	6.70%	9.20%	<0.001	6.30%	6.20%	0.86	7.30%	9.40%	<0.001
UOB, n (%)	11.10%	8.80%	<0.001	11.20%	9.40%	0.00	10.80%	8.80%	<0.001
GBp, n (%)	7.40%	8.90%	<0.001	6.20%	8.60%	<0.001	8.90%	9.70%	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood;

GBp: gallbladder polyps.

Table 4. Multivariable analyses of the factors associated with MAFLD

Variables	Univariable logistical regression			Multivariable logistical regression			
	OR	OR (95% CI)	P	OR	OR (95% CI)		P
MAFLD							
BMI (kg/m^2)							
<23	0.057	0.056	0.060	<0.001	0.125	0.119	0.130	<0.001
≥23							
SBP, mmHg	1.033	1.033	1.034	<0.001	1.003	1.003	1.005	<0.001
DBP, mmHg	1.053	1.052	1.054	<0.001	1.014	1.012	1.016	<0.001
FBG, mmol/L	1.541	1.520	1.559	<0.001	1.122	1.104	1.131	<0.001
TG, mmol/L	2.899	2.854	2.953	<0.001	1.651	1.627	1.691	<0.001
TC, mmol/L	1.378	1.365	1.392	<0.001	0.879	0.866	0.893	<0.001
LDL-C, mmol/L	1.267	1.255	1.277	<0.001	1.231	1.216	1.259	<0.001

HDL-C, mmol/L	0.799	0.785	0.813	<0.001	0.717	0.690	0.740	<0.001
ALT, U/L	1.040	1.038	1.040	<0.001	1.036	1.035	1.038	<0.001
AST, U/L	1.055	1.054	1.057	<0.001	0.979	0.977	0.981	<0.001
ALP, U/L	1.004	1.004	1.005	<0.001	0.998	0.998	1.000	<0.001
GGT, U/L	1.025	1.025	1.026	<0.001	1.002	1.002	1.002	<0.001
BUN, mmol/L	1.145	1.139	1.154	<0.001	1.019	1.007	1.032	<0.001
Scr, μmol/L	1.014	1.013	1.014	<0.001	0.995	0.994	0.996	<0.001
SUA, μmol/L	1.005	1.005	1.006	<0.001	1.003	1.002	1.003	<0.001
HCT, %	0.998	0.997	0.998	<0.001	1.006	1.003	1.008	<0.001
MCV, fl	0.997	0.997	0.997	<0.001	0.994	0.993	0.995	<0.001
UPRO, n (%)	1.407	1.342	1.462	<0.001	1.112	1.069	1.198	<0.001
UOB, n (%)	0.762	0.749	0.811	<0.001	1.000	0.933	1.033	0.47
GBp, n (%)	1.233	1.176	1.280	<0.001	1.026	0.981	1.090	0.21

Lean (BMI<23), MAFLD

SBP, mmHg	1.027	1.025	1.029	<0.001	1.999	0.995	1.002	0.51
DBP, mmHg	1.046	1.042	1.048	<0.001	1.018	1.012	1.024	<0.001
FBG, mmol/L	1.393	1.346	1.424	<0.001	1.098	1.064	1.133	<0.001
TG, mmol/L	2.771	2.642	2.891	<0.001	1.878	1.781	1.968	<0.001
TC, mmol/L	1.498	1.465	1.565	<0.001	0.891	0.860	0.941	<0.001
LDL-C, mmol/L	1.455	1.393	1.485	<0.001	1.372	1.301	1.430	<0.001
HDL-C, mmol/L	1.890	0.831	0.920	<0.001	0.695	0.631	0.741	<0.001
ALT, U/L	1.028	1.026	1.030	<0.001	1.025	1.024	1.030	0.27
AST, U/L	1.028	1.026	1.030	<0.001	0.971	0.969	0.980	<0.001
ALP, U/L	1.006	1.004	1.007	<0.001	1.000	0.998	1.001	<0.001
GGT, U/L	1.016	1.016	1.018	<0.001	1.001	1.001	1.004	<0.001
BUN, mmol/L	1.150	1.133	1.182	<0.001	1.022	0.990	1.059	0.16

Scr, μmol/L	1.010	1.008	1.012	<0.001	0.898	0.987	0.993	<0.001
SUA, μmol/L	1.005	1.005	1.006	<0.001	1.004	1.004	1.004	<0.001
HCT, %	0.996	0.995	0.998	<0.001	1.016	1.005	1.023	<0.001
MCV, fl	0.997	0.996	0.998	<0.001	0.993	0.986	0.995	<0.001
UPRO, n (%)	1.000	0.841	1.149	<0.001	0.995	0.795	1.130	0.57
UOB, n (%)	0.802	0.716	0.926	<0.001	0.947	0.757	1.004	0.06
GBp, n (%)	1.444	1.242	1.629	<0.001	1.221	0.992	1.337	0.06

MAFLD: metabolic associated fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood; GBp: gallbladder polyps.

FIGURE LEHENDS

Figure 1. The location of the three study cities in Liaoning Province.

Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018). ***P<0.001.

Figure 1. The location of the three study cities in Liaoning Province.

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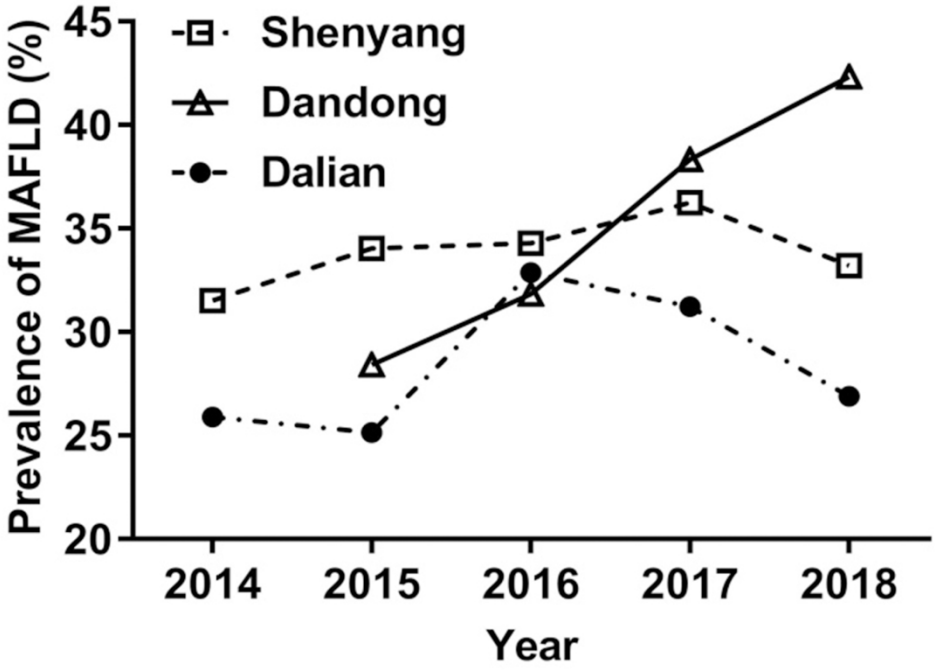

Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

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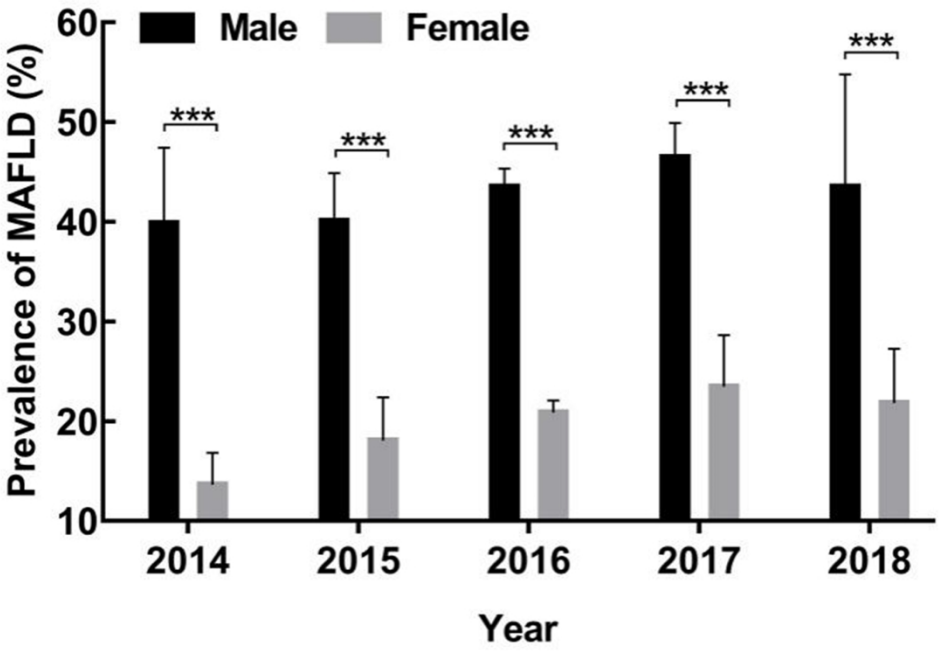

Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018). ***P<0.001.

80x55mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ***Case-control study***—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) ***Cohort study***—For matched studies, give matching criteria and number of exposed and unexposed ***Case-control study***—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) ***Cohort study***—If applicable, explain how loss to follow-up was addressed ***Case-control study***—If applicable, explain how matching of cases and controls was addressed ***Cross-sectional study***—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) ***Cohort study***—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	***Cohort study***—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Prevalence and risk factors of metabolic associated fatty liver disease during 2014-2018 from three cities of Liaoning province: An epidemiological survey

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Prevalence and risk factors of metabolic associated fatty liver disease during 2014-2018 from three cities of Liaoning province: An epidemiological survey

Running title: Prevalence of MAFLD in Liaoning, China

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Ethical statement: The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital of China Medical University ([2020]2020-257-2). The ethics committee waived the requirement for informed consent because of the retrospective nature of the study.

Author contributions

(I) Conception and design: LG, XHZ, YLL

(II) Administrative support: JS, DL, YLL

(III) Provision of study materials or patients: LG, XJ, NNW

(IV) Collection and assembly of data: HYT, XW, ZLZ

(V) Data analysis and interpretation: HF, JL

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

ABSTRACT

Objectives: To investigate the incidence and characteristics of metabolic associated fatty liver disease (MAFLD) in individuals undergoing physical examinations in Liaoning province (China).

Design: Retrospective study

Setting: Single-center.

Participants: Adults who underwent routine health examination at Xikang Medical Center in Liaoning province (Shenyang, Dandong, and Dalian cities) between January 2014 and December 2018.

Interventions: Not applicable.

Primary And Secondary Outcome Measures: Not applicable.

Results: Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28%. The total prevalence of MAFLD in Shenyang, Dandong, and Dalian cities over the past 5 years was 35.8%, 40.41%, and 31.7%, respectively. Men had a prevalence of 46.12%, which was higher than in women (21.80%). The percentage of MAFLD in body mass index (BMI) <23 and ≥23 kg/m^2 was 6.49 % and 53.23%, respectively. In all subjects, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase

(GGT), blood urea nitrogen (BUN), serum creatinine (sCr), and serum uric acid (SUA), hematocrit (HCT), mean corpuscular volume (MCV), and urine protein (UPRO) were independently associated with MAFLD (all P<0.001). In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, sCr, SUA, HCT, and MCV were independently associated with MAFLD (all P<0.001).

Conclusion: The prevalence of MAFLD in Liaoning province was found to be associated with sex, cities with different economic statuses, BMI, and multiple metabolic indicators.

Key words: metabolic associated fatty liver disease; prevalence; risk factors; body mass index; lean.

Strengths and limitations of this study

1. The study is a large-scale epidemiological survey.
2. It is one of the first epidemiological articles after NAFLD renamed as MAFLD.
3. The study provides time trends from three cities in China with varying economic development.
4. The data of MAFLD patients with T2DM are lacking in the study.
5. Although the majority of the metabolic risk factors have been discussed in the study, further comprehensive assessment is required.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is defined as the presence of ≥5% hepatic steatosis (HS) (1, 2). Recently, it was recommended to rename NAFLD as metabolic associated fatty liver disease (MAFLD), which might increase the awareness of the disease and decrease its stigma (3, 4). NAFLD is associated with chronic diseases, such as insulin resistance and/or type 2 diabetes mellitus (T2DM), dyslipidemia, hypertriglyceridemia, and hypertension (5-8). The prevalence of NAFLD was reported to be 24-45%, with an estimated prevalence of 76% in patients with T2DM (9). For non-obese patients, NAFLD is associated with the elevated triglyceride (TG) level, enlarged waist circumference, and insulin resistance (10).

Chinese individuals are at substantially higher risks of NAFLD, even those with noticeably lower body mass index (BMI, kg/m^2) values, compared with the US population (11). Factors, such as waist circumference, T2DM, increased TG level, low high−density lipoprotein (HDL)-cholesterol level, and metabolic syndrome are known as predictive factors for NAFLD in adults, of which the metabolic syndrome is considered as a strong predictive factor (12, 13). NAFLD is also associated with dyslipidemia characterized by high TG, high low-density lipoprotein (LDL), and low HDL-cholesterol levels (14). Determining the risk factors associated with a worse prognosis is essential to develop further effective therapeutic strategies.

Since the 21st century, the prevalence of NAFLD in China has significantly

increased to reach about one in three mainland Chinese residents (12). A recent meta-analysis showed that the incidence of NAFLD is higher in the northern China (35.78%) and lower in the northwestern China (21.52%) (15). Among provinces in the northern China, Heilongjiang has the highest incidence, with up to 50.48% (15). Nevertheless, the results might be biased due to the small number of studies, and the incidence of NAFLD in the northern China is still significantly higher than that in the southern provinces. In addition, the risk of NAFLD-related mortality has also increased significantly, mainly due to liver fibrosis-associated diseases (16). NAFLD has become an important public health concern, negatively influencing the Chinese population, as well as increasing the socioeconomic burden (11, 12, 15). Therefore, Chinese medical professionals and stakeholders urgently need to develop further accurate early diagnostic methods for NAFLD. Multiple studies have reported that NAFLD is a heterogeneous entity, and its development is related to sex, age, race, mild-to-moderate alcohol consumption, dietary intake, lifestyle, obesity, metabolism, genetic variations, and educational level (11, 12, 15, 16). With uneven economic development and diverse lifestyles among the different provinces in China, the epidemiology of NAFLD has shown remarkable regional differences. With understanding the epidemiology of NAFLD in Liaoning province (China), we can conduct targeted education and clinical research for precise prevention and control of NAFLD. Moreover, after NAFLD was renamed MAFLD, few studies investigated the prevalence of MAFLD.

There have been no data from large-scale epidemiological investigations of MAFLD in Liaoning province over the past 10 years. Therefore, the present retrospective study aimed to investigate the incidence and disease characteristics of MAFLD in Liaoning province. The physical examination data of residents of three cities (Shenyang, Dandong, and Dalian) in Liaoning province were collected from 2014 to 2018 with different economic levels.

METHODS

Study subjects

This is a retrospective study of adults who underwent routine health examination at Xikang Medical Center in Liaoning province (including clinics in Shenyang, Dandong, and Dalian) between January 2014 and December 2018. The study was conducted in accordance with the Declaration Helsinki, and the study protocol was approved by the Ethics Committee of the First Hospital of China Medical University ([2020]2020-257-2). The Ethics Committee waived the requirement for informed consent because of the retrospective nature of the study.

The three cities are from different parts of the Liaoning province (North, South, and East (Figure 1)), and they have different economic levels. Shenyang, located in the north of Liaoning province, is a highly developed inland city, while Dalian in the south of Liaoning province is a developed coastal city. Dandong, in the east of Liaoning province, is a poorly developed city bordering North Korea.

The inclusion criteria were as follows: 1) patients who aged >18 years old; 2) patients who lived in Shenyang, Dalian, or Dandong for at least 5 years; 3) participation in the annual physical examination; and 4) no missing data (as listed in Table 1). The exclusion criteria were as follows: 1) liver cirrhosis; 2) liver cancer; 3) any liver lesions; or 4) no ultrasound examination. For participants undergoing more than one examination during the study period, only the first examination was involved in this study. According to the guidelines, the diagnosis of MAFLD is no longer than an exclusive diagnosis. Therefore, the diagnosed patients did not rule out conditions, such as alcohol consumption and other liver diseases.

The selected patients were divided into MAFLD group and non-MAFLD group based on the ultrasound evidence of hepatic steatosis, in addition to one of the following two criteria, namely overweight/obesity (BMI ≥23 kg/m^2， according to the standards recommended by the World Health Organization for Asians (17) or BMI <23 kg/m^2 with at least two evidences of metabolic dysregulation, such as blood pressure ⩾130/85 mmHg, TG⩾1.70 mmol/L, and HDL-cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women) (18). Regrettably, 3156 patients with T2DM who received medical intervention were not included in this study, due to serious incomplete medical records.

Patient and Public Involvement

No patient was involved.

Physical examination

All physical examinations involved in this study are part of the routine examination. Blood pressure measurements, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), were performed twice after participants have sited, in a calm state for at least 5 min, using an electronic sphygmomanometer (HEM-7200; OMRON Healthcare, Kyoto, Japan). Height and weight were measured in the morning on an empty stomach.

Laboratory examination

All physical blood tests included in this study are part of the routine examination. Anterior cubital vein blood was drawn in the fasting state (at least 8 h). A midcourse morning urine specimen was taken as well. Routine blood panel, liver function, kidney function, serum uric acid (SUA) level, fasting blood glucose (FBG) level, blood lipids, and routine urine analysis were assessed using a 7600 autoanalyzer (Hitachi, Tokyo, Japan).

Color Doppler ultrasound of the liver and gallbladder

A liver ultrasound is part of the routine examination. It was performed by two experienced ultrasound radiologists with at least 5 years of experience using an IU 22 system (Philips Healthcare, Best, The Netherlands). A participant was diagnosed with hepatic steatosis when the ultrasound examination showed that the liver had fatty liver changes (hyperechogenicity due to the increased acoustic interface caused by the

intracellular accumulation of lipid vesicles, blurring of vascular margins, enlarged liver size, and increased acoustic attenuation (10, 19)) .

Statistical analysis

R 3.5.3 and R Commander 2.5-3 were used for statistical analysis. The categorical data were expressed as n (%) and were analyzed using the Chi-square test. The continuous variables conforming to the normal distribution (according to the Kolmogorov-Smirnov test) were expressed as mean ± standard deviation and were analyzed using the Student's t-test. Abnormally distributed continuous variables were presented as median (interquartile range (IQR)) and were analyzed using the Mann-Whitney U test. Factors associated with MAFLD were identified using univariate analysis. Variables with P-value <0.05 were included in a multivariate logistic regression model. P-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the subjects

A total of 284,129 subjects were examined during the study period, and 204,394 subjects met the eligibility criteria. Table 1 presents the characteristics of the subjects. The subjects' mean age was 39.6±13.6 years old. The number of male and female subjects was 111,782 and 92,612, respectively. The male subjects' mean age was 38.8±13.7 years old, and that of female subjects was 40.5±13.3 years old. Shenyang

included 78,329 subjects, who aged 39.3±12.7 years old. No routine health examination was performed in Dandong in 2014. Dandong included 42,039 subjects, who aged 47.8±14.1 years old. Finally, 84,026 subjects were from Dalian, who aged 36.3±12.7 years old.

The prevalence of MAFLD among the healthy population

Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28% (Table 1). The prevalence of MAFLD increased with age (P<0.001), which was higher in men than in women (P<0.001), higher in overweight/obese subjects than in lean ones (P<0.001), and was higher in Dandong, followed by Shenyang and Dalian (P<0.001) (Table 1). The prevalence of MAFLD in Shenyang, Dandong, and Dalian over the past 5 years was 36.83%, 40.42%, and 31.78%, respectively.

The prevalence of MAFLD over time

The total prevalence of MAFLD from 2014 to 2018 was 30.01%, 30.11%, 33.22%, 34.58%, and 32.19%, respectively. The prevalence of MALFD over the 5 years mainly increased in the age-based group of 30-39 years old (P=0.006), in men (P=0.029) and in women (P=0.035) (Table 2). The prevalence of MAFLD in Shenyang over the past 5 years was basically consistent with the general trend in Liaoning. The prevalence of MAFLD in Dandong significantly increased annually

over the past 4 years. The prevalence of MAFLD in Dalian substantially increased in 2016, while it declined in 2017 and 2018 (Figure 2). The prevalence rate in men and women over the past 5 years was basically consistent with the general trend of MAFLD in Liaoning (Figure 3). With the increase of age, the prevalence of MAFLD was elevated in Liaoning.

Biomarkers for MAFLD

Table 3 presents the biomarkers in all subjects and according to lean/overweight-obese. The number of subjects with overweight/obese MAFLD was 66,609, of whom the number of patients with T2DM was 3,550 (5.33%). The number of cases with lean MAFLD was 5147, of whom the number of patients with T2DM was 143 (2.78%). The number of cases who were diagnosed (for the first time) with fasting blood glucose level over 7 was 289. Compared with the non-MAFLD group, subjects in the MAFLD group had higher SBP, DBP, FBG, TG, total cholesterol (TC), LDL-C, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), blood urea nitrogen (BUN), serum creatinine (sCr), and serum uric acid (SUA), higher frequencies of urine protein (UPRO) and GBp, lower HDL-C, hematocrit (HCT), and mean corpuscular volume (MCV), and lower frequency of UOB (all $P<0.001$). The same tendencies were observed in lean subjects, while there was no significant difference in UPRO ($P=0.86$).

MAFLD-associated factors

Table 4 presents the results of the univariate and multivariate logistic regression analyses of the factors associated with MAFLD. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO were independently associated with MAFLD (all P<0.001), while UOB (P=0.47) and GBp (P=0.21) were not. In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV were independently associated with MAFLD (all P<0.001), while SBP (P=0.51), ALT (P=0.27), BUN (P=0.16), UPRO (P=0.57), UOB (P=0.06), and GBp (P=0.06) were not.

DISCUSSION

The present study showed that the prevalence of MAFLD in Shenyang, Dandong, and Dalian cities varied, and higher BMI value and age played significant roles in the development of the disease. In addition, biomarkers, such as DBP, FBG, TG, LDL-C, ALT, GGT, BUN, SUA, HCT, UPRO, GBs, and GBp were independently and positively correlated with the prevalence of MAFLD, whereas HDL-C and MCV were negatively correlated. Therefore, the prevalence of MAFLD in Liaoning was related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators.

The increasing trend in the prevalence of NAFLD follows the level of

industrialization and urbanization. At present, China is the fastest-growing major economy in the world, and there are problems associated with a westernized diet, sedentary lifestyle, and metabolism, which are correlated with MAFLD. Thus, there is a closer relationship between MAFLD and economy than NAFLD. Studies have shown that the increase in the total annual NAFLD prevalence in China is consistent with the improvement in the gross domestic product (GDP) per capita (20). An increase in morbidity in various regions of the mainland China could be related to the increase in GDP per capita, while areas with the highest GDP per capita (≥$13,000) did not exhibit an increased incidence of NAFLD (21). According to the National Bureau of Statistics of China, the GDP per capita of Liaoning province has ranked first in the Northeast China over the past 5 years, whereas it is still in the lower-middle level nationally. The present study revealed that the prevalence of MAFLD in Liaoning (35.1%) was slightly higher than the overall prevalence in China (29.2%) (12). The current study selected two economically developed cites (Dalian and Shenyang) and one city with a moderate development (Dandong). The prevalence of MAFLD in these three cities was inversely proportional to the level of urban economic development. The prevalence of MAFLD in Dalian was lower than that in Shenyang. This could be related to the fact that Dalian is a coastal city, with dietary habits different from those of inland cities.

Differences in age were also confirmed. The prevalence of MAFLD in the age-based group of 20-29 years old was 17.9%, while it was 45.6% in the age-based

group of >60 years old, which is in agreement with previous studies, which demonstrated that age could play a crucial factor in the prevalence of NAFLD (11, 12, 15).

The present study indicated that the overall prevalence of MAFLD in men was higher than that in women, which is basically consistent with the previously reported findings in other regions of China (22). The prevalence of MAFLD in middle-aged men was the highest and reached the peak at 40-49 years old (50.27%). This high prevalence might be related to high stress, irregular work and rest, and decreased metabolism among middle-aged men. The prevalence of MAFLD in women aging over 50 years old was significantly higher, which could be related to the age range of menopause.

Obesity is closely associated with metabolic diseases, such as MAFLD. The current study confirmed that BMI ≥23 kg/m^2 is an independent risk factor for MAFLD in Liaoning. Therefore, for overweight and obese individuals, it is necessary to improve diet and exercise management, even using drugs or surgery, if required. It has been reported that the global NAFLD prevalence in lean population was 5%-26% (23). In the present study, the prevalence of NAFLD in lean population was 10.75%, which is similar to previously reported results (24).

In this study, both lean-MAFLD and non-lean-MAFLD were closely related to metabolic indicators. Those metabolic indicators were also associated with T2DM, metabolic syndrome, obesity, and liver diseases, as supported by previous studies (11,

12, 15, 22-24). In addition to obesity, variations in the prevalence of MAFLD follow the epidemic trends of T2DM and MetS. The prevalence of MAFLD in hyperlipidemia and T2DM patients is higher, reaching 27%-92% and 28%-70%, respectively. Patients with MAFLD mainly have hyperlipidemia, hypertension, T2DM, and metabolic syndrome (25). In the current study, multivariate logistic regression analysis found that DBP, TG, LDL-C, FBG, and SUA were independent risk factors for MAFLD, while HDL-C was independently associated with MAFLD. Therefore, additional attention should be paid to hyperlipidemia, hypertension, and T2DM to assess their influences on the prevention and treatment of MAFLD. Regarding the correlation between SUA and MAFLD, SUA elevation was reported as one of the risk factors for MAFLD (26).

Although genetic susceptibility was not examined in the current study, it is involved in NAFLD. Polymorphisms in PNPLA3 (27), SREBF-2 (28), CETP (28, 29), and APOC3 (30) have been found to be associated with lean-NAFLD. In addition to genetic polymorphisms, lean-NAFLD cases have increased bile acid and FXR activity due to metabolic abnormalities and changes in intestinal microbial composition (31, 32). These factors should be assessed in the future studies.

Regarding the diabetes, because 3156 patients had previously received systemic treatment for diabetes, the current blood glucose levels and metabolic indicators were in the normal range, thus, in order to reduce the error in the analysis of risk factors, we excluded these patients. In addition, diabetic patients analyzed in the present study

were previously diagnosed, of whom 289 patients were found to have elevated fasting blood glucose levels for the first time. As physical examinations did not involve OGTT and repeated tests, we did not classify such patients as diabetic.

This study has some limitations. Although the examinations were performed at the same clinic, they were conducted at three different physical locations over the past 5 years. Biases due to the different locations and changes in practice over time could not be excluded. Due to the large number of physical examinations and no measurement of waist circumference and high-sensitivity C-reactive protein (hs-CRP), the diagnosis of MAFLD in some patients with normal BMI might be ignored. In addition, ultrasound is operator-dependent, and a bias in the diagnosis of MAFLD could not be excluded. Finally, this was a cross-sectional study that could not provide any causal relationship between MAFLD and the associated factors.

In conclusion, the prevalence of MAFLD in Liaoning was found to be associated with sex, cities with different economic statuses, BMI, and multiple metabolic indicators. Longitudinal studies are necessary to further determine factors associated with the development of MAFLD.

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.

2. Stal P. Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge with prognostic significance. World J Gastroenterol. 2015;21:11077-87.

3. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020;158:1999-2014 e1.

4. Fouad Y, Waked I, Bollipo S, et al. What's in a name? Renaming 'NAFLD' to 'MAFLD'. Liver Int. 2020;40:1254-61.

5. Pai RK. NAFLD Histology: a Critical Review and Comparison of Scoring Systems. Curr Hepatol Rep. 2019;18:473-81.

6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274-85.

7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012;142:1592-609.

8. Non-Alcoholic Fatty Liver Disease: Assessment and Management. National

Institute for Health and Care Excellence: Guidance. London2016.

9. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313:2263-73.

10. Shen FF, Lu LG. Advances in noninvasive methods for diagnosing nonalcoholic fatty liver disease. J Dig Dis. 2016;17:565-71.

11. Zhou J, Zhou F, Wang W, et al. Epidemiological Features of NAFLD From 1999 to 2018 in China. Hepatology. 2020;71:1851-64.

12. Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis. Hepatology. 2019;70:1119-33.

13. Caballeria L, Auladell MA, Toran P, et al. Risk factors associated with non-alcoholic fatty liver disease in subjects from primary care units. A case-control study. BMC Gastroenterol. 2008;8:44.

14. Hartmann P, Schnabl B. Risk factors for progression of and treatment options for NAFLD in children. Clin Liver Dis (Hoboken). 2018;11:11-5.

15. Wu Y, Zheng Q, Zou B, et al. The epidemiology of NAFLD in Mainland China with analysis by adjusted gross regional domestic product: a meta-analysis. Hepatol Int. 2020;14:259-69.

16. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;65:1557-65.

17. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157-63.

18. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic associated fatty liver disease: an international expert consensus statement. Journal of Hepatology. 2020;73(1):202-209.

19. Mahale AR, Prabhu SD, Nachiappan M, et al. Clinical relevance of reporting fatty liver on ultrasound in asymptomatic patients during routine health checkups. J Int Med Res. 2018;46:4447-54.

20. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of nonalcoholic fatty liver disease. Med Res Rev. 2019;39:328-48.

21. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol. 2017;67:862-73.

22. Zhu JZ, Zhou QY, Wang YM, et al. Prevalence of fatty liver disease and the economy in China: A systematic review. World J Gastroenterol. 2015;21:5695-706.

23. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. Clin Nutr. 2019;38:975-81.

24. Shi Y, Wang Q, Sun Y, et al. The Prevalence of Lean/Nonobese Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2020;54:378-87.

25. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis. 2019;20:163-73.

26. Ma Z, Xu C, Kang X, et al. Changing trajectories of serum uric acid and risk of non-alcoholic fatty liver disease: a prospective cohort study. J Transl Med. 2020;18:133.

27. Musso G, Cassader M, Bo S, et al. Sterol regulatory element-binding factor 2 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and lipoprotein and glucose dysmetabolism. Diabetes. 2013;62:1109-20.

28. Adams LA, Marsh JA, Ayonrinde OT, et al. Cholesteryl ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity. J Gastroenterol Hepatol. 2012;27:1520-7.

29. Petersen KF, Dufour S, Hariri A, et al. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N Engl J Med. 2010;362:1082-9.

30. Li C, Guo P, Okekunle AP, et al. Lean non-alcoholic fatty liver disease patients had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and overtime work as obese non-alcoholic fatty liver disease patients. J Gastroenterol Hepatol. 2019;34:256-62.

31. Safari Z, Gerard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cell Mol Life Sci. 2019;76:1541-58.

32. Suk KT, Kim DJ. Gut microbiota: novel therapeutic target for nonalcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol. 2019;13:193-204.

Table 1. Characteristics of the patients with non-MAFLD and MAFLD

Subgroups	Age (years), Mean±**SD**	All N=204,394	Non-MAFLD n=132,638	MAFLD n=71,756	Prevalence (%)	P
Age						<0.001
20-29		22,822	18,728	4094	17.94	
30-39		80,227	54,671	25,556	31.85	
40-49		44,464	27,913	16,551	37.22	
50-59		30,861	17,173	13,688	44.35	
≥60		26,020	14,153	11,867		
Sex						<0.001
Male	38.8±13.7	111,782	60,222	51,560	46.13	
Female	40.5±13.3	92,612	72,416	20,196	21.81	
BMI (kg/m^2)						<0.001
<23		79,271	74,124	5147	6.49	
≥23		125,123	58,514	66,609	53.23	
City						<0.0

					01
Shenyang	39.3±12.7	78,329	50,265	28,064	36.83
Dandong	47.8±14.1	42,039	25,048	16,991	40.42
Dalian	36.3±12.7	84,026	57,325	26,701	31.78
Overall	39.6±13.6	204,394	132,638	71,756	35.11

MAFLD: metabolic-associated fatty liver disease; BMI: body mass index.

Table 2. Changes in the prevalence of MAFLD over time (2014-2018)

Subgroups	Year, %					P
	2014	2015	2016	2017	2018	
Age (years)						
20-29	16.43	17.20	17.30	18.82	18.18	0.081
30-39	29.24	28.60	31.05	33.37	34.33	0.006
40-49	35.65	34.50	35.40	39.04	38.69	0.200
50-59	46.32	39.40	41.67	46.96	45.44	0.636
≥60	44.83	40.65	45.34	48.39	46.50	0.234
Sex						
Male	42.60	42.63	44.36	48.12	48.45	0.029
Female	14.85	19.33	21.49	24.63	22.67	0.035
BMI (kg/m^2)						
<23	5.08	5.35	6.68	7.36	6.80	0.058
≥23	54.93	50.37	52.15	55.08	53.76	0.510
City						
Shenyang	34.89	34.80	34.27	37.36	36.92	0.182
Dandong	-	30.06	34.29	42.66	44.17	0.039
Dalian	26.36	29.00	33.20	32.36	32.98	0.048
Overall	30.01	30.11	33.22	34.58	32.19	<0.001

BMI: body mass index.

Table 3. Comparison of the metabolic tests between non-MAFLD and MAFLD

Variables	Overall		P	Lean (BMI<23)		P	Overweight (BMI >=23)		P
	Non-MAFLD	MAFLD		Non-MAFLD	MAFLD		Non-MAFLD	MAFLD	
SBP, mmHg	118±18	129±19	<0.001	114±16	122±19	<0.001	123±18	129±19	<0.001
DBP, mmHg	70±11	77±13	<0.001	67±10	73±12	<0.001	72±12	77±13	<0.001
FBG, mmol/L	5.15±1.30	5.82±1.63	<0.001	5.04±1.22	5.63±1.65	<0.001	5.3±1.38	5.83±1.63	<0.001
TG, mmol/L	1.07±0.85	2.12±1.73	<0.001	0.91±0.64	1.79±1.46	<0.001	1.28±1.01	2.14±1.75	<0.001
TC, mmol/L	4.41±1.43	4.96±1.34	<0.001	4.29±1.41	4.94±1.36	<0.001	4.55±1.43	4.97±1.34	<0.001
LDL-C, mmol/L	1.99±1.34	2.42±1.43	<0.001	1.9±1.28	2.46±1.38	<0.001	2.09±1.40	2.42±1.43	<0.001
HDL-C, mmol/L	1.01±0.71	0.9±0.60	<0.001	1.06±0.73	0.99±0.64	<0.001	0.93±0.67	0.9±0.60	<0.001
ALT, U/L	19.37±17.28	36.58±27.98	<0.001	17.09±14.34	27.89±21.40	<0.001	22.19±19.98	37.2±28.29	<0.001
AST, U/L	19.59±11.18	25.85±13.56	<0.001	18.76±10.03	23.55±13.08	<0.001	20.62±12.38	26.02±13.57	<0.001
ALP, U/L	7.01±22.44	9.62±25.91	<0.001	5.51±20.85	8.48±24.35	<0.001	8.98±24.13	9.7±26.02	<0.001

GGT, U/L	18.42±24.10	39.36±42.82	<0.001	15.54±20.76	31.41±48.78	<0.001	21.99±27.27	37.71±42.34	<0.001
BUN, mmol/L	4.32±1.97	4.8±1.80	<0.001	4.17±1.90	4.65±1.77	<0.001	4.51±2.04	4.81±1.80	<0.001
Scr, μmol/L	58.57±26.43	66.63±24.76	<0.001	56.12±25.14	62.05±22.61	<0.001	61.62±27.66	66.96±24.88	<0.001
SUA, μmol/L	283.17±125.06	369.05±135.06	<0.001	263.87±116.14	330.07±123.40	<0.001	307.09±131.43	371.84±135.42	<0.001
HCT, %	21.57±21.35	20.32±22.42	<0.001	21.95±20.97	20.36±21.90	<0.001	21.1±21.80	20.32±22.46	<0.001
MCV, fl	47.2±44.74	41.66±44.42	<0.001	48.78±44.68	42.74±44.70	<0.001	45.23±44.74	41.58±44.40	<0.001
UPRO, n (%)	6.70%	9.20%	<0.001	6.30%	6.20%	0.86	7.30%	9.40%	<0.001
UOB, n (%)	11.10%	8.80%	<0.001	11.20%	9.40%	0.00	10.80%	8.80%	<0.001
GBp, n (%)	7.40%	8.90%	<0.001	6.20%	8.60%	<0.001	8.90%	9.70%	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood;

GBp: gallbladder polyps.

Table 4. Multivariable analyses of the factors associated with MAFLD

Variables	Univariable logistical regression			Multivariable logistical regression			
	OR	OR (95% CI)	P	OR	OR (95% CI)		P
MAFLD							
BMI (kg/m^2)							
<23	0.057	0.056	0.060	<0.001	0.125	0.119	0.130	<0.001
≥23							
SBP, mmHg	1.033	1.033	1.034	<0.001	1.003	1.003	1.005	<0.001
DBP, mmHg	1.053	1.052	1.054	<0.001	1.014	1.012	1.016	<0.001
FBG, mmol/L	1.541	1.520	1.559	<0.001	1.122	1.104	1.131	<0.001
TG, mmol/L	2.899	2.854	2.953	<0.001	1.651	1.627	1.691	<0.001
TC, mmol/L	1.378	1.365	1.392	<0.001	0.879	0.866	0.893	<0.001
LDL-C, mmol/L	1.267	1.255	1.277	<0.001	1.231	1.216	1.259	<0.001

HDL-C, mmol/L	0.799	0.785	0.813	<0.001	0.717	0.690	0.740	<0.001
ALT, U/L	1.040	1.038	1.040	<0.001	1.036	1.035	1.038	<0.001
AST, U/L	1.055	1.054	1.057	<0.001	0.979	0.977	0.981	<0.001
ALP, U/L	1.004	1.004	1.005	<0.001	0.998	0.998	1.000	<0.001
GGT, U/L	1.025	1.025	1.026	<0.001	1.002	1.002	1.002	<0.001
BUN, mmol/L	1.145	1.139	1.154	<0.001	1.019	1.007	1.032	<0.001
Scr, μmol/L	1.014	1.013	1.014	<0.001	0.995	0.994	0.996	<0.001
SUA, μmol/L	1.005	1.005	1.006	<0.001	1.003	1.002	1.003	<0.001
HCT, %	0.998	0.997	0.998	<0.001	1.006	1.003	1.008	<0.001
MCV, fl	0.997	0.997	0.997	<0.001	0.994	0.993	0.995	<0.001
UPRO, n (%)	1.407	1.342	1.462	<0.001	1.112	1.069	1.198	<0.001
UOB, n (%)	0.762	0.749	0.811	<0.001	1.000	0.933	1.033	0.47
GBp, n (%)	1.233	1.176	1.280	<0.001	1.026	0.981	1.090	0.21

Lean (BMI<23), MAFLD

SBP, mmHg	1.027	1.025	1.029	<0.001	1.999	0.995	1.002	0.51
DBP, mmHg	1.046	1.042	1.048	<0.001	1.018	1.012	1.024	<0.001
FBG, mmol/L	1.393	1.346	1.424	<0.001	1.098	1.064	1.133	<0.001
TG, mmol/L	2.771	2.642	2.891	<0.001	1.878	1.781	1.968	<0.001
TC, mmol/L	1.498	1.465	1.565	<0.001	0.891	0.860	0.941	<0.001
LDL-C, mmol/L	1.455	1.393	1.485	<0.001	1.372	1.301	1.430	<0.001
HDL-C, mmol/L	1.890	0.831	0.920	<0.001	0.695	0.631	0.741	<0.001
ALT, U/L	1.028	1.026	1.030	<0.001	1.025	1.024	1.030	0.27
AST, U/L	1.028	1.026	1.030	<0.001	0.971	0.969	0.980	<0.001
ALP, U/L	1.006	1.004	1.007	<0.001	1.000	0.998	1.001	<0.001
GGT, U/L	1.016	1.016	1.018	<0.001	1.001	1.001	1.004	<0.001
BUN, mmol/L	1.150	1.133	1.182	<0.001	1.022	0.990	1.059	0.16

Scr, μmol/L	1.010	1.008	1.012	<0.001	0.898	0.987	0.993	<0.001
SUA, μmol/L	1.005	1.005	1.006	<0.001	1.004	1.004	1.004	<0.001
HCT, %	0.996	0.995	0.998	<0.001	1.016	1.005	1.023	<0.001
MCV, fl	0.997	0.996	0.998	<0.001	0.993	0.986	0.995	<0.001
UPRO, n (%)	1.000	0.841	1.149	<0.001	0.995	0.795	1.130	0.57
UOB, n (%)	0.802	0.716	0.926	<0.001	0.947	0.757	1.004	0.06
GBp, n (%)	1.444	1.242	1.629	<0.001	1.221	0.992	1.337	0.06

MAFLD: metabolic associated fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood; GBp: gallbladder polyps.

FIGURE LEHENDS

Figure 1. The location of the three study cities in Liaoning Province.

Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018). ***P<0.001.

Figure 1. The location of the three study cities in Liaoning Province.

80x71mm (600 x 600 DPI)

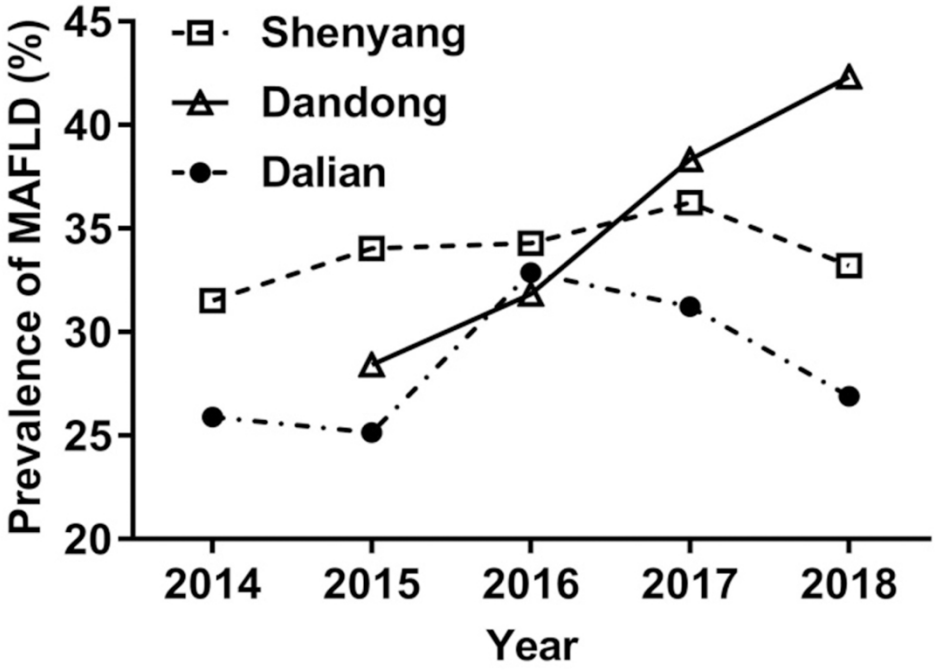

Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

80x61mm (600 x 600 DPI)

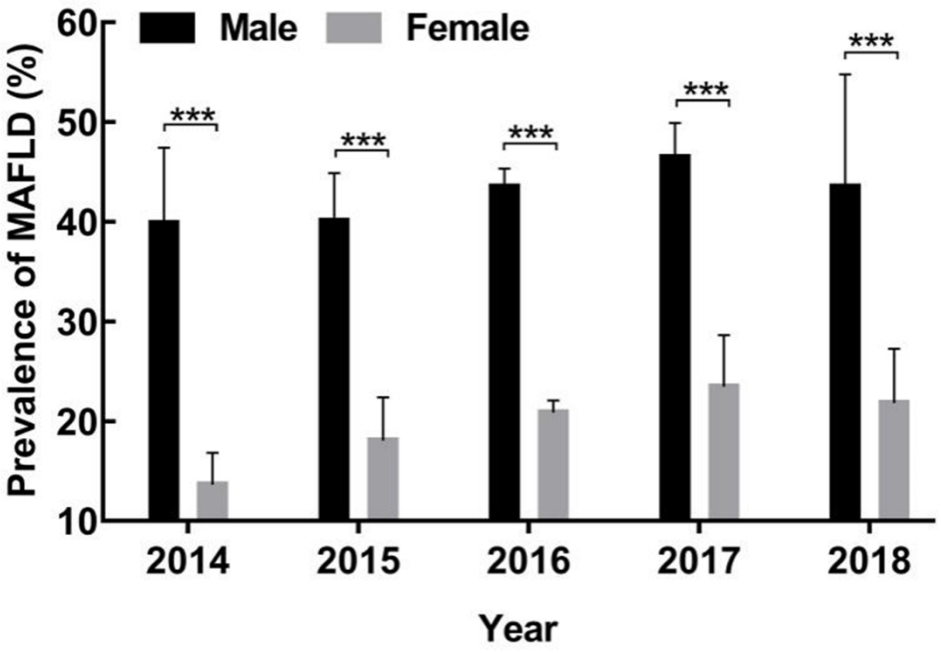

Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018).
***P<0.001.

80x55mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ***Case-control study***—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) ***Cohort study***—For matched studies, give matching criteria and number of exposed and unexposed ***Case-control study***—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) ***Cohort study***—If applicable, explain how loss to follow-up was addressed ***Case-control study***—If applicable, explain how matching of cases and controls was addressed ***Cross-sectional study***—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) ***Cohort study***—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	***Cohort study***—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.