International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

Analysis of Factors Related to Pulmonary Nodules in Patients With Fatty Liver: A Large-Scale Cohort Study Based on a Physical Examination Population

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Purpose: People with fatty liver are at high risk for pulmonary nodules, but the underlying mechanism is unclear. This study aimed to investigate the occurrence of lung nodules in fatty liver patients and explore influencing factors.

Patients and Methods: We retrospectively analyzed 57,119 individuals who underwent health checkups at the People's Hospital of Guangxi from May 2020 to May 2024. Patients with fatty liver were divided into pulmonary nodule and no pulmonary nodule groups. Univariate and multifactorial analyses were conducted using physical examination data, laboratory test indexes, and imaging information. Logistic regression analysis was used to identify independent predictors of pulmonary nodules in fatty liver patients.

Results: A total of 20,042 patients with fatty liver were included in the study, with 12,334 (61.5%) in the lung nodule group and 7708 (38.5%) in the non-lung nodule group. Age, gender, systolic and diastolic blood pressure were significantly higher in the pulmonary nodule group, while body weight, waist circumference, hemoglobin, uric acid, and glutamyltransferase were lower. Multifactorial logistic regression analysis showed that male gender, body weight, age, and diastolic blood pressure were significant factors influencing lung nodule development in fatty liver patients.

Conclusion: Fatty liver disease is independently associated with an increased incidence of pulmonary nodules, highlighting its importance in lung cancer screening and prevention.

Keywords: pulmonary nodules, fatty liver, health checkup, influencing factors, retrospective cohort study

Introduction

The prevalence of pulmonary nodules, a common type of lung lesion, ranges roughly from 10% to 20% worldwide.[1,2] With the widespread use of low-dose spiral CT (LDCT) in medical examinations, the detection rate of lung nodules has increased significantly, and although most lung nodules are benign, the risk of their potential malignant transformation has attracted much attention.[3] The development of pulmonary nodules is influenced by a variety of factors, among which metabolic factors have received much attention in recent years. Metabolic abnormalities, including obesity, dyslipidemia, hyperglycemia, hypertension, etc., are not only closely associated with a variety of chronic diseases, but also have been gradually recognized to be closely related to the formation and development of lung nodules, possibly by promoting inflammatory response, cell proliferation, and other pathways to increase the risk of lung nodules. In addition, poor lifestyle and dietary habits, such as long-term smoking, overeating, and excessive intake of spicy and irritating foods, may lead to an imbalance of the metabolic environment in the body, which in turn promotes the formation and malignancy of lung nodules.[4] These influences not only act independently, but also

Received: 27 September 2024
Accepted: 12 January 2025
Published: 16 January 2025

intertwine with other risk factors, such as age and gender, to form a complex network of lung nodule development.[5] Therefore, in-depth investigation of the pathogenesis of lung nodules, identification of their risk factors, and effective prevention and screening accordingly are of great significance in improving the early diagnosis of lung cancer and reducing mortality.

Fatty liver, is a metabolic disease mainly characterized by abnormal fat deposition in the liver. Its occurrence is closely related to metabolic abnormalities such as obesity, elevated blood lipids, insulin resistance, and hypertension.[6] Disturbances in fat metabolism in patients with fatty liver may lead to an increase in free fatty acids and inflammatory factors in the blood, which may reach the lungs through the blood circulation, causing changes in the microenvironment of the lungs and promoting the formation of lung nodules.[7] Secondly, insulin resistance and hyperglycemia in combination with fatty liver may exacerbate oxidative stress and inflammation throughout the body, and this chronic low-grade inflammatory state is an important predisposing factor for a variety of diseases, including pulmonary nodules.[8] Furthermore, patients with fatty liver disease often suffer from decreased liver function, which affects the liver's ability to process toxins and waste products in the body, and may indirectly affect the health of the lungs, promoting the development of pulmonary nodules.[9]

Although there is a lack of direct studies on the association between fatty liver and lung nodules, there is some indirect evidence suggesting a potential link. Zhu et al showed a higher incidence of lung cancer, especially adenocarcinoma, in patients with fatty liver.[10] Wu et al found that patients with fatty liver had a higher incidence of lung nodules than non-fatty liver populations, and that these nodules may be more malignant pathologically.[11] These findings suggest that fatty liver may be an important risk factor for the development of lung nodules. However, the mechanism of how fatty liver specifically affects the development of pulmonary nodules is not fully understood, and further studies are needed to elucidate the complex relationship.

Therefore, this study will systematically assess the occurrence of pulmonary nodules in patients with fatty liver disease and explore the influencing factors behind them through large-scale data collection and analysis based on the physical examination population. Through this study, the high-risk group of pulmonary nodules can be identified more precisely, providing a scientific basis for the development of personalized preventive and intervention measures.

Materials and Methods

General Information

We collected data from 57,119 healthy individuals who underwent health examinations at the Health Management Center of Guangxi Zhuang Autonomous Region People's Hospital from May 2020 to May 2024. According to the criteria outlined in the "Guideline for the Diagnosis and Treatment of Non-alcoholic Fatty Liver Disease (2018 Updated Version)", a total of 20,042 individuals were diagnosed with fatty liver disease.[12] Among them, 12,334 had fatty liver disease with lung nodules (referred to as the lung nodule group), and 7708 had fatty liver disease without lung nodules (referred to as the non-lung nodule group). The inclusion and exclusion criteria were as follows: Inclusion criteria: (1) aged 18 years and above; (2) underwent chest LDCT examination; (3) underwent abdominal ultrasound examination. Exclusion criteria: (1) history of lung cancer or pulmonary tuberculosis; (2) severe dysfunction of important organs such as the heart, liver, and kidneys; (3) women who were pregnant, preparing for pregnancy, or lactating; (4) patients with viral hepatitis, drug-induced hepatitis, or autoimmune hepatitis (Figure 1). This study was approved by the Ethics Committee of Guangxi Zhuang Autonomous Region People's Hospital and the Ethics Committee of Guangxi Medical Sciences Institute (Approval No. KY-SY-2021-1). All participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Physical Examination

Anthropometric data, including height, weight, Systolic Blood Pressure(SBP), Diastolic Blood Pressure(DBP), waist circumference(WC), and hip circumference(HC), were collected by professional medical staff for each participant.

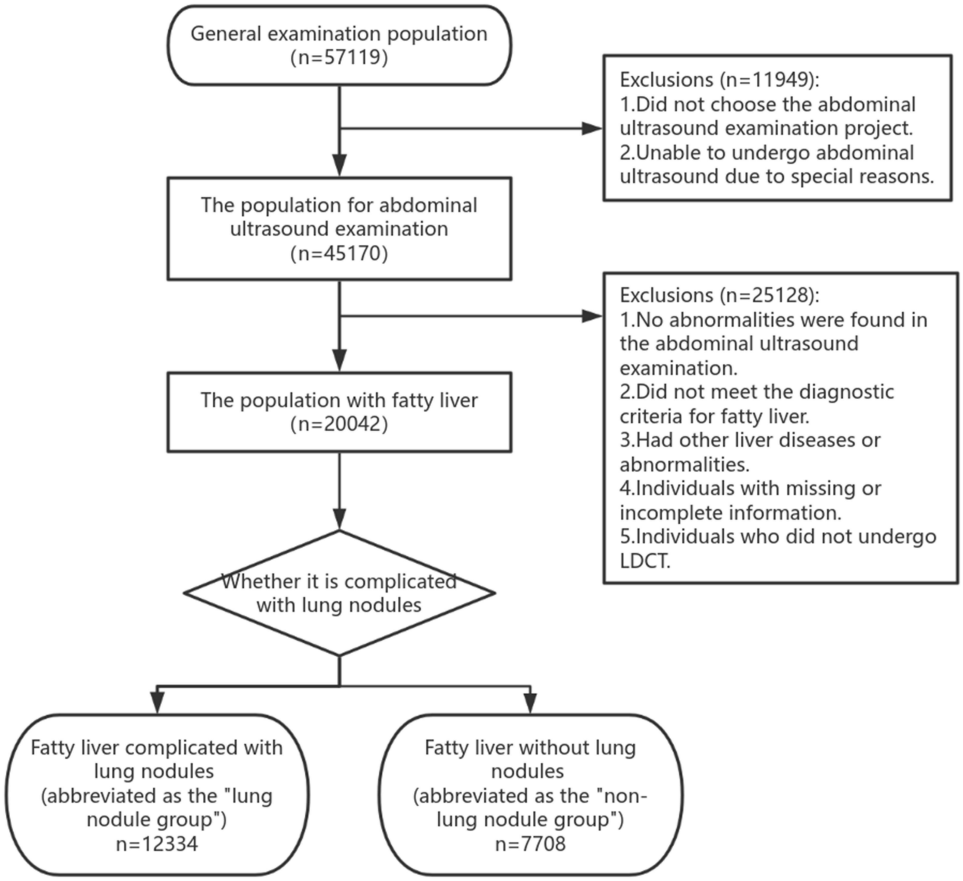

Figure 1 Flowchart for Screening Participants from the General Examination Population.

Laboratory Tests

After fasting for at least 8 hours, morning fasting serum samples were collected from all participants. The collected biomarkers included triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), serum creatinine (Cr), uric acid(UA), endogenous creatinine clearance rate (Ccr), hemoglobin (HGB), platelet count (PLT), white blood cell count (WBC), glycated hemoglobin (HbA1c), 2-hour postprandial blood glucose (2h-PG), fasting insulin (FINS), and high-sensitivity C-reactive protein (hs-CRP). The results of serum biomarkers were obtained from the hospital information system.

Ultrasound Examination

All participants underwent ultrasound examination of the liver, gallbladder, pancreas, and spleen after fasting for more than 8 h. The diagnosis of NAFLD was mainly based on the diagnostic criteria of the Guidelines for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease (2018 Update),[12] and at least 2 of the following 3 abdominal ultrasound manifestations were required for the diagnosis of fatty liver by ultrasound: (1) diffuse enhancement of hepatic echogenicity and greater hepatic echo than that of the kidneys or the spleen; (2) blurring of blood vessels; (3) gradual attenuation of liver echoes. Abdominal ultrasound is performed using a color Doppler ultrasound imager, and is examined by an ultrasonographer with intermediate or advanced qualifications, and a unified diagnosis is made in accordance with the above diagnostic criteria.

Imaging Examination

Chest LDCT scans were performed on all participants using a 64-slice spiral CT scanner (Siemens SOMATOM Go TopX). The scans were interpreted by two senior radiologists from our hospital in conjunction with CAD. The diagnostic

results were based on the "Chinese Expert Consensus on the Diagnosis and Treatment of Lung Nodules (2018 Version)".[13] Lung nodules were defined as at least one non-calcified nodule with a maximum diameter of ≤30mm in the lung. Nodules with a diameter of <5mm were defined as micro-nodules, those between 5mm and 10mm were defined as small nodules, and those >10mm were defined as large nodules.

Statistical Analysis

Statistical analysis of the data was performed using SPSS 24.0 software. Count data were described using frequency and percentage (%), while measurement data were described using mean ± standard deviation. Univariate analysis was conducted using independent sample *t*-tests (for continuous variables) and χ^2-tests (for categorical variables) to assess the correlation between the occurrence of lung nodules in fatty liver patients and common clinical variables. For continuous variables with non-normal distribution, the Wilcoxon rank-sum test was used for comparison. Variables with statistically significant differences in univariate analysis were included in multivariate logistic regression analysis to identify independent risk factors for the occurrence of lung nodules in fatty liver patients. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to quantify the impact of various factors on the risk of lung nodule occurrence. A P-value <0.05 was considered statistically significant.

Results

General Characteristics of the Study Population

A total of 57,119 healthy individuals were recruited for this study, based on the inclusion and exclusion criteria, a total of 20,042 patients with fatty liver disease (12,334 from the lung nodule group and 7708 from the non-lung nodule group) were selected for final analysis. Among them, there were 32,874 males (57.55%) and 24,245 females (42.45%), with a mean age of 49.79±14.58 years. The detection rate of lung nodules in patients with fatty liver was 61.5% (12,334 cases), with 11,274 cases (19.74%) identified as low-risk lung nodules and 681 cases (1.19%) as moderate-to-high-risk lung nodules. This indicates a certain correlation between fatty liver and lung nodules, but further analysis is needed to identify specific influencing factors (Table 1). In Figure 2, we show low-dose CT image maps presenting examples of low-risk, intermediate-risk, and high-risk lung nodules, respectively; while in Figure 3, images of normal liver versus fatty liver are shown in comparison.

Table 1 General Information of 57,119 Physical Examination Participants

Variable	Total (n = 57,119)
Age (years)	49.79 ± 14.58
Gender	
- Male	32,874 (57.55%)
- Female	24,245 (42.45%)
Height (cm)	163.96 ± 8.09
Weight (kg)	65.73 ± 12.37
SBP (mmHg)	127.26 ± 16.30
DBP (mmHg)	76.93 ± 11.18
WC (cm)	83.62 ± 11.93
HC (cm)	95.68 ± 7.52
TG (mmol/L)	1.69 ± 1.74
2h-PG (mmol/L)	7.19 ± 2.80
HGB (g/L)	143.15 ± 16.07
ALT (U/L)	24.67 ± 22.91

(*Continued*)

Table 1 (Continued).

Variable	Total (n = 57,119)
AST (U/L)	25.14 ± 16.49
UA (μmol/L)	377.14 ± 97.36
Cr (μmol/L)	77.02 ± 26.24
Pulmonary Nodule Risk Category	
- Low Risk	11,274 (19.74%)
- Intermediate-to-High Risk	681 (1.19%)
Fatty Liver Disease	
- Absent	23,226 (40.66%)
- Present	20,042 (35.09%)
Pulmonary Nodules	
- Absent	23,312 (40.81%)
- Present	33,807 (59.19%)

Univariate Analysis of Lung Nodule Detection in Patients With Fatty Liver

To evaluate the influencing factors of lung nodules in patients with fatty liver, we divided the population into two groups based on whether lung nodules were detected by LDCT and conducted independent correlation analyses. The results showed that age, systolic blood pressure, and diastolic blood pressure were significantly higher in the lung nodule group than in the non-lung nodule group ($P<0.05$), while the proportion of males, body weight, waist circumference, hemoglobin, uric acid, and gamma-glutamyl transferase were significantly lower in the lung nodule group than in the non-lung nodule group ($P<0.05$). There were no significant differences in height, hip circumference, triglycerides, high-density lipoprotein, low-density lipoprotein, postprandial 2-hour blood glucose, or glycated hemoglobin between the two groups (Table 2).

Multivariate Logistic Regression Analysis of Lung Nodule Occurrence in Patients With Fatty Liver

To further identify the independent influencing factors of lung nodule occurrence in patients with fatty liver, we included indicators with statistically significant differences in a multivariate logistic regression analysis. The results indicated that gender, age, body weight, and diastolic blood pressure were important influencing factors for lung nodule occurrence in patients with fatty liver. Specifically, males were less likely to develop lung nodules compared to females (OR=0.833, 95% CI: 0.752–0.923, $P<0.001$). For each additional year of age, the risk of lung nodule occurrence increased by 1% (OR=1.01, 95% CI: 1.007–1.013, $P<0.001$). Increased body weight was also identified as a risk factor for lung nodule occurrence (OR=1.005, 95% CI: 1.000–1.010, P=0.041). For every one kg increase in body weight, the risk of developing lung nodules in patients with fatty liver disease increases by approximately 0.5%, and for every 1 mmHg increase in diastolic blood pressure, the risk of developing lung nodules increases by approximately 0.7% (OR=1.007, 95% CI: 1.003–1.012, P=0.001) (Table 3).

Comparison of Relevant Indicators Between Low-Risk and Moderate-to-High-Risk Lung Nodule Groups in Patients With Fatty Liver

Based on the aforementioned results indicating a correlation between fatty liver and the occurrence of lung nodules, we further compared the conditions of low-risk and moderate-to-high-risk lung nodules in patients with fatty liver to investigate whether fatty liver affects the malignancy of lung nodules. The results showed significant differences in gender distribution between the two groups, with the proportion of males in the moderate-to-high-risk group being significantly lower than that in the low-risk group ($P<0.001$). This finding suggests that gender may be an important factor affecting the risk level of lung nodules. The body weight in the moderate-to-high-risk group was significantly lower than that in the low-risk group (P=0.005). Waist circumference, as an important indicator for measuring abdominal

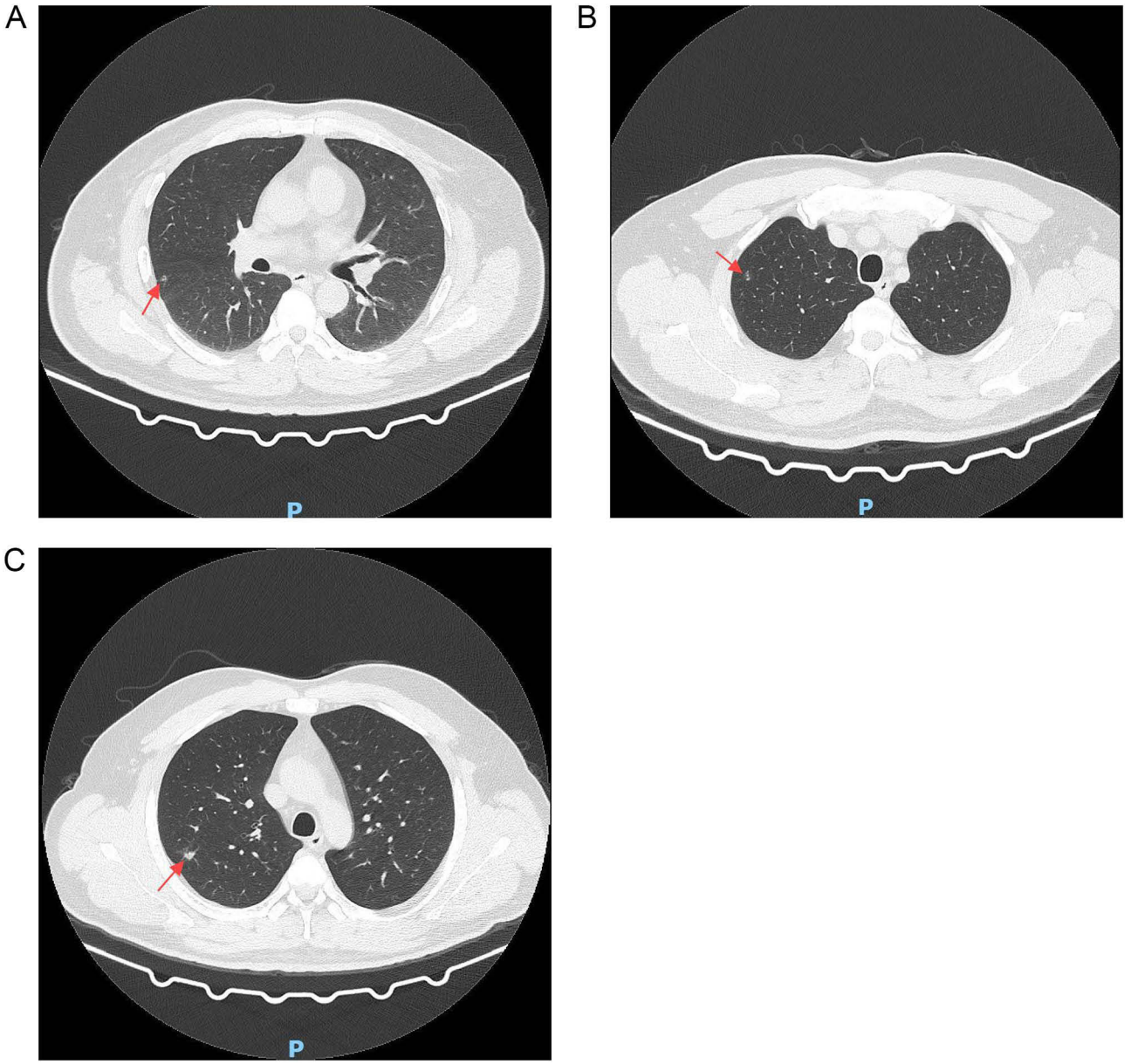

Figure 2 Comparison images of low-risk, intermediate-risk and high-risk pulmonary nodules in the lungs on low-dose CT scans.(**A**) low-risk pulmonary nodule.(**B**) Medium-risk lung nodule.(**C**) High-risk lung nodules.The red arrow points to the location of the lesion.

obesity, also showed significant differences between the two groups (P=0.015), with the mean waist circumference in the moderate-to-high-risk group being slightly smaller than that in the low-risk group. Additionally, there were statistically significant differences in height and systolic blood pressure between the two groups (P<0.05). In terms of biochemical indicators, there were no significant differences between the two groups in triglycerides, high-density lipoprotein, low-density lipoprotein, postprandial 2-hour blood glucose, glycated hemoglobin, platelet count, white blood cell count, uric acid, creatinine, urea nitrogen, endogenous creatinine clearance rate, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, and fasting insulin. However, the hemoglobin (HGB) level in the moderate-to-high-risk group was significantly lower than that in the low-risk group (P=0.021), which may reflect specific hematological changes in the moderate-to-high-risk group. These differences suggest that, for patients with fatty liver, lung nodules of different risk levels may be associated with different clinical characteristics (Table 4).

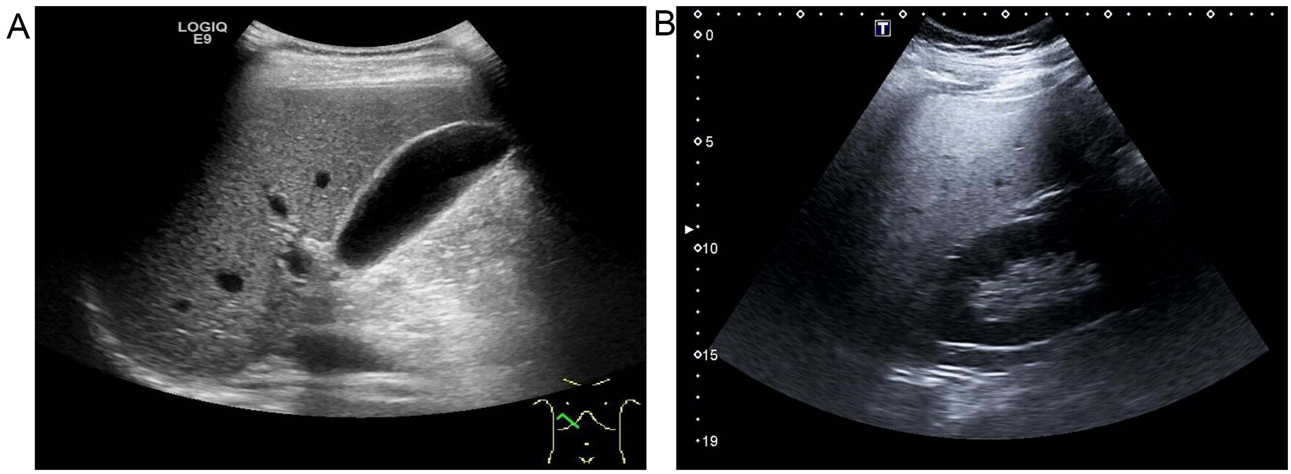

Figure 3 Ultrasonographic images of normal liver and fatty liver.(**A**) Ultrasound image of a normal liver.(**B**) Echogram of fatty liver.

Multivariate Logistic Regression Analysis of Low-Risk and Moderate-to-High-Risk Lung Nodules in Patients With Fatty Liver

Further multivariate logistic regression analysis revealed that gender is an important independent factor affecting the risk level of lung nodules. After adjusting for other variables, male gender was found to be a protective factor against the transition from low-risk to moderate-to-high-risk lung nodules (OR=0.511, 95% CI: 0.299–0.874, P=0.014), indicating that males are less likely to develop moderate-to-high-risk lung nodules compared to females. However, indicators such as body weight, height, systolic blood pressure, waist circumference, and hemoglobin did not show significant effects on the risk level of lung nodules in the regression analysis (Table 5).

Table 2 Risk Factors for the Occurrence of Lung Nodules in Patients With Fatty Liver

	Pulmonary Nodules	**Non-Pulmonary Nodules**	
Variable	**(n=12334)**	**(n=7708)**	**P-value**
Age (years)*	52.00 (42.00–61.00)	50.00 (39.00–60.00)	0.000 **
Height (cm)*	166.30 (160.30–171.40)	166.40 (160.90–171.30)	0.225
Weight (kg)	72.657±11.577	73.169±11.543	0.003 *
WC (cm)*	90.00 (84.00–95.00)	90.00 (85.00–95.00)	0.018 *
HC (cm)	98.61±6.02	98.74±6.08	0.168
SBP (mmHg)	132.21±15.49	131.39±15.48	0.000 **
DBP (mmHg)	80.88±11.05	80.46±11.14	0.010 *
TG (mmol/L)*	1.74 (1.27–2.52)	1.72 (1.23–2.48)	0.081
HDL (mmol/L)	1.28±0.28	1.29±0.27	0.762
LDL (mmol/L)	3.50±0.81	3.51±0.80	0.892
2h-PG (mmol/L)	7.82±3.08	7.78±3.19	0.597
HbA1c (mmol/L) *	5.60 (5.30–5.90)	5.60 (5.30–5.90)	0.072
HGB (g/L)	148.27±14.77	148.89±14.72	0.0075 *
PLT (g/L)	263.94±61.18	265.27±62.26	0.141
WBC (109/L)	6.74±1.61	6.76±1.61	0.373
UA (μmol/L)	417.79±95.17	423.49±95.92	0.000 **
Cr (μmol/L) *	80.00 (68.00–90.00)	80.00 (68.00–90.00)	0.335
BUN (μmol/L)	5.118±1.267	5.09±1.28	0.135

(*Continued*)

https://doi.org/10.2147/IJGM.S495396

Table 2 (Continued).

Variable	Pulmonary Nodules (n=12334)	Non-Pulmonary Nodules (n=7708)	P-value
Ccr (μmol/L) *	86.00 (76.80–97.00)	87.00 (75.20–98.70)	0.929
ALT (U/L) *	24.00 (21.00–29.00)	24.00 (20.00–29.00)	0.855
AST (U/L) *	24.00 (18.00–35.00)	25.00 (18.00–37.00)	0.055
GGT (U/L) *	33.00 (23.00–51.00)	34.00 (23.00–53.00)	0.044 *
FINS (uIU/mL)	10.62±6.43	10.81±5.99	0.682
hs-CRP (mg/L)*	2.01 (0.87–3.66)	1.89 (1.15–3.33)	0.91
Gender**			0.000 **
-Male	8975 (72.8%)	5865 (76.1%)	
-Female	3359 (27.2%)	1843 (23.9%)	

Notes: * indicates independent sample *T*-test for the variable; ** indicates Wilcoxon rank-sum test for the variable. * p<0.05,**p<0.01.

Abbreviations: WC, waist circumference; HC, hip circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; 2h-PG, 2-hour postprandial blood glucose; HbA1c, glycated hemoglobin; HGB, hemoglobin; PLT, platelet count; WBC, white blood cell count; UA, uric acid; Cr, serum creatinine; BUN, blood urea nitrogen; Ccr, endogenous creatinine clearance rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; FINS, fasting insulin; hs-CRP, high-sensitivity C-reactive protein.

Table 3 Logistic Regression Analysis Results of Risk Factors for the Occurrence of Lung Nodules in Patients With Fatty Liver

Variable	Regression Coefficient	Standard Error	z-value	OR	95% CI	P-value
(Intercept)	−0.217	0.267	−0.816	0.805	0.477–1.357	0.415
Male	−0.183	0.052	−3.501	0.833	0.752–0.923	0 **
Weight	0.005	0.002	2.041	1.005	1.000–1.010	0.041 *
UA	0	0	−1.117	1	0.999–1.000	0.264
Age	0.01	0.002	6.456	1.01	1.007–1.013	0 **
SBP	−0.001	0.002	−0.616	0.999	0.996–1.002	0.538
WC	−0.003	0.003	−1.092	0.997	0.991–1.002	0.275
DBP	0.007	0.002	3.236	1.007	1.003–1.012	0.001 **
HGB	−0.001	0.001	−0.451	0.999	0.997–1.002	0.652
GGT	0	0	−0.162	1	0.999–1.001	0.872

Notes: * p<0.05,**p<0.01.

Abbreviations: UA, uric acid; SBP, Systolic Blood Pressure; WC, waist circumference; DBP, Diastolic Blood Pressure; HGB, hemoglobin; GGT, gamma-glutamyl transferase.

The Correlation Between Fatty Liver Disease and Lung Nodules of Different Risk Levels

We further investigated the specific risk factors for the development of lung nodules in patients with fatty liver disease. There was a significant difference in the risk stratification of lung nodules between the fatty liver group and the non-fatty liver group (P=0.004), with a significantly lower proportion of patients with fatty liver developing medium- to high-risk lung nodules compared to those without fatty liver. The proportion of patients with medium-risk lung nodules in the fatty liver group was 2.0%, while it was 2.8% in the non-fatty liver group; the proportions of patients with high-risk lung nodules were 2.5% and 3.2%, respectively. Similarly, there was a significant difference in the outcomes of lung nodule lesions between the two groups (P=0.004), with significantly lower incidences of precursor lesions (2.5% vs 3.1%) and malignant nodules (1.5% vs 1.7%) in patients with fatty liver compared to those without. These findings suggest that

Table 4 Comparison of Relevant Indicators Between Low-Risk and Moderate-to-High-Risk Lung Nodule Groups in Patients With Fatty Liver

	Low-Risk Pulmonary Nodules	Intermediate-to-High-Risk Pulmonary Nodules	
Variable	**(n=4178)**	**(n=195)**	**P-value**
Age (years)*	52.699±12.794	54.215±13.078	0.106
Height (cm)*	165.512±8.131	164.297±7.963	0.050 *
Weight (kg)	72.375±11.687	69.849±11.181	0.005 **
WC (cm)*	90.00 (84.00–95.000)	89.00 (81.25–94.00)	0.015 *
HC (cm)	98.585±6.092	97.835±5.809	0.13
SBP (mmHg)	132.437±15.382	134.761±16.794	0.048 *
DBP (mmHg)	80.749±10.840	80.978±11.570	0.783
TG (mmol/L)*	1.73 (1.25–2.47)	1.70 (1.32–2.54)	0.625
HDL (mmol/L)	1.292±0.282	1.323±0.286	0.136
LDL (mmol/L)	3.508±0.806	3.622±0.840	0.058
2h-PG (mmol/L)	7.929±3.165	7.465±2.954	0.142
HbA1c (mmol/L) *	5.60 (5.40–6.00)	5.60 (5.30–5.90)	0.228
HGB (g/L)	147.684±14.838	145.138±15.273	0.021 *
PLT (g/L)	265.266±63.697	269.143±60.239	0.412
WBC (109/L)	6.745±1.651	6.707±1.802	0.76
UA (μmol/L)	413.096±95.475	404.691±93.816	0.236
Cr (μmol/L) *	80.00 (68.00–90.00)	77.00 (63.00–91.00)	0.144
BUN (μmol/L)	5.150±1.298	5.042±1.204	0.263
Ccr (μmol/L) *	86.00 (75.20–94.90)	86.00 (73.45–105.95)	0.79
ALT (U/L) *	24.00 (21.00–29.00)	24.00 (20.00–28.00)	0.352
AST (U/L) *	24.00 (17.00–35.00)	23.50 (17.00–34.75)	0.542
GGT (U/L) *	32.00 (22.00–49.00)	31.00 (22.00–52.00)	0.921
FINS (uIU/mL)	9.552±5.637	7.530±2.946	0.427
hs-CRP (mg/L)*	2.372±1.638	3.001±1.171	0.323
Gender**			0.000 **
-Male	2946 (70.5%)	112 (57.4%)	
-Female	1232 (29.5%)	83 (42.6%)	

Notes: * indicates independent sample *T*-test for the variable; ** indicates Wilcoxon rank-sum test for the variable *p<0.05,**p<0.01.

Table 5 Multivariate Logistic Regression Analysis of Influencing Factors in Low-Risk and Moderate-to-High-Risk Lung Nodule Groups in Patients With Fatty Liver

Variable	Regression Coefficient	Standard Error	z-value	OR	95% CI	P-value
(Intercept)	−6.426	3.127	−2.055	0.002	0.000–0.743	0.04
Male	−0.672	0.274	−2.453	0.511	0.299–0.874	0.014*
Weight	−0.012	0.016	−0.736	0.988	0.958–1.020	0.461
Height	0.025	0.018	1.396	1.026	0.990–1.063	0.163
SBP	0.008	0.005	1.485	1.008	0.997–1.019	0.138
WC	−0.008	0.017	−0.495	0.992	0.960–1.025	0.621
HGB	0	0.007	0.068	1	0.987–1.014	0.946

Note: * p<0.05.

although fatty liver disease is independently associated with an increased incidence of lung nodules, it may not necessarily be a risk factor for more severe or malignant lung nodules (Table 6).

Discussion

The molecular mechanisms underlying the development of lung nodules due to fatty liver disease are still under intensive investigation, and no definitive conclusions have yet been reached. Based on existing literature, it is speculated that

Table 6 Correlation Between Fatty Liver and Lung Nodules of Different Risk Levels

	No Fatty Liver	Fatty Liver	
Variable	**(n=23226)**	**(n=20042)**	**P-value**
Pulmonary Nodule Risk Classification			0.004 **
- N-Miss	18184	15,669	
- Low risk	4740 (94.0%)	4178 (95.5%)	
- Moderate risk	139 (2.8%)	86 (2.0%)	
- High risk	163 (3.2%)	109 (2.5%)	
The Types Of Pulmonary Nodule Lesions			0.004**
- N-Miss	9084	7707	
- Benign	13465 (95.2%)	11,847 (96.0%)	
- Precursor lesions	442 (3.1%)	309 (2.5%)	
- Malignant	235 (1.7%)	179 (1.5%)	

Note: **p<0.01.

patients with fatty liver disease are prone to hepatocyte injury and inflammatory responses due to excessive fat content in the liver.[14] This inflammatory response may trigger local immune cell infiltration, including cells that may migrate to the lungs, thereby initiating an immune response in the lungs and leading to the formation of nodules.[15] Another possibility is that immune cells such as alveolar macrophages, upon stimulation by certain factors (eg, fat metabolites), become activated and may induce chronic inflammation and tissue damage, increasing the risk of lung diseases.[15,16] This activation may be related to specific molecular signaling pathways, but the exact mechanisms are still being studied. Additionally, patients with fatty liver disease may experience hemodynamic changes that predispose them to the formation of microthrombi. When these thrombi detach and circulate in the bloodstream, they may obstruct the capillaries in the lungs, leading to pulmonary circulation disorders and a series of symptoms.[17,18] Although this is more related to physical processes, it also involves the molecular mechanisms of blood coagulation and thrombosis. It is worth noting that this study is the first large-sample cohort study in China to directly explore the correlation between fatty liver and lung nodules, filling a research gap in this field and providing a new perspective for further revealing the pathogenesis of lung nodules.

This study found that the detection rate of lung nodules in patients with fatty liver was significantly higher than that in individuals without fatty liver ($p<0.05$), indicating a potential association between fatty liver and the occurrence of lung nodules. This finding is consistent with the indirect research results of Wu et al, suggesting that fatty liver may be a potential risk factor for the development of lung nodules.[11] Through multivariate logistic regression analysis, we identified male gender, age, body weight, and diastolic blood pressure as important factors for the occurrence of lung nodules in patients with fatty liver.

The gender factor exhibited an interesting trend in our study results. Compared to females, males had a lower likelihood of developing lung nodules, which contradicts some reports indicating higher lung disease risks for males. This discrepancy may be attributed to specific hormonal factors in females. Increasing evidence suggests that estrogen can act on signaling pathways such as TNF-α/NF-κB, EGFR/HER2, ERK/MAPK, and PI3K/AKT, which play crucial roles in biological effects like cell proliferation, migration, and invasion. By activating these signaling pathways, estrogen can further promote the malignant behavior of lung cancer cells.[19–21] Some studies have shown that estrogen can activate the expression of certain oncogenes, such as KRAS and BRAF, while potentially inhibiting the expression of tumor suppressor genes like TP53. Aberrant expression of these genes may lead to uncontrolled cell proliferation and inhibited apoptosis, thereby promoting the occurrence and development of lung cancer.[22,23] Given estrogen's role in promoting cell proliferation and inhibiting apoptosis, we speculate that it may exacerbate the imbalance of the lung microenvironment in female patients with fatty liver disease, thus increasing the risk of lung nodules. In light of these findings, clinicians should pay attention to potential gender differences in the risk of lung nodules and formulate targeted prevention strategies accordingly. For example, more aggressive screening or monitoring measures may be needed for female patients with fatty liver disease to detect and intervene in potential lung nodule risks at an early stage.

Our study also found that age is a risk factor for the occurrence of lung nodules. This finding aligns with research by Chang-Zheng Shi et al, which demonstrated that the incidence of lung nodules increases with age.[24] Studies by Jaime L Schneider et al also pointed out that age is one of the important risk factors for the development of lung nodules. As individuals age, the lung tissue undergoes physiological and pathological changes, such as decreased lung function and thickening of alveolar walls, all of which may increase the risk of lung nodule formation.[25] Patients with fatty liver disease may face more complex health challenges as they age, as fatty liver itself indicates a disruption in the metabolic system, and aging further exacerbates this disrupted state.[26] The immune system function gradually weakens, leading to a decreased ability of the body to clear potential pathogens, which may make the lungs more susceptible to inflammation or infection, thereby promoting the formation of lung nodules.[27] Additionally, aging is accompanied by an increase in oxidative stress levels due to the decline in the function of the body's antioxidant defense system.[28] Oxidative stress can damage DNA, proteins, and lipids, resulting in cellular damage and the accumulation of mutations, which may initiate or promote the formation of lung nodules. Furthermore, genetic damage accumulates with age, potentially involving the activation of proto-oncogenes or the inactivation of tumor suppressor genes, further increasing the risk of lung nodules and lung cancer.[29] All these mechanisms work together to make the elderly population a high-risk group for lung nodules and lung cancer. This reminds us that in lung cancer screening and monitoring, elderly patients should be prioritized, regardless of whether they have fatty liver disease. In future research, we should delve deeper into the specific mechanisms by which aging promotes the formation of lung nodules and identify potential interventions that can mitigate these effects.

Weight gain is also considered a risk factor for the development of lung nodules in patients with fatty liver disease. Studies by Chiara Porro et al[30] have demonstrated the link between obesity and an increased risk of lung nodules. Obesity not only leads to fat deposition in the liver, resulting in fatty liver disease, but also induces systemic chronic low-grade inflammation. Macrophages and other immune cells in adipose tissue are activated, releasing a large amount of pro-inflammatory cytokines such as TNF-α, IL-6, and CRP.[31] These pro-inflammatory cytokines can act on various organs throughout the body, including the lungs, through blood circulation, causing persistent inflammatory responses. This inflammatory environment can promote the development of lung nodules by increasing oxidative stress, activating inflammatory pathways, and stimulating cell proliferation. When managing patients with fatty liver disease, we can help them lose weight and improve their metabolic status by developing dietary and exercise plans. This not only contributes to improving the overall health of patients with fatty liver disease but also helps reduce the risk of lung nodules in this population, providing important support for the prevention and early intervention of lung nodules.

In addition, hypertension may be another important risk factor for the occurrence of lung nodules, which aligns with the research by Zinuo Yuan et al[32] linking hypertension to an increased risk of lung nodules and lung cancer. In a hypertensive state, blood vessel walls and surrounding tissues may be damaged, leading to the release of inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[33] These inflammatory factors not only participate in the pathological process of hypertension but may also reach the lungs through blood circulation, causing inflammatory responses in lung tissues, thus promoting the proliferation and fibrosis of lung cells, and ultimately leading to the formation of nodules. Hypertension can also cause thickening of pulmonary artery walls, luminal stenosis, and subsequent pulmonary artery hypertension, resulting in lung tissue ischemia, hypoxia, and disrupted blood circulation and oxygen supply in the lungs, which further contributes to the formation of lung nodules. The WHO emphasizes that aggressive antihypertensive therapy for hypertensive patients can prevent the occurrence and development of metabolic diseases such as fatty liver disease.[34] When managing and monitoring blood pressure in patients with fatty liver disease, antihypertensive therapy can be used to reduce the release of inflammatory factors, thereby alleviating the inflammatory burden on the liver and mitigating inflammatory responses in lung tissues.[35] Furthermore, by improving hemodynamics, it can lower portal vein pressure and pulmonary artery pressure, potentially reducing the risk of lung nodules. In our future research, we should further explore the mechanisms by which hypertension promotes the formation of lung nodules and determine whether antihypertensive therapy can reduce the incidence of lung nodules.

When further comparing the clinical characteristics of low-risk and moderate-to-high-risk lung nodules in patients with fatty liver, we found that the proportion of males in the moderate-to-high-risk group was significantly lower than that in the low-risk group, suggesting that gender may be an important factor affecting the risk level of lung nodules.[36]

Additionally, body weight and waist circumference in the moderate-to-high-risk group were significantly lower than those in the low-risk group, which may be related to differences in the pathogenesis and clinical manifestations of lung nodules of different risk levels. However, the hemoglobin level in the moderate-to-high-risk group was significantly lower than that in the low-risk group, and the specific mechanism of this finding is unclear and requires further research to explore. These findings are consistent with the relevant risk factors for the malignant transformation of lung nodules reported in the existing literature,[24] further supporting the necessity of differentiated management of lung nodules of different risk levels in clinical practice.

According to our findings, although patients with fatty liver disease may be more prone to developing lung nodules, these nodules tend to fall into lower-risk categories. We hypothesize that cancer cells, characterized by rapid proliferation, require substantial energy and nutrients for this process. Therefore, cancer cells in patients with malignant lung nodules may consume a large amount of the body's energy reserves, including fat. Theoretically, this would reduce the amount of fat available for deposition in the liver in these patients, thereby lowering the likelihood of developing fatty liver disease. Verifying this hypothesis requires more clinical data and experimental research. Exploring the potential molecular mechanisms between fatty liver disease and the malignant transformation of lung nodules is also an important direction for future research.

Although this study provides strong evidence for the correlation between fatty liver and lung nodules through a large-sample cohort study, there are still some limitations. First, this study did not collect information on participants' smoking history, which is a known important risk factor for lung nodules and lung cancer. Omission of this information may result in confounding effects. Future studies should include smoking history and other relevant factors to more comprehensively assess the relationship between fatty liver and lung nodules. Second, this study did not conduct a survey on dietary and lifestyle habits, which are also believed to be closely related to the occurrence of metabolic diseases and lung nodules. Thirdly, given the retrospective method of analysis used in this study, all relevant information has been collected. At present, no quantitative scoring assessment of fatty liver has been implemented. Looking forward to future studies, we plan to delve into a more detailed dissection and exploration of the quantitative characteristics of fatty liver. Fourthly, although we have identified several factors that can influence the risk of lung nodules in individuals with fatty liver disease, whether adjusting these factors can reduce the risk of lung nodules still requires further confirmation through future prospective studies. Future prospective cohort studies can further validate the findings of this study and explore the possible causal mechanisms between fatty liver and lung nodules.

Conclusion

This study indicates that there is a significant correlation between fatty liver and the occurrence of lung nodules, and male gender, age, body weight, and diastolic blood pressure are important influencing factors for the occurrence of lung nodules in patients with fatty liver. In lung cancer screening and surveillance, more aggressive screening or surveillance measures may be needed for female patients with fatty liver disease; lung screening should be prioritized for older patients with or without fatty liver disease; in managing patients with fatty liver disease, physicians need to help them lose weight and improve their metabolic status through diet and exercise programs; and attention should be paid to people with high blood pressure, with antihypertensive treatments, to reduce the risk of lung nodules in this group. It is also important to focus on people with high blood pressure, and to aggressively pursue antihypertensive treatments to reduce the risk of pulmonary nodules in this population, which provides important support for prevention and early intervention of pulmonary nodules.

Data Sharing Statement

The relevant datasets are included in the article.

Ethics Approval and Informed Consent

This study was approved by the Ethics and Human Subject Committee of The People's Hospital of Guangxi Zhuang Autonomous Region.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Guangxi Key Research and Development Program "Construction and Application of a Multidisciplinary Health Intervention System for Early Lung Cancer Screening in the Guangxi Health Examination Population" (Guike AB22080094) and the Research on the Construction and Application of a Health Intervention System for Early Lung Cancer Screening, a subject of the Guangxi Medical and Health Appropriate Technology Development and Promotion and Application (S2021035).

Disclosure

The authors report no conflicts of interest in this work.

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