Original Article

# Association between non-alcoholic fatty liver disease and the risk of pulmonary nodules in patients with intestinal polyps

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**Background:** Associations between metabolic risk factors and lung cancer remain elusive, and evidence on the linkage between non-alcoholic fatty liver disease (NAFLD) and pulmonary nodules is limited. This study sought to examine the independent association between NAFLD and the risk of pulmonary nodules.

**Methods:** Cross-sectional analyses of 1,119 patients with intestinal polyps hospitalized at the Department of Gastroenterology, Minhang District Central Hospital of Shanghai, China, were conducted. NAFLD was diagnosed based on hepatic ultrasonography or computed tomography (CT) findings of hepatic steatosis, with exclusion criteria ensuring patients had no history of significant alcohol consumption, viral infections, or hepatic autoimmune diseases. The currently accepted definition of a pulmonary nodule is a solid or sub-solid shadow ≤3 cm in diameter that appears as a solid or semi-solid pattern on a chest CT scan (our specific treatment is pulmonary nodule size: 5 mm to 3 cm). Adjusted 95% confidence intervals (CIs) and odds ratios (ORs) for NAFLD and the clinical features connected with pulmonary nodule risk were determined using a multivariable logistic regression analysis.

**Results:** Among the 979 intestinal polyp patients, the prevalence rates of NAFLD and pulmonary nodules were 25.9% and 32.8%, respectively. Patients with pulmonary nodules exhibited higher rates of NAFLD (31.5% *vs.* 23.3%, P=0.006) and obesity (41.4% *vs.* 32.5%, P=0.006) compared to those without pulmonary nodules. After removing all the possible confounding variables, the adjusted ORs for NAFLD, an older age, smoking, and obesity were 1.370 (95% CI: 1.006–1.867, P=0.04), 1.022 (95% CI: 1.010–1.033), 1.599 (95% CI: 1.033–2.475), and 1.410 (95% CI: 1.057–1.880), respectively (all P values <0.05). NAFLD showed a significant association with an increased risk of pulmonary nodules.

**Conclusions:** NAFLD was independently linked to an increased incidence of pulmonary nodules in intestinal polyp patients, which emphasizes the importance of screening and managing these conditions in lung cancer prevention.

**Keywords:** Non-alcoholic fatty liver disease (NAFLD); pulmonary nodules; obesity; lung cancer; intestinal polyps

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a variety of clinical conditions, such as simple steatosis, non-alcoholic steatohepatitis, and cirrhosis brought on by hepatic fat buildup (1). The global incidence of NAFLD is estimated to be around 30%, with rates typically falling between 25% and 35% across most regions. Notably, the prevalence in Latin America is particularly high, reaching up

to 44.37% (2). Due to its effects on extra-hepatic disorders [e.g., type 2 diabetes mellitus (T2DM), cardiovascular disease, and chronic kidney disease], hepatocellular carcinoma, and chronic liver disease, NAFLD has become a significant public health burden (3-5). Further, NAFLD has been found to be connected with a variety of cancers, including not only hepatocellular carcinoma but also extra-hepatic cancers, such as esophageal, gastric, colorectal, pancreatic, renal, breast, and prostate cancers (6-9).

Both the incidence and prevalence rates of lung cancer are increasing worldwide (10-12). Due to differences in smoking patterns and socio-economic prerequisites, these rates vary across countries; however, it has been acknowledged as an epidemic (10-12). Lung cancer is the most common malignant tumor and the primary cause of cancer-related death in most developed countries (13). Important characteristics of lung cancer, compared with other types of cancer, include a rapid onset period, a higher malignancy, and a more difficult diagnosis of the disease in its early stages (14). Due to developments in and the increasing utility of computer tomography (CT) in most countries, the detection of pulmonary nodules is now the most important early indicator of lung cancer (15,16). It is well documented that smoking and genetic risk factors are risk factors of lung cancer (17,18). Further, a narrative review showed that the association between obesity and lung cancer risk and prognosis depends on age, gender, race, and the metrics used to measure obesity (19). It also indicates that central obesity is associated with an increased risk of lung cancer and a worse prognosis (20). However, there is poor evidence of an association between NAFLD and pulmonary nodules.

The primary goal of the current study of 1,119 intestinal polyp patients was to identify any independent relationships between NAFLD and pulmonary nodule risk. The secondary goal was to investigate separate correlations between other clinical risk factors and the risk of pulmonary nodules. (A definitive diagnosis of lung cancer requires pathological support and usually involves invasive procedures such as biopsy or surgery. Lung nodules are usually an early sign of lung cancer and can be easily detected by imaging modalities such as CT scanning, therefore we chose to investigate the correlation between lung nodules and NAFLD). We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-754/rc).

### Highlight box

**Key findings**

- This study discovered a significant independent association between non-alcoholic fatty liver disease (NAFLD) and an increased risk of pulmonary nodules in patients with intestinal polyps.
- Among the patients studied, those with pulmonary nodules demonstrated higher rates of NAFLD and obesity, even after adjusting for confounders.

**What is known and what is new?**

- NAFLD is prevalent globally and associated with various extra-hepatic diseases and cancers. Pulmonary nodules are main initial findings of lung cancer, with smoking and genetic factors recognized as traditional risk factors.
- This manuscript contributes novel insights by establishing NAFLD as an independent risk factor for pulmonary nodules, a finding not widely recognized or investigated before this study.

**What is the implication, and what should change now?**

- The linkage between NAFLD and pulmonary nodules underscores the necessity for clinicians to consider NAFLD in the risk assessment for lung cancer.
- Screening for pulmonary nodules in patients with NAFLD should be integrated into clinical practice to aid in early detection and prevention strategies for lung cancer.
- Further research is needed to understand the pathophysiological mechanisms underlying this association and to guide targeted interventions.

## Methods

### *Study population*

From January 1, 2020 to April 30, 2021, all patients with intestinal polyps hospitalized at the Department of Gastroenterology, Minhang District Central Hospital of Shanghai, China, were recruited for the present study. Of these patients, 1,119 with complete data on clinical measurements were included in the final analysis. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) with intestinal polyps; (II) had successfully undergone chest computer tomography (CT) plain scanning, hepatic ultrasonography scanning, and thyroid ultrasonography scanning examinations; and (III) with serum biochemical and other laboratory measurements available. Patients were excluded from the study if they met any of the following exclusion criteria: (I) aged <18 years; (II) had not undergone colonoscopy examinations (patients with incomplete colonoscopy cannot be identified for the

presence of colonic polyps); (III) had colorectal cancer, inflammatory bowel disease, ischemic enteritis, non-specific enteritis, lung cancer, familial adenomatous polyposis, colectomy, or other types of cancer (as malignant tumors or inflammation of the colon interfered with the analysis of the results of our study); (IV) had an excessive alcohol intake (total ethanol >30 g/day for men or >20 g/day for women), or viral, drug, autoimmune, or other liver diseases; (V) had total parenteral nutrition, hypothyroidism, coeliac disease, β lipoprotein deficiency, or Cushing's syndrome (patients with these can also cause fatty liver, limiting this criterion to those with a clear NASH diagnosis); and/or (VI) had incomplete clinical data or refused to take part in the investigation. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Human Research Ethics Committee of Minhang District Central Hospital of Shanghai, China (approval No. 2020-Approval-003-01K). A written informed consent form was signed by each participant.

### *Measurements*

In-person interviews were conducted to gather information about the lifestyle choices, past and current medical histories, and prescription regimens of each patient. After removing their shoes and bulky clothing, each patient's height and body weight were measured using a calibrated scale. The body mass index (BMI) was calculated by dividing height in square meters by weight in kilos [differences in statistical stratification analyses when stratified for degree of obesity (e.g., increase in BMI) were not statistically significant]. According to the World Health Organization's guidelines for the Asian Pacific population, patients were classified as obese if their BMI was ≥25.0 kg/m$^2$ (21). After sitting for at least 15 minutes, each patient's arterial blood pressure (BP) was evaluated using a mercury sphygmomanometer. The national guidelines for hypertension management in China [2019] were followed to take the BP readings, and hypertension was diagnosed as diastolic BP ≥90 mmHg or systolic BP ≥140 mmHg, or the management of pre-existing hypertension (22).

After a minimum of eight hours of fasting, venous blood samples were taken in the morning. The clinical laboratory at the Minhang District Central Hospital of Shanghai, China, conducted all the biochemical tests. Blood routine examination, C-reactive protein, fasting plasma glucose (FPG), glycosylated hemoglobin A1c, liver function (aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, direct-, and indirect-bilirubin), and lipid profiles [total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and serum uric acid] were determined using an automatic biochemical analyzer (Roche Cobas 8000, Switzerland).

Diabetes was defined as follows: (I) a self-reported history of diabetes previously diagnosed by health care professionals; (II) FPG ≥126 mg/dL (7.0 mmol/L); or (III) 2-hour plasma glucose [2-h PG, oral glucose tolerance test (OGTT)] ≥200 mg/dL (11.1 mmol/L). These standards are outlined in the Chinese Diabetes Society Guidelines for the prevention and treatment of T2DM in China [2020]. According to the same guidelines, the patients had to meet three of the four following criteria to be classified as having metabolic syndrome: (I) being overweight or obese (a BMI ≥25.0 kg/m$^2$); (II) had hyperglycemia [FPG ≥110 mg/dL (6.1 mmol/L), 2-h PG ≥140 mg/dL (7.8 mmol/L), or had been previously diagnosed with T2DM]; and (III) had hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or had previously been diagnosed and treated for hypertension); and/or (IV) had dyslipidemia [a TG level ≥150 mg/dL (1.7 mmol/L), or HDL-c <35 mg/dL (0.9 mmol/L) in males and <39 mg/dL (1.0 mmol/L) in females] (23).

### *Imaging, ultrasonography*

Sonographic characteristics, such as liver parenchymal brightness, deep beam attenuation, hepatorenal echo contrast, and vascular blurring, were used to identify hepatic steatosis (24,25). Hepatic ultrasonography scanning was carried out by an experienced radiologist using a Philips_iE_Elite/Canon_Aplio_500/Mindray_DC8_pro/Mindray_Resona7S/Canon_Xario_200/Sonoscape_S50 scanner (supplied by Shanghai Green Sky Technology and Trade Co., Ltd., model: FibroScan 502 Touch, product number: F62199) with a 4-MHz transducer. Hepatic CT scanning was also performed, and hepatic steatosis was identified based on widely reduced liver density or a CT liver/spleen ratio of <1.0 (26). Other abdominal organs (gallbladder, pancreas, spleen, and kidney), carotid and thyroid ultrasonography scanning, as well as CT tests in the chest and abdomen were conducted using standard protocols and techniques. Chest CT plain scanning was conducted using a 32-row CT scanner, and the scanning parameters were as follows: total radiation exposure dose: ≤5 mSv; KVp: 120, mAs: <60; frame rotation speed: ≤0.5 seconds; detector

quasi diameter: ≤1.5 mm; scanning layer thickness: 7 mm; scanning spacing ≤ layer thickness; scanning range: from the apex of the lung to the costal septal angle (including all lungs) with a scanning sampling time of ≤10 seconds and patients trained to hold their breath at the end of deep inspiration.

### *Colonoscopy examinations and treatments*

Colonic polyps are lesions that grow from the mucosa of the colon and are elevated on the mucosal surface, and the manifested elevated lesions located on the mucosal surface of the colon can be visualized by colonoscopy. In this study, all polyps underwent endoscopic excision of the entire polyp and pathological sections were taken to determine the pathological type of the polyp. All patients undergoing colonoscopy received a low residue diet the day before and finished taking laxatives and completing bowel preparation prior to colonoscopy. The colonoscopy was performed by inserting a flexible tube with a miniature electronic camera at the end. With the patient lying on the left side, the colonoscope slowly entered the colon through the anus, slowly advanced to the ileocecal region, and then slowly retracted, using a camera probe to synchronize the images of the colon mucosa on a monitor in order to check for lesions in the colonic region. Once a polyp lesion was found, it was first exposed to the center of the field of vision, a special instrument (loop liner) was then inserted through the aperture on the colonoscope, and a steel wire ring was extended next to the polyp to enclose it and tighten it, and the polyp was gently lifted into the intestinal lumen to keep the steel wire ring away from the intestinal mucosa as far as possible, and high-frequency electric power was pulsed through the steel wire ring for electrocautery until the root of the polyp was cut off and the polyp was dislodged. The specimen was recovered and sent for pathological examination. To prevent delayed bleeding of the wound, metal clips can be used to close the wound.

### *Definitions of NAFLD and pulmonary nodules*

NAFLD diagnosis was based on hepatic ultrasonography or CT indicating hepatic steatosis, excluding patients with significant alcohol consumption, viral hepatitis, or autoimmune liver disorders as per established diagnostic guidelines (27-30). A pulmonary nodule is a small, focal, quasi-circular lung shadow with increased radiologic density, which can be solitary or multiple. It does not accompany lung atelectasis, hilar enlargement, or pleural effusion. An isolated pulmonary nodule typically presents without specific symptoms, often appearing as a single, well-defined, high-density shadow with a diameter ≤3 cm, surrounded by aerated lung tissue. Radiologic manifestations of pulmonary nodules include solid intrapulmonary nodules, partially solid intrapulmonary nodules (mixed ground-glass opacity nodules), and pure ground-glass opacity nodules (31).

### *Statistical analysis*

For the continuous variables, the data were presented as the mean ± standard deviation (SD). For the categorical variables, the data were presented as an approximation of normal distributions or as the number and percentage. The differences between the patients with pulmonary nodules (yes *vs.* no) were compared using the Chi-squared test for the categorical variables and the *t*-test for the normally distributed continuous variables. Univariable and multivariable logistic regression analyses were used to determine the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of NAFLD and the clinical characteristics with the risk of pulmonary nodules. The SPSS 26.0 program (IBM Corporation, Armonk, NY, USA) was used for all the analyses. The threshold for statistical significance was set at $P<0.05$, and every P value was two-sided.

## Results

Of the 979 patients (after excluding patients with missing data) with intestinal polyps, 433 were women and 546 were men with mean ages ± SD of 61.3±0.5 and 61.0±0.6 years, respectively (P value =0.95).

### *Demographic and clinical characteristics stratified by pulmonary nodule status*

Among the patients, 143 (33.0%) women and 178 (32.6%) men were identified as having pulmonary nodules (P=0.88). The total prevalence rate of pulmonary nodules among the 979 patients with intestinal polyps was 32.8%. *Table 1* presents the demographic and clinical characteristics by pulmonary nodules (yes *vs.* no) among all the patients. Generally, the patients with pulmonary nodules were observed to have significantly higher average age, body weight, and BMI, and a higher likelihood of smoking compared to those without pulmonary nodules (all P values

**Table 1** Demographic and clinical characteristics of patients stratified by pulmonary nodule status

| Variables | Pulmonary nodules | | P value |
|---|---|---|---|
| | No | Yes | |
| Demographics | 658 (67.2) | 321 (32.8) | – |
| Sex | | | 0.88 |
| Men | 368 (55.9) | 178 (55.5) | |
| Women | 290 (44.1) | 143 (44.5) | |
| Age (years) | 60.2±0.5 | 63.4±0.6 | <0.001*** |
| A history of smoking | 55 (8.4) | 40 (12.5) | 0.04* |
| Clinical characteristics | | | |
| Weight (kg) | 64.9±0.4 | 66.4±0.7 | 0.04* |
| BMI (kg/m$^2$) | 23.8±0.2 | 24.4±0.2 | 0.01* |
| Obesity (BMI ≥25.0 kg/m$^2$) | 214 (32.5) | 133 (41.4) | 0.006** |
| Fasting plasma glucose (mmol/L) | 5.45±0.06 | 5.58±0.10 | 0.20 |
| GGT (U/L) | 35.3±2.7 | 35.1±2.9 | 0.95 |
| Triglyceride (mmol/L) | 1.70±0.07 | 1.73±0.09 | 0.81 |
| Total cholesterol (mmol/L) | 4.25±0.04 | 4.32±0.06 | 0.30 |
| HDL-cholesterol (mmol/L) | 1.16±0.02 | 1.13±0.02 | 0.23 |
| LDL-cholesterol (mmol/L) | 2.83±0.04 | 2.89±0.05 | 0.33 |
| NAFLD | 153 (23.3) | 101 (31.5) | 0.006** |

Data are presented as mean ± standard deviation or n (%). *, P<0.05; **, P<0.01; ***, P<0.001. BMI, body mass index; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease.

**Table 2** Demographic and clinical characteristics of patients stratified by NAFLD status

| Variables | NAFLD | | P value |
|---|---|---|---|
| | No | Yes | |
| Demographics | 725 (74.1) | 254 (25.9) | – |
| Sex | | | 0.69 |
| Men | 407 (56.1) | 139 (54.7) | |
| Women | 318 (43.9) | 115 (45.3) | |
| Age (years) | 61.1±0.5 | 61.8±0.8 | 0.46 |
| A history of smoking | 66 (9.1) | 29 (11.4) | 0.27 |
| Clinical characteristics | | | |
| Weight (kg) | 63.7±0.4 | 70.1±0.7 | <0.001*** |
| BMI (kg/m$^2$) | 23.5±0.1 | 25.6±0.2 | <0.001*** |
| Obesity (BMI ≥25.0 kg/m$^2$) | 206 (28.4) | 141 (55.5) | <0.001*** |
| Fasting plasma glucose (mmol/L) | 5.35±0.06 | 5.86±0.10 | <0.001*** |
| GGT (U/L) | 32.6±2.4 | 41.9±3.5 | 0.03* |
| Triglyceride (mmol/L) | 1.50±0.06 | 2.20±0.12 | <0.001*** |
| Total cholesterol (mmol/L) | 4.20±0.04 | 4.44±0.07 | 0.002** |
| HDL-cholesterol (mmol/L) | 1.18±0.01 | 1.05±0.02 | <0.001*** |
| LDL-cholesterol (mmol/L) | 2.80±0.04 | 2.96±0.06 | 0.01* |
| Pulmonary nodules | 220 (30.3) | 101 (39.8) | 0.006** |

Data are presented as mean ± standard deviation or n (%). *, P<0.05; **, P<0.01; ***, P<0.001. NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol.

<0.05). The prevalence of NAFLD in the patients with pulmonary nodules (31.5%) was significantly higher than that in the patients without pulmonary nodules (23.3%, P=0.006).

### *Demographic and clinical characteristics stratified by NAFLD status*

*Table 2* shows the differences in the clinical and demographic characteristics of the patients stratified by NAFLD status (yes *vs.* no). Among the 979 patients, 254 (25.9%) were diagnosed with NAFLD. Generally, compared to those without NAFLD, patients with the condition had significantly higher body weight, BMI, FBG level, gamma-glutamyl transpeptidase level, TG level, TC level, and LDL-c level, and a markedly lower HDL-c level, indicating a greater likelihood of obesity (all P values <0.05). Furthermore, the predominance of pulmonary nodules in those with NAFLD (39.8%) was significantly higher than that in the patients without NAFLD (30.3%, P=0.006).

### *Univariable unadjusted ORs with 95% CIs for risk of pulmonary nodules in all patients*

We performed univariable logistic regression analyses to calculate the unadjusted ORs and 95% CIs for NAFLD

**Table 3** Univariable logistic regression analysis for pulmonary nodules

| Variables | Pulmonary nodules | | |
|---|---|---|---|
| | OR | 95% CI | P value |
| Age | 1.021 | 1.010–1.032 | <0.001* |
| Smoker (yes *vs.* no) | 1.555 | 1.011–2.394 | 0.04* |
| BMI | 1.048 | 1.008–1.089 | 0.01* |
| Obesity (BMI ≥25.0 kg/m$^2$) (yes *vs.* no) | 1.468 | 1.114–1.933 | 0.007* |
| NAFLD (yes *vs.* no) | 1.515 | 1.126–2.039 | 0.006* |

*, P<0.05. OR, odds ratio; CI, confidence interval; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease.

**Table 4** Multivariable logistic regression analysis for pulmonary nodules

| Variables | Pulmonary nodule | | |
|---|---|---|---|
| | OR | 95% CI | P value |
| Age | 1.022 | 1.010–1.033 | <0.001* |
| Smoker (yes *vs.* no) | 1.599 | 1.033–2.475 | 0.03* |
| Obesity (BMI ≥25.0 kg/m$^2$) (yes *vs.* no) | 1.410 | 1.057–1.880 | 0.01* |
| NAFLD (yes *vs.* no) | 1.370 | 1.006–1.867 | 0.04* |

*, P<0.05. OR, odds ratio; CI, confidence interval; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease.

and other clinical risk factors about the risk of developing pulmonary nodules (*Table 3*). An older age, BMI, smoker, and obesity were all significantly associated with an increased risk of pulmonary nodules (all P values <0.05). An increased risk of pulmonary nodules was significantly correlated with NAFLD (yes *vs.* no) [OR =1.515 (95% CI: 1.126–2.039), P=0.006].

### *Multivariable adjusted ORs with 95% CIs for risk of pulmonary nodules in all patients*

We employed multivariable logistic regression to estimate the adjusted ORs and 95% CIs for the association between NAFLD and other clinical variables with the occurrence of pulmonary nodules (*Table 4*). Even after accounting for potential confounders, our multivariable analysis showed that obesity, smoking history, and older age were significantly associated with a higher risk of pulmonary nodules (all P values <0.05). Additionally, NAFLD (yes *vs.* no) remained significantly linked to a greater risk of pulmonary nodules [modified OR =1.370 (95% CI: 1.006–1.867), P=0.04].

## Discussion

The current study revealed that the incidence rates of lung nodules and NAFLD were 32.8% and 25.9%, respectively, in 979 individuals with intestinal polyps. Patients with pulmonary nodules showed a significantly higher prevalence of NAFLD and obesity. In the multivariable logistic regression analysis, after correcting for all the possible confounding variables, NAFLD was shown to be independently linked with an elevated incidence of pulmonary nodules. In addition, older age, smoking, and obesity were also independently associated with a higher risk of pulmonary nodules. Obesity, in particular, is associated with a higher risk of various pulmonary diseases. Increased chest wall and abdominal fat due to obesity can reduce lung volume and impair pulmonary ventilation. Obesity is a major risk factor for the development of multiple respiratory diseases, including asthma, pulmonary hypertension, sleep apnea, obesity hypoventilation syndrome, pneumonia, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and lung cancer (32).

With their rapidly increasing prevalence, incidence, and related economic burdens, both NAFLD and lung cancer have become heavy threats to public health worldwide. NAFLD is not only associated with hepatocellular carcinoma, it is also associated with extra-hepatic cancers. Lung cancer has become the leading cause of cancer-related death worldwide (33). The most common type of lung cancer, pulmonary adenocarcinoma, is defined by gland and/or duct formation and/or significant mucus production. It is typically thought to be the histological subtype of non-small-cell lung cancer that is most commonly diagnosed, and its incidence has been sharply rising over the past few decades (34). Pulmonary adenocarcinoma has a comparatively better prognosis than other forms of lung cancer; however, the 5-year overall survival rate for lung cancer is poor even with extensive therapeutic interventions (35,36). The 5-year survival rate of lung cancer in China is only 19.7%, but about 75% of patients are already in advanced stages at the time of diagnosis, missing the best time for radical surgical treatment (37). Current treatment strategies include surgical resection, chemotherapy, targeted therapy and radiotherapy. However, despite these options,

the prognosis remains poor. Therefore, there is an urgent need for a paradigm shift in treatment approaches (38). Based on a retrospective study of 3,664 lung cancer patients, Zhu *et al.* found that NAFLD and obesity were independently correlated with an elevated risk of pulmonary adenocarcinoma, particularly in female non-smokers, which emphasizes the need for more research into the mechanisms behind the association between NAFLD and pulmonary adenocarcinoma (39). Based on a comparative study of 10 cohort investigations with a whole sample of 182,202 middle-aged individuals (24.8% with NAFLD) and a 5.8-year median follow-up period, Mantovani *et al.* reported that the patients with NAFLD were 30% more likely to develop lung cancer [hazard ratio =1.30 (95% CI: 1.14–1.48)] (40). However, research on the association between NAFLD and the risk of pulmonary nodules is limited. In this study, through an analysis of clinical data, we identified an independent association between NAFLD and a higher risk of pulmonary nodules in individuals with colorectal polyps. The adjusted OR was 1.370 (95% CI: 1.006–1.867). As far as we know, this study appears to be among the earliest to report the separate relationship between NAFLD and the occurrence of pulmonary nodules among individuals with intestinal polyps.

A "two-hit" hypothesis has been proposed for the development of NAFLD (41). The two "hits" are mostly attributed to hyperinsulinemia, free radical generation, and inflammatory mediators. Metabolic syndrome, hypertension, and T2DM have been shown to be associated with NAFLD, and insulin resistance is a major contributor to metabolic syndrome and enhances the development of NAFLD (42-44). Chronic inflammation has been found to be involved in the development of lung cancer (45). Therefore, these factors may also be involved in the associations between NAFLD and pulmonary nodules in patients with intestinal polyps, however, future studies are needed to elucidate the specific mechanisms underlying these associations.

Obesity is associated with a risk of pulmonary disease, such as asthma and COPD and affects lung function adversely (46). However, information on the relationship between obesity and the risk of pulmonary nodules is limited (47). With an adjusted OR of around 1.41, the current study revealed a significant relationship between obesity and an increased risk of pulmonary nodules. Obesity is highly correlated with NAFLD (48). However, in the current investigation, we discovered that the risk of pulmonary nodules was independently correlated with both NAFLD and obesity. In addition to exploring hyperinsulinemia, insulin resistance, and chronic inflammation, future research should investigate other potential pathophysiological mechanisms that might independently link NAFLD, obesity, and the risk of pulmonary nodules.

There are a few limitations in this study. First, as it was a cross-sectional study, we were unable to ascertain the time sequences of the correlations between NAFLD, obesity, and pulmonary nodules. Second, the sample size was small, and all the 979 patients with intestinal polyps were sampled from one hospital in Shanghai, China; therefore, the generalizability of the results to other populations is limited. Third, hepatic CT or ultrasonography were used to identify NAFLD; however, quantitative data were lacking and only information on the diagnosis of hepatic steatosis was provided. Additionally, the decision to include only patients screened for the first time with intestinal polyps introduced selection bias, potentially skewing the representativeness of the findings. Therefore, these limitations underscored the need for future studies, particularly prospective studies with cohort study designs, larger sample sizes, and enhanced precision, need to be conducted for NAFLD in the future.

## Conclusions

In the current research, NAFLD and pulmonary nodules were common in patients with intestinal polyps. An independent correlation was found between NAFLD and a higher incidence of lung nodules. Additionally, an older age, smoking, and obesity were also found to be independently associated with the risk of pulmonary nodules. Consequently, our results suggest that in the prevention of lung cancer, the screening and management of NAFLD and pulmonary nodules are important for patients with intestinal polyps.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-754/rc

*Data Sharing Statement:* Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-754/dss

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-754/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Human Research Ethics Committee of Minhang District Central Hospital of Shanghai, China (approval No. 2020-approval-003-01K). A written informed consent form was signed by each participant.



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