

The relationship between lung cancer and hepatosteatosi s in patients with biopsy-confirmed lung cancer diagnosis

 Murat Asik,¹  Mehmet Ali Agirbasli,²  Kendal Erincik¹

¹Department of Radiology, Istanbul Medeniyet University Faculty of Medicine, Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkiye

²Department of Cardiology, Istanbul Medeniyet University Faculty of Medicine, Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkiye

ABSTRACT

OBJECTIVE: The purpose of this study is to evaluate whether hepatosteatosi s is associated with lung cancer in patients undergoing lung nodule biopsy.

METHODS: 359 patients (248 males, 69.1%) who underwent lung biopsy between the years 2016 and 2022 were included in this retrospective study. The average age of the patients was 64.59±14.05 (range=30–90) years. These patients were undergoing follow-up for a lung lesion and had undergone thoraco-abdominal CT scans. Attenuation measurements were performed on non-contrast CT scans from the liver and spleen parenchyma.

RESULTS: Pathology results showed that the majority of diagnoses were malignant (n=265, 73.8%). Statistical analysis revealed a significantly higher number of patients with malignancy among those with hepatosteatosi s compared to those without hepatosteatosi s (73% vs. 57%, p=0.006). Furthermore, patients with malignancy were more frequently male (73 vs. 27%, p=0.010), older (65.80±12.83 years vs. 61.20±16.63 years; p=0.06) and had a higher prevalence of diabetes mellitus (DM) (43.7 vs. 31.9%, p=0.046). Logistic regression analysis indicated that advanced age, DM, and hepatosteatosi s were associated with an increased risk of malignancy (p=0.049, 95% CI (1.000–1.036), p=0.044, 95% CI (0.0347–0.98736), p=0.013, 95% CI (1.154–3.323), respectively).

CONCLUSION: The study findings suggest that hepatosteatosi s might be associated with lung cancer. Therefore, due to its possible relationship with lung cancer, it should be taken very seriously, considering the chance of early diagnosis and treatment.

Keywords: Computed tomography; hepatosteatosi s; lung cancer; metabolic factors; lung biopsy.

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Lung cancer is the leading cause of cancer-related deaths worldwide [1]. It is a complex disease influenced by genetic, non-modifiable, modifiable, and preventable risk factors. Modifiable risk factors for lung cancer can be categorized as environmental and personal factors. For instance, air pollution and smoking are well-known environmental and personal risk factors for lung cancer [2, 3]. Additionally, the increasing prevalence of obesity globally raises concerns about the metabolic causes of lung cancer [4].

Obesity, resulting from changing lifestyles and dietary habits, is a significant global public health issue. It is believed to be a contributing factor to various types of cancer, including lung cancer. Ongoing studies aim to improve our understanding of the underlying mechanisms connecting obesity and lung cancer. Obesity and metabolic syndrome can lead to genetic mutations and epigenetic changes that promote the development of lung cancer [4]. Hepatosteatosi s, also known as fatty

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Correspondence: Murat ASIK, MD. Istanbul Medeniyet Universitesi Tip Fakultesi, Prof. Dr. Suleyman Yalcin Sehir Hastanesi, Radyoloji Klinigi, Istanbul, Turkiye.

Tel: +90 535 555 38 97 e-mail: muratasik81@gmail.com

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liver disease, is a prevalent condition affecting approximately one in four adults worldwide [5]. It is closely associated with obesity and metabolic syndrome. Hepatosteatosi is a complex multifactorial disease influenced by metabolic, environmental, and genetic factors. If left untreated, it can progress to chronic liver disease and cirrhosis. Moreover, hepatosteatosi, being the most common cause of chronic liver disease globally, increases the risk of developing cancer in various organs, including hepatocellular carcinoma (HCC) and colorectal cancer [6].

Ultrasonography (US) is commonly used to subjectively diagnose hepatosteatosi. However, it does not provide an objective quantitative value for assessing the condition. There are studies showing that ultrasonography can be used to objectively evaluate hepatosteatosi using the attenuation imaging technique. However, it's worth noting that not all ultrasound devices have these features [7]. On the other hand, computed tomography (CT) has comparable sensitivity and specificity to the US in detecting hepatosteatosi. Unlike the US, non-enhanced CT enables the numerical quantification of hepatosteatosi by measuring the density of liver parenchyma in Hounsfield units (HU) [8].

Studies suggest that weight loss, achieved through an appropriate diet to prevent hepatosteatosi, may reduce the risk of HCC and even lung cancer [9, 10]. In this study, the relationship between lung cancer and hepatosteatosi was investigated in patients diagnosed with lung cancer as a result of transthoracic biopsy and hepatosteatosi diagnosed with non-contrast abdominal CT.

MATERIALS AND METHODS

Patient Population

This retrospective, single-center study was conducted after obtaining approval from the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (date: 11.01.2023, number: 2023/0031). The study included a total of 359 consecutive patients (248 males, 69.1%) who underwent CT-guided percutaneous transthoracic lung biopsy at our hospital between the years 2016 and 2022.

The patients arrived at our clinic from an external center with a biopsy request and chest and abdomen CT images. Consequently, obtaining anamnesis information, physical examination findings, and laboratory values (such as AST, ALT) before the biopsy was not possible.

Highlight key points

- Since lung cancer is one of the most common cancer types with the highest mortality, it is very important to reveal the preventable risk factors.
- As a result of the relationship of hepatosteatosi with inflammation, it is thought that it may cause lung cancer as well as in other systems (such as HCC, colorectal cancer).
- Considering the relationship between hepatosteatosi and cancer, it is more important to diagnose and follow up objectively.

The decision to perform a biopsy based on CT imaging for patients who applied to our clinic with a biopsy request was made through the multidisciplinary council's decision.

Our study was conducted in accordance with the Declaration of Helsinki. Informed consent forms were obtained from all patients after detailed information about the procedure was given by the interventional radiologist who would perform the biopsy procedure. In the follow-ups before the biopsy, all patients were informed (by the clinician or radiologist) and informed consent forms were obtained.

Transthoracic Lung Biopsy Procedure

Before the biopsy procedure, the patients' respiratory function tests, bleeding coagulation tests, and comorbidity conditions were evaluated. In the pre-biopsy evaluation, the platelet level was aimed to be $\geq 50,000/\text{mm}^3$ and International Normalized Ratios ≤ 1.5 .

Then, considering the largest size of the lesion, its location in the lung parenchyma, its proximity to the main bronchus and vascular structures, and its distance to the pleura, it was decided to perform a 128-detector CT-guided FNAB or tru-cut biopsy. (OPTIMA 660 General Electric Medical Systems, Milwaukee, WI, USA). After reviewing the previous images, the projection of the lesion on the skin was estimated and metallic markers were placed on the skin. The position and entry point to be biopsied were determined and after the skin was disinfected with povidone-iodine, local anesthesia was performed with 1% lidocaine from the skin to the pleural surface. If FNAB was performed, half of the sample smear preparations were fixed in air and the other half in 90% alcohol. If a core biopsy was performed, they were placed in 10% formaldehyde solution and sent for pathological examination.

Data Collection

All patient data were collected retrospectively from the hospital information system, and CT images were retrieved from the Picture Archiving and Communication System (PACS) for further analysis. Pathological diagnoses were determined based on the findings from fine-needle aspiration biopsy (FNAB) or core biopsy. Data about whether the patients smoked or not, BMI values and diabetes mellitus (DM) diagnosis were obtained from hospital records. In addition, lipid profiles including triglycerides, LDL cholesterol, and HDL cholesterol, as well as liver function tests such as AST and ALT, were obtained from the available biochemical test results.

The inclusion criteria for our study were as follows: patients who underwent transthoracic lung biopsy due to a lung mass and had a histopathological diagnosis, and patients who had undergone abdominal CT scans for radiological follow-up within 1–6 months before the biopsy. However, patients with only contrast-enhanced abdominal CT scans or those without non-contrast abdominal CT scans, as well as those without histopathological results from lung biopsy, were excluded from the study.

Multi-slice abdominal CT examination was performed using 128-channel CT (GE Healthcare Optima CT660, USA) with/without intravenous contrast agent. The CT images were obtained using a 512×512 matrix detector, acquisition 24×1.2 mm, slice thickness 2.5 mm, pitch 0.98, 75 mAs and 120 Kv. In our clinic, routine triphasic abdominal CT examinations are performed for the purpose of metastasis screening in patients with lung masses during their outpatient follow-ups. For patients who had undergone triphasic abdominal CT scans (non-contrast - arterial - venous phase) within 1–6 months prior to the biopsy, measurements of liver and spleen parenchyma densities were performed using HU on non-contrast images, and the recorded values were used for analysis (Fig. 1).

Measurement of Liver Parenchyma Attenuation

Evaluation of hepatosteatosis in the patients was performed by two radiologists (M.A. and K.E.) with ten and five years of experience. Non-contrast CT scans were used for the assessment. For patients who were being monitored for suspected metastasis prior to the biopsy, abdominal CT scans were performed capturing images in dynamic phases including non-contrast, arterial, and



FIGURE 1. Density measurement in liver and spleen parenchyma in axial image on non-contrast abdominal CT.

venous phases. In the non-contrast images, the liver and spleen densities were measured in HU. Liver parenchymal attenuation was measured on non-contrast CT images by calculating the average value from three separate regions of interest (ROIs) selected from different localizations within the liver and spleen parenchyma. ROIs, approximately 10 mm in diameter, were selected with measurements from the right lobe of the liver, excluding the gallbladder and vascular structures. The diagnosis of hepatic steatosis was determined using specific CT criteria: liver parenchymal attenuation that was 10 HU lower than spleen attenuation, absolute liver attenuation of less than 40 HU, or a liver-to-spleen attenuation ratio less than 1. These criteria were used to identify and classify cases of hepatic steatosis [8].

Statistical Method

The normality of the variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics, such as mean ± standard deviation for parametric data or median (interquartile range) for non-parametric data, were used to summarize continuous variables. Percentages were used for categorical variables.

To compare two groups with parametric distribution, the Student t-test was employed, while the Mann-Whitney U test was used for groups with non-parametric distribution. The chi-square test was utilized for comparing categorical variables between groups.

The individual effects of risk factors for lung cancer were analyzed using t-tests, while the synergistic effects of multiple factors were assessed using multivariate lo-

TABLE 1. Demographic characteristics and pathological diagnoses of the patients

Variables	Benign n (%)	Malign n (%)	
Gender			
Female	39 (41.5)	72 (27.2)	
Male	55 (58.5)	193 (72.8)	
Age (mean±SD)	61.20±16.63	65.80±12.83	
Hepatosteatosi			
Present	49 (57)	172 (72.9)	
Absent	37 (43)	64 (27.1)	
Hypertension			
Present	44 (50.6)	119 (46.3)	
Absent	43 (49.4)	118 (53.7)	
Type II DM			
Present	38 (43.7)	175 (68.1)	
Absent	49 (56.3)	82 (31.9)	
Liver function test			
AST	25.88±29.81 (0–31 U/L)	22.69±25.17 (0–31 U/L)	
ALT	22.55±25.54 (0–37 U/L)	19.49±21.69 (0–37 U/L)	
Pathological diagnosis			
Anthracosis	6 (13.6)	Adenocarcinoma	150 (55.6)
Infection	38 (86.3)	Squamous cell carcinoma	64 (23.8)
		Small cell lung carcinoma	26 (9.7)
		Metastasis	28 (10.4)

SD: Standard deviation; DM: Diabetes mellitus; AST: Aspartate transaminase; ALT: Alanin aminotransferaz.

gistic regression. Univariate analyses were conducted to identify potential variables associated with disease severity and mortality, presenting odds ratios (OR) and 95% confidence intervals (CI). Multivariable logistic regressions were performed to examine the association of clinical characteristics and biochemical results with the study endpoints. A significance level of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 26.0 software (IBM SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 359 patients were enrolled in the study, comprising 248 males (69.1%) and 111 females. The mean age of the patients was 64.59 ± 14.05 years (range=30–90). The mean BMI value was found to be 25.97 ± 4.62 SD in our patients. While 64.5% of the patients were overweight and obese, 35.5% were of normal weight ($< 25 \text{ kg/m}^2$).

All patients underwent transthoracic fine needle or core biopsy guided by CT for the diagnosis of a mass associated with metastasis or primary lung cancer. Among the patients, 163 (45.4%) had hypertension, and 120 (33.4%) had type II diabetes mellitus (DM). The demographic characteristics and pathological diagnoses obtained from the biopsy are presented in Table 1.

Out of the total patient population, 241 individuals (67.13%) were diagnosed with hepatosteatosi. On CT, the density measured from the liver parenchyma and the difference in density between the liver and spleen parenchyma were measured as 56.50 ± 11.10 , 12.53 ± 7.81 , respectively. Upon dividing the patients based on the pathology results into benign ($n=94$, 26.2%) and malignant ($n=265$, 73.8%) groups.

Interestingly, among the patients with hepatosteatosi, there was a higher number of individuals diagnosed with malignancy compared to those without hepatosteatosi, and this difference was statistically significant (73 vs. 57%, $p=0.006$) (Fig. 2). Furthermore, it was observed

TABLE 2. Logistic regression analysis and results of factors that increase the risk of lung malignancy

	sig.(p)	OR	95% CI for OR	
			Lower	Upper
Steatosis	0.013	1.958	1.154	3.323
Type II DM	0.044	0.585	0.347	0.987
Age	0.049	1.018	1.000	1.036
Constant	0.576	0.713		

DM: Diabetes mellitus; OR: Odds ratio; CI: Confidence interval.

that patients diagnosed with malignancy had a higher incidence of type II DM when compared to the group with benign lesions (43.7 vs. 31.9%, $p=0.046$).

The incidence of malignancy was higher in males compared to females (73 vs. 27%, $p=0.010$). Although there was a trend suggesting that the group with malignancy was older than the patients with benign lesions, this difference did not reach statistical significance (mean age 65.80 ± 12.83 years vs. 61.20 ± 16.63 years, $p=0.06$).

When the factors affecting malignancy are examined with the univariate test, it is seen that steatosis, which is one of the modifiable factors, is statistically significant ($p=0.006$). Among the factors that could not be modified, it was seen that the most effective ones were male gender, age and Type 2 DM ($p=0.010$, $p=0.018$, $p=0.046$, respectively).

When logistic regression analysis was performed, it was seen that hepatosteatois and type II DM, among metabolic factors, and age, among non-metabolic factors, were associated with lung cancer. ($p=0.013$, 95% CI (1.154–3.323), $p=0.044$, 95% CI (0.0347–0.98736), $p=0.049$, 95% CI (1.000–1.036), respectively) (Table 2).

Additionally, when the relationships between hepatosteatois and primary lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma) were analyzed, a statistically significant difference was observed between them ($p=0.033$). The highest rate of steatosis was seen in adenocarcinoma, followed by squamous cell carcinoma and small cell lung carcinoma (62.1%, 30.1% and 7.8%, respectively).

DISCUSSION

This study reports that hepatosteatois is commonly seen in patients who underwent biopsy for a lung lesion and were diagnosed with malignancy. In addition to hep-

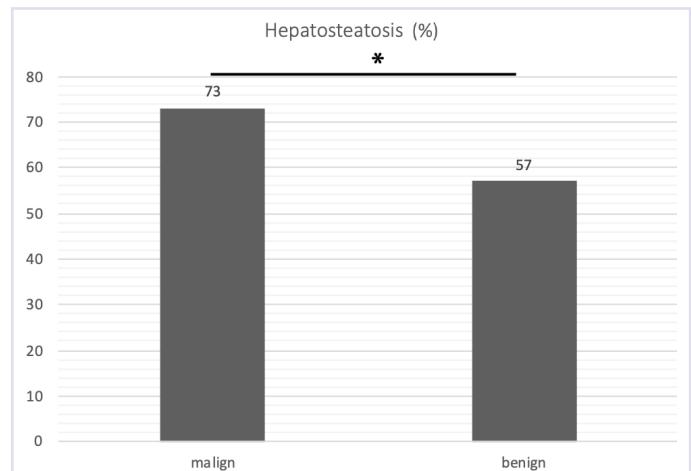


FIGURE 2. Hepatosteatois is present in the majority of patients diagnosed with malignancy and there is a statistically significant difference (73% vs. 57%, $*p=0.006$).

atosteatois, advanced age and type II DM have also been shown to be associated with the risk of lung malignancy. In patients who have not undergone US but are followed up with abdominal CT, the diagnosis of hepatosteatois can be reliably and objectively diagnosed with CT [8].

Lung cancer is one of the leading causes of death worldwide [1]. The most well-known etiological factor is a smoking history; however, it is also known that there are other preventable causes such as obesity. Additionally, lung cancer subtypes, such as adenocarcinoma, have been shown to have a lower prevalence of smoking history compared to other types of lung cancer [2]. Therefore, other potential risk factors apart from smoking, should be investigated.

Studies have drawn attention to the increased risk of various cancer types in obese individuals compared to non-obese individuals [11]. Currently, the incidence of obesity is exponentially increasing globally due to sedentary lifestyles and dietary factors. Obesity can lead to epidermal growth factor receptor (EGFR) mutations, which are associated with lung adenocarcinoma. In recent years, studies have shown that obesity is involved in the etiology of many cancers, and has also been implicated in the development of lung cancer [4, 10, 11].

Visceral fat accumulation caused by obesity is commonly associated with hepatosteatois. Hepatosteatois is closely linked to obesity and metabolic syndrome. The co-occurrence of colon, breast, and liver cancer is well-known in patients with hepatosteatois. Moreover, hepatosteatois is thought to play a role in the development

of lung cancer [10]. However, there is currently a lack of sufficient and conclusive studies on this matter.

Hepatosteatosi can be diagnosed radiologically. The most commonly used imaging method, US, can be utilized for the diagnosis of hepatosteatosi [12]. Additionally, CT imaging, which exhibits high sensitivity and specificity similar to US and MRI, can also be employed for diagnosing hepatosteatosi [13]. Moreover, CT allows for obtaining objective results with numerical values measured in HU. Thus, CT can be safely utilized in the diagnosis of hepatosteatosi. The objective determination of hepatosteatosi through CT, commonly used in the follow-up of cancer patients, provides numerical values that contribute to the diagnosis. In light of our study's findings, it is crucial to highlight the presence of hepatosteatosi in CT reports, particularly in individuals diagnosed with hepatosteatosi and who possess additional risk factors such as DM, advanced age, and male gender, as they face an elevated risk of developing lung cancer. Our study provides evidence linking hepatosteatosi identified through CT with malignancy. This approach enables the implementation of early interventions in patients with such risks. According to the guidelines, if hepatosteatosi is incidentally detected in a person through imaging methods, further evaluation should be conducted, considering the potential risks associated with hepatosteatosi, such as type II diabetes mellitus, cardiovascular diseases, and cancer [14, 15].

Due to its association with obesity and metabolic syndrome often coexists with other diseases in these patients, in addition to visceral fat accumulation [16]. For instance, the co-occurrence of type II DM and hypertension is common. Therefore, in our population of patients diagnosed with lung cancer, it is important to investigate the synergistic effect of hepatosteatosi with other factors, beyond visceral fat accumulation. However, no statistically significant result was found regarding hypertension.

Furthermore, logistic regression analysis revealed an increased risk of lung cancer in patients with hepatosteatosi, advanced age, and type II DM.

Considering that hepatosteatosi is the easiest to diagnose among these three factors and is also treatable, it emerges as a prominent factor. Therefore, hepatosteatosi should be regarded as a condition that needs to be taken into account in CT examinations and carefully mentioned in reports.

In the literature, it has been observed that hepatosteatosi tends to decrease after the age of 60 but is more

commonly seen in middle-aged individuals [14]. Its higher prevalence at an early age and its status as a widespread disorder globally indicate that hepatosteatosi is an important condition that should be taken seriously in terms of diagnosis and follow-up.

Our study confirms previous observations that hepatosteatosi is a multisystem disorder. It disrupts the microstructural architecture and causes inflammation, eventually leading to cirrhosis in the liver. Given the liver's connections with systemic circulation, it is believed that the inflammation caused by hepatosteatosi can impact multiple body systems through a multisystemic effect [17]. It has been shown that tumor necrosis factor-alpha (TNF- α) levels increase in hepatosteatosi and contribute to oxidative stress and apoptosis, leading to biological effects in various tissues [18]. Inflammation, particularly chronic inflammation, has been identified as an influential factor in the development of new tumors and the progression of existing tumors. Moreover, immune activation and inflammation have been shown to play a significant role in the development and prognosis of lung cancer [19]. In fact, a study utilizing canakinumab, an interleukin beta inhibitor, demonstrated a reduction in the incidence of lung cancer and lung cancer-related mortality among individuals using canakinumab [20]. Supporting this hypothesis, there are studies in the literature indicating that hepatosteatosi can contribute to cancer development in various organs, including the gastrointestinal system, breast, prostate, thyroid, kidney, and lungs [21–26]. Additionally, previous reports have highlighted the common co-occurrence of hepatosteatosi and lung cancer, which aligns with our findings [21].

Our study had several limitations that need to be acknowledged. The first important limitation was that only patients with a lung mass whose biopsy was performed and whose histopathological diagnosis was made were included in the study. The second limitation was the limited number of patients due to the single-center nature of our study. A larger and more diverse sample would have enhanced the generalizability of our results. Furthermore, our study was retrospective in nature, introducing inherent limitations associated with data collection and potential biases. Since the majority of patients were referred to our clinic for lung biopsy, the effect of smoking could not be included in the logistic regression test because the smoking history could not be clearly obtained in the majority of our patient group. Hepatosteatosi was diagnosed by retrospectively eval-

uating the abdominal CT taken during the follow-up of these patients who underwent biopsy. The duration of hepatosteatosis and the regularity of follow-up examinations were unknown, which may have influenced our findings. Lastly, due to the lack of long-term follow-up after the initial diagnosis, we were unable to conduct comprehensive surveys and investigations to assess the long-term outcomes and potential associations. This limitation restricts our ability to draw definitive conclusions regarding the relationship between hepatosteatosis and lung cancer over time. Finally, the cause-and-effect relationship between hepatosteatosis and cancer is far more complex than previous assumptions. Peroxisome proliferator-activated receptor-delta (PPAR- δ) and several transcription factors regulate metabolism, inflammation, and tumorigenesis. It remains unclear, whether hepatosteatosis versus malignancy triggers the pathophysiology in these patients [27].

Conclusion

Our study findings showed that the frequency of hepatosteatosis was statistically significantly higher in the majority of our patient group followed up with a diagnosis of lung cancer. This suggests that hepatosteatosis, a metabolic risk factor, may be associated with lung cancer. Studies with larger sample size, prospective design, and long-term follow-up are needed to overcome the limitations of our current study and elucidate the complex relationship between hepatosteatosis and different types of lung cancer.

Ethics Committee Approval: The Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 11.01.2023, number: 2023/0031).

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