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Lymphocyte To HDL-C Ratio in Metabolic Dysfunction-Associated Steatotic Liver Disease

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ABSTRACT

We aimed to evaluate the lymphocyte/HDL cholesterol ratio as a new potential indicator in patients diagnosed with metabolic dysfunction-associated steatotic liver disease by ultrasonographic imaging. This ratio is easily calculated method.
One hundred and seventy-three patients who came to our outpatient clinic between 1 February-15 November 2022 were included in the study. After measuring the height, weight and waist circumference of all patients, blood sample was drawn from the antecubital vein following a fasting period of at least 8 hours. The patients' sex, age (years), and AST(U/L), ALT (U/L), albumin (g/dl), glucose(mg/dl), insulin(mlU/L), HDL-C (high-density lipoprotein-C) (mg/dl), lymphocyte (10^9/L) values were recorded. Ultrasonographic imaging was used as the diagnostic method for hepatosteatosis in all cases. The fatty liver on ultrasonography was graded as grade 1-2-3.
Forty-eight (28.2%) patients had no fatty liver findings in ultrasonography. Patients with fatty liver findings were sorted as 52 patients (30.1%) with grade 1, 47 patients (27.2%) with grade 2, and 26 patients (15.0%) with grade 3 fatty liver. Among the cases with and without metabolic dysfunction-associated steatotic liver disease, the difference was significant between body mass index(**p=0.001**), waist circumference(**p=0.001**), and glucose(**p=0.036**) means. Among the cases with and without metabolic dysfunction-associated steatotic liver disease, the difference was not significant between age, AST, ALT, albumin, insulin, insulin resistance, HDL-C, lymphocytes, and lymphocytes/HDL-C ratio.
Although there is no significant result, it is the first study to evaluate that lymphocyte/HDL-C ratio in metabolic dysfunction-associated steatotic liver disease, which is a common public health issue. More research is needed before stating that the lymphocyte/HDL-cholesterol ratio can be a new potential indicator of metabolic dysfunction-associated steatotic liver disease.

Keywords: Prognostic markers, Lymphocyte/HDL-C ratio, metabolic dysfunction-associated steatotic liver disease.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a public health problem, increasing worldwide (1). It is characterized by atypical fat accumulation in the liver not related to alcohol consumption and can present a broad range of clinical conditions, including fatty liver, steatohepatitis, liver cirrhosis, and hepatocellular carcinoma. It is one of the leading causes of chronic liver disease in Western societies today (2). Sedentary life, unhealthy diet and especially excessive fructose consumption, increase de-novo lipogenesis and contribute to the development of MASLD in all age groups (3). Along with metabolic risk factors, age, sex, and ethnicity are risk factors that significantly affect the development of MASLD. MASLD is more common in men, elderly people, and Hispanics. Patients are most often diagnosed in their 40s and 50s, the prevalence of the disease increases with age (4). Patients with MASLD have higher mortality rates and shorter survival times compared to the general population (5).

Diagnosing the metabolic dysfunction-associated steatotic liver disease, the gold standard method is liver biopsy (2). Considering the liver biopsy is invasive, costly, and prone to complications, routine liver biopsy is not preferred much. Ultrasonography recently has become widespread and a more accessible method and is very successful in detecting fatty liver.

Lymphocyte/high-density cholesterol ratio (LHR) is a new inflammatory biomarker that has been shown to be associated with a cardiovascular risk factor (6).

In this study, we wanted to investigate whether LHR is associated with metabolic dysfunction-associated steatotic liver disease or not.

High lymphocyte counts cause slow-progressing chronic inflammation in the body, stimulates lymphocyte migration and increases lipogenesis

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(7). Increased lymphocyte counts impair endothelial function while nitric oxide and prostacyclin production is increased (6). Adipocytes increase the migration of lymphocytes, and lymphocytes increase lipid formation (8).

HDL-C is a lipid biomarker with antithrombotic, antioxidant, anti-inflammatory and antiapoptotic features (8). HDL-C has inhibitory effects on inflammation, oxidation, and thrombosis (7).

For all these reasons; Lymphocyte/HDL-C ratio (LHR) may be a potential new indicator of inflammation (9).

In this study, we aim to predict whether we can use the lymphocyte/high-density cholesterol ratio is an indicator of metabolic dysfunction-associated steatotic liver disease.

Materials and Methods

University medical faculty ethics committee gave permission for the study.

The study was conducted by including patients who applied to the University Medical Faculty Hospital Gastroenterology and Endocrinology outpatient clinics between February 1 and November 15, 2022.

It is a descriptive and comparative study. The records of patients with metabolic measurements, laboratory results and ultrasound examinations between the specified dates were retrospectively analyzed. Patients who came to the endocrinology and gastroenterology clinic that day and underwent liver USG were included in the study. Patients who underwent liver USG were grouped according to liver steatosis and non-steatosis. After measuring the height, weight and waist circumference of all patients, blood sample was drawn from the antecubital vein following a fasting period of at least 8 hours, and liver parenchyma evaluation was performed by the same gastroenterology physician with a Philips Affinity 50G (Philips, Netherlands) ultrasonography device.

Fatty liver was diagnosed by diffuse increase in hepatic parenchymal echogenicity relative to spleen or kidney on USG. The grading of fat in the liver was done as follows:

Grade 1: Mild diffuse increase in echogenicity,

Grade 2: Decreased clarity of the portal vein wall and diaphragm, accompanied by a moderate rise in echogenicity.

Grade 3: With advanced echogenicity, posterior part of the liver, diaphragm and the portal vein wall cannot be seen.

The patients' sex, age (years), AST(U/L), ALT (U/L), albumin (g/dl), glucose(mg/dl), insulin(mlU/L), HDL-C (high-density lipoprotein-C) (mg/dl), lymphocyte(10^9 /L) values were recorded.

We obtained insulin resistance values by dividing the product of glucose and insulin values by 405 (The homeostasis model assessment (HOMA) of insulin resistance (IR)), and LHR were calculated with same blood sample.

Patients with chronic kidney failure, chronic liver failure, heart failure, cancer, diabetes, chronic inflammatory diseases, heavy alcohol use, drug use that can cause fatty liver were excluded from the study to have objective laboratory results and physical examination measures.

Statistical Analysis: The data were analyzed using SPSS version 22 compatible with Windows. A p-value of less than 0.05 was considered statistically significant. The health records of the patients were accessed through the hospital archive and no sample was selected for the study. All patients with appropriate records were included in the study. Therefore, the results do not represent the community because the study only includes people admitted to the hospital, but it makes an important contribution to the literature. Continuous variables were presented as means ± standard deviation, while counts or percentages (%) were used for categorical variables. Kolmogorov Smirnov and Shapiro Wilk Test were used to determine the suitability of the data with the normal distribution. We compared age, body mass index, waist circumference, AST, ALT, albumin, glucose, insulin, insulin resistance, HDL-C, lymphocyte and lymphocyte/HDL ratio with Student's-t Test, Mann-Whitney U Test and Chi-Square test on patients with fatty and non-fatty liver.

Results

One hundred and seventy-three patients were included in the study. Fifty-eight percent of the cases (33.5%) of the cases were female and 115 (66.5%) were male. The mean age of participants was 45.8 ± 14.4. Body mass index waist circumference, AST, ALT, albumin, glucose, insulin, insulin resistance, HDL-C, lymphocyte, lymphocyte/HDL-C ratio mean and standard deviations were measured. 48 patients showed no

Table 1: Demographic, Clinical and Laboratory Features of The Cases

n:173	Mean ± standard deviation
Female (n, %)	(58, 33.5%)
Male (n, %)	(115, 66.5%)
Age (Years)	45.8 ± 14.4
Body mass index(kg/cm²)	27.51± 4.73
Waist circumference(cm)	96.46± 12.61
AST (IU/mL)	26.6 ± 15.0
ALT (IU/mL)	27.2 ± 23.0
Albumin (g/dL)	4.4 ± 0.3
Glucose (mg/dL)	104.8 ± 22.6
Insulin(mlU/L)	9.76 ± 5.35
İnsulin resistance	2.55±1.60
HDL-C(mg/dl)	51.7±12.3
Lymphocyte(10^9 /L)	2528.43±871.11
Lymphocyte HDL-C ratio	52.28±24.50
Fatty liver Grade 0(n, %)	(48, 28.0%)
Fatty liver Grade 1(n, %)	(52, 30.0%)
Fatty liver Grade 2(n, %)	(47, 27.0%)
Fatty liver Grade 3(n, %)	(26, 15.0%)

Table 2: The Relation Between Sex, Age, Body Mass Index, Waist Circumference, AST, ALT, Albumin, Glucose, Insulin, Insulin Resistance, HDL-C, Lymphocyte, Lymphocyte/HDL Ratio and Patients' Liver Fat Status

	Without MASLD(n 48, 27.7%) Mean ± standard deviation	**With MASLD(n 125, 72.3%)** Mean ± standard deviation	**p**
Female (n, %)	13, 27.08%	45, 36.00%	0.266(x2)
Male (n, %)	35, 72.91%	80, 64.00%	
Age (years)	40.70±13.97	47.79±14.19	0.108*
Body mass index(kg/cm²)	23.24±3.32	29.15±4.14	**0.001****
Waist circumference(cm)	84.79±9.8	100.94±10.53	**0.001****
AST (IU/mL)	22.14±5.31	28.38±17.11	0.745**
ALT (IU/mL)	18.06±8.14	30.83±25.85	0.074**
Albumin (g/dL)	4.57±0.31	4.44±0.35	0.620*
Glucose (mg/dL)	95.40±12.63	108.39±24.51	**0.036****
İnsulin(mlU/L)	7.26±3.04	10.73±5.73	0.256**
İnsulin resistance	1.70±0.79	2.88±1.71	0.196**
HDL-C(mg/dl)	54.90±12.39	50.62±12.25	0.250*
Lymphocyte(10^9 /L)	2417.44±837.00	2570.16±183.25	0.777**
Lymphocyte HDL-C ratio	47.25±23.01	54.04±24.86	0.401**

x² Pearson Chi-Square
***** Student's t-test
******Mann-Whitney U test

liver fat on ultrasound, 52 patients had grade 1 fatty liver, 47 patients had grade 2, and 26 patients had grade 3 fatty liver (Table 1).

Of the cases without fatty liver on ultrasonography, 13 were female and 35 were male. The mean and standard deviations of age,

body mass index, waist circumference, AST, ALT, albumin, glucose, insulin, insulin resistance, HDL-C, lymphocyte, and lymphocyte/HDL-C ratio were measured.

Of the cases with fatty liver on ultrasonography, 45 were female and 80 were male. The mean and standard deviations of age, body mass index, waist circumference, AST, ALT, albumin, glucose, insulin, insulin resistance, HDL-C, lymphocyte, and lymphocyte/HDL-C ratio were measured.

Among the cases with and without MASLD, there was a significant difference between body mass index ($p=0.001$), waist circumference ($p=0.001$), and glucose ($p=0.036$) means.

Among the cases with and without MASLD, the difference between age, AST, ALT, albumin, insulin, insulin resistance, HDL-C, lymphocytes, and lymphocytes/HDL-C ratio was not significant (Table 2).

Discussion

This study did not reveal that cases with metabolic dysfunction-associated steatotic liver disease had significantly higher LHR values compared to cases without metabolic dysfunction-associated steatotic liver disease.

However, in an outpatient setting, this study is the first to demonstrate whether the lymphocyte/HDL-C ratio can be used as an aid in the diagnosis of metabolic dysfunction-associated steatotic liver disease.

No laboratory test can replace liver biopsy in diagnosing metabolic dysfunction-associated steatotic liver disease. Liver biopsy is an invasive, expensive, and team-requiring procedure and it may lead to complications such as bleeding and pain.

This study, although there is no significant result, it is the first study showing that lymphocyte/HDL-C ratio can be used as an indicator in metabolic dysfunction-associated steatotic liver disease, which is a public health issue.

We investigated, age, body mass index and waist circumference, which are non-invasive prognostic factors of fatty liver, as well as albumin, glucose, insulin resistance and lymphocyte/HDL-C ratio. More research is needed before stating that the lymphocyte/HDL-cholesterol ratio can be a new potential indicator of metabolic dysfunction-associated steatotic liver disease.

We wanted to draw attention to the importance of lymphocyte/HDL-C ratio, which is a new biomarker of inflammation in the diagnosis of MASLD. However, based on this study, it appears that LHR cannot be used as a biomarker in MASLD.

Globally, the most common liver disease is MASLD with a prevalence of 25% (10). Fibrosis is more common in MASLD that progresses to metabolic-dysfunction associated steatohepatitis (MASH) (11). Liver fibrosis level is a reliable finding that can assist us in forecasting the clinical progression of MASLD and liver-related mortality (12). Patients with advanced fibrosis and cirrhosis are more likely to develop hepatocellular carcinoma and liver failure (13). Significant alcohol consumption and secondary causes of liver disease are excluded in metabolic-dysfunction associated steatohepatitis (14).

As our study has supported, instead of non-alcoholic liver disease, the definition of metabolic dysfunction-associated fatty liver disease has recently come to the fore (15).

In our study, even though there is no significant relation, MASLD increased with age. One study suggested that metabolic dysfunction-associated fatty liver disease peaks between the ages of 40-50 years in men and 60-69 years in women (15). Golabi P et al. also showed in their study that the frequency of metabolic dysfunction-associated fatty liver disease increases with age (16).

In our study, the body mass index was higher in cases with MASLD. Fabbrini E et al, Fan R et al, Yılmaz Y et al. reported that obesity and increased body mass index are risks for MASLD (17).

Waist circumference was also measured higher in individuals with MASLD in our study, which supported by Alam S et al (18).

In this study, AST and ALT levels were found higher in patients with metabolic dysfunction-associated fatty liver disease. In many studies, this was considered an indicator of advanced liver fibrosis (11).

Albumin is a marker of liver reserve (19). In our study, we found low albumin levels in patients with metabolic dysfunction-associated fatty liver disease. This may be a predictor that leads to liver fibrosis and failure (19).

Miyake T et al. showed metabolic dysfunction-associated fatty liver disease as a risk factor for glucose intolerance (20). In this study, the blood glucose level in patients with MASLD was higher than in patients without MASLD.

Decreased insulin sensitivity is a feature of MASLD. The progression of MASLD is associated with insulin resistance (21), and like our study, MASLD and insulin resistance move in the same direction. In a study by Chen et al., attempts to reduce insulin resistance also led to improvement in metabolic dysfunction-associated fatty liver disease (22). In a study using the Mediterranean diet, both insulin resistance and fat accumulation in the liver were reduced (10). As seen in our study, an increase in insulin resistance, may be a laboratory indicator of fatty liver disease.

LHR has been presented as a new indicator of inflammation and it has been studied as a biomarker in metabolic syndrome and chronic obstructive pulmonary disease (7). Chen et al have shown that LHR is an independent predictor of metabolic syndrome (7). However, a study in which LHR is a biomarker in MASLD has not been done so far. In a study investigating parameters related to MASLD, HDL cholesterol level was found to be low (23). In this study, we investigated whether LHR is a definitive marker in the diagnosis of MASLD.

The limitations of our study are that methods such as liver biopsy, magnetic resonance, elastography, as well as other inflammation markers such as C-reactive protein are not examined in the diagnosis of MASLD, and the results are not compared with LHR.

In conclusion, more research is needed to use LHR as a simple, easy and effective indicator of metabolic dysfunction-associated fatty liver disease.

Conflict of Interest: The authors declared no conflict of interest.

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