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The Evalution of Correlatıons Between the Incıdence of Gallstones in Patıents wıth Cırrhosıs and Fındıngs of Hypersplenısm wıth the Splenıc Ultrasound Elastography Fındıngs.

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Abstract: Background: Cirrhosis is often associated with hypersplenism and an increased incidence of gallbladder stones, contributing to complications and mortality in affected patients. Ultrasound elastography has emerged as a non-invasive tool for assessing tissue stiffness, including spleen stiffness, which may reflect the presence of hypersplenism. This study aims to explore the correlations between spleen stiffness measured by ultrasound elastography, hypersplenism, and gallbladder stone incidence in patients with cirrhosis.
Methods: A total of 88 participants were included, consisting of healthy volunteers (n=28), patients with liver cirrhosis and signs of hypersplenism (LC+H, n=37), and patients with liver cirrhosis without hypersplenism (LC-H, n=23). Clinical and biochemical parameters were recorded, and ultrasound elastography was performed to assess spleen stiffness. Statistical analysis was conducted to evaluate correlations between spleen stiffness, hypersplenism, and gallbladder stone incidence.
Results: Hypersplenism was present in 61.7% of cirrhosis patients. Patients with hypersplenism showed lower hemoglobin and platelet values compared to those without hypersplenism. Gallbladder stones were more prevalent in patients with cirrhosis and hypersplenism (54%) compared to those without (26%). Spleen stiffness measured by elastography did not differ significantly between patient groups but showed a positive correlation with gallbladder stone frequency in the hypersplenism group.
Conclusion: Spleen stiffness measured by ultrasound elastography shows a positive correlation with gallbladder stone incidence in cirrhosis patients with hypersplenism. Early identification of increased spleen stiffness may aid in the early detection and management of gallstone-related complications in cirrhosis.

Key Words: Liver cirrhosis, gallstones, hypersplenism, elastograph

İNTRODUCTİON

Cirrhosis is a condition of liver failure secondary to chronic viral hepatitis (B, C, and Delta), autoimmune hepatitis, non-alcoholic steatohepatitis, alcohol use, and other causes [1]. While bone marrow suppression, lack of growth factors, and immunological pathologies have been implicated in the pathophysiology of hematological problems in cirrhosis, hypersplenism is widely accepted as a primary factor [2, 3]. Another common occurrence in cirrhosis patients is the increased incidence of gallbladder stones, which is reported to be approximately two times higher compared to the normal population. These stones, often bilirubin pigment stones, are attributed to increased hemolysis secondary to hypersplenism [4-6].

Hypersplenism is characterized by an abnormally increased functional spleen, resulting in increased destruction of blood cells and decreased erythrocyte lifespan. Confirmation of hypersplenism typically requires meeting criteria such as decreased blood cell counts, compensatory hyperplasia in bone marrow examination, splenomegaly, and normalization of blood cells after splenectomy. However, these criteria are not always practical for patients with cirrhosis [7].

In recent years, ultrasound elastography examination has emerged as a dynamic ultrasound technique that measures tissue strain by applying minimal external compression, providing information about tissue stiffness. Studies have demonstrated the non-invasive assessment of liver stiffness and fibrosis in patients with chronic liver disease [8, 9]. Splenic elastography has also been identified as a promising clinical marker in portal hypertension cases [10].

The purpose of this study is to investigate the correlation between spleen stiffness and the presence of hypersplenism and gallbladder stones in cases of cirrhosis secondary to various etiologies.

MATERİALS AND METHODS

Approval for the study was obtained from the Fırat University Faculty of Medicine Clinical Studies Ethics Committee under decision number 10, dated 15.03.2012. The kits utilized in this study were provided by the authors, with no support received from any institution or organization for this purpose.

Patient Selection:

The study included male and female patients over 18 years of age who were under follow-up with diagnoses of chronic viral hepatitis (B, C, D), alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, cryptogenic cirrhosis, and cirrhosis due to other etiologies, and who presented to the Fırat University Faculty of Medicine Gastroenterology Clinic.

Diagnosis of liver cirrhosis was based on liver biopsy results if available, or clinical (e.g., ascites, splenomegaly, presence of esophageal varices) and laboratory findings if biopsy was not performed. Each patient underwent abdominal ultrasonography to assess the presence and extent of ascites, gallbladder stones, spleen size, and elastography.

The study comprised a total of 88 participants, including 28 healthy volunteers as the control group, 37 patients with liver cirrhosis and signs of hypersplenism (LC+H), and 23 patients with liver cirrhosis but without hypersplenism (LC-H). Prior to the procedures, a patient consent form was prepared, and each participant or their legal guardian filled out and signed the form under the supervision of the attending physician. The control group comprised male and female individuals over 18 years of age with no history of chronic hepatitis or diabetes mellitus, no obesity, no previous gallbladder, spleen, or liver surgeries, and no chronic illnesses.

Exclusion criteria included pregnant women, individuals in a coma, patients diagnosed with hematolytic-hematological disorders, and those with conditions causing splenomegaly other than liver cirrhosis. The study recorded the name, surname, age, gender, height, and weight of each participant for analysis purposes. Additionally, clinical features and biochemical parameters of the patient groups, including complete blood count, AST, ALT, ALP, GGT, LDH, INR, LDL, total protein, albumin, urea, creatinine, total bilirubin, direct bilirubin, and fasting blood sugar, were recorded and evaluated from their medical records.

Ultrasound Elastographic Examination:

Following the diagnostic ultrasonography (USG) examination, elastography volumes were obtained and recorded by applying rhythmic minimal pressure on the abdominal wall for 5-10 seconds. This procedure is non-invasive and typically takes 15-30 seconds following the normal diagnostic procedure. Subsequently, the acquired volumes were evaluated at the workstation, and maximum, minimum, and mean spleen strain values were measured. Additionally, resistive index (RI) and pulsatility index (PI) measurements were conducted on the splenic artery, and spleen volume measurements were performed.

Statistical Analysis:

The statistical analysis of the data was conducted using the SPSS statistical program. For parametric data, Student's t-test, analysis of variance (ANOVA), and post-hoc Tukey tests were employed, while the Mann-Whitney U test was utilized for non-parametric data. Categorical data were analyzed using the chi-square test. Pearson correlation analysis was employed todetermine the relationship between the variables. A significance level of $P<0.05$ was considered statistically significant.

RESULTS

Hypersplenism was present in 61.7% of the patients. Among all patients with liver cirrhosis (LC), 36 were males (60%) and 24 were females (40%). In the patient group with signs of liver cirrhosis and hypersplenism (LC+H), 19 were males (51%) and 18 were females (49%). The patient group with liver cirrhosis but no signs of hypersplenism (LC-H) consisted of 18 men (78%) and 5 women (22%). In the control group, 13 were men (46.4%) and 15 were women (53.6%). There was no statistically significant difference between the patient and control groups in terms of gender ($p>0.05$). The average age of all patients with LC was 58.48±1.8 years. It was 60±2.2 years in the patient group with liver cirrhosis and signs of hypersplenism, and 56±3.1 years in the patient group with liver cirrhosis but no signs of hypersplenism. In the control group, it was found to be 38.11±1.39 years. A statistically significant difference was found between the patient and control groups in terms of average age ($p<0.001$) (Table 1).

Table 1. Meanandstanderrorvalues of laboratoryresultsanddemographicinformation of thepatientandcontrolgroups

	LC (n: 60)	**Control (n: 28)**	***P***
Hemoglobin (g/dL)	11,1±0,3	13,58±0,2	<0,001
Hematocrit (%)	34,9±1,0	42,0±0,7	<0,001
WBC (mm3)	4839±352	6666±291	<0,001
Platelet (mm3)	105871±7585	262892±10448	<0,001
Glucose (mg/dL)	114±9	75±1,8	<0,001
ALT (U/L)	41±4,4	26±2,6	<0,004
AST (U/L)	63±5,4	24±1,3	<0,001
GGT (U/L)	84±10,1	18±2,1	<0,001
ALP (U/L)	124±10,1	66±4,6	<0,001
LDH (U/L)	230±10,0	211±9,3	<0,01
INR	1,3±0,2	1,0±0,01	<0,001
Total Protein(g/dL)	6,6±0,1	7,1±0,1	<0,01
Albumin (g/dL)	3,1±0,8	4,5±0,5	<0,001
T.bilirubin (mg/dL)	2,04±0,2	0,7±0,06	<0,01
LDL	73±4,5	118±6,3	<0,001
BMI	26±0,6	25±0,6	>0,4
Age	58±1,8	38,1± 3	<0,001

A statistically significant difference was found between the patient and control groups participating in the study in terms of laboratory findings. There was no statistically significant difference between the body mass indexes of the patients based on demographic characteristics only (p>0.4) (Table 2).

Table 2. Meanandstandarderrorvalues of laboratoryresultsforpatientgroupswithandwithoutsigns of hypersplenism

LC+H	**(n: 37)**	**LC-H (n: 23)**	*P*
Hemoglobin (g/dL)	10,3±0,4	12,32±0,5	>0,05
Hematocrit (%)	32,5±1,3	38,6±1,1	<0,001
WBC (mm3)	4644±451	5153±573	>0,05
Platelet (mm3)	85.927±8526	137956±11631	<0,001
Glucose (mg/dL)	114±10	113±16	>0,05
ALT (U/L)	38±5	47±8	>0,05
AST (U/L)	65±8	59±6	>0,05
GGT (U/L)	73,08±10,3	102,09±20,3	>0,05
ALP (U/L)	106,±7,9	153±22	>0,05
LDH (U/L)	228±13,8	233,7±14,2	>0,05
INR	1,4±0,04	1,3±0,05	>0,05
Total Protein(g/dL)	6,5±0,1	6,7±0,1	>0,05
Albumin (g/dL)	3,0±0,1	3,3±0,1	>0,05
T.bilirubin (mg/dL)	2,1±0,3	1,8±0,3	>0,05
LDL	66,8±3,9	86,2±9,5	>0,05
BMI	26,5±1,0	25,7±0,7	>0,05
Age	60±2,2	56,04±3,1	>0,05

A statistically significant difference was observed between hemoglobin and platelet values in the patient groups with and without signs of hypersplenism (<0.001). Hemoglobin and platelet values were observed to be lower in the patient group with signs of hypersplenism. There was no significant difference between the groups in terms of other laboratory findings. No significant difference was observed between the demographic characteristics of the groups (>0.05) (Table 3).

Table 3. Meanandstandarderrorvalues of laboratoryresults of the patient group with hypersplenism finding sand the control group

	LC+H (n: 37)	**Control (n: 28)**	***p***
Hemoglobin (g/dL)	10,3±0,4	13,5±0,2	>0,05
Hematocrit (%)	32,5±1,3	42,0±0,7	<0,001
WBC(mm3)	4644±451	7359±291	>0,05
Platelet (mm3)	85.927±8526	262892±10448	<0,001
Glucose (mg/dL)	114±10	75±1,8	<0,001
ALT (U/L)	38±5	26±2,6	<0,001
AST (U/L)	65±8	24±1,3	<0,001
GGT (U/L)	73,08±10,3	18,3±2,1	<0,001
ALP (U/L)	106,±7,9	66±4,6	<0,001
LDH (U/L)	228±13,8	211±9,3	>0,05
INR	1,4±0,04	1,0±0,01	<0,001
Total Protein(g/dL)	6,5±0,1	7,1±0,1	>0,05
Albumin (g/dL)	3,0±0,1	4,5±0,06	<0,001
T.bilirubin (mg/dL)	2,1±0,3	0,1±0,06	<0,001
LDL	66,8±3,9	118±6,3	<0,001
BMI	26,5±1,0	25,3±0,7	>0,05
Age	60±2,2	38,1±1,3	<0,001

There was no statistically significant difference between the patient group with signs of hypersplenism and the control group in terms of Hb, WBC, LDH, and total protein results from laboratory data, but a significant difference was seen in other results. There was a significant difference between the average age of the two groups ($p<0.001$). The average age of the LC+H group was older (Table 3).

In the semi-quantitative elastography measurements performed on the cases, no significant difference was observed in the maximum, minimum, and average tension values between the LC+H group and the LC-H group. No significant difference was observed between the LC+H group and the LC-H group in RI and PI measurements made on the splenic artery and splenic volume measurements. A statistically significant difference was found between the groups in terms of gallbladder stone (GBS) frequency ($p<0.05$) (Table 4).

Tablo 4. Elastographyaverages, GBS frequency and statistical analysis results for patient groups with and without signs of hypersplenism

	LC+H	**LC-H**	***P***
Maximum strain	92,6(±3,2)	84,6(±5,0)	>0,05
Minimumstrain	78,5(±3,7)	67,9(±5,4)	>0,05
Meanstrain	86,6(± 3,7)	74,5(±6,0)	>0,05
PI	1,5(±0,1)	1,3(±0,08)	>0,05
RI	0,7(±0,03)	0,6(±0,02)	>0,05
Splenicvolume	810,4(±105,1)	561 (±77,5)	>0,05
GBS frequency(n,%)	20(%54)	6(%26)	<0,05

In the semi-quantitative elastography measurements performed on the cases, no significant difference was observed between the maximum, minimum, and mean strain values between the LC group and the control group ($p>0.06$-$p>0.08$-$p>0.5$). Again, no significant difference was observed between the patient group and the control group in the RI and PI measurements made on the splenic artery ($p>0.07$). The difference in splenic volume measurements between the patient and control groups was statistically significant ($p<0.05$). A statistically significant difference was found between the groups in terms of GBS frequency ($p<0.05$) (Table 5).

Table 5. Elastographymeans, GBS frequencyandstatisticalanalysisresultsforthepatientandcontrolgroups

	KC-S	**Kontrol**	***P***
Maximum strain	89±2,8	99±5,2	>0,06
Minimumstrain	74±3,1	85±5,7	>0,08
Meanstrain	81±3,3	85±5,7	>0,5
PI	1,4±0,09	1,2±0,07	>0,07
RI	0,7±0,02	0,6±0,01	>0,07
Splenic volume	709±71,5	240±19,0	<0,00
GBS frequency(n,%)	26(%44,1)	0(%0,0)	<0,00

No significant correlation was found between the maximum spleen strain value and GBS in the total patient group with liver cirrhosis ($p>0.05$). A significant positive correlation was also detected between the RI value applied to the splenic artery and GBS ($p<0.05$) (Table 6).

A positive correlation was found between the maximum spleen strain value and the frequency of GBS in the group of patients with LC+H ($p>0.05$). A significant positive correlation was detected between the group's minimum spleen strain value and the frequency of GBS ($p<0.05$). Again, a significant positive correlation was found between the mean spleen strain value and the frequency of GBS ($p<0.05$) (Table 6).

Table 6. Correlation of spleen elastography findings of LC-H, LC+H, LC+T groups with the frequency of GBS

	GBS					
	LC-H		LC+H		LC+T	
	P	R	p	R	p	R
Maximum strain	0,99	0,00	0,03	0,39	0,95	0,01
Minimumstrain	0,94	0,01	0,01	0,45	0,55	0,08
Meanstrain	0,97	0,00	0,02	0,41	0,77	0,04
Splenic volume	0,04	0,43	0,08	0,31	0,84	-0,02
RI	0,60	-0,12	0,85	0,03	0,00	0,86
PI	0,34	-0,21	0,41	0,15	0,00	1

In the group of patients with LC-H, no correlation was found between the maximum spleen strain value and GBS ($p>0.05$). There was no correlation between the group's minimum spleen strain value and SCT ($p>0.05$). A positive correlation was detected between the splenic volume values of the group and the frequency of GBS ($p<0.05$) (Table 6).

DİSCUSSİON

In patients with liver cirrhosis, increased spleen stiffness, which may be measured with sonoelastography, can be considered as a risk factor for future gallstones. Splenomegaly may lead to hypersplenism, characterized by conditions such as thrombocytopenia, increased risk of infection, and anemia, contributing to increased mortality in both surgical and medical treatment settings for patients with cirrhosis (11, 12). Ashraf and Naeem's study (13) demonstrates that hypersplenism is prevalent in chronic liver patients (68%), with most cases of pancytopenia attributed to hypersplenism. Similarly, in our study, hypersplenism was observed in 61% of 7 patients, consistent with this finding.

Shi et al. (14) found a statistically significant negative correlation between spleen size and hemoglobin and platelet count in patients with cirrhosis and hypersplenism. This suggests that peripheral blood cell count reflects the severity of hypersplenism and should be considered in cirrhosis staging. In our study, while a statistically significant negative correlation between spleen size and platelet count was observed in patients with hypersplenism, this correlation was not found with hemoglobin levels.

The incidence of gallstones in chronic liver disease, particularly cirrhosis, is known to be higher than in the normal population (15-17). In our study, gallstones were observed in 44% of the patient group, whereas none were found in the control group. Among patients with liver cirrhosis and hypersplenism findings, 54% had gallbladder stones, compared to 26% in patients with liver cirrhosis but no signs of hypersplenism.

Spleen stiffness is typically measured using MRI Elastography, ARFI, and Transient Elastography to evaluate portal hypertension and esophageal varices in patients with chronic liver disease (20-24). Hu et al. (25) evaluated the diagnostic value of spleen and liver elasticity in liver fibrosis and found an excellent correlation between spleen and liver stiffness, suggesting that spleen stiffness measurement may be suitable for indirectly assessing liver fibrosis. In our study, semi-quantitative elastography measurements were performed, revealing no significant difference in maximum, minimum, and mean spleen strain values between the LC group and the control group. However, spleen volume measurements and RI and PI measurements of the splenic artery were larger in the patient group, with a statistically significant difference in spleen volume measurements ($p < 0.00$) between the patient and control groups.

Onur et al. (26) conducted semi-quantitative elastography on the liver of patients diagnosed with hepatocellular carcinoma and cirrhosis, finding that the mean strain index value of patients with hepatocellular carcinoma was significantly higher than in benign lesions. This suggests that semi-quantitative elastography may aid in distinguishing malignant focal solid liver lesions from benign ones (26).

Ye et al. (27) measured spleen and liver stiffness in patients with liver fibrosis using ARFI elastography and found a significant correlation between liver and spleen stiffness and fibrosis, as well as between spleen stiffness and the degree of esophageal varices. They concluded that spleen stiffness measured by ARFI could serve as a non-invasive method to determine the presence and severity of esophageal varices.

In our study, a significant positive correlation was found between the RI value applied to the splenic artery and gallstones in the total patient group ($p < 0.05$). Furthermore, a positive correlation was found between maximum spleen strain value, minimum spleen strain value, mean spleen strain value, and the frequency of gallbladder stones in the group of patients with LC+H. No correlation was found between these elastography values and the frequency of gallbladder stones in the group of patients with LC-H. To our knowledge, no other study in the literature has evaluated the correlation between semi-quantitative elastography findings and the frequency of gallbladder stones.

The main limitations of elastography include its operator dependency, variation between observers, and the requirement for training and experience to master the appropriate technique (28). Our study had several limitations, including inadequate pressure applied to patients with ascites and patient breathing incompatibility.

Additionally, the wide range of stress index values and the semi-quantitative method's need for additional calculations and time after obtaining the elasticity map are notable disadvantages.

In conclusion, our study found a significant positive correlation between maximum, minimum, and average spleen tension sonoelastography values and the frequency of gallbladder stones in the hypersplenism group. Increased spleen stiffness measured by sonoelastography in patients with liver cirrhosis can be considered a risk factor for future gallstones. Since surgical intervention is rarely required in advanced-stage cirrhosis cases and carries inherent risks, early examination and consideration of these factors upon diagnosis may be beneficial in patient management.

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