

# The Utility of Lactate Dehydrogenase Isoenzyme Pattern in the Diagnostic Evaluation of Malignant and Nonmalignant Ascites

Alper Sevinc, MD; Ramazan Sari, MD; and Ersin Fadillioğlu, MD  
Gaziantep, Antalya and Malatya, Turkey

**Objective:** Lactate dehydrogenase (LDH), a tetrameric protein composed of four monomers, is expressed as five isoenzymes. Serum LDH isoenzymes may be useful in differential diagnosis of ascites etiology since tissue damage releases isoenzymes contained therein, leading to a change in their pattern.

**Materials and Methods:** We determined ascitic fluid LDH level and LDH isoenzyme activities in patients with malignant and nonmalignant ascites in a total of 76 patients (43 males and 33 females).

**Results:** LDH level, LDH-4 activity and LDH-5 activity were found to be significantly higher, and LDH-1 activity was found to be lower in malignant ascites when compared with nonmalignant ascites. LDH-1 activity was detected to be significantly higher in the sterile cirrhotic ascites when compared with spontaneous bacterial peritonitis, malignant ascites, tuberculous ascites and congestive heart failure-related ascites. LDH-2 activity was found to be higher in spontaneous bacterial peritonitis when compared with the other groups. LDH-3 activity was detected to be higher in spontaneous bacterial peritonitis, malignant ascites and tuberculous ascites when compared with the sterile cirrhotic ascites. In the diagnosis of malignant ascites, the sensitivity and specificity were 96% and 76% for LDH level, 90% and 70% for LDH-1 activity, 94% and 62% for LDH-4 activity, and 100% and 56% for LDH-5 activity, respectively.

**Conclusion:** Ascitic LDH and its isoenzyme pattern may be helpful for the differential diagnosis of the most common causes of ascites: cirrhosis, spontaneous bacterial peritonitis, congestive heart failure, tuberculosis and malignancy.

**Key words:** lactate dehydrogenase ■ isoenzymes ■ ascitic fluid ■ malignancy

## INTRODUCTION

The lactate dehydrogenase (LDH) molecule is a tetramer composed of four polypeptide chains. There are five component isoenzymes as a result of the five different combinations that are produced by two polypeptide chains encoded by separate genes (M and H). LDH-1 is composed of four H subunits, and LDH-5 of four M subunits. The prevailing type of LDH varies according to tissue type. In the heart, the H gene is more active than the M gene, the latter being strongly expressed in the skeletal muscle. As the number of the M over H chains increases, the LDH isoenzyme becomes more efficient in catalyzing the conversion of pyruvate to lactate (LDH-5), while an increase in H over M chains (LDH-1) favors the conversion of pyruvate to acetyl-coenzyme A that enters into the citric acid cycle. Serum LDH isoenzymes may be useful in differential diagnosis of ascites etiology since tissue damage releases isoenzymes contained therein, leading to a change in their pattern.<sup>1-3</sup>

Ascites can present a challenging diagnostic problem. The differential diagnosis is diverse, but most common causes include cirrhosis, spontaneous bacterial peritonitis, tuberculosis, congestive heart failure and malignancy. A complete separation between malignant ascites and nonmalignant ascites has not been always possible. Exfoliative cytology for malignant cells despite its high specificity is unreliable as positive results are obtained only in 40–60% of cases. Therefore, LDH isoenzyme analysis may contribute to cytologic evaluation of serosal fluid and may suggest a malignant etiology even in cytologically negative neoplastic pleural effusions. Measurements of ascitic fluid LDH levels are useful as one of the parameters in the separation of exudative from transudative effusions.<sup>4</sup> In addition to their higher enzyme concentrations, many of the tissues show different isoenzyme composition. In cardiac muscle, kidney and erythrocytes, the electrophoretically faster-moving isoenzymes LDH-1 and LDH-2 predominate, whereas in liver and skeletal muscle the more cathodal LDH-4 and LDH-5 isoenzymes

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predominate (although skeletal muscle may also contain midzone and anodic LDH isoenzymes). Isoenzymes of intermediate mobility are found in many tissues, such as endocrine glands, spleen, lung, lymph nodes, platelets and nonpregnant uterine muscle. The value of serosal LDH isoenzyme pattern is controversial.<sup>5-9</sup>

Ascitic cytology is highly specific but has a diagnostic sensitivity of only 40–60%. No laboratory test completely distinguishes malignant ascites from ascites associated with cirrhosis or other benign etiologies. The objective of the present study was to determine the ascitic fluid LDH level and LDH isoenzyme activities in patients with malignant and nonmalignant ascites (spontaneous bacterial peritonitis, sterile cirrhotic ascites, tuberculous ascites, congestive heart failure-related ascites) to see whether ascitic fluid biochemical examinations might help in the analysis of ascites.

## MATERIAL AND METHODS

A total of 76 patients (43 males and 33 females) with ascites were investigated for their ascitic fluid LDH levels and its isoenzyme activities. Paracentesis were performed to all of the patients to highlight the underlying etiology of ascites. Biochemical, hematological and microbiological investigations were also performed. Complete blood count, biochemical examinations, ultrasonography and cytologic examination of the ascitic fluid were determined:

### Group 1—Malignant Ascites

Twenty-one patients (12 males and nine females), aged  $52.2 \pm 9.1$  years formed group 1. The diagnosis of malignancies was based on histopathological examination of liver, omentum or mass. These patients included five ovarian, four hepatoma, three colon, three mesothelioma, two gastric, two breast, one cholangiocellular and one pancreas carcinoma cases. Eight of these patients were detected to have liver metastasis by ultrasonographic biopsy.

### Group 2—Nonmalignant Ascites

Fifty-five patients (31 males and 24 females),

aged  $50.9 \pm 12.4$  years formed group 2. Group 2 included total four subgroups: spontaneous bacterial peritonitis (group 2a), sterile cirrhotic ascites (group 2b), tuberculous ascites (group 2c), and congestive heart failure-related ascites (group 2d).

**Group 2a—Spontaneous bacterial peritonitis (SBP).** Thirteen patients with SBP (eight males and five females) aged  $51.5 \pm 10.4$  years with a previous history of chronic liver disease formed group 2a. Chronic liver disease was due to hepatitis B in nine cases and hepatitis C in four cases. According to Child-Pugh classification, eight of the patients were group C and five were group B. SBP group was formed of patients either having a positive microbiological culture or having a neutrophil count of  $>250/\text{mm}^3$  in the ascitic fluid. Ascitic fluid culture positivity was detected in 10 patients (*E. coli* in seven, *enterococci* in three).

**Group 2b—Chronic liver disease with sterile ascites.** Fifteen patients (nine males and six females), aged  $54.4 \pm 11.2$  years formed group 2b. Hepatitis B was positive in 10 and hepatitis C was positive in five, and one patient was on alcohol abuser. According to Child-Pugh classification nine patients were group C and six were group B. Malignancy and infections was ruled out in all these patients.

**Group 2c—Tuberculous ascites.** Forming group 2c were 13 patients (seven males and six females) aged  $49.6 \pm 12.0$  years who were diagnosed by histopathological examination of the peritoneum after diagnostic laparoscopy.

**Group 2d—Congestive heart failure-related ascites.** A total of 14 patients (seven males and seven females) aged  $64.2 \pm 10.8$  years who were diagnosed by echocardiography formed group 2d. Spontaneous bacterial peritonitis, chronic liver disease, tuberculosis and malignancy were ruled out in these patients.

Polypropylene tubes were used for ascitic fluid collection and storage. Biochemical parameters were analyzed by Olympus AU 600 (Olympus, Hamburg, Germany) with Olympus kits. LDH isoenzymes were determined by an LDH isoenzyme electrophoresis kit (Hydradel ISO-LDH, Sebia, PN 4130) and expressed as a percentage of LDH activity. Sebia's Hyrys densit-

**Table 1. Ascitic Fluid LDH Levels and Its Isoenzyme Activities in Malignant and Nonmalignant Ascites**

	Malignant Ascites (n=21)	Nonmalignant Ascites (n=55)	P Value
Ascites LDH (U/l)	439.1 $\pm$ 169.1	261.2 $\pm$ 135.7	<0.001
Ascites LDH-1 (%)	21.2 $\pm$ 4.0	43.9 $\pm$ 5.2	<0.01
Ascites LDH-2 (%)	29.5 $\pm$ 3.6	23.8 $\pm$ 2.5	0.076
Ascites LDH-3 (%)	22.6 $\pm$ 1.4	18.8 $\pm$ 1.1	0.095
Ascites LDH-4 (%)	15.6 $\pm$ 2.8	5.9 $\pm$ 1.3	<0.001
Ascites LDH-5 (%)	11.4 $\pm$ 2.5	5.1 $\pm$ 1.2	<0.001

ometer (PN 1010) was used for densitometric measurements. The precision of the analytical method for LDH was assessed by repeated assays of two pools of 10 different nonmalignant ascites fluid. Ascitic fluids (n=10) were stored at -20°C during the experiments. On the other hand, the diagnostic value of ascitic fluid LDH activity was assessed in terms of sensitivity and specificity.

### Statistical Analysis

Statistical analysis was performed with SPSS statistical software. Data is presented as the means  $\pm$  standard deviations. Intergroup comparisons were analyzed by Mann-Whitney U and Kruskal-Wallis 1-Way Anova for nonparametric tests. Spearman test was used for correlation.  $P < 0.05$  values were considered to be statistically significant.

### RESULTS

LDH levels and isoenzyme activities were studied in the ascitic fluid in malignant ascites and nonmalignant ascites. Data regarding LDH and its isoenzymes of malignant and nonmalignant ascites were summarized in Table 1. LDH level and LDH isoenzyme activities of subgroups were shown in Table 2.

### LDH Levels

In all groups, the highest and lowest ascitic fluid LDH levels were detected in group 2c and group 2b, respectively. Ascitic fluid LDH was found to be significantly higher in malignant ascites when compared with nonmalignant ascites ( $p < 0.001$ ). Ascitic fluid LDH levels were found to be significantly higher in group 2c when compared with group 2a ( $p < 0.01$ ) and group 2b ( $p < 0.01$ ), in group 1 ( $p < 0.01$ ) and group 2d ( $p < 0.01$ ) when compared with group 2b.

### LDH-1 Activity

The highest and lowest ascitic fluid LDH-1 activities were detected in group 2b and group 2c, respectively. Ascitic fluid LDH-1 activity was found to be significantly lower in malignant ascites when compared with nonmalignant ascites ( $p < 0.01$ ). Ascitic fluid LDH-1 activity was found to be higher in group 2a when compared with group 1 ( $p < 0.01$ ) and group 2c ( $p < 0.01$ ); in group 2b when compared with group 1 ( $p < 0.001$ ), group 2a ( $p < 0.001$ ), group 2c ( $p < 0.001$ ) and group 2d ( $p < 0.001$ ); in group 2d when compared with groups 1 ( $p < 0.01$ ) and 2c ( $p < 0.01$ ).

### LDH-2 Activity

There was no statistically significant difference between malignant and nonmalignant ascites groups ( $p = 0.076$ ). Ascitic fluid LDH-2 was found to be higher in group 2a when compared with groups 1 ( $p < 0.001$ ), 2b ( $p < 0.001$ ), 2c ( $p < 0.001$ ) and 2d ( $p < 0.001$ ); in group 1 ( $p < 0.01$ ), group 2c ( $p < 0.01$ ) and group 2d ( $p < 0.01$ ) when compared with group 2b.

### LDH-3 Activity

There was no statistically significant difference between malignant and nonmalignant ascites groups ( $p = 0.095$ ). Ascitic fluid LDH-3 activity was found to be higher in group 2a when compared with group 2b ( $p < 0.001$ ) and group 2d ( $p < 0.001$ ); in group 1 when compared with group 2b ( $p < 0.01$ ) and group 2d ( $p < 0.01$ ); in group 2c when compared with group 2b ( $p < 0.001$ ) and group 2d ( $p < 0.001$ ).

### LDH-4 Activity

Ascitic fluid LDH-4 activity was not detected in patients with sterile cirrhotic ascites. Ascitic fluid LDH-4 activity was found to be significantly higher in malignant ascites when compared with the nonmalignant ascites group ( $p < 0.001$ ). Ascitic fluid

**Table 2. Ascitic Fluid LDH Level and Its Isoenzyme Activities in All Groups**

	Group 1 (n=21)	Group 2a (n=15)	Group 2b (n=13)	Group 2c (n=13)	Group 2d (n=14)
Ascites LDH (U/l)	439.1 $\pm$ 169.1	93.5 $\pm$ 35.7	62.8 $\pm$ 7.8	740.5 $\pm$ 270.4	185.4 $\pm$ 66.6
Ascites LDH-1 (%)	21.2 $\pm$ 4.0	32.7 $\pm$ 3.2	78.7 $\pm$ 4.8	16.9 $\pm$ 5.9	42.4 $\pm$ 6.2
Ascites LDH-2 (%)	29.5 $\pm$ 3.6	36.7 $\pm$ 1.5	14.0 $\pm$ 1.2	20.1 $\pm$ 1.5	26.2 $\pm$ 2.4
Ascites LDH-3 (%)	22.6 $\pm$ 1.4	28.9 $\pm$ 3.1	7.1 $\pm$ 3.6	32.3 $\pm$ 1.1	10.4 $\pm$ 1.8
Ascites LDH-4 (%)	15.6 $\pm$ 2.8	0.3 $\pm$ 0.3	0	18.5 $\pm$ 4.5	5.6 $\pm$ 2.1
Ascites LDH-5 (%)	11.4 $\pm$ 2.5	0	0	12.1 $\pm$ 3.1	8.6 $\pm$ 2.3

LDH-4 activity was found to be higher in group 1 ( $p<0.001$ ) and group 2c ( $p<0.001$ ) when compared with group 2a; in group 1 ( $p<0.01$ ), group 2c ( $p<0.01$ ) and group 2d ( $p<0.01$ ) when compared with group 2b; in group 1 ( $p<0.01$ ) and group 2c ( $p<0.01$ ) when compared with group 2d.

### LDH-5 Activity

Ascitic fluid LDH-5 activity was not detected in patients with spontaneous bacterial peritonitis and sterile cirrhotic ascites. Ascitic fluid LDH-5 activity was found to be significantly higher in malignant ascites when compared with nonmalignant ascites ( $p<0.001$ ). Ascitic fluid LDH-5 activity was detected to be higher in group 1 ( $p<0.01$ ), group 2c ( $p<0.01$ ) and group 2d ( $p<0.01$ ) when compared with group 2a; in group 1 ( $p<0.01$ ), group 2c ( $p<0.01$ ) and group 2d ( $p<0.01$ ) when compared with group 2b.

There were positive correlations between ascitic fluid LDH level, LDH-2, LDH-3, LDH-4 and LDH-5 activities with ascitic fluid albumin, globulin and protein levels. There was a negative correlation between ascitic fluid LDH-1 activity with ascitic fluid albumin, globulin and protein levels (Table 3).

In the diagnosis of malignant ascites, the sensitivity and specificity were 96% and 76% for ascitic fluid LDH level (cut-off value  $\geq 200$  U/L), 90% and 70% for ascitic fluid LDH-1 activity (cut-off value  $\leq 30\%$ ), 94% and 62% for ascitic fluid LDH-4 activity (cut-off value  $\geq 60\%$ ), 100% and 56% for ascitic fluid LDH-5 activity (cut-off value  $\geq 5\%$ ), respectively.

The coefficient of variations for within-day repeatability and day-to-day reproducibility were 6.6% and 9.7%, respectively, for LDH.

### DISCUSSION

LDH is an enzyme in the glycolytic pathway and its released as the result of cell damage. LDH isoenzyme analysis, which requires small volume samples, is quick and easy to perform. LDH isoenzymes may be useful in differential diagnosis since tissue damage releases isoenzymes contained therein,

leading to a change in their pattern.<sup>1-3</sup> Previous studies of the diagnostic utility of serous fluid LDH isoenzyme pattern reported controversial results. Several studies describe relative values of LDH isoenzymes in different pathologic states, concluding that serous fluid LDH isoenzymes were not diagnostic.<sup>5-9</sup> The commonly used criteria of Light et al.<sup>4</sup> for the differentiation of serous effusion establish the exudative or transudative nature of the serous fluid but do not determine its specific etiology. LDH isoenzymes may be released from cells that have infiltrated the body fluids other than serum. For example, in viral and tuberculous meningitis causing lymphocytosis, it may create an elevation of LDH-1 through LDH-3.<sup>1</sup>

All the hundreds of different enzymes present in the human body are synthesized intracellularly, and most of them carry out their functions within the cells in which they are formed. With a few exceptions, the clinical chemist is principally concerned with changes in the levels (i.e., activity or mass) in serum, plasma or ascites of enzymes that are predominantly intracellular and that are normally present in the body fluids in low levels only. By measuring changes in the levels of these enzymes in a disease, it is possible to infer the location and nature of pathological changes in the tissues of the body. Therefore, it is necessary to understand the factor that affects the rate of release of enzymes from their cells of origin and the rate at which they are cleared from the circulation, so that changes in levels in disease can be interpreted correctly. These are: leakage of enzymes from cells (viruses, organic chemicals, shock, hypoxemia) and altered enzyme production (enzyme induction, proliferation).

Patients with malignant diseases show increased LDH activity in serum and malignant effusions; the LDH pattern usually shows a nonspecific increase in LDH-4 and LDH-5. LDH and its isoenzyme LDH-5 have been successfully used as prognostic markers for melanoma, various types of leukemia, testicular cancer and some solid tumors.<sup>3,8,10-13</sup> Schneider and

**Table 3. The Correlation between Ascitic Fluid LDH Isoenzymes with Ascitic Fluid Albumin, Globulin and Protein Levels**

	Ascitic fluid albumin Level (g/l)		Ascitic fluid globulin Level (g/l)		Ascitic fluid protein Level (g/l)	
	r value	p value	r value	p value	r value	p value
Ascitic fluid LDH level (U/l)	0.650	0.025	0.620	0.001	0.755	0.002
Ascitic fluid LDH-1 activity (%)	-0.700	0.035	-0.565	0.005	-0.645	0.015
Ascitic fluid LDH-2 activity (%)	0.450	0.047	0.585	0.042	0.495	0.025
Ascitic fluid LDH-3 activity (%)	0.550	0.037	0.750	0.035	0.640	0.035
Ascitic fluid LDH-4 activity (%)	0.400	0.045	0.440	0.040	0.485	0.030
Ascitic fluid LDH-5 activity (%)	0.600	0.025	0.450	0.030	0.555	0.038

colleagues<sup>12</sup> reported that peritoneal fluid and serum LDH levels in ovarian cancer patients were significantly higher than those in patients with benign ovarian tumor or other gynecological malignancies. Interestingly, peritoneal fluid LDH demonstrated higher diagnostic sensitivity (87%) and greater diagnostic accuracy (90%) than serum LDH (60% and 77%, respectively) or serum CA-125 (73% and 83%, respectively). Vergnon et al. reported<sup>8</sup> a high LDH-5 activity in 60% of patients with malignant effusion. It has also been shown that malignant lymphomas and small-cell lung carcinoma differ from other malignancies by a low LDH-5 isoenzyme secretion. Alternatively, the extent of the serosal inflammatory response to malignancy and the variable degree of serosal polymorphonuclear leukocytosis may determine the relative levels of LDH-4 and LDH-5 isoenzymes.<sup>8</sup>

The LDH isoenzymes are unable to discriminate between hepatocellular carcinoma and cirrhosis or between abdominal neoplasia with and without liver metastases.<sup>1,5,8</sup> In Lossos et al.'s study<sup>5</sup>, there was more than one LDH isoenzyme pattern in the malignancy-associated effusions. In our study, elevated LDH level and LDH-4 and LDH-5 activities were also found to be in malignant ascites than nonmalignant ascites. A marked heterogeneity of malignant etiologies and a relatively small number of the malignant group in the present study precluded separation between two LDH isoenzyme patterns according to the cytopathological diagnosis. Moreover, we detected low LDH-1 activity in malignant ascites group than nonmalignant ascites group. This could be due to the various neoplastic tissues that secrete different LDH isoenzymes. Cobben et al.<sup>9</sup> reported that the malignant pleural effusion group showed a low percentage of LDH-1, whereas the percentages of LDH-4 and LDH-5 were higher compared to transudative pleural effusion group, supporting our view.

Elevations of LDH activity are especially high in toxic hepatitis with jaundice; slightly lower values are observed in viral hepatitis which are often associated with elevations of LDH-3.<sup>14,15</sup> Serum LDH-5 is often markedly elevated in patients with either primary liver disease, viral hepatitis or liver anoxia secondary to decreased oxygen perfusion.<sup>11</sup> Rotenberg et al.<sup>14</sup> reported, in patients with acute liver disorders, both the serum LDH and LDH-5 proportions were sensitive for liver injury. On the other hand, LDH-5 proportion was much less sensitive than LDH in patients with chronic liver disorders. In our study, we did not evaluate serum LDH isoenzymes, as we could not detect ascitic fluid LDH-5 activity in those patient groups. Interestingly, we had also found elevated ascitic fluid LDH-1 activity in patients with cirrhotic ascites. Ascitic fluid LDH-1 was found to be higher

in the sterile cirrhotic group when compared with other groups. Moreover, LDH-3, LDH-4 and LDH-5 activities were higher in other groups when compared with sterile cirrhotic ascites. Therefore, ascitic fluid LDH isoenzyme activity may be more helpful in the diagnosis of sterile cirrhotic ascites.

LDH-5 values may be moderately elevated in congestive cardiac failure with hepatic congestion as a result of hepatic anoxia. Prabhakaran and Henderson<sup>10</sup> reported two cases of congestive cardiac failure with unusually high activities of serum LDH and LDH-5. The LDH-5 component was 87% of the total serum activity. We had also found the highest ascitic fluid LDH-5 activity in the group of congestive heart failure supporting this view.

In patients with suspected tuberculous peritonitis, the elevated ascitic fluid LDH levels have high sensitivity for the disease.<sup>16</sup> In viral and tuberculous meningitis with lymphocytosis, an elevation of LDH-3 was detected.<sup>1</sup> Zhang<sup>17</sup> reported that both LDH level and isoenzymes in pleural fluid between the tuberculous and malignant groups did not correlate significantly. Contrary to these findings, we detected highest ascitic fluid LDH levels and LDH-3 activity in patients with tuberculosis. In addition, we found high ascitic fluid LDH-4 and LDH-5 activities in the tuberculous and malignant groups. However, these isoenzymes activities were similar in these groups.

Suzuki et al.<sup>18</sup> studied the usefulness of fibrin degradation products (FDP) and lactic dehydrogenase isoenzyme patterns in assessing the clinical course of peritonitis. They concluded that the failure of normalization of FDP and LDH isoenzyme patterns suggests an incomplete recovery from peritonitis. They also proposed that FDP and LDH isoenzymes were useful in assessing the course of relapsing and persistent episodes of peritonitis. In our study, ascitic fluid LDH-2 and LDH-3 activities were found to be significantly elevated in the SBP group than in the sterile cirrhotic ascites group. Ascitic fluid LDH-2 and LDH-3 activities might be helpful in discriminating whether the ascitic fluid is infected or not.

Paavonen et al.<sup>3</sup> reported that the LDH concentration correlated somewhat with the pleural protein content. They concluded that the pleural LDH isoenzyme distribution, both in benign and malignant conditions, differed from that in serum, having shifted towards LDH-4 and LDH-5. These data possibly suggested that visceral or parietal pleural cells were rich in LDH isoenzymes 4 and 5. In our study, we also detected positive correlations between ascitic fluid LDH, LDH-2, LDH-3, LDH-4 and LDH-5 activities with ascitic fluid albumin, globulin and protein levels. However, there were negative correlations between ascitic fluid LDH-1 and ascitic fluid albumin, globulin and protein levels.

In conclusion, LDH and its isoenzyme activities in the ascitic fluid may contribute to the differential diagnosis of ascitic fluid etiology. In patients with malignant ascites, ascitic fluid LDH and LDH isoenzyme activities have high sensitivity and low specificity for the disease groups. However, owing to the relatively small study population, further studies are indicated to confirm the utility of LDH isoenzyme patterns in the diagnostic evaluation of ascites for malignant and non-malignant etiologic categories.

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