

Ascitic Fluid Lactate Dehydrogenase (LDH) – A Marker for Spontaneous Bacterial Peritonitis

S Sandhya*, Rinchu Loomba**, V Loomba***, N Malhotra***

Abstract

Ascites is defined as pathological accumulation of fluid in the peritoneal cavity. Evaluation of the cause of ascites is important for therapeutic and prognostic reasons. Bacterial infection of the ascitic fluid without any intra-abdominal surgically treatable source of infection is called spontaneous bacterial peritonitis (SBP). For evaluation of SBP, we rely upon serum ascitic fluid albumin gradient (SAAG), leucocyte count and fluid culture. At times, the diagnosis may not be clear and there may not be any other parameter to rely upon.

Aims and objectives: To study the significance of ascitic fluid lactate dehydrogenase (LDH) levels in SBP and to correlate the ascitic fluid LDH values to their corresponding blood values in SBP.

Material and methods: The study was a hospital-based cross-sectional study conducted in a tertiary care hospital of North India. Patients admitted with ascites due to any underlying aetiology were included in the study. Abdominal paracentesis was done under aseptic conditions, the ascitic fluid and corresponding blood samples sent for routine samples and LDH estimation.

Results and analysis: 170 patients were included in the study with the mean age of 54.38 years. Ascitic fluid LDH (AFLDH) was significantly raised in SBP as compared to non SBP patients ($p < 0.0001$). For SBP, AFLDH ≥ 127.5 IU/L had sensitivity of 76.5%, specificity of 75.2%, PPV of 28.3% and NPV of 96.2%. For SBP, AFLDH/SeLDH ratio with a cut-off value of ≥ 0.50 had specificity of 81.2%, sensitivity of 47.1%, PPV of 25.7% and NPV of 93%. For AFLDH in SBP, the area under the curve was 0.820 with 95% CI 0.737 - 0.904 (p value < 0.001).

Conclusion: Raised AFLDH may be a useful parameter in diagnosis of SBP. So, in nutshell we can say that if the AFLDH is < 127.5 IU/L, then chances of having SBP are very less.

Key words: Cirrhosis, portal hypertension, ascites, lactate dehydrogenase, spontaneous bacterial peritonitis.

Introduction

Ascites is defined as pathological accumulation of fluid in the peritoneal cavity. Normally, the peritoneal fluid volume is around 5 mls. in men and 5 - 18 mls. in women (depending on the phase of menstrual cycle). At least 1,500 mls of fluid needs to be present in the peritoneal cavity to be detected on clinical examination (much more in obese patients)¹. Mild ascites may not cause symptoms, whereas moderate to massive ascites may lead to abdominal distension, development of abdominal hernias or respiratory distress². Evaluation of the cause of ascites is important for therapeutic and prognostic purposes. Development of ascites in patients with cirrhosis of liver is associated with a mortality rate of 15% at one year and 44% at five years. Combined analysis of clinical profile along with the laboratory analysis of the ascitic fluid samples is needed to reach to the diagnosis³. Bacterial infection of the ascitic fluid without any intra-abdominal, surgically treatable, source of infection is called spontaneous bacterial

peritonitis (SBP). The prevalence rate of SBP in patients with cirrhosis is 1.5 - 3.5% in the outpatient and 10% in hospitalised patients. With early diagnosis and treatment, the mortality rate in SBP has reduced from 90% to nearly 20%. For evaluation of SBP, we rely upon serum ascitic fluid albumin gradient (SAAG), leucocyte count and fluid culture. When the SAAG is > 1.1 gm/dl, its called transudative ascites (High SAAG) and is found in cirrhosis, right heart failure, and Budd Chiari syndrome. When the SAAG is < 1.1 gm/dl, its called exudative ascites (Low SAAG) and is found in patients with infections like tuberculosis, pancreatic ascites or malignancy⁴. SBP is an example of infected transudate characterised by SAAG > 1.1 gm/dl and neutrophil count of > 250 cells/mm^{3,5} in the ascitic fluid with or without culture positivity. Despite the use of sensitive methods, ascitic fluid culture is negative in 60% of the patients with clinical manifestations suggestive of SBP and increased ascitic fluid neutrophil count. The gold standard for ascitic neutrophil count is manual microscopy, which is labour intensive and associated with interobserver variability. So, at times, while

*Senior Resident, ***Professor and Unit Head, Department of Medicine, **Associate Professor, Department of Biochemistry, Christian Medical College and Hospital, Ludhiana - 141 008, Punjab.

Corresponding Author: Dr Rinchu Loomba, Associate Professor, Department of Biochemistry, Christian Medical College and Hospital, Ludhiana - 141 008, Punjab. Tel: 9855601410, E-mail: rinchuloomba@gmail.com.

using these parameters the diagnosis may not be clear and there may not be any other parameter to rely upon. As in Light's criteria used for pleural fluid analysis, LDH analysis has been explored for the ascitic fluid analysis. It has been reported that in patients with malignant ascites, ascitic fluid LDH (AFLDH) has high sensitivity but low specificity for the diagnosis of the disease⁶. According to Gokturk *et al*, LDH values were higher in patients with SAAG < 1.1 gm/dl as compared to those with SAAG > 1.1 ($p < 0.001$)⁷. However, the role of LDH in diagnosis of SBP has not been studied.

Aims and objectives

- To study the diagnostic significance of ascitic fluid lactate dehydrogenase (LDH) levels in evaluation of spontaneous bacterial peritonitis (SBP).
- To correlate between the ascitic fluid LDH levels and their corresponding blood levels in SBP.

Material and methods

The study was a hospital-based cross-sectional study carried-out in a tertiary care hospital of North India. The study was approved by the Institutional Ethics Committee on January 4th 2018 (Ref: 201801-033-IEC/CMCL-APPRVL-PG.THESIS/Medicine). Patients admitted with ascites due to any underlying aetiology over a period of 18 months were included in the study and abdominal paracentesis was done after taking an informed consent in writing. The ascitic fluid and corresponding blood samples were sent for routine investigations and LDH estimation. LDH values of ascitic fluid and blood were correlated with the clinical, pathological and radiological findings.

Sample size: Sample size was 170 patients.

Inclusion criteria: All patients above the age of 18 years who had presented with ascites were included in the study after taking an informed consent in writing.

Exclusion criteria: Pregnant women and recent post-partum (within 6 months of delivery) were excluded.

The estimation of LDH was carried-out on C501 module of fully automated analyzer Cobas 6,000 by Roche. Other appropriate investigations were sent, as needed, for each patient.

Statistical analysis

Categorical variables were presented as number and percentage and continuous variables were presented as mean \pm SD and median. Normality of the data was tested by Kolmogorov-Smirnov test. If normality was rejected, then non parametric tests were used. The differences in AFLDH

and AFLDH/SeLDH ratio between SBP and non-SBP group were compared using Mann-Whitney U test (as the data sets were not normally distributed). Receiver Operative Characteristics (ROC) curve was used to calculate the area under the curve and to define a cut-off value to predict SBP. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using appropriate formulas. A p value of < 0.05 was considered statistically significant. The data was entered in MS Excel spreadsheet and analysis was done using Statistical package for social sciences (SPSS) version 21.0.

Results

The study was carried-out in the medical wards of a tertiary care hospital of North India over a period of 18 months. A total of 170 patients with ascites were included in the study. The mean age was 54.38 years and had 70.59% males. Abdominal distension was the commonest presenting symptom in 90.59% patients, weight loss in 61.18%, fever in 56.47% and pain abdomen in 12.94% patients (Fig. 1). Historically, 56.57% patients had jaundice and 31.17% patients had hepatic encephalopathy.

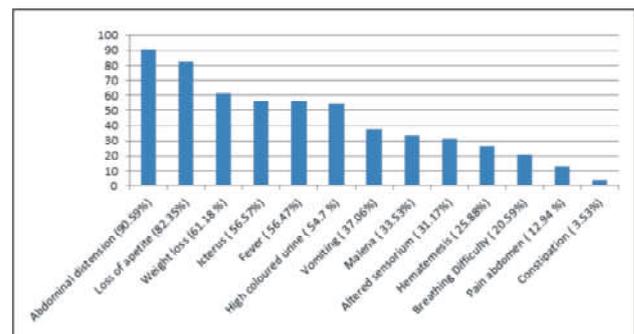


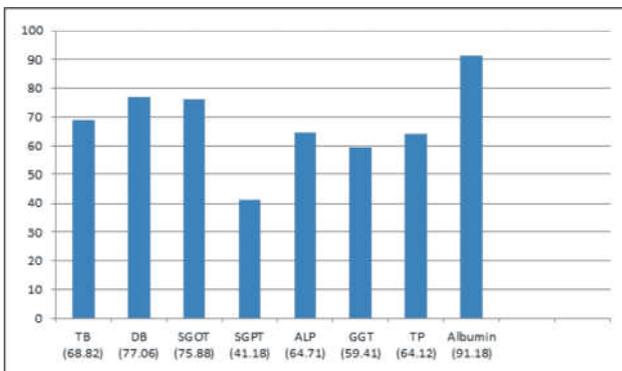
Fig. 1: Presenting Symptoms in % age.

Clinical examination revealed shifting dullness in 95.29% patients, fluid thrill in 81.17% patients, and pedal oedema in 61.76% patients. Signs of liver cell failure were present in nearly one-third (33.53%) of the patients, hepatomegaly in 20% and splenomegaly in 7.64% patient. Nearly one-third of the patients (30.58%) had asterixis and two-third had anaemia (Table I).

Liver function tests were abnormal in majority of the patients (Fig. 2). Hypoalbuminaemia (91.18%) was the commonest abnormality followed by hyperbilirubinaemia (77.06%). Thrombocytopenia was present in 64.12% and coagulopathy in 74.70%. Child Pugh grade C was present in 62.35% patients and grade B in the remainder (37.64%). On ultrasound examination, coarse nodular liver was present in 70%, splenomegaly in 40% and right side pleural effusion in 15.29%.

Table I: Presenting signs.

Presenting signs	Frequency (N = 170)	Percentage (%)
Shifting dullness	162	95.29
Fluid thrill	138	81.17
Pallor	115	67.65
Oedema	105	61.76
Icterus	89	52.35
Lacrimal gland enlargement	57	33.53
Gynaecomastia	53	31.17
Asterixis	52	30.58
Clubbing	41	24.11
Hepatomegaly	34	20
Dupuytren's contracture	33	19.41
Parotid gland enlargement	31	18.24
Splenomegaly	13	7.64
Spider naevi	11	6.47
Testicular atrophy	10	5.88
Palmar erythema	5	2.94

**Fig. 2: Abnormal LFT (%).**

Alcohol was the cause of liver dysfunction in 60.58% patients (85.83% males) and hepatotropic viruses (HBV, HCV, and HIV) were detected in 17% patients. In 24 (14.11%) patients, ascitic fluid examination revealed high SAAG (> 1.1 gm/dl) with neutrophil count > 250/mm³ (Table II). There were 20 patients with malignancy. Amongst the remaining 150 patients, 16 fulfilled the criteria for SBP (n = 16). Diabetes mellitus was the commonest co-morbidity in 21.76% patients followed by hypertension in 17.05% patients (Table II).

Table II: Diagnosis

Diagnosis	Frequency (N = 170)	%age
Alcoholic liver disease	103	60.58
Diabetes mellitus	37	21.76
Hypertension	29	17.05
Spontaneous bacterial peritonitis	24	14.11
Cryptogenic	23	13.52
Malignancy	20	11.76
Hepatitis C virus	21	12.35
Tuberculosis	16	9.41
Hepatitis B virus	6	3.53
HIV	2	1.18
Hepatitis E virus	2	1.18
Cardiogenic	6	3.52
Hypothyroidism	5	2.94
Secondary peritonitis	3	1.76

Ascitic fluid LDH was estimated in all these 150 patients. It was found that patients with SBP had significantly raised ascitic fluid LDH (p = 0.001). The median (IQR) in SBP group was 201 IU/L (118 - 921.5) as compared to 74 IU/L (48 - 128) in non-SBP group (Table III).

Table III

	SBP (N = 16)	Non-SBP (N = 134)	
	Median (IQR)	Median (IQR)	p value
AFLDH	201 (118 - 921.5)	74 (48 - 128)	0.001
AFLDH/SeLDH	0.50 (0.31 - 1.11)	0.24 (0.15 - 0.42)	< 0.001

Table IV: Test result variable(s).

	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lowerbound	Upperbound
AFLDH	0.820	0.043	0.000	0.737	0.904
AFLDH - SeLDH	0.749	0.060	0.001	0.631	0.866

The AFLDH \geq 127.5 IU/l was found to be suggestive of SBP. It had specificity of 75.2% and sensitivity of 76.5%, PPV was 28.3% and NPV was 96.2%. For AFLDH, the area under the curve was 0.820 with 95% CI 0.737 - 0.904 (p value < 0.001) (Table IV). The ratio of AFLDH to Se LDH was also significantly raised in the SBP group. The median (IQR) AFLDH/SeLDH ratio was 0.50 (0.31 - 1.11) in the SBP group as compared to 0.24 (0.15 - 0.42) in the non-SBP group (p < 0.001). AF LDH/Se LDH ratio had a cut-off value of \geq 0.50.

0.50. The specificity was 81.2%, sensitivity was 47.1%, PPV was 25.7% and NPV was 93% (Table IV).

Discussion

Higher level of AFLDH indicates high degree of peritoneal inflammation. In patients with malignancy, tuberculosis and pancreatic ascites, LDH is usually high (> 500 IU/L) and in liver related disorders it is generally low⁸. Tuberculosis and other conditions which have raised LDH have exudative ascites in contrast to SBP, which has transudative ascites. It means that if the ascitic fluid is transudative and the LDH is raised, then the chances of SBP are high.

Boyer *et al* observed that the AFLDH levels were higher in malignant ascites (913 +/- 2,283 IU/L) as compared to ascites associated with liver disease (169 +/- 9 IU/L). Gokturk *et al* observed that AF LDH was higher in patients with SAAG < 1.1 gm/dl as compared to patients with SAAG > 1.1 gm/dl⁷. Touny *et al* reported that out of 41 patients of cirrhosis with ascites, 5 fulfilled the criteria of SBP. Out of these 5 patients, 3 had culture positive neutrophilic ascites and 2 had culture negative neutrophilic ascites. The ratio of AFLDH/SeLDH > 0.75 was present in the SBP group as compared to < 0.58 in non-SBP group⁹. Mortada *et al* reported that out of 30 patients of ascites, 13 had SBP and the AF LDH was significantly higher in this group as compared to the non-SBP group (p < 0.002). AF LDH/Se LDH > 0.5 had a sensitivity of 80%, specificity of 88%, PPV 66.7%, NPV 93.7% and accuracy of 63.3%¹⁰.

Bedside criterion of neutrophil count > 250/mm³ for the diagnosis of SBP is labour intensive and associated with inter-observer variability. So, to overcome these limitations, LDH can serve as a reliable parameter.

Conclusions

Ascitic fluid LDH can be a good biochemical marker for spontaneous bacterial peritonitis. AFLDH \geq 127.5 IU/l can be suggestive of SBP. It has specificity of 75.2%, sensitivity of 76.5%, PPV of 28.3% and NPV of 96.2%. AFLDH/ SeLDH ratio had a cut-off value of \geq 0.50. The specificity was 81.2%, sensitivity was 47.1%, PPV was 25.7% and NPV was 93%.

References

1. Tasneem H, Shahbaz H, Sherazi BA. Causes, management and complications of ascites: a review. *Int Curr Pharm J* 2015; 4: 370-7.
2. Mahmood G, Debnath CR, Mandal AK. Evaluation of 100 cases of ascites. *Mymensingh Med J* 2009; 1: 62-6.
3. Khan FY. Ascites in the state of Qatar: aetiology and diagnostic value of ascetic fluid analysis. *Singapore Med J* 2007; 48: 434.
4. Karoo R, Lloyd T, Garcea G *et al*. How valuable is ascetic cytology in the detection and management of malignancy? *Postgrad Med J* 2003; 79: 292-4.
5. Koulaouzidis A, Bhat S, Karagiannidis A *et al*. Spontaneous bacterial peritonitis. *Postgrad Med J* 2007; 83: 379-83.
6. Huang LL, Xia HH, Zhu SL. Ascitic fluid analysis in the differential diagnosis of ascites, focus on cirrhotic ascites. *J Clin Transl Hepatol* 2014; 2: 58-64.
7. Gokturk HS, Demir M, Ozturk NA *et al*. The role of ascitic fluid viscosity in the differential diagnosis of ascites. *Can J Gastroenterol* 2010; 24: 255-9.
8. Buer Reginato TJ, Andrade Oliveira MJ, Moreira LC *et al*. Characteristics of ascitic fluid from patients with suspected spontaneous bacterial peritonitis in emergency units at a tertiary hospital. *Sao Paulo Med J* 2011; 129 (5): 315-9.
9. M el-Touny, L Osman, T Abd-el Hamid *et al*. Re-evaluation of the value of ascitic fluid pH Lactate Dehydrogenase and total proteins in the diagnosis of spontaneous bacterial peritonitis. *J Trop Med Hyg* 1989; 92 (1): 6-9.
10. El-Shabrawi MHF, Sisi OEI, Kamal N. Diagnosis of spontaneous bacterial peritonitis in infants and children with chronic liver disease: A cohort study. *Ital J Pediat* 2011; 37 (1): 26.

ADVERTISEMENT TARIFF

Journal, Indian Academy of Clinical Medicine

Advertisement Tariff effective January, 2020

Position	Single Issue	Consecutive Four Issues
(a) Back cover	₹ 20,000/-	₹ 60,000/-
(b) Inside back and inside front cover	₹ 15,000/-	₹ 45,000/-
(c) Full page	₹ 10,000/-	₹ 30,000/-
(d) Half page	₹ 6,000/-	₹ 18,000/-

Note: Artworks/positives (processing)/art pulls of advertisements for Back cover, Inside front cover, Inside back cover and Full page should not exceed 28 cm (H) x 21 cm (W) – (for bleed); and 25 cm (H) x 18 cm (W) – (for non-bleed). For half page advertisements the artwork should not exceed 12 cm (H) x 18 cm (W).

Size of the Journal is 28 cm x 21 cm.

For advertisement assistance & queries, contact:

Dr. Amit Aggarwal, Secretary, JIACM

Mobile: +91-9716112232