

Clinical Profile in Patients of Amoebic Liver Abscess with and without Hyperbilirubinemia: A Prospective Cohort Study

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ABSTRACT

Introduction: In tropical countries like India, two-thirds of liver abscess cases are amoebic. Along with abdominal pain, fever, and other non-specific clinical features, jaundice is commonly observed in Amoebic Liver Abscess (ALA) cases. However, the understanding of jaundice in a patients with ALA is limited, and it is associated with a poor prognosis.

Aim: To compare the morbidity and mortality of ALA patients with and without hyperbilirubinemia, as well as their clinical outcomes.

Materials and Methods: The present prospective cohort study was conducted at a tertiary teaching institute in northern India. It included 150 patients aged between 20 and 60 years with a confirmed diagnosis of ALA. The patients were divided into two groups based on the presence or absence of hyperbilirubinemia.

Those with jaundice resulting from other causes or a history of hepatitis were excluded. Variables examined in the study included age, sex, alcohol intake, basic laboratory parameters, ultrasound-assessed abscess size and number, and duration of hospital stay.

Results: Among the 150 cases, 22 (14.6%) had elevated serum bilirubin levels (>1 mg/dL). Additionally, 122 (81.33%) had a history of alcohol intake, and 117 (78%) had a single abscess cavity. In ALA patients with hyperbilirubinemia, 12 (54.55%) had abnormal creatinine values, and 6 (27.26%) experienced complications such as rupture and peritonitis. One mortality occurred in a patient with ALA and jaundice.

Conclusion: ALA patients with jaundice exhibited larger abscess cavities, a higher complication rates, a longer hospital stays, and a poor prognoses.

Keywords: Amoebiasis, Extraintestinal amebiasis, *Entamoeba histolytica*, Hepatic-entamoebiasis, Jaundice

INTRODUCTION

Liver abscess is a prevalent condition in surgical practice, occurring worldwide but with a higher incidence in countries like India, tropical regions of Africa, Mexico, and Central America [1]. It can be caused by bacterial, parasitic, fungal, or mixed infections, leading to the formation of a pus-filled mass in the liver parenchyma. Different types of liver abscess, including amoebic, pyogenic, fungal, and mixed types, can occur [2,3]. ALA is the most common extra-intestinal manifestation of amebiasis, affecting 3-9% of cases [4]. Amebiasis is a parasitic infection caused by ingestion of *Entamoeba histolytica* cysts through contaminated food or water. ALA is particularly prevalent in tropical countries like India, where 50-70% of liver abscess cases are amoebic in nature [5]. The high incidence of ALA in tropical developing countries may be attributed to factors such as poor sanitation, overcrowding, poverty, and inadequate nutrition [6,7].

The typical symptoms and signs associated with ALA include right hypochondriac abdominal pain that worsens with coughing, jolting, and deep breathing; fever of varying degrees with or without rigours; tender hepatomegaly; and intercostal tenderness [8]. Common laboratory findings include leukocytosis, anemia, and elevated liver enzymes. Chest X-rays may reveal an elevated right hemidiaphragm, pleural effusion, and basal atelectasis. Abdominal USG is a preferred diagnostic modality for ALA, showing hypoechoic lesions with poor rim echoes, predominantly affecting the right lobe [8].

Jaundice is frequently observed in ALA patients and is considered a poor prognostic indicator. Serum bilirubin levels >3.5 mg/dL, encephalopathy, and hypoalbuminemia are independent risk factors for mortality in ALA cases [8,9]. The causes of hyperbilirubinemia in ALA are not fully understood but are thought to be either due to cholestasis resulting from the mechanical pressure of the abscess cavity on biliary channels or parenchymal destruction of liver cells [10]. Previous studies have shown increased morbidity and mortality in ALA patients with jaundice, attributed to liver cell necrosis and

subsequent damage to biliary canaliculi and associated vascular channels [9,10]. However, there is limited research available [10,11] that specifically addresses the clinical, laboratory, and radiological profiles of ALA patients in correlation with jaundice. Therefore, the aim of this study is to assess the morbidity and mortality of ALA patients with and without hyperbilirubinemia, considering their clinical, biochemical, microbiological, and radiological profiles.

MATERIALS AND METHODS

This prospective cohort study was conducted at Dr. Baba Saheb Ambedkar Medical College and Hospital in Delhi, India, from October 2016 to December 2017. Ethical approval was obtained from the Institutional Ethical Committee (IEC approval letter No.- F.5(59)/2013/BSAH/DNB/Committees/11423) prior to the start of the study.

Inclusion criteria: Patients between the ages of 20 and 60 years who were diagnosed with ALA and provided consent were enrolled in the study.

Exclusion criteria: Patients with cholangitis, gall bladder and Common Bile Duct (CBD) stones, hepatitis, CBD stricture, medical renal disease, critically ill patients requiring ICU admission, pregnant women, and patients with a history of malignancy were excluded.

Sample size: A convenient sample of 150 patients with serum bilirubin levels above 1 mg/dL was included in Group-1, while the remaining patients with normal serum bilirubin levels were included in Group-2. The variables studied in both groups included age, sex, alcohol intake, previous history of hepatitis, and the site, size, and number of liver abscesses observed on Ultrasonography (USG).

Procedure

A detailed history, physical examination, routine laboratory investigations, chest X-ray, and USG abdomen were conducted as a baseline measures for all eligible patients. The laboratory tests and their normal ranges are presented in [Table/Fig-1]. USG abdomen

was performed in both supine and lateral positions to assess the morphological characteristics of the liver abscess. Chest X-rays were obtained to evaluate for pleural effusion, basal atelectasis, or any pulmonary complications related to ALA. The diagnosis of ALA was confirmed by amoebic serology in all cases.

Parameters	Laboratory test	Normal value
Total bilirubin	Sample blank, and factor method	0.1 to 1 mg/dL
Direct bilirubin	Sample blank, and factor method	Less than 0.3 mg/dL
ALT (SGPT)	IFCC (liquid-stable) method	4-36U/L
AST (SGOT)	IFCC (liquid-stable) method	8-33U/L
Alkaline Phosphatase (ALP)	DGKC method	44-147IU/L
Serum urea	DAM method	5-20 mg/dL
Serum creatinine	Jaffe's kinetic method	0.6-103 mg/dL
Random blood sugar	Reducing method	100-140 mg/dL
Thrombocytopenia	Haematology analysers	150,000-450,000/microliter

[Table/Fig-1]: Tests used for different laboratory parameters.

In either group, percutaneous aspiration or catheter drainage of the ALA was considered if patients did not show improvement in symptoms after five days of medical therapy, if the abscess cavity diameter exceeded 300 cm, if there was a thin rim of parenchymal tissue (<10 mm) around the abscess, if the abscess was located near the right porta hepatis, or if there was evidence of mechanical obstruction to the biliary tree or Inferior Vena Cava (IVC). Outcomes were assessed based on symptom and sign improvement, reduction in bilirubin level, and decrease in abscess cavity size on USG examination.

STATISTICAL ANALYSIS

Categorical variables were presented as numbers and percentages (%), while continuous variables were presented as mean \pm SD and median. The data was entered into a Microsoft excel spreadsheet and analysed using Statistical Package for Social Sciences (SPSS) version 21.0. The normality of the data was assessed using the Kolmogorov-Smirnov test. Non-parametric tests were used for variables that did not follow a normal distribution. The independent t-test was used to compare quantitative variables, while the Mann-Whitney U test was used for variables with non-normal distribution. Qualitative variables were analysed using either the Chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

RESULTS

Out of the 150 patients with ALA included in the present study, 22 had a raised level of serum bilirubin and were included in Group-1, while the remaining 128 patients had normal serum bilirubin levels and were included in Group-2. The baseline characteristics of subjects in both groups were comparable and summarised in [Table/Fig-2]. The majority of cases (n=68/46%) were seen in the age group of 36 to 45 years in both groups. The male-to-female sex ratio in Group-1 was 21:1, while in Group-2 it was 9.66:1. Symptoms such as pain, abdomen, and fever were comparable in both groups with no statistical difference (p-value=1.00). Hepatomegaly was observed in the USG examination, and a significant number of patients (81.8%) in Group-1 had hepatomegaly compared to Group-2.

The histories of alcohol intake by the patients in both groups were comparable, with no statistically significant difference. Group-1 had a higher prevalence of thrombocytopenia, deranged blood sugar, urea, and serum creatinine, and these differences were statistically significant compared to Group-2 [Table/Fig-2]. In Group-1, 2 (9.09%) patients had deranged PT-INR, while none of the patients in Group-2 had deranged PT-INR. A larger number of patients (16, 72.73%) in Group-1 with hyperbilirubinemia had a large (>300 cc) abscess.

Baseline parameters		Group-1 (n=22)	Group-2 (n=128)
Age distribution (In years)	20-35	9 (40.91%)	32 (25.00%)
	>35-45	10 (45.45%)	59 (46.09%)
	>45-55	1 (4.55%)	32 (25.00%)
	>55	2 (9.09%)	5 (3.91%)
Gender	Female	1 (4.55%)	12 (9.38%)
	Male	21 (95.45%)	116 (90.63%)
Alcohol intake	122 (81.33%) (all male)	17 (77.27%)	105 (82.03%)
Symptoms and signs	Fever	21 (95.45%)	119 (92.97%)
	Pain abdomen	22 (100%)	125 (98%)
	Icterus	18 (81.8%)	0 (0%)
	Hepatomegaly	18 (81.8%)	75 (58.5%)
	Ascites	5 (22.7%)	7 (5.4%)
Laboratory parameters	TLC >11000/mm ³	1 (4.55%)	55 (42.97%)
	Total Bilirubin (mg/dL)		
	>1-3	6 (27.27%)	0
	>3-5	10 (45.45%)	0
	>5	6 (27.27%)	0
	Deranged ALT (U/L) (n=4-36U/L)	9 (40.90%)	34 (26.56%)
	Deranged AST (U/L) (n=8-33U/L)	15 (68.18%)	54 (42.18%)
	Deranged ALP (U/L) (n=44-147 IU/L)	19 (86.36%)	65 (50.78%)
	Deranged urea (n=5-20 mg/dL)	16 (72.73%)	28 (21.88%)
	Deranged S. Creatinine (n=0.6-1.3 mg/dL)	12 (54.55%)	9 (7.03%)
On USG examination	Deranged RBS (n=100-140 mg/dL)	9 (40.91%)	20 (15.63%)
	Thrombocytopenia (<150,000/microliter)	5 (22.73%)	3 (2.34%)
	Size (CC) of the abscess- <100 cc	0 (0.00%)	19 (14.84%)
	-100-300 cc	6 (27.27%)	50 (39.06%)
Lobes of the liver involved	->300 cc	16 (72.73%)	59 (46.09%)
	Multiple abscess	10 (45.45%)	23 (17.97%)
	Right lobe	12 (54.55%)	89 (69.53%)
	Left lobe	0 (0.00%)	21 (16.41%)
Lobes of the liver involved	Both right and left lobe	9 (40.91%)	18 (14.06%)
	Caudate lobe	1 (4.55%)	0 (0.00%)

[Table/Fig-2]: Baseline characteristics of all study subjects.

Depending on the clinical condition and severity of the disease, patients were managed using conservative medical management, percutaneous needle aspiration, or catheter drainage. All patients in Group-1 required some form of intervention for the management of liver abscesses. Only one patient in Group-1 required exploratory laparotomy for a ruptured liver abscess. Intercostal tube drainage for symptomatic relief in patients with pleural effusion was required in 2 (9.1%) patients in Group-1 and 5 (3.91%) patients in Group-2, which was statistically significant (p-value=0.007). However, there was no significant difference in the rate of complications between the two groups (p-value=0.06). Pus cultures from 17 patients were positive for secondary bacterial infection, with *E. coli* being the most common pathogen (12, 70.59%).

One patient with a ruptured liver abscess, severe peritonitis, and septicemia in Group-1 died during the course of treatment. Among the remaining 149 patients, the mean length of hospital stay was 13.31 \pm 5.3 days (range: 7-62 days), with a median of 13 days. There was a statistically significant difference in the duration of hospital stay between Group-1 and Group-2 (p-value <0.0001) [Table/Fig-3].

Patients in both groups responded well to therapeutic management, either through medical or surgical intervention, and the response time

		Group-1 (n=22)	Group-2 (n=128)	p-value
Modes of managements	Medical only	0 (0.00%)	14 (10.94%)	0.007
	Percutaneous drainage (Needle/Catheter)	21 (95.45%)	114 (89.06%)	
	Expl. Laparotomy	1 (4.55%)	0 (0.00%)	
Complications	Rupture in to peritoneal cavity	3 (13.63%)	8 (6.25%)	0.06
	Rupture in to pleural cavity	2 (9.09%)	5 (3.90%)	
	Generalised peritonitis	1 (4.54%)	0 (0.00%)	
	Overall (n=150)	6 (27.27%)	13 (10.15%)	
Length of hospital stay*	<10 days	0 (0.00%)	37 (28.91%)	0.0001
	10-20 days	16 (76.19%)	91 (71.09%)	
	>20 days	5 (23.81%)	0 (0.00%)	

[Table/Fig-3]: Comparison of modes of management, complications and duration of hospital stay in both groups.

*One patient died during treatment and after 72 hours, only 21 patients remained in Group-1

was found to depend on the size of the abscess. Larger abscesses took more time to respond. In Group-1, the response to treatment varied and was found to be related to the level of serum bilirubin at admission. After 72 hours of management, 15 (71.42%) patients in Group-1 had serum bilirubin levels of 1-3 mg/dL compared to 6 (27.27%) at baseline (p-value=0.013), which is statistically significant. A summary of different outcomes at admission and after 72 hours of treatment is presented in [Table/Fig-4].

Outcomes		On admission	After 72 hours of treatment*	p-value
Fever	Both groups (n=150)	140 (93.33%)	11 (7.33%)	0.013
Pain abdomen (Mean VAS score)		147 (98.00%)	18 (12%)	
Serum bilirubin (Group-1 only, n=22)	1-3 mg/dL	6 (27.27%)	15 (71.42%)	
	3-5 mg/dL	10 (45.45%)	6 (28.57%)	
	>5 mg/dL	6 (27.27%)	0 (0.00%)	
Size of abscess on USG (Both groups, n=150)	<100cc	19 (12.67%)	72 (48%)	<0.001
	100-300 cc	56 (37.33%)	66 (44%)	
	>300 cc	75 (50.00%)	11 (7.33%)	

[Table/Fig-4]: Comparison of outcomes on admission and after 72 hours of treatment.

*One patient died during treatment and after 72 hours only 21 patients remained in Group-1

DISCUSSION

In the present study, the mean age of patients was 40.37±8.94 years, and 91.33% were male and 8.63% were female. Out of a total of 150 patients, 14.66% were found to have jaundice. Jaundice in patients with ALA is a common finding, and according to the literature, it may be between 6 and 29% [10,11]. The incidence of jaundice in ALA reported in the literature has a lot of variation, and this trend is increasing with time. For example, Chhetri MK et al.,

reported it at 6% in their series, Vakil BJ et al., reported 7.8%, Chen HL et al., reported 21.43%, and Jha AK et al., reported as high as 28% in their series [12-15]. The increasing trend of higher incidences of jaundice reported in ALA may be due to the wide availability and access to laboratory investigations now. It has been observed that in a series where a higher incidence of jaundice among patients with ALA was reported, it was also associated with more incidences of complications, morbidity, and even mortality [11,13]. In this study also, the authors found the same result with more morbidity, and overall, one reported mortality was reported in a patient with ALA with jaundice.

The demographic findings of the current study match fairly with the findings of other studies. For example, Sharma N et al., reported a mean age of 40.5±2.1 years in their series, while Mukhopadhyay M et al., reported 91.67% male and 8.33% female in their series of patients with ALA [16,17]. In the current study, symptoms like fever and pain in the abdomen were present in 93.33% and 98%, respectively, which was also comparable to the findings of other studies. Sharma N et al., reported 94% of patients with fever and 90% of patients with pain in the abdomen, while in a series by Mukhopadhyay M et al., it was reported to be 80.56% and 83.33%, respectively [16,17]. In 67.33% of patients, involvement of the right lobe of the liver and the finding of a single abscess cavity in 78% of patients in this study are on par with the literature and findings of an earlier study [16].

Many studies have found a strong association between alcohol consumption and hyperbilirubinemia in patients with ALA [14,15,18,19]. They found that the majority of patients with a history of chronic alcoholism have hyperbilirubinemia compared to non-alcoholic ones [15,18,19]. In the present study, the authors found the same result. Out of the total 150 cases of ALA, 81.3% of patients and 90.90% of patients with jaundice had a history of alcohol intake. Most of the reported series found a raised TLC count in patients with ALA, and it was more pronounced in patients with ALA with jaundice [20,21]. In the present study, there were also 62.67% of the total 150 patients with ALA and 95.45% of the patients with ALA with jaundice found to have leukocytosis. Comparison of findings of similar studies are summarised in [Table/Fig-5] [12-17].

Most of the studies done earlier found deranged kidney function and a higher associated high blood sugar level in a patient with ALA who had jaundice [19,21]. In the present study, among ALA patients who had jaundice, 72.73% had elevated serum urea, 54.55% had raised serum creatinine, and 40.91% had an elevated random blood sugar value. Comparing these results with patients with ALA without jaundice, we found a statistically significant difference. Katzenstein D et al., and Gupta RK correlated the high value of Alkaline Phosphatase (ALP) with the duration of ALA, which returned to normal after the resolution of the abscess. Abnormally high ALP is associated with ALA and is considered the most reliable and consistent biochemical indicator of ALA [22,23]. Also, a raised level of ALP is found to be associated with an increase in the size

S. No.	Author's name and year	Place of study	Number of subject	Parameters assessed	Conclusion
1.	Chhetri MK et al., [12]	India	60	Factors associated with ALA	6% of total cases had jaundice.
2.	Vakil BJ et al., [13]	India	190	Clinical and laboratory investigations were performed while assessing the atypical manifestation of ALA	58 (30.52%) patients presented with atypical symptoms including jaundice in 7.8%.
3.	Chen HL et al., [14]	Southeastern Taiwan	14	Clinical and laboratory investigations for assessing the epidemiological profile of the patients of ALA in Taiwan	3 (21.43%) had jaundice and 78.6% were alcoholic.
4.	Jha AK et al., [15]	Bihar, India	198	Factors associated with ALA	55 (28%) had jaundice and 168 (85%) were alcoholic.
5.	Sharma N et al., [16]	Chandigarh, India	86	Clinical and laboratory investigations in patients of ALA presented in the emergency department	11 (12.7%) had jaundice and 40 (46.5%) were alcoholic.
6.	Mukhopadhyay M et al., [17]	West Bengal, India	72	Epidemiological, clinical profile, and complications of the patients with ALA	11 (15.27%) had jaundice and 44 (61.11%) were alcoholic.
7.	Present study	Delhi, India	150	Clinical and laboratory investigations to assess the morbidity and mortality of patients with and without hyperbilirubinemia in ALA	22 (14.66%) had jaundice and 122 (81.33%) were alcoholic.

[Table/Fig-5]: Comparison of findings in different studies on similar topics [12-17].

of the abscess cavity in patients with ALA [24]. The findings of the present study correlate well with these earlier findings. In the present study, 86.36% of patients with jaundice and 50.78% of ALA patients without jaundice had raised ALP, while 61.90% of overall patients with an abscess cavity size greater than 300 cm had raised ALP.

Most of the patients with uncomplicated ALA with a size of abscess less than 100 cm were managed in this series with medical management, while larger abscesses with or without complications required drainage procedures in the form of percutaneous needle aspiration or catheter drainage. Most of the studies reported earlier that medical management is the mainstay of treatment for ALA and itself is sufficient for uncomplicated abscesses of size less than 5 cm [1,6,8,12,25]. Patients with ALA with jaundice reported a higher rate of complications than the cases without jaundice. The authors found complications like rupture in the pleural cavity in 4.66% of cases, rupture in the peritoneal cavity in 7.33% of cases, and generalised peritonitis and death in 0.6% of cases. These findings of the present study are comparable with those of earlier studies [10,17]. The authors found that patients of ALA with jaundice have a longer duration of hospital stay in comparison to patients without jaundice, which is well understood by the fact that ALA patients with jaundice have a serious nature of illness with a higher rate of complications.

Limitation(s)

The samples for this study were chosen from a single source, and they were already diagnosed cases of ALA. The selected cases were divided into two groups based on the presence or absence of jaundice without randomisation. This study was a simple observational study without randomisation or intervention, and the authors observed the limited jaundiced population found in our small series of ALA. Further study is required that should be based on a randomised sample representing a wider population.

CONCLUSION(S)

In conclusion, the current study observed that hyperbilirubinemia, or jaundice, is not a rare manifestation of ALA. Patients with ALA who have diabetes and a history of chronic alcohol intake are more likely to develop jaundice and other complications. Deranged laboratory parameters in terms of leucocytosis, raised serum urea, and creatinine are more frequently associated with patients with ALA and jaundice. Raised serum bilirubin and alkaline phosphatase in a patient with ALA are associated with a longer duration of hospital stay, higher complications, and a poor prognosis.

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