Original Article

Assessment of Risk Factors in Pyogenic Liver Abscesses in Children

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Abstract

Background: Pyogenic liver abscess (LA) is a significant contributor to morbidity and mortality in developing countries like India. The risk factors predisposing to the LA specifically in children are not known. Studies done in the past largely remain inconclusive and have identified only probable causes. The cause of LA in children with no coexisting illness remains unknown. **Methodology:** This prospective observational study was conducted at a tertiary teaching hospital located in New Delhi, India. All children between 2 months and 12 years of age with sonographically confirmed LA presenting to the hospital were included and managed with appropriate intravenous antibiotics and relevant investigations. **Results:** A total of 52 children were included. The mean age was 6 years and 4 months, and the male: female ratio was 1.4:1. Around 50% of the patients were malnourished. Fever, abdominal pain and loss of appetite were the most common symptoms. Nine patients (17%) were managed conservatively, 13 (25%) needed percutaneous needle aspiration and 30 (57.69%) required drainage using a pigtail catheter. Poor socioeconomic status and anaemia were found to be the most commonly associated risk factors. Selective immunoglobulin A (IgA) deficiency was the most common primary immunodeficiency disorder followed by T-cell defect. On multivariate analysis, it was seen that in those with clinical icterus, gamma-glutamyl transferases >350 IU/m, and those with impending rupture, the time to defervescence was significantly different ($P = 0.05$). **Conclusion:** Poor socioeconomic status causing malnutrition emerged as a significant risk factor for LA in children. Selective IgA deficiency was the most common immunodeficiency seen in a few children. Adopting a conservative approach like aspiration and percutaneous drainage led to lower mortality and good recovery rates.

Keywords: Liver abscess, percutaneous drainage, primary immunodeficiency, risk factors

Introduction

Pyogenic liver abscesses (LAs) are serious infections in children, associated with significant mortality and morbidity with a higher incidence in developing countries like India, compared to developed countries where it is uncommon.[1,2] The overall incidence of LAs in India is 79/100,000 with a mortality rate of <15%.[2,3] Most of the LAs in children are pyogenic (80%), the most common causative organism being *Staphylococcus* followed by amoebic LAs.[4,5]

The diagnosis is made with a clinical history and radiological confirmation of LA using ultrasound and computed tomography (CT) which are important tools for diagnosis. Different treatment guidelines exist for pyogenic LAs employing concomitant use of antibiotics and percutaneous drainage. Various multicentric studies from India and other developing countries have shown better efficacy of percutaneous drainage over conservative management with reduction of hospital stay and consequent lesser morbidity and mortality.[2,6,7]

There is a paucity of data regarding risk factors in children. Some studies have highlighted the causative role of intestinal infestations, chronic cholangitis, umbilical vein catheter (in neonates), systemic bacteraemia, hepatic trauma and chronic granulomatous disease.[1,7,8] The association of malnutrition and worm infestation with LA has been reported in children from developing countries.[2,7,9] Studies focusing on various prognostic markers influencing the outcomes in LAs in the paediatrics population are also very few.

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Received: 24-01-2022 **Revised:** 22-06-2022 **Accepted:** 30-06-2022 **Available Online:** 19-01-2023

Access this article online

Quick Response Code:

Website: https://journals.lww.com/AJPS

DOI: 10.4103/ajps.ajps_15_22

How to cite this article: Pandey A, Rajeshwari K, Kumar D, Gupta G. Assessment of risk factors in pyogenic liver abscesses in children. Afr J Paediatr Surg 2023;20:218-23.

In this study, we have evaluated the occurrence of risk factors for LAs in children and compared multiple clinical and laboratory parameters including immunological profiles influencing the outcome.

Methodology

This prospective observational study was conducted at a tertiary hospital Located in New Delhi, India, from April 2020 to March 2021, after obtaining Institutional Ethical Clearance (No. 17/IEC/MAMC/2018/03). All children between 2 months and 12 years of age were included after informed written consent. The basic patient information-demographic details, dietary history, clinical history and examination and details of antibiotic treatment were recorded as per a pre-structured pro forma. Anthropometric measurements were recorded using standard methodology. All plausible risk factors such as malnutrition (WHO criteria), anaemia, worm infestation, poor socioeconomic status (using modified Kuppuswamy Scale), septic foci, immunodeficiency and pneumonia were identified based on history and clinical examination and relevant investigations. Haematological and biochemical parameters that were assessed include-complete blood counts, liver function tests, kidney function tests, serum electrolytes, USG, Chest X-ray, aspiration of pus and relevant staining and culture for microorganisms using standard microbiological techniques, blood culture, amoebic serology, HIV antibody testing and primary immunodeficiency (PID) workup including, T-cell marker ($CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+$:$CD8^+$), B-cell marker ($CD\ 19^+$) and NK cell markers ($CD3^+$, $CD56^+$, $CD3^+$, $CD16^+$ and $CD3^+$, $CD56^+$, $CD16^+$) using flow cytometry, neutrophil oxidative index using quantitative dihydrorhodamine flow cytometric assay and the mean fluorescence intensity and quantitative immunoglobulin profile (IgA). Sample for HIV testing and PID workup was taken only if clinically directed (recurrent/deep skin or organ infection, recurrent pneumonia, 2 or more deep-seated infections or septicaemia, 2 or more sinusitis and within a 1 year, >4 new ear infection within a year, persistent thrush or fungal skin infection, need for intravenous antibiotics and family history of PID). A thorough literature search was done and all published risk factors for LAs were identified.

Data were analyzed using IBM SPSS statistical software for windows version 19, Armonk, New York, USA. The continuous variables were measured by calculating the mean, median and standard deviation. Quantitative variables were compared using an unpaired *t*-test/Mann–Whitney test and Qualitative variables were correlated using the Chi-square test/Fisher's exact test.

Results

A total of 52 children with LAs presented to the department of paediatrics during the study period were included and investigated. The mean age of presentation was 6 years and 4 months (range- 2 years 1 month – 10 years 10 months), and the male-to-female ratio was 1.4:1. The demographic characteristics of these children are described in Table 1.

An estimated 88.46% of total cases belonged to lower socioeconomic status. Out of 52 children, 19 children were <5 years of age, and 52.62% of them were malnourished (moderate – 42.10%, severe-10.52%). Thirty-three children out of 52 were more than 5 years of age and over 50% of them were underweight.

Fever (100%), pain abdomen (98%) and loss of appetite (80%) were the most common symptoms. The mean duration of symptoms before presentation was 13.07 ± 7 days. Other clinical features are described in Table 2.

The radiological and other laboratory characteristics are mentioned in Table 3. Out of 52 cases, 42 (80.7%) had a

Table 1: Demographic characteristics

Characteristics	Number, *n* (%)
Age group (years)	
<2	0
2-4	16 (30.5)
4-<6	7 (13.5)
6-<8	14 (27)
>8	15 (29)
Sex	
Male	1.4
Female	1
Nature of residence	
Urban	42 (80.8)
Rural	10 (19.2)
Religion	
Hindu	26 (50)
Muslim	26 (50)
Socioeconomic status	
Upper	0
Upper middle	2 (3.8)
Lower middle	4 (7.6)
Upper lower	35 (67.3)
Lower	14 (21.2)
Dietary history (inadequate)	
Calories	30 (58)
Protein	26 (50)
Consumption of milk and milk products	42 (80)
Nutritional status of children (<5 years)	Total=19
Normal	9 (47.32)
Moderate malnutrition	8 (42.10)
Severe malnutrition	2 (10.52)
Stunted	7 (36.84)
Wasted	6 (31.57)
Nutritional status of children (> 5 years)	Total=33
Underweight	17 (51.51)
Normal	15 (45.45)
Overweight	1 (3.03)
Obese	0

Table 2: Clinical symptoms and signs

Symptoms	Number, *n* (%)
Fever	52 (100)
Pain abdomen	51 (98)
Right upper abdominal pain	49 (94)
Loss of appetite	42 (80)
Cough	17 (32)
Vomiting	16 (30.7)
Abdominal distension	6 (11)
Burning micturition	6 (11)
Altered sensorium	3 (5.7)
Jaundice	3 (5.7)
Signs	
Hepatomegaly	50 (96)
Liver tenderness	46 (88)
Toxic look	22 (42)
Decreased air entry (pleural effusion)	17 (32)
Tachypnea	15 (28.8)
Ascites	5 (9.6)
Icterus	3 (5.7)

Table 3: Radiological and laboratory parameters

Radiological	Number, *n* (%)
Number and size of abscesses	
Single	42 (80.7)
Two	7 (13.4)
>Two	3 (5.7)
>50 cc	39 (75)
<50 cc	13 (25)
Lobe right	
Segment 6	32 (61.5)
Segment 7	7 (13.4)
Segment 8	2 (3.8)
Segment 5	1 (1.9)
Left lobe	10 (19.2)
Associated findings	
Pleural effusion	17 (32.6)
Ascites	5 (9.6)
Impending rupture	13 (25)
Haematological	
Moderate anaemia (7-10 g/dl)	32 (61.5)
Severe anaemia (<7 g/dl)	10 (19.2)
Elevated leucocytosis (>15,000 cell/mm^3)	38 (73)
Thrombocytopenia (<1.5 lakhs/mm^3)	10 (19.2)
Biochemistry	
Prolonged INR	
>1.1	43 (82)
>1.4	17 (32.6)
Hyperbilirubinaemia (>1.2 mg/dl)	6 (11.5)
Liver functions	
Elevated ALT (>44 IU/L)	26 (50)
Elevated AST (>44 IU/L)	27 (51.9)
Hypoalbuminaemia (<3.4 gm/dl)	43 (82.69)

INR: International normalised ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 4: Showing organisms isolated from 52 enrolled cases of liver abscess

Number of abscesses	Organism isolated	Frequency
Single abscess	*E. coli*	6
	S. aureus	4
	Coagulase-negative *Staphylococcus*	4
	Acinetobacter spp.	2
	P. aeruginosa	2
	Burkholderiacephacia	1
	K. pneumonia	1
Multiple abscess	*S. aureus*	3
	E. coli	2
	Coagulase-negative *staphylococcus*	2
Total	27*	

*One patient has dual growth of *E. coli* and *S. aureus* from single pus culture with *S. aureus* growth in blood culture. *E. coli: Escherichia coli, S. aureus*: *Staphylococcus aureus, P. aeruginosa: Pseudomonas aeruginosa, K. pneumonia: Klebsiella pneumoniae*

Table 5: Risk factors in enrolled 52 cases

Risk factor	Number, *n* (%)
Poor socioeconomic status	47 (90)
Anaemia (haemogram <11 g/dl)	44 (84)
Malnutrition	27 (52)
Worm infestation	18 (34)
Systemic bacteraemia	14 (26)
Severe anaemia (haemogram <7 g/dl)	10 (19)
Immunodeficiency (*n*=20)[#]	9 (45)
Selective IgA deficiency	4 (20)
T-cell defect	3 (15)
Chronic granulomatous disease	2 (10)
Class switch/hyper IgM disorder	2 (10)
Coexisting enteric fever	2 (3.8)
Genetic syndrome*	1 (1.9)

[#]immunodeficiency workup was done in 20 patients only, *craniofacial cleft with corneal opacities

single abscess at presentation. The most common site of the abscess was segment 6 of the right lobe (61.5%). The mean volume of abscess at presentation was 138.96 ± 91 ccs in 52 enrolled cases. Out of 52 cases, 29 (55.7%) demonstrated high-risk characteristics during the admission period. Seventeen out of 52 patients had pleural effusion, followed by septicaemia (*n* = 14, 26.9%), impending rupture (*n* = 13, 23%), multiorgan dysfunction (*n* = 9, 17%) and jaundice (*n* = 3, 5.7%).

As far as management is concerned, out of 52 cases, 9 patients (17%) were managed conservatively, 13 (25%) needed percutaneous needle aspiration and 30 (57.69%) required drainage using a pig-tail catheter. In nine patients, catheter displacement occurred which required replacement, whereas in 3 patients, persistent bile drainage occurred which subsided spontaneously. Antibiotics were started for all patients as per the unit protocol. The mean duration of parenteral

Table 6: Various prognostic factors affecting outcomes (duration of defervescence)

Parameter to compare	Duration for defervescence (days)		*P*
Number of abscesses	Single (8.92)	Multiple (9.3)	0.45
ALP	<350 IU/L (8.54)	>350 IU/L (11.1)	0.05
TLC	<15,000 cell/mm^3 (7.54)	>15,000 cell/mm^3 (9.4)	0.10
Rupture/impending	Absent (8.3)	Present (11)	0.01
Culture	Positive (8.09)	Negative (9.96)	0.04
Albumin	>3.5 g/dl (7.33)	<3.5 g/dl (8.91)	0.78
Bilirubin	<1.2 mg/dl (8.67)	<1.2 mg/dl (13)	0.72
Blood urea	<40 mg/dl (9.13)	>40 mg/dl (9)	0.60
Clinical icterus	Present (14.67)	Absent (8.65)	0.04

TLC: Total leucocytes count, ALP: Alkaline phosphatase

antibiotics was 19.45 ± 7.32 days (range 10 days to 36 days) and of oral antibiotics was 13.92 ± 0.56 days with most patients receiving 14 days of oral antibiotics. The mean duration from the start of treatment to subsidence of fever was 8 ± 5 days and the mean duration of hospital stay was 19.9 ± 7.7 days (range from 10 days to 42 days).

Out of 52 cases, 37 (71%) had a pyogenic LA and amoebic LAs were seen in 9 (17.3%) cases. Out of 52 culture samples sent, 21 (57%) were found positive for bacterial aetiology and 1 sample had cultivated a mix of organisms as described in Table 4.

Risk factors were assessed in all 52 cases, except for the immunological workup which was done in 20 patients only who consented to give the sample tested at another hospital. Poor socioeconomic status and anaemia were found to be the most commonly associated risk factors. Selective IgA deficiency was the most common PID disorder (20%) followed by T-cell defect (15%). Other risk factors are enlisted in Table 5.

Out of 52, one patient expired on day 2 of admission, who presented with septic shock and multiorgan dysfunction.

On multivariate analysis, it was seen that in those with clinical icterus, gamma-glutamyl transferases (GGT) >350 IU/m, and those with impending rupture, the time to defervescence was significantly different [Table 6]. On comparing the culture-positive and culture-negative cases, the duration of hospital stay was significantly more in culture-positive cases ($P = 0.05$).

Discussion

This study was done at the department of paediatrics of a tertiary level teaching hospital in New Delhi, India. A total of 52 children with LAs were enrolled in the study after informed written consent. The mean age of children presenting with LAs was 6 years and 4 months with the youngest child being 2 years 1 month and the oldest child being 10 years and 10 months. The findings in this study were in accordance with other published studies mentioning the mean age of children presenting with the LA as varied from 3 to 8 years.[4,10] Large recent multicentric studies focusing on LAs in children from India are scanty. Although there is a paucity of data regarding the distribution of LA cases among varying age groups in children, recent data showed LA preponderance among children more than 5 years of age in India. A study by Ramachandran *et al*.[11] and Roy Choudhury *et al*.[7] showed a median age of 7.3 years and 6.76 years respectively. Furthermore, recent data showed an upward shift in median age from 3 years in a study by Kumar *et al*.[3] in 1998 to 6.76 years in the latest study by Roy Choudhury *et al*.[7] in 2016. In our study, there was a male preponderance with a male-to-female ratio of 1.4:1. Similar results were also been observed by various studies in the past.[1,3,12,13]

Most of the patients in this study resided in urban areas (80.8%) where 46 out of 52 patients (88.46%) belonged to lower socioeconomic status. Similar results were also seen by Ghosh *et al*.[1] (67.5% of patients were from low socioeconomic class) and Ba *et al*.[9] (69% of patients belonged to low socioeconomic strata).

Dietary history was taken in these 52 enrolled patients with the help of 24 h recall method. It was observed that 58% (30 out of 52 patients) had an inadequate caloric intake with about half (26 out of 52 patients) having inadequate protein intake. There is a paucity of large-scale data regarding the presence of caloric deficit amongst patients with a LA in children, especially from India. The association of malnutrition with various infectious illnesses in children is well known.

The mean duration of symptoms before presentation was 13.07 ± 7 days. Many other studies[3,5,14] have also demonstrated fever as the major clinical presentation in LAs. Prolonged fever (>7 days) was present in 71% of patients. In a study by Hsu *et al*.[15] (a study done in Central Taiwan), 46% of patients presented with prolonged fever. A plausible explanation for this large proportion of prolonged fever in our patients might be due to a delay in diagnosis due to delayed presentation to our hospital as compared with patients from developed countries. Similar results were also shown by a retrospective study in Iran (another developing country) by Salahi *et al*.,[16] with the median time of delay between the beginning of symptoms and diagnosis was 13 days. Most patients presenting with pain abdomen had localised pain in the right upper abdomen (96%) which might be due to stretching of the liver capsule. Hepatomegaly (96%) and liver tenderness (88%) were the most common signs seen at the presentation. Similar results were observed by Roy Choudhury *et al*.[7] (hepatomegaly in 97% and liver tenderness in 95%) and Ramachandran *et al*.[11] The classical triad of fever, hepatomegaly and liver tenderness was seen in 86.5% of patients. The clinical signs seen in this study were similar to many studies published from both developing and developed countries[1-5,7,11-18]

In our study, all LAs were diagnosed on ultrasound with a sensitivity of 100%. Various other studies have also shown

similar efficacy of ultrasound ranging from 85% to 95%.[2] CT scan was not needed in any case for diagnostic purposes.

In our study, the most common site of the abscess was segment 6 of the right lobe (32 cases, 61.5%) followed by the left lobe in 10 cases (19.2%). The mean volume of abscess at presentation was 138.96 ± 91 ccs in 52 enrolled cases which was similar to that observed by Waghmare *et al*.[19] (164 cc). The predilection for the right side of the lobe was also seen in studies by Kumar *et al*.[3] (66.7%), Hsu *et al*.[15] (86.7%), Ramachandran *et al*.[11] (92%), and many others[2-7,17] This could be explained by the volume of the right portal venous flow and also that the right portal vein continues in the same direction as the common portal vein while the left portal vein takes a more horizontal direction.[2] Furthermore, the blood flow volume is more and biliary canaliculi are denser in the right lobe thus leading to more congestion.[1] Single abscess on initial evaluations was also seen in the majority of the above studies[2-7,19]

High-risk characteristics were also evaluated during the initial evaluation by an ultrasonogram. These high-risk characteristics were first mentioned by Srivastava *et al*.[10] in his study and included both radiological and non-radiological parameters. Rupture/impending rupture was seen in 13 out of 52 cases (25%) of cases. High-risk characteristics include pleural effusion, septicaemia, rupture/impending rupture, multi-organ dysfunction, jaundice and gastrointestinal bleed. High-risk characteristics were present in 29 out of 52 (55.7%) patients with pleural effusion being most common (32.7%), followed by septicaemia and rupture/impending rupture.

Haematological features showed that 80.7% of patients had moderate to severe anaemia and leucocytosis in 73% of patients. Various studies[3,7,11,12,15,19] have observed anaemia and leucocytosis as a common features in LAs. Biochemical parameters were also evaluated at the time of admission with hypoalbuminemia and deranged international normalised ratio (INR) (defined as INR more than 1.1) observed in 82.69% and 82% respectively. Other laboratory features are summarised in Table 3.

Out of 52 cases, 37 (71%) had a pyogenic LA and 9 (36.7%) had an amoebic LA. The preponderance of pyogenic LAs was also shown by Srivastava *et al*.[10] (64% pyogenic and 28.3% amoebic LA) and Salahi *et al*.[16] (88% pyogenic LA and 5.5% amoebic LA).

In our study, 48% revealed organisms on pus culture, whereas blood culture yields were 25% only. Similar results were seen in a study by Hsu *et al*.[15] where the sensitivity of blood and pus cultures were 20% and 85.7%, respectively in contrast with many Indian studies[1,7,19] which have poor yields The high pus culture yield in this study was due to early aspiration and very careful use of standard microbiological techniques.

The most common species isolated was *Staphylococcus spp.*, other organisms isolated were *Escherichia coli, Acinetobacter spp, Pseudomonas aeruginosa.* and *Burkholderiacepacia.*

Risk factors assessed in our study are enumerated in Table 5. There is a paucity of data regarding risk factors for LA in children. Most of the studies have focussed on adult patients with the presence of various risk factors. Risk factors studied by Ba *et al*.[9] includes anaemia (69.2%), malnutrition (42.4%) and abdominal trauma (15.3%). Malnutrition was the major risk factor in studies by Kumar *et al*.,[3] Hendricks *et al*.[14] and Waghmare *et al*.[19]

An immunological workup could be undertaken in only 20 out of 52 cases. Selective IgA deficiency was the most common PID disorder seen followed by T-cell defect, chronic granulomatous disorder and hyper M disorder. There is a paucity of data regarding the association of various immunological disorders with the LA.

The mean duration of subsidence of fever and duration of hospitalisation after initiation of treatment was 8 ± 5 days and 19.9 ± 7.7 days, respectively comparable with studies by Roy Choudhury *et al*.[7] and Srivastava *et al*.[10]

Patients were managed in consultation with the Paediatric Surgery Department. 17.3% of cases underwent conservative management only and the rest (82.69%) required some sort of drainage procedure in conjunction with antibiotic therapy (25% required needle aspiration and 57.69% required drainage with a pigtail catheter). None of our patients required open surgical drainage which is in contrast with experience from other studies where open surgical intervention was required varying from 17.9% to 20.7%.[2,17,20,21] Indications of open surgical intervention which has been advocated in previous studies are ruptured abscess on presentation, multiloculated abscess, abscess with thick pus, multiple abscesses not responding to treatment, large left lobe abscess, and failed percutaneous drainage.[2] Thus, we recommend that percutaneous drainage may be tried in these conditions before going for an open surgical technique. Previous reports advocating surgical drainage have been published largely by paediatric surgeons.[2,6,7,10,11] Publications from India on large series of LAs treated by paediatricians are few. Thus, it appears that good closed drainage and appropriate antibiotics will be sufficient in the majority of cases with surgical drainage only for those with rupture and severe peritonitis. Other recent publications also support this view.[22] Adopting a conservative approach like aspiration and percutaneous drainage led to lower mortality and good recovery rates in this study. The risk associated with anaesthesia and open surgical drainage in these malnourished children was minimised with aspirations or percutaneous drainage procedures done under local anaesthesia and minimal sedation.

There is a paucity of data regarding predictors of poor prognosis among children. In children, only raised GGT and open surgical procedures were associated with poor outcomes.[11,23] In this study, elevated baseline GGT (>350 IU/L), clinical icterus, culture positivity and high-risk characters as rupture/impending rupture were only statistically significant indicators of morbidity (duration of defervescence, the P = 0.05,0.04, 0.04 and 0.01, respectively).

A unique finding observed in this study was that immunodeficiencies in children may present for the first time with LAs without previous history of recurrent infections or diarrhea. Larger studies on children will further unravel the various manifestations of immunodeficiency in Indian children. It is plausible that severe malnutrition compounds pre-existing immunodeficiency. Furthermore, these children respond to standard medical management of LA is another important finding emerging from this analysis.

Limitations of the study

The small sample size was a limiting factor in this study.

Strengths of the study

It is one of the first studies from India evaluating risk factors in LA in children and comparing outcomes with multiple clinical, biochemical and radiological parameters. Furthermore, the first study to evaluate immunological profiles in children with LAs in India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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