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Original Article

Differential diagnosis of acute liver failure in India

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Abstract

Background: **Acute liver failure (ALF) is a condition with rapid deterioration of liver function resulting in hepatic encephalopathy and/or coagulopathy in patients with previously normal liver. Complicated forms of certain infectious diseases like falciparum malaria, leptospirosis, dengue fever, ricketsial fever, typhoid fever, haemophagocytosis, herpes simplex virus, cytomegalovirus, tuberculosis or amoebic liver abscess can present with altered mentation and/or bleeding manifestations in presence of jaundice and mimic ALF due to acute viral hepatitis (AVH).** ***Methods:*** **We describe our experience in last 2 years with 28 patients of ALF due to above mentioned conditions (ALF-ID) and compared them with 28 patients with ALF due to AVH (ALF-AVH).** ***Results:*** **In ALF-ID, typhoid fever was present in 1, haemophagocytosis in 1, ricketsial infection in 4 (scrub typhus = 2, endemic typhus = 2), amoebic liver abscess in 4, leptospirosis in 5, dengue fever in 5 and falciparum malaria in 8 patients. In ALF-AVH, hepatitis E and B co-infection was responsible in 1, hepatitis A and E co-infection in 1 and hepatitis E, B and C co-infection in 1, hepatitis E in 18, hepatitis A in 2 and hepatitis B in 5 patients. Differentiation of various forms of ALF-ID from ALF-AVH depends on various clinical, haematological and biochemical parameters, in addition to specific diagnostic tests. Patients with ALF-AVH had mortality rate of 50% (14/28) and ALF-ID had mortality rate of 25% (7/28).** ***Conclusions:*** **In developing countries, ALF-mimicking infections should be looked for in differential diagnosis of ALF. Early identification and treatment of these infections is important in reducing mortality.**

Key words: Acute liver failure, severe malaria, dengue fever, leptospirosis, enteric fever, amoebic liver abscess, ricketsial infection, haemophagocytosis, infectious diseases,

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Abbreviations
Acute liver failure (ALF), international standardized ratio of prothrombin time (INR), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), infectious diseases (ID), falciparum malaria (FM), Leptospirosis (LP), dengue fever (DF), ricketsial fever (RF), typhoid fever (TF), haemophagocytosis (HP), herpes simplex virus (HSV), cytomegalovirus (CMV), amoebic liver abscess (ALA), acute viral hepatitis (AVH), ALF due to infectious diseases other than A-E hepatitis viruses (ALF-ID), ALF due to acute viral A-E hepatitis (ALF-AVH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), prothrombin time (PT), lactate dehydrogenase (LDH), creatine kinase (CK), erythrocyte sedimentation rate (ESR), statistically significant (S), statistically not significant (NS), times upper limit of normal value (xULN),

Introduction

Acute liver failure (ALF) is a condition with rapid deterioration of liver cell function resulting in hepatic encephalopathy and/or coagulopathy in patients with previously normal liver. The definition of ALF includes evidence of coagulation abnormality (international standardized ratio of prothrombin time (INR) > 1.5) and any degree of mental alteration in a patient without pre-existing cirrhosis and with an illness of < 26 weeks duration.[1] Common causes of ALF are hepatitis viruses or drugs. In Western Countries, drug induced ALF predominates, comprising 19-75% of total cases of ALF, followed by viruses comprising 4-36% of ALF;[2] whereas in India, 91-100% cases are due to viruses, while drug toxicity is responsible for 0-7.4% cases.[3-11] In adults, among viral etiologies, hepatitis A virus (HAV) comprises of 2-5.5% cases, hepatitis B virus (HBV) 11-40% cases, hepatitis C virus (HCV) 0-7.2% cases, hepatitis D virus (HDV) 0-11.1% cases, hepatitis E virus (HEV) 23-56.5% cases, mixed infections in 4-22% cases and non A-E viruses in 15-62.4% cases.[3,6-9,12-14] In children, HAV is responsible

for ALF in 10-71% cases, HEV in 2.7-25%, HBV in 0-10.7%, HCV in 0-2.5%, HDV in 16.7%, mixed infection in 10-22% and non A-E infections in 17.9%.[15] There is no specific treatment available for ALF for most of the causes, and mortality due to ALF even with a liver transplantation remains high.

In recent years, a subgroup of patients is often looked at, who harbor complicated forms of common infectious diseases (ID) and present as ALF.[16-21] These infections are falciparum malaria (FM), Leptospirosis (LP), dengue fever (DF), ricketsial fever (RF), typhoid fever (TF), haemophagocytosis (HP), herpes simplex virus (HSV), cytomegalovirus (CMV), adenovirus, Epstein-Barr virus, Varicella-Zoster virus, tuberculosis or amoebic liver abscess (ALA). Complicated forms of all of them can present with altered mentation and/or bleeding manifestations in presence of jaundice and mimic ALF due to acute viral hepatitis (AVH). Early recognition of these conditions is essential, as most of them can be completely treated with specific therapies.

In tropical countries like India, where these infections are common; differentiation of ALF due to infectious diseases other than A-E hepatitis viruses (ALF-ID) from ALF due to acute viral A-E hepatitis (ALF-AVH) becomes crucial to provide specific therapy for ALF-ID in addition to supportive treatment for ALF. This study was planned to recognize features that can alert clinicians to suspect these infections in a patient with ALF and differentiate ALF-ID from ALF-AVH.

Material and methods

Study design and study population

This prospective case-controlled study was carried out at our institution during the 2-year study period from January 2004 to December 2005. All the consecutive patients presenting as ALF were evaluated for presence of various infectious diseases. Patients with ALF-ID were included in the study. During the study period, equal numbers of the consecutive patients with AVH who fulfilled criteria for ALF (ALF-AVH) were included in the study for comparison.

Baseline evaluation

All the patients underwent detailed history taking with special emphasis on recent travel, exposures to drugs or toxins, sexual activities, prodromal symptoms of viral hepatitis, history of fever, psychiatric illness, other concomitant diseases, previous history suggestive of chronic liver disease and detailed history of alcohol consumption. Clinical examination included assessment and documentation of mental status, stigmata of chronic liver disease, jaundice, right upper quadrant tenderness, measurement of liver span, splenomegaly and ascites. Baseline laboratory evaluation included liver function tests [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutyl transferase, total/conjugated bilirubin, albumin and globulin, prothrombin time (PT) and INR], renal function tests [including creatinine, blood urea nitrogen], serum chemistry [including sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, lactate dehydrogenase (LDH), creatine kinase (CK)], blood glucose, arterial blood gas analysis, arterial lactate, arterial ammonia, complete blood count (including haemoglobin, leukocyte count, platelet count, erythrocyte sedimentation rate (ESR), reticulocyte count), blood group typing, amylase and lipase level and pregnancy test (if female). All the patients underwent ultrasonography of abdomen with special reference to liver size and echotexture, features of portal hypertension and presence of ascites and pleural effusion. Computerized tomography of head was performed in cases with worsening in mental status to exclude intracranial haemorrhage and other causes. To define aetiology, following tests were performed: serology for viral markers (HIV, IgM anti HAV, HBsAg, IgM anti HBc, anti HCV, IgM anti HEV and anti HDV), serum acetaminophen level, toxicology screening, autoimmune markers (ANA, ASMA, Anti LKM1, p-ANCA), tests for Wilson disease (serum ceruloplasmin, slit lamp study, urinary copper), liver biopsy (in suspected autoimmune hepatitis, Wilson disease, metastatic/ malignant infiltration, lymphoma or herpes simplex hepatitis). In addition, all the patients were checked for specific diagnostic tests for infectious diseases causing ALF-ID: peripheral smears for malarial parasites and Plasmodium Falciparum antigen (for FM); IgM Dengue virus antibody (for DF); IgM Leptospirosis antibody and urine test for Leptospirosis (for LP); IgM herpes simplex virus antibody (for HSV); IgM cytomegalovirus antibody (for CMV); Widal test and blood culture for Salmonella (for TF); Weil-Felix reaction (for RF) and blood culture for bacteria and fungus. IHA test for amoebiasis and culture of the aspirate were performed in case of liver abscess on imaging (for ALA). Transjugular liver biopsy and/or bone marrow biopsy were performed as and when necessary to define aetiology. HP was diagnosed on basis of peripheral smear picture and bone marrow biopsy examination.

Treatment and outcome

All the patients received standard supportive treatment for ALF. Patients with ALF-ID received, in addition, the specific treatment for the infection.

Statistical analysis

Statistical analysis was performed using the chi square test and student t test. P value less than 0.05 was considered statistically significant (S) and more than 0.05 statistically not significant (NS).

Results

In ALF-AVH, HEV and HBV co-infection was responsible in 1, HAV and HEV co-infection in 1 and HEV, HBV and HCV co-infection in 1, HEV in 18, HAV in 2 and HBV in 5 patients. In ALF-ID, TF was present in 1, HP in 1, RF in 4 (scrub typhus = 2, endemic typhus = 2), ALA in 4, LP in 5, DF in 5 and FM in 8 patients.

Demographic, clinical, biochemical and haematological parameters at baseline evaluation of both the groups are tabulated in *table I*.

Statistically significant features which were exclusive to ALF-ID, were not specific for any single infection presenting as ALF-ID and were not seen in ALF-AVH were as follows: high grade fever (> 102° F), splenomegaly, ALT or AST < 5 times upper limit of normal value (xULN), higher AST or LDH than ALT and INR < 1.5 (normal PT).

Other statistically significant exclusive features of ALF-ID were specific to the underlying infection: skin rash, myalgia, conjunctival suffusion, severe abdominal pain, pleural effusion, pulmonary parenchymal involvement, CK > 10 xULN, LDH > 10 xULN, severe anaemia (haemoglobin < 9 gm %), leukocytosis (leukocyte count > 11000 cells/cmm), high reticulocyte count (> 2%) and ESR > 50 mm at end of 1 hour.

Non-significant but exclusive features to ALF-ID were: meningism and lymphadenopathy.

Other statistically significant features seen more commonly in ALF-ID, but were not exclusive to ALF-ID, were as follows: shorter duration of jaundice before encephalopathy, persistent fever after appearance of jaundice, longer duration of fever before appearance of jaundice, overt bleeding manifestations (including petechiae), headache, haemodynamic instability (pulse rate > 90 beats/min and systolic blood pressure < 90 mm Hg), hepatomegaly, hypoalbuminaemia (Serum albumin < 3 gm/dL), renal failure (creatinine > 2 mg/dL), anemia (haemoglobin < 11 gm%), thrombocytopenia (platelet count < 150,000 or < 100,000 cells/cmm).

Statistically significant features seen more commonly in ALF-AVH were as follows: grade III-IV encephalopathy, INR > 2, ALT and AST > 5 xULN or > 10 xULN, hypoglycaemia, normal haemoglobin (> 12 gm %), leukocyte (4000-11,000 cells/cmm) and platelet (150,000-500,000 cells/cmm) count.

Patients with ALF-AVH had mortality rate of 50% (14/28) and ALF-ID had mortality rate of 25% (7/28) (p = S).

Table II shows characteristics of individual infections responsible for ALF-ID, taking in account exclusive or significant features in *table I*.

Discussion

In developing countries like India, ID like FM, TF, LP, and DF can present in a complicated form with febrile jaundice with encephalopathy features and may mimic ALF; and so they should be looked for in all the cases presenting as ALF. Baseline routine clinical and laboratory data help in raising suspicion for presence of such ID. After reaching specific diagnosis, specific therapy for ID in addition to supportive management of ALF is important in reducing mortality.

In a patient presenting with jaundice and encephalopathy (altered mentation) and/or coagulopathy (deranged coagulation parameters with/without systemic bleeding), primary diagnostic consideration is ALF-AVH, which is the commonest form of ALF in India. But, as seen in our study, presence of high grade fever, splenomegaly, mild ALT and AST elevation (< 5 xULN), AST/ALT ratio > 1, LDH/ALT ratio > 1 and normal PT should make a clinician suspicious about presence of ID other than AVH. Additional such features are persistent fever after appearance of jaundice, longer duration of fever, presence of hepatomegaly, and abnormal haemoglobin, leukocyte and platelet counts. In patients with suspected ALF-ID, presence of peculiar features to respective ID can help to narrow down further investigations. Mortality rates were lower for ALF-ID than ALF-AVH in our study, despite statistically insignificant delay in diagnosis and subsequent start of specific therapy between the two groups.

It is known since long that in the tropics, viral hepatitis needs to be differentiated from other common ID such as typhoid, amoebic or malarial hepatitis.[22]

Previously various series have looked at differentiation of hepatitis due to ID from acute viral hepatitis. One such retrospective series compared 27 patients with typhoid hepatitis with 27 AVH and concluded lower ALT/LDH ratio (< 4) was the best discriminator and other features more common to typhoid hepatitis were high grade fever, relative bradycardia, left shift of leukocytes, lower ALT and AST and elevated ALP.[23] Another study suggested to look for TF in presence of febrile jaundice and hepatomegaly.[24] One of the series on FM suggested that in a patient with fever and jaundice with or without altered sensorium, disproportionate hyperbilirubinaemia with only mild elevation of liver enzymes differentiate malaria cases from AVH. As the mortality in late presenters of FM is high, early diagnosis in such cases with institution of specific therapy may be life saving.[25] In a series assessing liver involvement in 732 FM cases, a severe form of malarial hepatitis was identified in 13 patients presenting with coma, deep jaundice and renal failure with mortality of around 30%.[26] An another similar series identified complications of renal failure, respiratory failure and septicaemia and so resultant mortality to be higher in patients with malarial hepatitis as compared to patients without hepatitis.[27] Another series looking at histological features in malarial hepatitis found that predominant conjugated hyperbilirubinemia, increased levels of AST and ALT, and hepatocellular necrosis on biopsy study are strong evidence of severe hepatocyte dysfunction in FM presenting as jaundice.[28]

Table I. Comparison of ALF-AVH and ALF-ID.

Characteristics	ALF-AVH	ALF-ID	P
Numbers of patients	28	28	-
Demographic features			
Mean age, (range) years	38.2 ± 11.2 (8-62)	36.8 ± 10.2 (9-72)	NS
Sex ratio, male: female	16:12	18:10	NS
Clinical features Defining ALF at baseline			
Mean time from onset of symptoms to diagnosis and start of treatment, (range) days	12.2 ± 4.2 (5-17)	10.1 ± 4.6 (2-16)	NS
Jaundice, n (%)	28 (100)	28 (100)	NS
Serum bilirubin > 2 xULN, n (%)	28 (100)	28 (100)	NS
Serum bilirubin > 10 xULN, n (%)	15 (53.5)	14 (50)	NS
Encephalopathy, n (%)	24 (85)	28 (100)	NS
Grade III-IV encephalopathy, n (%)	8 (28.5)	1 (3.5)	S
Mean duration of jaundice before encephalopathy, (range) days	15.1 ± 3.2 (7-22)	5.1 ± 2.1 (1-10)	S
INR > 2, n (%)	17 (60.7)	4 (14.2)	S
INR < 1.5, n (%)	0 (0)	22 (78.5)	S
Other clinical features seen at baseline			
Fever, n (%)	22 (78.5)	28 (100)	S
High grade fever > 102° F, n (%)	0 (0)	24 (85)	S
Persistent fever after appearance of jaundice, n (%)	3 (10.7)	25 (89.2)	S
Mean duration of fever before jaundice, (range) days	4.2 ± 0.8 (3-7)	7.7 ± 0.9 (2-20)	S
Systemic bleeding, n (%)	4 (14.2)	9 (32.8)	S
Anorexia, n (%)	27 (96.4)	14 (50)	S
Diarrhoea, n (%)	2 (7.1)	5 (17.8)	NS
Vomiting-nausea, n (%)	16 (57.1)	13 (46.2)	NS
Abdominal discomfort, n (%)	8 (28.5)	11 (39.2)	NS
Severe abdominal pain, n (%)	0 (0)	6 (21.4)	S
Meningism, n (%)	0 (0)	2 (7.1)	NS
Headache, n (%)	4 (14.2)	18 (64.2)	S
Bodyache, n (%)	20 (71.4)	20 (71.4)	NS
Myalgia, n (%)	0 (0)	5 (17.8)	S
Hemodynamic instability, n (%)	2 (7.1)	9 (32.1)	S
Skin rash, n (%)	0 (0)	3 (10.7)	S
Lymphadenopathy, n (%)	0 (0)	2 (7.1)	NS
Conjunctival suffusion, n (%)	0 (0)	3 (10.7)	S
Hepatomegaly, n (%)	2 (7.1)	23 (82.1)	S
Splenomegaly, n (%)	0 (0)	12 (42.8)	S
Ascites, n (%)	10 (35.7)	10 (35.7)	NS
Pedal edema, n (%)	2 (7.1)	4 (14.2)	NS
Pleural effusion, n (%)	0 (0)	9 (32.8)	S
Pulmonary parenchymal abnormalities or symptoms, n (%)	0 (0)	6 (21.4)	S
Biochemical parameters at baseline			
ALT < 5 xULN, n (%)	0 (0)	19 (67.8)	S
ALT > 5 xULN, n (%)	28 (100)	9 (32.1)	S
ALT > 10 xULN, n (%)	28 (100)	1 (3.5)	S
AST < 5 xULN, n (%)	0 (0)	17 (60.7)	S
AST > 5 xULN, n (%)	28 (100)	11 (39.2)	S
AST > 10 xULN, n (%)	28 (100)	1 (3.5)	S
AST (xULN) > ALT (xULN), n (%)	0 (0)	20 (71.4)	S
ALP > 3 xULN, n (%)	1 (3.5)	3 (10.7)	NS
LDH > 10 xULN, n (%)	0 (0)	8 (28.5)	S
LDH (xULN) > ALT (xULN), n (%)	0 (0)	20 (71.4)	S
CK > 10 xULN, n (%)	0 (0)	3 (10.7)	S
Serum albumin < 3 gm/dL, n (%)	3 (10.7)	19 (67.8)	S
Serum Creatinine > 2 mg/dL, n (%)	5 (17.8)	17 (60.7)	S
Blood glucose < 60 mg/dL, n (%)	12 (42.8)	4 (14.2)	S
Serum sodium < 135 mEq/L, n (%)	5 (17.8)	8 (28.5)	NS
Hematological parameters at baseline			
Normal haemoglobin, n (%)	26 (92.8)	14 (50)	S
Haemoglobin < 12 gm %, n (%)	2 (7.1)	14 (50)	S
Haemoglobin < 9 gm %, n (%)	0 (0)	9 (32.1)	S
Normal leukocyte count, n (%)	26 (92.8)	16 (57.1)	S
Leukocytosis, n (%)	0 (0)	10 (35.7)	S
Leukocytopenia, n (%)	2 (7.1)	2 (7.1)	NS
Normal platelet count, n (%)	26 (92.8)	14 (50)	S
Platelet count < 150000 cells/cmm, n (%)	2 (7.1)	14 (50)	S
Platelet count < 100,000 cells/cmm, n (%)	1 (3.5)	12 (42.8)	S
Reticulocyte count > 2%, n (%)	0 (0)	11 (39.2)	S
Normal ESR, n (%)	5 (17.8)	2 (7.1)	NS
ESR >50 mm at end of 1 hour, n (%)	0 (0)	10 (35.7)	S
New or worsening complications during hospitalization			
Encephalopathy, n (%)	10 (35.7)	3 (10.7)	S
Coagulopathy or systemic bleeding, n (%)	4 (14.2)	4 (14.2)	NS
Renal failure, n (%)	2 (7.1)	2 (7.1)	NS
Multi-organ failure, n (%)	6 (21.4)	3 (10.7)	S
Secondary infection, n (%)	3 (10.7)	1 (3.5)	NS
Hemodynamic stability, n (%)	4 (14.2)	6 (21.4)	NS
Outcome			
Mortality, n (%)	14 (50)	7 (25)	S

Table II. Comparison of different infections causing ALF-ID.

Characteristics, n (%)	RF (n = 4)	DF (n = 5)	LP (n = 5)	FM (n = 8)	ALA (n = 4)	TF (n = 1)	HP (n = 1)
Grade III-IV encephalopathy	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
INR > 2	0 (0)	2 (40)	0 (0)	2 (25)	0 (0)	0 (0)	0 (0)
INR < 1.5	4 (100)	3 (60)	4 (80)	6 (75)	3 (75)	1 (100)	1 (100)
Systemic bleeding	1 (25)	4 (80)	2 (40)	2 (25)	0 (0)	0 (0)	0 (0)
Anorexia	4 (100)	2 (40)	2 (40)	1 (12.5)	3 (75)	1 (100)	1 (100)
Severe abdominal pain	0 (0)	0 (0)	0 (0)	2 (25)	4 (100)	0 (0)	0 (0)
Meningism	0 (0)	0 (0)	1 (20)	1 (12.5)	0 (0)	0 (0)	0 (0)
Headache	2 (50)	4 (80)	4 (80)	8 (100)	0 (0)	1 (100)	0 (0)
Myalgia	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Hemodynamic instability	1 (25)	3 (60)	1 (20)	3 (37.5)	0 (0)	1 (100)	0 (0)
Skin rash	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lymphadenopathy	2 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Conjunctival suffusion	0 (0)	0 (0)	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatomegaly	3 (75)	4 (80)	3 (60)	7 (87.5)	4 (100)	1 (100)	1 (100)
Splenomegaly	1 (25)	3 (60)	0 (0)	6 (75)	0 (0)	1 (100)	1 (100)
Ascites	1 (25)	5 (100)	2 (40)	0 (0)	1 (25)	0 (0)	1 (100)
Pleural effusion	1 (25)	4 (80)	1 (20)	0 (0)	2 (50)	0 (0)	1 (100)
Pulmonary abnormalities	1 (25)	1 (20)	2 (40)	0 (0)	2 (50)		
	0 (0)	0 (0)					
ALT < 5 xULN	3 (75)	1 (20)	2 (40)	8 (100)	4 (100)	0 (0)	1 (100)
ALT > 10 xULN	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AST < 5 xULN	2 (50)	0 (0)	3 (60)	8 (100)	4 (100)	0 (0)	0 (0)
AST > 10 xULN	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LDH > 10 xULN	0 (0)	2 (40)	0 (0)	6 (75)	0 (0)	0 (0)	0 (0)
CK > 10 xULN	0 (0)	0 (0)	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoalbuminemia	2 (50)	5 (100)	5 (100)	4 (50)	2 (50)	0 (0)	1 (100)
Renal failure	3 (75)	3 (60)	3 (60)	6 (75)	1 (25)	1 (100)	0
Hypoglycaemia	0 (0)	0 (0)	0 (0)	4 (50)	0 (0)	0 (0)	0 (0)
Hyponatremia	3 (75)	0 (0)	2 (40)	1 (12.5)	0 (0)	1 (100)	1 (100)
Normal haemoglobin	0 (0)	3 (60)	5 (100)	1 (12.5)	4 (100)	1 (100)	0 (0)
Severe anemia	2 (50)	1 (20)	0 (0)	5 (62.5)	0 (0)	0 (0)	1 (100)
Normal leukocyte count	4 (100)	4 (80)	0 (0)	8 (100)	0 (0)	0 (0)	0 (0)
Leukocytosis	0 (0)	1 (20)	5 (100)	0 (0)	4 (100)	0 (0)	0 (0)
Leukocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)
Normal platelet count	4 (100)	0 (0)	5 (100)	1 (12.5)	4 (100)	1 (100)	0 (0)
Platelet count < 100,000 cells/cmm	0 (0)	5 (100)	0 (0)	6 (75)	0 (0)	0 (0)	1 (100)
Reticulocyte count > 2%	0 (0)	3 (60)	0 (0)	8 (100)	0 (0)	0 (0)	0 (0)
Normal ESR	0 (0)	2 (40)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ESR >50 mm	0 (0)	0 (0)	2 (40)	3 (37.5)	4 (100)	1 (100)	0 (0)
Mortality	1 (25)	2 (40)	1 (20)	2 (25)	0 (0)	0 (0)	1 (100)

Previously from India, ALF due to FM and TF is described in various series.[16-19,29] Few series are reported from India looking at differentiation of complicated FM and TF respectively from ALF-AVH. One such series suggested disproportionate anaemia, renal failure and only mildly elevated liver enzymes should help in differentiating FM from ALF-AVH.[17] In another study comparing 25 patients with complicated FM and 25 patients of ALF-AVH suggested that longer duration of fever, hepatomegaly, splenomegaly, lower haemoglobin, thrombocytopenia, lower AST and ALT levels and normal PT were commonly present with FM.[18] In one prospective series, analysis of 11 patients of complicated TF and 36 ALF-AVH, hepatomegaly, thrombocytopenia, elevated ALP, AST > ALT and only mildly prolonged PT suggested a diagnosis of TF.[19] Both these series have achieved survival rate of 100% with TF and 76% with FM as compared to ALF-AVH group (16.6% and 24%, respectively).[18,19] Our study also showed survival benefit to ALF-ID group as compared to ALF-AVH. In a study on severe FM presenting as multi-organ failure, multiple organ involvement was associated with increased mortality and hepatic failure was associated with around 50% mortality rate.[30]

Continuation of fever despite appearance of jaundice, presence of hepatosplenomegaly, thrombocytopenia, evidence of hemolysis (low hemoglobin and haptoglobin levels; high indirect bilirubin, LDH and reticulocyte count), normal PT and serum proteins, mild-moderate (< 5 xULN) ALT elevations (AST > ALT), renal failure, demonstration of falciparum ring forms or antigen in blood, and response to antimalarial drugs differentiate complicated FM (with renal failure, shock, acidosis, disseminated intravascular coagulation and cerebral malaria) from ALF-AVH.[16,18,31-33]

TF is diagnosed in presence of high grade fever, right hypochondrial pain, tender hepatomegaly, relative lymphocytosis with leucopenia, thrombocytopenia, mild-moderate ALT abnormalities (AST > ALT), elevated ALP, normal PT, presence of biliary complications like cholecystitis or pyogenic abscess, presence of positive culture for salmonella from blood, stool or urine, positive Widal test or rising titers of Widal test and response to Quinolone or Cephalosporin antibiotics.[19,34,35]

LP should be suspected in the presence of hectic fever, severe myalgia, headaches, severe prostration, manifestations like gastrointestinal bleeding, purpura or epistaxis, exposure to water or soil potentially contaminated with animal waste (recreational activities like hiking or swimming; animal contact; work in farms during heavy rain falls), conjunctival suffusion, tender hepatomegaly, presence of meningism, mild anemia, leukocytosis with neutrophilia, thrombocytopenia, high conjugated bilirubin with mild-moderate elevations of ALT, worsening renal failure, abnormal urine analysis and severely elevated CK. A positive IgM leptospira antibody test or isolation of leptospira from CSF or blood during the first week of fever and from urine during the second week confirms the diagnosis. The disease responds to Penicillin, Ampicillin or Doxycyclin therapy.[20,34,36,37]

Recently, few case reports are published on occurrence of ALF in DF and dengue hemorrhagic fever, which are endemic in India.[38,39] DF is diagnosed in presence of high grade fever of > 3 days duration, gastrointestinal symptoms, hemorrhagic manifestations, facial flushing, worsening drowsiness, shock with narrow pulse pressure, hepatomegaly, circulatory disturbances (restlessness, cold extremities, capillary refill time > 2 sec and tachycardia), positive tourniquet test (> 10 petechiae/2.5 cm^2 skin area), profound thrombocytopenia, normal leukocyte count and ESR, evidence of hemoconcentration, evidence of capillary leakage (pleural effusion, ascites and/or hypoproteinemia), mild to severe elevation (> 10 xULN) in AST or ALT levels, absence of hypoglycemia and hyponatremia, and positive test of IgM dengue antibody.[21,40-43]

Ricketsial fever is rarely associated with liver failure. As seen in our study, these infections are characterized by fever, headache, anorexia, gastrointestinal symptoms, bodyache, skin rash, lymphadenopathy, hepatomegaly, petechiae, hypoalbuminemia, hyponatremia, renal failure, pneumonitis, encephalitis, normal leukocyte and platelet counts, mild-moderate ALT or AST elevation and normal PT.[44]

ALA rarely presents with hyperbilirubinemia and/or encephalopathy, which are identified as poor prognostic factors and independent risk factors for mortality in a previous Indian series.[45] In our study, ALA was associated with fever, hepatomegaly, anorexia, severe right hypochondrial pain, pleural effusion and pulmonary parenchymal abnormalities, normal PT, mild-moderate ALT or AST elevation, leukocytosis, normal haemoglobin and platelet count and high ESR. All these features are well described in patients with ALA previously.[46]

Hepatomegaly and deranged liver functions are previously described in fatal HP.[47]

High index of suspicion and awareness are required to identify various common infections causing symptom complex similar to ALF. This help in identifying a patient with ALF who may have low mortality if specific treatment for such infection is given in time.

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