



Clinical Approach to Patients with Acute Viral Hepatitis A and Factors Associated with Poor Prognostic Outcome

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Abstract

Background: *Hepatitis A is the most common infectious etiology of acute viral hepatitis. There has been an increase in incidence of disease in many parts of the world, along with more complications and many unwanted secondary effects. The main aim of study is to identify the clinical profile, unwanted secondary effects and risk factors associated with worst outcome.*

Material and Methods: *A Prospective observational study was conducted on 100 consecutive patients who attended the Civil Hospital, Gurdaspur, Punjab. The patients were kept under follow up for four months. Clinical evaluations and relevant investigations were conducted on those patients.*

Results: *Most of the patients were between 18 to 40 years. Thrombocytopenia, transverse myelitis, Loss of appetite, arthralgias, pancreatitis and acute renal injury were some of the unwanted secondary effects. Three patients died.*

Conclusions: *There were no correlation between SGPT levels and complications. Prior NSAID, Chemicals & alcohol intake is associated with adverse outcome.*

Keywords: *Acute Viral Hepatitis A, NSAIDS, Hepatic encephalopathy.*

Background

Hepatitis A virus (HAV) is a leading cause of acute liver inflammation or hepatitis. It can cause relapsing signs and symptoms but not a chronic infection. HAV is a non enveloped 27nm, heat, acid and ether resistant, single stranded, positive sense RNA virus. It belongs to the family Picornaviridae and the genus *Hepatovirus*. It has characteristics of the enteroviruses. Viral transmission occurs in a fecal-oral route. An estimated 1.5 million people are infected with hepatitis A virus infection occur in the world each year¹. Hepatitis A viral infection can be super infected or co infected with other viral infections and it is one of the most widespread liver

infections in the world, particularly in developing countries. The virus is more prevalent in areas with poor sanitary conditions & with low socioeconomic conditions. The most common source of hepatitis A is direct person-to-person contact and, to a lesser extent, direct fecal contamination of food or water.³ Hepatitis A Virus is concentrated in mollusks raised in contaminated water, hence consumption of undercooked shellfish is an uncommon but possible source of hepatitis A.

The clinical manifestations of HAV infection are widely variable, depending on the host response. They range from silent infection and spontaneous resolution to fulminant hepatic failure. The

incubation period of HAV ranges from 15-50 days (mean 28 days). The prodromal phase is characterized by nonspecific symptoms such as fatigue, weakness, loss of appetite, nausea, vomiting, abdominal discomfort and fever. Headache, arthralgias, myalgias, rash, or diarrhea can follow. Jaundice begins within 1-2 weeks from the onset of the prodrome. Extrahepatic manifestations are uncommon and include evanescent rash, vasculitis, glomerulonephritis, arthritis, immune complex disease, toxic epidermal necrolysis, myocarditis, optic neuritis, transverse myelitis, polyneuritis, polyarteritis nodosa (PAN), thrombocytopenia, aplastic anemia, and red cell aplasia². The course of hepatitis A infection is benign in most of those infected. It is occasionally severe, or fulminant in adults, particularly in those with associated chronic liver disease.

After initial studies on the clinical features of the disease and subsequent development of safe and effective vaccines in the early 1990s, research on acute hepatitis A faded away. However, according to improvements in health sanitation and living conditions, changes in the epidemiology of HAV have paradoxically increased the disease burden in many regions of the world, especially in adult population and complications and unwanted secondary effects of acute viral hepatitis A are also more prevalent in adult population.

Aims and Objectives

1. To study the clinical profile of Acute viral hepatitis A.
2. To study the unwanted secondary effects of Acute viral hepatitis A.
3. To study the risk factors associated with worst outcome.

Materials and Methods

Study Design

Prospective hospital based observational study.

The Centre and Period of Study

Civil Hospital, Gurdaspur, Punjab

The study was conducted between FEBURARY 2020 and JULY 2021

Study Population

Patients admitted in department of general medicine wards, satisfying inclusion criteria.

Inclusion Criteria

- Patients with clinical and biochemical profile suggestive of acute viral hepatitis with positive serological viral marker for hepatitis A-IgM HAV.

Exclusion Criteria

- Patients with serology positive for HBsAg & IgM anti HCV
- Chronic liver disease or USG abdomen showing features of chronic liver disease
- Chronic kidney disease or USG showing features suggestive of chronic kidney disease
- Patients on hepatotoxic drugs
- Patients with serious co morbid illness

Sample Size

Study will include a total of 100 subjects meeting the inclusion criteria.

Data Collection

Computer data sheet for demographics, direct interview and questionnaires and detailed clinical examinations and relevant laboratory investigations.

It is a prospective hospital based observational study. Total of 100 consecutive patients admitted due to acute viral hepatitis in medical wards of Civil Hospital, Gurdaspur, Punjab FEBURARY 2020 to JULY 2021 were enrolled for the study. Patients were selected according to inclusion and exclusion criteria.

All patients underwent a detailed history, daily based clinical examination after obtaining their informed consent. Hematological and biochemical investigations were conducted on all patients including complete blood counts, ESR ,peripheral blood smear, renal and liver function tests, PT-INR, BT, CT, APTT, LIPID PROFILE, blood sugar, urine examination, ECG, 2D echocardiography to rule out myocarditis , IgM HAV, HBsAg, AntiHCV. Radiological investigation include USG abdomen to rule out underlying chronic liver or kidney disease.

All patients were managed symptomatically and complications were managed according to standard treatment protocol of the hospital. All patients are being following upto the next 3 months or liver enzymes become normal, whichever is earlier.

Statistical Analysis

The results were entered into a microsoft excel sheet and then analyzed using the SPSS statistical software version 29 and conclusions drawn accordingly. The statistical significance of different variables was calculated on the basis of Chi – Square test.

Ethical Concerns

Strict confidentiality was maintained regarding the identity of each individual patient. The patients were given option to participate in the study or not to participate with the help of an informed consent form. The patients were neither be exposed to any invasive procedures nor be given drugs as part of the study.

Results

Of the 100 patients, 48% belonged to the 18-26 years age group, 42% belonged to the 26-34 years age group, maximum age observed was 56 years and minimum age observed was 18 years with an average of 25.7 ± 7.2 years (Fig 1).

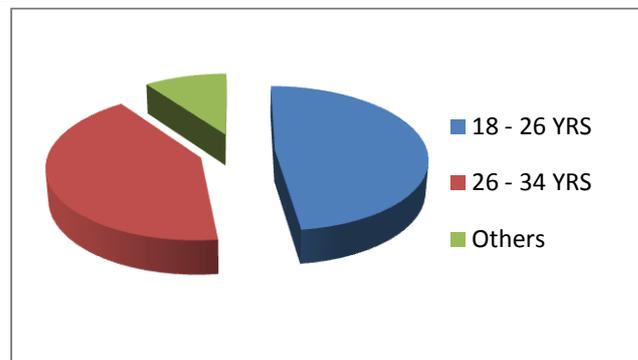


Fig 1: Age distribution

Out of 100 patients 94% had documented fever and 6 % presented without fever and 35 % had continuing fever even after the onset of clinical jaundice. Thus hepatitis A may present as long duration fever. Out of 100 patients , 28 patients had thrombocytopenia , 14 patients had arthralgias /arthritis ,5 patients had AKI , , 8 patients had rash , one patient had acute transverse myelitis and thrombocytosis. Out of 100 patients 10 % of the patients had hepatic encephalopathy , 5 % of the patients had symptomatic bleeding , 6 % of the patients had ascites , 3 patients had pancreatitis , 20 % of patients had cholestatic hepatitis ,7% of patients developed AKI and one patient had transverse myelitis. (Fig 2). Out of these 3 patients expired. 64% of the patients recovered without any complications, 33% had at least one complication. (Fig 3)

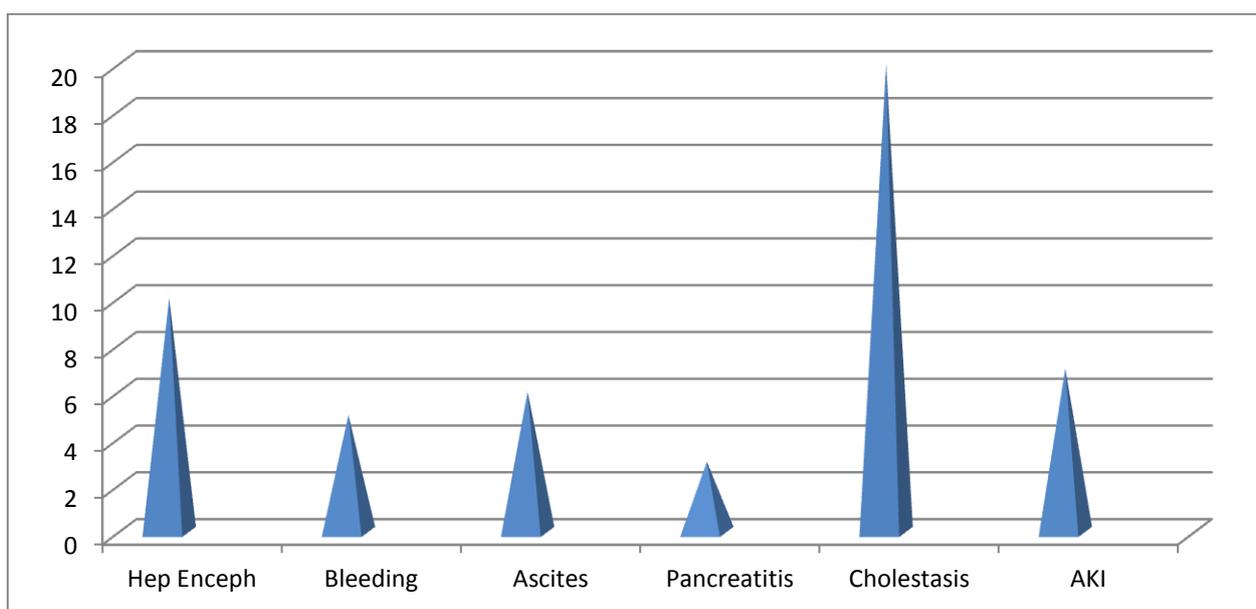


Fig 2: Clinical Presentation

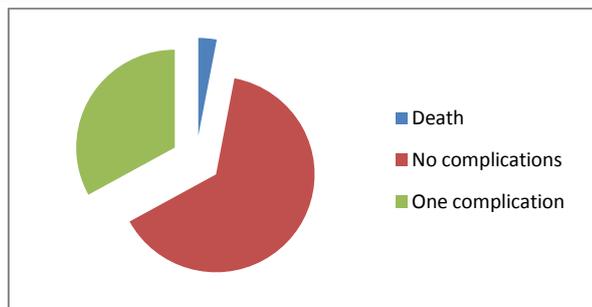


Fig 3. Complications

Factors Associated with Bad Outcome

In this study, the median age of the patients was 25.7 ± 7.2 years, and substantial numbers of patients were below 45 yr. We compared the severity of hepatitis between the groups of the

patients younger and older than 45 yr. The clinical manifestations including complications and laboratory data showed that the clinical course in terms of hepatic dysfunction and renal complication were worse in the group of the patients between 25-34 years.

Presence of alcoholism and poor prognosis is closely related. Among alcoholic patients 66.2% had at least one complication with a statistically significant p value of 0.003. Most common complication noted was fulminant hepatic failure followed by acute pancreatitis.

Alcohol and Outcome

Table 1: Association of presence of alcohol intake and outcome

Alcohol	Recovered	Recovered	Complicated	Complicated	Total
	Count	Percent	Count	Percent	
Yes	6	28.2	11	67.8	17
No	60	70.4	23	29.6	83
Total	66		34		100

X²=8.6058 P=0.003351

NSAID intake also had a significant relation with adverse outcome (p 0.0053) and among patients who took NSAID 53.5% had complications compared to non NSAID group, who had a

complication rate of 27.9%. Most common complication noted in NSAID group was fulminant hepatic failure with symptomatic bleeding.

Table 2: Association of NSAID intake and adverse outcome

NSAID intake	Recovered	Recovered	Complicated	Complicated	Total
	Count	Percent	Count	Percent	
Yes	8	45.5	13	53.5	21
No	56	73.1	23	27.9	79
Total	64		36		100

X²=7.7423 P=0.0053

There was no statistical correlation was found between WBC count and adverse outcome (p=0.624) and even though 33% of the patients had thrombocytopenia, no significant relation was found between platelet count and adverse outcome (p=0.116). Regarding SGPT value and outcome, 40% peak SGPT values was within 2001-4000, 30% within 4001-8000, 15% within 1001-2000, 6% within 501-1000, 4% below <500 and 5% >8000 IU. Maximum value of SGPT observed was 12000 IU and minimum value was 420IU. No

significant correlation was found between SGPT value and adverse outcome. (p=0.347).

Intake of indigenous medication was found to be associated with adverse outcome and it was associated with development of cholestatic hepatitis. Out of 100 patients, 30 patients had taken indigenous medication for the treatment of hepatitis A. It was in powder and tablet form and content of the medication was not known. Among the patients who took indigenous medication 45% developed cholestatic hepatitis with significant statistical correlation (P<0.00054).

Table 3 Association of intake of indigenous medication and prolonged cholestasis

Indigenous medications	Cholestasis	Cholestasis	No Cholestasis	No Cholestasis
Yes	14	45	16	55
No	6	7.3	64	92.7
Total	20		80	

$\chi^2=11.956$ P is 0.00054

Out of 100 patients, 12 patients developed fulminant hepatic failure. Out of these 9 patients recovered and 3 patients expired. From the recovered patients, 8 patients had grade 1-2 hepatic encephalopathy.

Discussion

Acute hepatitis A is a most common viral infection found throughout the world and is spread principally via the oral fecal fashion. The clinical spectrum of acute hepatitis A virus (HAV) infection is varied and includes silent infection detected only by viral serologic testing, subclinical infection revealed by abnormal liver function tests, clinically apparent hepatitis, and rarely, fulminant hepatitis, which is associated with coma and occasionally death. While most infants and children have silent or subclinical infections, the majority of adults develop symptoms and signs of acute disease. Atypical manifestations such as relapse, cholestasis, rash, and arthralgia also have been described in patients with hepatitis A, but the pathophysiology of these phenomena has not been elucidated.

A hundred of patients with clinical and biochemical profile suggestive of acute viral hepatitis A and satisfying inclusion criteria were studied from February 2020 to July 2021. Of the 100 patients, 48% belonged to the 18-26 years age group, 42% belonged to the 26-34 years age group, 6% belonged to the 34-42 years age group and 4% belonged to the 52-60 years age group. Maximum age observed was 56 years and minimum age observed was 18 years with an average of 25.7 ± 7.2 years. So most of the patients were belonging to younger adult group (21-32 years) indicates that Gurdaspur is moderately prevalent for hepatitis A. This is the most active group of total populations and may be

related to life style habits like food intake from outside and also most of the older adults have serologically positive antibodies against hepatitis A, indicating that subclinical infections are common. In Koff et al⁷ study, surveys in many communities showed a high prevalence of antibodies to hepatitis A virus (HAV) in people over the age of 50 years. However, few of that age can recall a previous episode of hepatitis, indicating that subclinical infections are common. The outcome of infection with HAV depends on the age at which infection occurs and, perhaps, the infectious dose. HAV infection tends to be asymptomatic in children <5 years of age and imparts lifelong immunity. Thus, in high prevalence areas where most of the population is exposed at a very young age and develops immunity without symptoms, we expect to see fewer symptomatic cases. If exposure to infection occurs for the first time at older ages, patients are more likely to develop symptomatic disease. Our patients were mostly from low economic background but still turned out to be not immune to hepatitis A infection. Our study implies that hepatitis A still remains an important cause of acute viral hepatitis in adults, at least in Gurdaspur. In view of this, a recommendation for mass vaccination against hepatitis A needs to be considered and debated.

Of the 100 patients, 65% were males and 35% were females. This also may be related to difference in lifestyle habits among males and females like food intake from outside. Out of 100 patients 94% had documented fever and 6 % presented without fever. Of these 28 % of the patients had 1-3 days of fever, 52% had 4-6 days of fever , 14% had prolonged fever >6 days and 6 % had no fever. Maximum duration of fever observed was 14 days for 6 patients. Out of total

100 sample patients, 35% had continuing fever even after the onset of clinical jaundice. Thus hepatitis A may present as long duration fever.

Of the 100 patients 31 patients had significant nausea/vomiting and anorexia requiring anti-emetics and intravenous fluids. 44% had a definite history of contact in the form of clustering of cases, either in family members or in locality.⁸

A multicentre study conducted by Kwon, So Young et al.⁹ in Korea showed fever in 71.5% with an average duration of 5 ± 2 days. Out of 100 patients, 13% had definite history of alcohol intake at least once in a week, 22 patients had received NSAID prior to the admission and 25 had history of intake of indigenous medication.

Out of 100 patients, 28 patients had thrombocytopenia, 14 patients had arthralgia/arthritis, 5 patients had AKI, 3% patients had pancreatitis, 8 patients had rash, acute transverse myelitis and thrombocytosis for one patient each. Jung YM et al.¹⁰ study showed 4.7% pancreatitis and 1.5% AKI as atypical manifestations. Kwon SY, et al.⁹ study showed 17.8% of arthralgia, 4.4% skin rash and 2.7% of AKI as atypical manifestations.

Out of 100 patients, 78 patients had normal WBC count between 4000-11000 cells/mm³, 10 patients had low WBC count below 4000 cells/mm³ and 12 patients had high WBC count more than 11000 cells/mm³ with a mean value of 5604 ± 1809 . Kwon SY, et al.⁹ study showed mean WBC count of 5101 ± 2509 cells/mm³. 47% had platelet count >2 lakhs, 21% within 1.5-1.9 lakhs, 20% within 1-1.49 lakhs, 12% had platelet count below 1 lakh with a mean value of 1.89 ± 0.68 . Out of these 32 patients had thrombocytopenia (platelet count <1.5 lakh). Kwon SY, et al. study showed mean platelet value of 1.77 ± 0.84 .

Out of 100 patients, 6 patients had microscopic hematuria. Out of 100 patients, 53% had peak total bilirubin value <5 mg/dl, 34% belonging to 5.1-10 mg/dl, 5% 10.1-15mg/dl and 8% of patient's bilirubin was >15 mg/dl. Mean peak total bilirubin was 6.3 ± 2.8 . This was consistent with

mean peak total bilirubin value of Kwon SY, et al. study, which was 7.3 ± 5.3 .

Out of 100 patients, 40% peak SGPT values were within 2001-4000, 30% within 4001-8000, 15% within 1001-2000, 6% within 501-1000, 4% below <500 and 5% >8000 IU. Mean peak SGPT value was 2858 ± 812 , this was consistent with mean peak SGPT value of Kwon SY, et al. study, which was 2963 ± 542 .

Out of 100 patients 10% of the patients had hepatic encephalopathy, 5% of the patients had symptomatic bleeding, 6% of the patients had ascites, 3% of the patients had pancreatitis, 20% of patients had cholestatic hepatitis, 7% of patients developed AKI and one patient had transverse myelitis.

Out of these 3 patients expired. 64% of the patients recovered without any complications, 33% had at least one complication. Korean study by Kwon SY, et al. showed 0.47% of mortality and 1.92% of cholestatic hepatitis and 0.91% fulminant hepatic failure. In our study all complications rate and mortality are high, may be because being a tertiary care centre most of the complicated cases are referred from periphery.

As age advances, the rate of complications are not increasing in our study and Chi square test shows that age and adverse outcome is not statistically significant ($p=0.295$). This is probably due to the decreased sample size. In the observation made by Acharya S K et al.¹³ 83.2% mortality is seen in patients above 40 yrs. The prognosis of hepatitis A is dependent on the age of patient. Young children less than 5 yr are usually asymptomatic, while most elder children and adults develop symptoms with jaundice and high levels of serum aminotransferase¹¹. Recent studies revealed the seroprevalence of anti-HAV is less than 50% in adult population of 20 yr to 40 yr.¹² In this study, the median age of the patients was 25.7 ± 7.2 , and substantial numbers of patients were below 40 yr. We compared the severity of hepatitis between the groups of the patients younger and older than 40 yr. The clinical manifestations including complications and laboratory data showed that the

clinical course in terms of hepatic dysfunction and renal complication was worse in the group of the patients between 25-33 years. These epidemiologic and clinical results suggest that the change of epidemiologic pattern of hepatitis A in our population may lead to increase the disease burden and increase in healthcare cost.

Presence of alcoholism and bad outcome is closely related. Among alcoholic patients 66.2% had at least one complication with a statistically significant P value of 0.0033. Most common complication noted was fulminant hepatic failure followed by acute pancreatitis.

NSAID intake also had a significant relation with adverse outcome (p 0.0053) and among patients who took NSAID 53.5% had complications compared to non NSAID group, who had a complication rate of 27.9%. Most common complication noted in NSAID group was fulminant hepatic failure with symptomatic bleeding.

35 % of the patients had abnormal coagulation profile in the form of PT with INR >1.5. Of these 5% patients had symptomatic bleeding in the form of gastrointestinal and cutaneous bleeding manifestations. As the PT INR value increases, the rate of complications and adverse outcome also increases (P= 0.009). There was no statistical correlation was found between WBC count and adverse outcome (P=0.624) and even though 28 % of the patients had thrombocytopenia, no significant relation was found between platelet count and adverse outcome (P=0.116).

Regarding SGPT value and outcome, 40% peak SGPT values was within 2001-4000, 30% within 4001-8000, 15% within 1001-2000, 6% within 501-1000, 4% below <500 and 5% >8000 IU. Maximum value of SGPT observed was 12000 IU and minimum value was 420 IU. No significant correlation was found between SGPT value and adverse outcome (P=0.347).

Intake of indigenous medication was found to be associated with adverse outcome and it was associated with development of cholestatic hepatitis. Out of 100 patients, 30 had taken

indigenous medication for the treatment of hepatitis A. It was in powder and tablet form and content of the medication was not known. Among the patients who took indigenous medication 45% developed cholestatic hepatitis with significant statistical correlation (P value 0.00054).

Out of 100 patients, 12 patients developed fulminant hepatic failure. Out of these 9 patients recovered and 3 patients expired. From recovered patients, 8 patients had grade 1-2 hepatic encephalopathy and one patient had grade 3 hepatic encephalopathy. Advanced stage of hepatic encephalopathy at the time of presentation carries worse prognosis. Reason for high incidence of fulminant hepatic failure following acute hepatitis A in this study is not clear or it may be due to high prevalence of hepatitis A in our population.

All patients who developed fulminant hepatic failure treated with early initiation of broad spectrum antibiotics, bowel sterilization, prophylactic fresh frozen plasma transfusion and branched chain amino acid therapy.

Conclusions

- 1) More than 50% of the patients were belonging to younger age group, indicating that Gurdaspur is moderately endemic for hepatitis A.
- 2) Symptomatic hepatitis A in adulthood occurs frequently in Gurdaspur, and the changing epidemiologic pattern of the disease may increase disease severity and incidence of complications.
- 3) Hepatitis A may rarely present as long duration fever.
- 4) Atypical manifestations are rather common in Hepatitis A (most common being thrombocytopenia).
- 5) Prior NSAID & alcohol intake is associated with adverse outcome.
- 6) Use of indigenous medication is strongly correlating with development of cholestatic hepatitis.

- 7) Reduced liver span & INR value has significant association with adverse outcome.
- 8) There is increased risk of complications with high peak bilirubin level.
- 9) There is no significant correlation between incidence of complications and SGPT level.

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