# Atypical Presentation of Hepatitis A in Children

Irum Aslam[1], Sundus Irshad[1], Muhammad Abu Talib[1], Ghazi Khosa[1], Aslam Sheikh[1] and Nagina Shahzadi[2]

[1]*Department of Paediatric Gastroenterology, Hepatology and Nutrition, The Children's Hospital and the Institute of Child Health, Multan, Pakistan*

[2]*Department of Paediatric Gastroenterology, Hepatology and Nutrition, The Children's Hospital and the Institute of Child Health, Faisalabad, Pakistan*

## ABSTRACT

**Objective:** To determine the frequency of atypical presentation of hepatitis A virus (HAV) infection in children.

**Study Design:** A cross-sectional study.

**Place and Duration of the Study:** Department of Paediatric Gastroenterology, Hepatology and Nutrition, The Children's Hospital and the Institute of Child Health, Multan, Pakistan, from November 2023 to April 2024.

**Methodology:** Children of either gender, aged 1-18 years, who visited the outpatients or emergency department, and were diagnosed with HAV infection were included in the study. HAV infection was diagnosed based on clinical and laboratory findings. Atypical manifestations of HAV were also documented. The Chi-square test for categorical data and the Independent sample t-test or Mann-Whitney U test for the comparison of quantitative variables were applied, considering $p < 0.05$ as statistically significant.

**Results:** In a total of 246 children, 144 (58.5%) were boys. The mean age was 6.52 ± 4.25 years. Atypical presentation of HAV infection was recorded in 60 (24.4%) children. The most frequent atypical presentations were ascites, pleural effusion, thrombocytopenia, and cholestasis, noted in 21 (35.0%), 16 (26.7%), 13 (21.7%), and 9 (15.0%) children, respectively. A relatively younger age was found to have a significant association with atypical presentation of HAV ($p = 0.014$). When compared to children with typical HAV manifestations, children with atypical manifestations had significantly less serum bilirubin ($p < 0.001$), higher INR ($p < 0.001$), and lower haemoglobin ($p = 0.004$).

**Conclusion:** Atypical manifestations of HAV are common among children, with ascites, pleural effusion, thrombocytopenia, and cholestasis being the most frequent occurrences. A relatively younger age was significantly associated with atypical HAV manifestations. Distinct laboratory parameters were observed among children with atypical manifestations of HAV.

**Key Words:** *Ascites, Cholestasis, Hepatitis A virus, Pleural effusion, Thrombocytopenia*.

**How to cite this article:** Aslam I, Irshad S, Talib MA, Khosa G, Sheikh A, Shahzadi N. Atypical Presentation of Hepatitis A in Children. *J Coll Physicians Surg Pak* 2025; **35(11)**:1424-1428.

## INTRODUCTION

Hepatitis A is an acute, self-limiting liver infection that was first identified in 1973 and remains one of the most prevalent types of acute viral hepatitis worldwide.[1,2] Despite the availability of an effective vaccine, hepatitis A virus (HAV) continues to be a major cause of acute viral hepatitis. According to the World Health Organization, more than 100 million infections of HAV occur annually, causing approximately 1.5 million clinical cases.[3] The causative virus is primarily associated with poor hygiene and is transmitted through the faecal-oral route, making it most common in developing regions such as Africa, Central and South America, and Southeast Asia.[4,5]

*Correspondence to: Dr. Irum Aslam, Department of Paediatric Gastroenterology, Hepatology and Nutrition, The Children's Hospital and the Institute of Child Health, Multan, Pakistan*
*E-mail: irum.aslam18@gmail.com*

*Received: November 16, 2024; Revised: February 05, 2025; Accepted: October 29, 2025*
*DOI: https://doi.org/10.29271/jcpsp.2025.11.1424*

Regional data report high endemicity for HAV infection, with most children under the age of six years exposed to HAV.[6] Over 90% of children contract HAV by the age of ten years. While HAV is asymptomatic in about 70% of those under six, it may cause significant morbidity in adolescents and adults, presenting with jaundice in 40–70% of cases.[6]

Environmental, social, and economic factors contribute to geographical variations in the distribution of HAV.[7] The infection is typically asymptomatic, and cases of fulminant hepatitis are relatively rare.[8,9] Only 4-16% of infected children exhibit symptoms, compared to 75-95% of adults.[10,11] Atypical manifestations of HAV may include prolonged cholestasis, extra-hepatic symptoms, and recurrent hepatitis. Data exhibit that about 20% of children with HAV report atypical presentation, with ascites, hepatic encephalopathy, and acute liver failure being the most frequent manifestations.[12]

This study aimed to go beyond documenting known atypical presentations by assessing their frequency and clinical spectrum in a specific high-burden region. Although atypical manifestations have been described in the literature, their frequency, impact, and diagnostic challenges in South Punjab remain underexplored. Identifying and knowing these atypical

presentations can prevent misdiagnosis, delayed treatment, unnecessary interventions, increased morbidity, and avoidable healthcare expenditure, while preventing disease spread in the population. Therefore, this research aimed to determine the frequency of atypical presentation of HAV infection in children visiting the tertiary childcare facility of South Punjab, Pakistan.

## METHODOLOGY

This cross-sectional study was performed in the Department of Paediatric Gastroenterology, Hepatology and Nutrition, the Children's Hospital and the Institute of Child Health, Multan, Pakistan, from November 2023 to April 2024. The study was approved by the Institutional Ethical Committee of the Children's Hospital and the Institute of Child Health, Multan, Pakistan (Letter No. 2007; dated: 12-10-2023). The sample size of 246 children was calculated, taking the anticipated prevalence of HAV as 20%,[12] with 95% confidence interval (CI) and 5% margin of error. Non-probability consecutive sampling technique was used. Children of either gender, aged 1-18 years, who presented to the OPD or emergency department and were diagnosed with HAV infection were included. HAV infection was diagnosed based on acute onset of clinical symptoms (*e.g.*, fever, anorexia, nausea, vomiting, abdominal pain, dark urine, and/or jaundice), supported by relevant laboratory investigations and positive serum anti-HAV IgM. Children presenting with a symptom duration of less than eight weeks at initial evaluation were considered for the diagnosis of acute HAV, while cases with prolonged or recurrent symptoms were further evaluated to distinguish chronic cholestasis of HAV and recurrent hepatitis from underlying chronic liver disease (CLD). Exclusion of CLD was based on a prior history of liver dysfunction, clinical signs suggestive of chronicity (*e.g.*, hepatosplenomegaly, ascites), persistent abnormal liver function tests (LFTs) beyond six months, and ultrasound findings showing cirrhosis or portal hypertension. Patients with persistent symptoms lasting more than 8 weeks were also evaluated for evidence of prior HAV infection, confirmed by positive anti-HAV IgM test within the last twelve weeks of presentation, to identify the atypical manifestations of HAV infection such as prolonged cholestasis and recurrent hepatitis A. Patients with a confirmed prior HAV diagnosis and a consistent clinical course were classified as having atypical presentations of HAV, including prolonged cholestasis or recurrent hepatitis. Children were also included if they had been diagnosed with acute HAV infection as per the inclusion criteria and subsequently developed symptoms of cholestasis persisting for at least 12 weeks, with no prior clinical or laboratory evidence of CLD, no current stigmata of CLD (other than overlapping ones), and exclusion of other common causes of CLD by investigations such as hepatitis B, hepatitis C, Wilson's disease, or autoimmune hepatitis. Similarly, patients diagnosed with acute HAV who had recurrence of symptoms within a total follow-up period of 12 weeks during the study were also included. Informed written consent was obtained from the parents or caregivers of all children.

Upon enrolment, data including age, gender, residence, and clinical symptoms were collected. LFTs, including alanine transaminase (ALT), aspartate aminotransferase (AST), and bilirubin levels, were conducted in all cases to assess hepatic involvement. Recurrent hepatitis was defined as the reappearance of acute hepatitis symptoms, along with a renewed elevation of ALT or AST levels occurring at least 4 weeks after the initial clinical and biochemical recovery from a documented episode of HAV infection. This was identified either through prospective follow-up (for patients enrolled between November 2023 and January 2024) or through retrospective chart review and referral records (for patients enrolled from February to April 2024). Only cases with documented prior improvement followed by relapse within the study timeframe were included. No cases were followed beyond April 2024. Hepatic encephalopathy was diagnosed based on altered mental status, confusion, or coma occurring within eight weeks of symptom onset, suggestive of acute viral hepatitis. Acute liver failure was defined as coagulopathy, indicated by an INR of 1.5 or greater, that is unresponsive to vitamin K supplementation and often accompanied by hepatic ence-phalopathy. In some cases, an INR of 2.0 or greater, regardless of the presence of encephalopathy, was also considered diagnostic. Prolonged cholestasis was defined as a peak serum bilirubin level greater than 10mg/dL (with direct bilirubin higher than 50% of the total bilirubin) and hyperbilirubinaemia or jaundice lasting for more than 12 weeks in the absence of haemolysis and renal failure, with ALT levels below 500U/L.[13]

Atypical manifestations of HAV were the occurrence of prolonged cholestatic hepatitis, recurrent hepatitis, or complications such as hepatic encephalopathy and acute liver failure. Other atypical features included thrombocytopenia (platelet count <150,000/µL), leucopaenia (WBC count <4,000/µL), and extrahepatic manifestations such as rash (non-specific, transient, and erythematous skin eruption), pleural or pericardial effusion, acute reactive arthritis, and neurological symptoms.

Although features such as coagulopathy, hepatic encephalopathy, acute liver failure, thrombocytopenia, or leucopaenia are recognised as complications of HAV in the literature, these were recorded at initial presentation and thus categorised as clinical presentations in this study context. While the study was cross-sectional, atypical cases—such as prolonged cholestatic hepatitis or recurrent hepatitis—were identified through prospective follow-up for patients enrolled between November 2023 and January 2024, and through retrospective review of clinical records for patients presenting from February to April 2024. Only those with a documented clinical course of at least 8–12 weeks prior to presentation were classified as having atypical features. No patient was followed beyond April 2024. Ultrasound examinations ruled out cirrhosis or fibrosis, while LFTs confirmed persistent cholestasis without progression to chronic liver impairment.

**Table I: Comparison of typical and atypical presentation of HAV infection with respect to characteristics of children (n = 246).**

| Characteristics | | Presentation | | p-values |
|---|---|---|---|---|
| | | Typical (n = 186) | Atypical (n = 60) | |
| Gender | Boys | 113 (60.8%) | 31 (51.7%) | 0.214 |
| | Girls | 73 (39.2%) | 29 (48.3%) | |
| Age (years) | 1-5 | 83 (47.5%) | 39 (65.0%) | 0.014 |
| | >5-12 | 65 (34.9%) | 16 (26.7%) | |
| | >12-18 | 38 (20.4%) | 5 (8.3%) | |
| Residence | Rural | 119 (64.0%) | 32 (53.3%) | 0.141 |
| | Urban | 67 (36.0%) | 28 (46.7%) | |

*The Chi-square test was applied.*

**Table II: Comparison of laboratory parameters with respect to atypical and typical manifestations of HAV infection (n = 246).**

| Laboratory measures | Typical (n = 186) | Atypical (n = 60) | p-values |
|---|---|---|---|
| ALT (IU/L) | 657.0 (427.0-952.0) | 684.0 (452.0-850.0) | 0.761 |
| Total bilirubin (mg/dl) | 13.2 (7.4-14.9) | 8.2 (4.8-12.2) | <0.001 |
| International normalised ratio (SD) | 1.6 (1.1-2.0) | 2.02 (1.2-2.6) | <0.001 |
| Haemoglobin (g/dl) | 12.2 (11.8-13.1) | 12.1 (10.2-11.9) | 0.004 |

*Values are given in median and interquartile range. The Mann-Whitney U test was applied.*

For data analysis, IBM SPSS, Statistics version 26.0, was used. Data following a normal distribution were presented as mean ± SD, while data with a skewed distribution were presented as median (IQR). The normality of the data distribution was assessed using the Shapiro-Wilk test. Categorical data were expressed as frequencies and percentages. Further analysis was performed to assess the association of age, gender, and residential status with the frequency of atypical presentation. The Chi-square test was applied for categorical data, while the independent sample t-test or Mann-Whitney U test was used for the comparison of quantitative variables. A p-value of <0.05 was considered statistically significant.

## RESULTS

Among a total of 246 children, 144 (58.5%) were boys, representing a boy-to-girl ratio of 1.4:1. The mean age was 6.52 ± 4.25 years, ranging between 1 and 16 years. The residential status of 151 (61.4%) children was rural. Atypical presentations of HAV infection were noted in 60 (24.4%) children. The most frequent atypical presentations were ascites (21, 35%), pleural effusion (16, 26.7%), thrombocytopenia (13, 21.7%), and cholestasis (9, 15%. Jaundice, hepatomegaly, fever, and abdominal pain were the most frequent typical presentations of HAV infection, noted in 175 (94.1%), 134 (72.0%), 104 (55.9%), and 81 (43.5%) children, respectively. Figure 1 and 2 are showing the frequency of atypical and typical manifestations of HAV infection in the studied children.

A relatively younger age was found to have a significant association with atypical presentation of HAV infection, as 65% children with atypical presentation were aged 1-5 years compared to 47.5% with typical presentation (p = 0.014). Gender and residential status did not show any statistically significant association with the presentation of HAV infection (Table I).

When compared to children with typical manifestations of HAV infection, children with atypical manifestations had significantly less serum bilirubin (p <0.001), higher INR (p <0.001), and lower haemoglobin (p = 0.004), as shown in Table II.

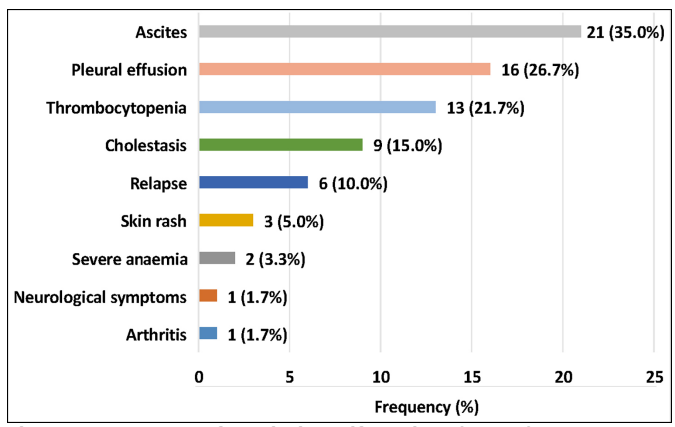


**Figure 1: Frequency of atypical manifestations (n = 60).**

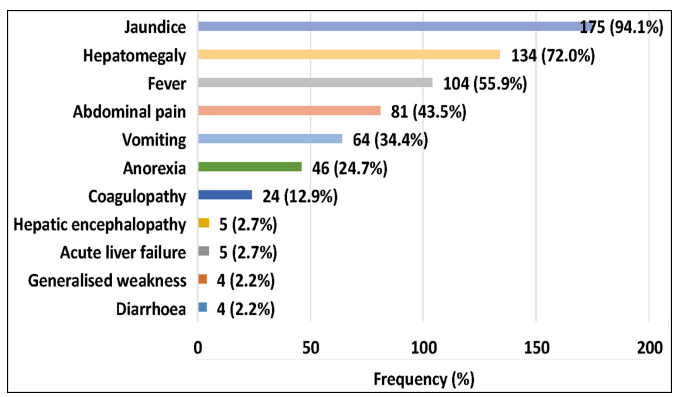


**Figure 2: Frequency of typical manifestations of HAV infection in children (n = 186).**

## DISCUSSION

The study evaluating atypical presentations of HAV infection in children was conducted to better comprehend deviations from the typical clinical course. Atypical manifestations of HAV were

present in 24.4% children. The most frequent atypical presentations were ascites (35.0%), pleural effusion (26.7%), thrombocytopenia (21.7%), and cholestasis (15%). Present findings, showing atypical manifestations of HAV infection in 24.4% children, are slightly lower than reported in a local study by Cheema *et al*. from Lahore, which found that 35.3% of children with HAV infection exhibited atypical manifestations.[14] The same study showed that ascites (20%), pleural effusion (15%), and thrombocytopenia (10%) were the most frequent findings, and these observations were consistent to the present study's findings. Samanta *et al*., analysing 229 children, reported that 15% of children with acute HAV had atypical features, contributing to increased morbidity.[15] Similarly, a study from India reported that 22% of children with HAV presented with atypical manifes-tations.[16] Other studies have also reported neurological, nephrological, and cardiovascular presentations of HAV; however, these were not clearly evident in this study.[17,18] The present study reported that thrombocytopenia was present in 21.7% cases of HAV infection. Immune thrombocytopenic purpura may present as the sole manifestation of acute HAV infection, without accompanying signs such as jaundice, vomiting, or abdominal pain.[19]

In this study, no significant association was found between gender and atypical presentation of HAV. This contrasts with the findings of Kalyoncu *et al*., who revealed that male children were significantly more affected by atypical presentation ($p = 0.03$).[20] The discrepancy may be due to differences in sample size, demographic factors, study design, or criteria used to defining atypical presentations. Kalyoncu *et al*. analysed only 22 children with HAV, which may not represent the full spectrum of the disease within a specific region. Regional healthcare practices and access could also impact observed gender associations, possibly explaining why Kalyoncu *et al*. found significance while the current study did not.[20]

The higher burden of atypical presentations in HAV observed in this research may be because of the fact that the study centre is a major tertiary childcare health facility of this region, and many of the cases are referred or have complications when they reach the healthcare facility. The exact mechanisms underlying atypical manifestations of HAV remain unclear; however, existing literature proposes that immune complex depositions are mainly responsible for these occurrences.[21,22] Investigating the burden of HAV in children, along with its potential complications and the diagnostic challenges associated with atypical presentations, aids in improving healthcare practices. Recognising variations in symptoms is crucial for accurate and timely diagnosis, thereby contributing to public health efforts and disease control. With the availability of vaccines, understanding atypical presentations—in vaccinated children—may help in evaluating vaccine efficacy.

This study demonstrated notable differences in laboratory parameters between children with typical and atypical manifestations of HAV. ALT levels did not differ significantly between the groups, indicating that hepatocellular injury is common to both forms of presentation. This finding is consistent with previous studies, such as those by Kalyoncu *et al*.[20] which emphasised that ALT is not a reliable discriminator for atypical courses. Total bilirubin levels were significantly higher in the typical group compared to atypical cases, which contrasts with the findings from a study in Bangladesh that showed markedly elevated bilirubin levels.[23] This difference may reflect variations in the spectrum of atypical presenta-tions across populations. Conversely, INR was significantly deranged in atypical cases, highlighting a higher frequency of coagulopathy and acute liver failure. This finding aligns with observations from Kalyoncu *et al*.,[20] who noted a strong association between atypical HAV and coagulation disturbances, reflecting more severe hepatic dysfunction and a higher risk of morbidity.

This study revealed that HAV infection is linked to various atypical manifestations, both hepatic and extrahepatic, affecting multiple organ systems. Clinicians should remain vigilant for these manifestations to ensure early diagnosis and appropriate management. All cases of HAV should be investigated for complications, with a specific focus on identifying atypical features. The findings emphasise that HAV-related severity and complications can affect younger children. This study adds valuable insights to the existing literature on atypical manifestations of HAV in children, especially as limited local work has explored this aspect. However, being a single-centre study with a relatively modest sample size, without data on clinical outcomes, were notable limitations of this study.

## CONCLUSION

Atypical manifestations of HAV are common among children, with ascites, pleural effusion, thrombocytopenia, and cholestasis being the most frequent occurrences. A relatively younger age was significantly associated with atypical manifestations. Distinct laboratory parameters were also observed among children with atypical HAV manifestations.

### ETHICAL APPROVAL:

The study was approved by the Institutional Ethical Committee of the Children's Hospital and the Institute of Child Health, Multan, Pakistan (Letter No. 2007; dated: 12-10-2023). The study was conducted in accordance with the Declaration of Helsinki.

### PATIENTS' CONSENT:

Informed consent was obtained from the patients to publish the data concerning this study.

### COMPETING INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

IA: Collected and arranged data, performed analysis, drafted

and revised the manuscript, and ensured data integrity.
SI, NS: Contributed to data synthesis, drafting, and proof-reading.
AT, GK, AS: Conceived and designed the study, proofread, and critically revised the manuscript.
All authors approved the final version of the manuscript to be published.

## REFERENCES


1. Feinstone SM, Kapikian AZ, Purceli RH. Hepatitis A: detection by immune electron microscopy of a virus like antigen associated with acute illness. *Science* 1973; **182(4116)**:1026-8. doi: 10.1126/science.182.4116.1026.
2. Castaneda D, Gonzalez AJ, Alomari M, Tandon K, Zervos XB. From hepatitis A to E: A critical review of viral hepatitis. *World J Gastroenterol* 2021; **27(16)**:1691-715. doi: 10.3748/wjg.v27.i16.1691.
3. Cao G, Jing W, Liu J, Liu M. The global trends and regional differences in incidence and mortality of hepatitis A from 1990 to 2019 and implications for its prevention. *Hepatol Int* 2021; **15(5)**:1068-82. doi: 10.1007/s12072-021-10232-4.
4. Feinstone SM. History of the discovery of hepatitis A virus. *Cold Spring Harb Perspect Med* 2019; **9(5)**:a031740. doi: 10.1101/cshperspect.a031740.
5. Franco E, Meleleo C, Serino L, Sorbara D, Zaratti L. Hepatitis A: Epidemiology and prevention in developing countries. *World J Hepatol* 2012; **4(3)**:68-73. doi: 10.4254/wjh.v4.i3.68.
6. Gholizadeh O, Akbarzadeh S, Ghazanfari HM, Gholami M, Amini P, Yekanipour Z, *et al*. Hepatitis A: Viral structure, classification, life cycle, clinical symptoms, diagnosis error, and vaccination. *Can J Infect Dis Med Microbiol* 2023; **2023**:4263309. doi: 10.1155/2023/4263309.
7. Migueres M, Lhomme S, Izopet J. Hepatitis A: Epidemiology, high-risk groups, prevention and research on antiviral treatment. *Viruses* 2021; **13(10)**:1900. doi: 10.3390/v13101900.
8. Abutaleb A, Kottilil S. Hepatitis A: Epidemiology, natural history, unusual clinical manifestations, and prevention. *Gastroenterol Clin North Am* 2020; **49(2)**:191-9. doi: 10.1016/j.gtc.2020.01.002.
9. Prasidthrathsint K, Stapleton JT. Laboratory diagnosis and monitoring of viral hepatitis. *Gastroenterol Clin North Am* 2019; **48(2)**:259-79. doi: 10.1016/j.gtc.2019.02.007.
10. Jeong SH, Lee HS. Hepatitis A: Clinical manifestations and management. *Intervirology* 2010; **53(1)**:15-9. doi: 10.1159/000252779.
11. Tong MJ, el-Farra NS, Grew MI. Clinical manifestations of hepatitis A: Recent experience in a community teaching hospital. *J Infect Dis* 1995; **171 Suppl 1**:S15-8. doi: 10.1093/infdis/171.supplement_1.s15.
12. Munmun SR, Yadav AS, Benzamin M, Karim ASMB, Rukunuzzaman M, Mazumder MW, *et al*. Atypical presentations of hepatitis A infection in children. *Paediatrica Indonesia* 2021; **61(6)**:317-21.
13. Jayappa M, Kumar P, Goyal JP. Prolonged cholestasis after acute viral hepatitis: successfully treated with oral steroid. *BMJ Case Rep* 2020; **13(5)**:e234430. doi: 10.1136/bcr-2020-234430.
14. Cheema HA, Fayyaz Z, Parkash A, Malik HS. Atypical presentations of hepatitis A in children presenting to the Children Hospital Lahore, Pakistan. *Infect Dis J* 2014; **23(3)**:709-13.
15. Samanta T, Das AK, Ganguly S. Profile of hepatitis A infection with atypical manifestations in children. *India J Gastroenterol* 2010; **29(1)**:31-3. doi: 10.1007/s12664-010-0006-3.
16. Singh SK, Borkar V, Srivastava A, Mathias A, Yachha SK, Poddar U. Need for recognizing atypical manifestations of childhood sporadic acute viral hepatitis warranting differences in management. *Eur J Pediatr* 2019; **178(1)**:61-7. doi: 10.1007/s00431-018-3262-3.
17. Baltadzhiev I, Geneva I, Popivanova N. Guillain-Barre syndrome in a child with ongoing viral hepatitis A. *Iran J Child Neurol* 2018; **12(3)**:133-8.
18. Allen O, Edhi A, Hafeez A, Halalau A. A very rare complication of hepatitis A infection: Acute myocarditis - a case report with literature review. *Case Rep Med* 2018; **2018**:3625139. doi: 10.1155/2018/3625139.
19. Tanir G, Aydemir C, Tuygun N, Yildirim I. Transient sinus bradycardia in a child during the course of acute hepatitis A. *Turk J Gastroenterol* 2007; **18(3)**:195-7.
20. Kalyoncu D, Nafiye U, Seda GG. Hepatitis A in children: Evaluation of atypical manifestations. *Paediatrica Indonesia* 2020; **60(5)**:239-43. doi: 10.14238/pi60.5.2020.239-43.
21. Wang M, Feng Z. Mechanisms of hepatocellular injury in hepatitis A. *Viruses* 2021; **13(5)**:861. doi: 10.3390/v13050861.
22. Walker CM. Adaptive immune responses in hepatitis A virus and hepatitis E virus infections. *Cold Spring Harb Perspect Med* 2019; **9(9)**:a033472. doi: 10.1101/cshperspect.a033472.
23. Alam R, Karim ASMB, Mazumder MW, Das SR, Benzamin M, Sonia ZF, *et al*. Atypical manifestations of acute viral hepatitis A in children in Bangladesh: Are these really uncommon? *Indian J Gastroenterol* 2021; **40(5)**:470-6. doi: 10.1007/s12664-021-01200-9.