

THE CLINICAL AND LABORATORY FEATURES OF ACUTE VIRAL HEPATITIS

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Abstract

Acute hepatitis A remains an important cause of acute viral hepatitis in Central Asia. Liver injury in hepatitis A is largely immune-mediated, so combined assessment of biochemical markers and inflammatory cytokines may help to describe severity.

In this single-centre sample, hepatocellular injury markers and IL-6 reflected the severity of hepatitis A far better than bilirubin, TNF- α , IL-1 β or routine haematological indices. These findings are hypothesis-generating and require confirmation in larger, independent cohorts.

Keywords: Acute viral hepatitis; hepatitis A; interleukin-6; TNF- α ; aminotransferases; disease severity; Karakalpakstan.

Introduction

Acute viral hepatitis is among the most relevant medical and social problems in infectious disease practice because of their wide distribution, the variability of their clinical course, the effect on liver function and, in a minority of patients, the development of severe complications. Hepatitis A virus (HAV) is a non-enveloped RNA virus of the family Picornaviridae that is transmitted mainly by the faecal–oral route. Liver damage in hepatitis A is thought to result less from direct cytopathic effects of the virus than from the host antiviral immune response and the associated inflammatory reaction, which largely determine the clinical and laboratory picture.

After the virus reaches the liver, Kupffer cells and tissue macrophages are activated. Their activation is accompanied by increased production of IL-1 β , which in turn enhances expression of pro-inflammatory cytokines such as TNF- α and IL-6. A marked rise in cytokine concentrations may impair hepatic microcirculation, increase vascular permeability, cause endothelial dysfunction and, through oxidative stress and lipid peroxidation, accelerate damage and apoptosis of hepatocytes.

In practice, severity is judged by standard biochemical markers: ALT and AST (hepatocellular cytolysis), total and direct bilirubin (cholestasis) and total protein and albumin (synthetic function). Interpreting these together with immunological parameters may give a more complete picture of the intensity of inflammation and of how aggressively the disease is progressing. Such combined analysis is of particular interest in the Aral Sea region of the Republic of Karakalpakstan, where environmental conditions, water supply and climate have specific features that may affect the epidemiology of faecal–oral infections, and where age structure, background comorbidity and the timing of first contact with medical services may influence the course of the disease.





The aim of this study was to describe the clinical and laboratory features of acute hepatitis A in patients with mild, moderate and severe disease and to evaluate the relationship between biochemical markers and serum cytokines (IL-6, TNF- α , IL-1 β) and disease severity.

Materials and Methods

This was a retrospective, single-centre, cross-sectional analysis of 90 patients with acute hepatitis A hospitalised in Republican Infectious diseases of children, Nukus, Republic of Karakalpakstan, Uzbekistan. Admission dates ranged from 13 December 2023 to 16 October 2025. Diagnosis was confirmed by a positive anti-HAV IgM test; all patients were negative for HBsAg and anti-HCV. Patients were assigned by the treating physicians to three groups of 30 according to disease severity: mild (group 1), moderate (group 2) and severe (group 3).

Recorded variables were age, sex, body mass index (BMI), day of illness at first examination, length of hospital stay, comorbidities, epidemiological contact with a known case, symptoms (weakness, malaise, right upper quadrant pain, nausea, vomiting, dyspepsia, loss of appetite, weight loss, dark urine, jaundice of skin and sclera, pale stools, rash), liver enlargement (cm below the costal margin), body temperature, pulse rate and respiratory rate, and outcome at discharge. For liver enlargement reported as a range, the midpoint was used; “normal” was coded as 0 cm.

Biochemical tests (total protein, glucose, urea, creatinine, total, direct and indirect bilirubin, ALT, AST) and haematological tests (haemoglobin, erythrocytes, colour index, leukocytes, segmented and band neutrophils, lymphocytes, ESR) were performed on. Serum IL-6, TNF- α and IL-1 β were measured by enzyme-linked immunosorbent assay using and are reported in pg/mL.

Normality was assessed with the Shapiro–Wilk test; most variables departed from normality, so data are presented as median. Three groups were compared with the Kruskal–Wallis test; where significant, pairwise comparisons used the Mann–Whitney U test with Bonferroni adjustment (three comparisons). Categorical variables were compared with the chi-square test. Associations were assessed with Spearman’s rank correlation coefficient (ρ). The discriminative ability of selected markers for severe versus non-severe disease was explored with the area under the ROC curve (AUC). Missing values (pulse and respiratory rate, $n = 2$ each; creatinine, colour index and band neutrophils, $n = 1$ each) were excluded pairwise. One patient had a discharge date earlier than the admission date, so that patient was excluded from the length-of-stay analysis only ($n = 29$ in group 3). A two-sided $p < 0.05$ was considered significant. Analyses were performed in Python (SciPy).

Results

The study included 90 patients (43 male, 47 female; median age 13 years [11.25; 15], range 9–34 years; 13 patients were aged 18 years or older). Of these, 84 lived in the city of Nukus. The proportion of male patients increased with severity (33.3%, 50.0% and 60.0% in groups 1–3, respectively), but the difference was not significant ($p = 0.113$). Age, BMI, day of illness at first examination, length of hospital stay, frequency of anaemia as a comorbid condition and epidemiological contact with a known case did not differ significantly between groups (Table 1). All patients improved by the time of discharge; there were no deaths.



Table 1. Baseline characteristics of patients by disease severity

Characteristic	Mild (n = 30)	Moderate (n = 30)	Severe (n = 30)	p
Age, years	14 [13; 16]	12.5 [11; 15]	14 [11; 15]	0.098
Male sex, n (%)	10 (33.3)	15 (50.0)	18 (60.0)	0.113
BMI, kg/m ²	22.0 [20.2; 23.6]	21.1 [19.1; 24.5]	21.3 [18.6; 24.0]	0.743
Day of illness at first examination	3 [3; 4.75]	4 [3; 6]	3 [3; 4]	0.338
Hospital stay, days	13.5 [11; 16.75]	13 [11.25; 14]	15 [13; 16]*	0.145
Anaemia as comorbidity, n (%)	21 (70.0)	22 (73.3)	25 (83.3)	0.457
Contact with a known case, n (%)	6 (20.0)	6 (20.0)	4 (13.3)	0.738

Clinical features

All 90 patients presented with general weakness, malaise, right upper quadrant pain, nausea, vomiting, dyspepsia, loss of appetite, weight loss, dark urine, jaundice of the skin and sclera and pale stools; no patient had a rash. Because these symptoms were present in every patient, they did not discriminate between severity groups. Liver enlargement was similar across groups (median 2.25 cm [2.25; 2.44], 2.25 cm [2.06; 2.44] and 2.25 cm [2.25; 2.75]; $p = 0.413$). Body temperature remained around normal values in all groups (median 36.6 °C; maximum 37.5 °C; $p = 0.568$), and pulse rate (median 100/min) and respiratory rate (median 19/min) did not differ ($p = 0.466$ and $p = 0.292$).

Biochemical parameters

Aminotransferase activity rose stepwise with severity (Table 2). Median ALT was 295 U/L in mild, 664 U/L in moderate and 868 U/L in severe hepatitis ($H = 72.9$; $p < 0.001$), and median AST was 98.5, 200 and 380 U/L ($H = 63.8$; $p < 0.001$); all pairwise differences were significant after adjustment ($p < 0.001$). Total bilirubin (40.0, 50.0 and 52.0 $\mu\text{mol/L}$; $p = 0.049$) and direct bilirubin (21.9, 30.0 and 31.0 $\mu\text{mol/L}$; $p = 0.048$) showed borderline overall differences, with no significant pairwise differences after Bonferroni correction. Indirect bilirubin, total protein, urea and creatinine did not differ between groups. Glucose differed marginally ($p = 0.016$), driven by a higher value in the moderate than in the mild group (adjusted $p = 0.028$); all medians were within 4.1–4.35 mmol/L.

Table 2. Biochemical parameters and cytokines by disease severity

Parameter	Mild (n = 30)	Moderate (n = 30)	Severe (n = 30)	p
ALT, U/L	295 [223; 351]	664 [563; 760]	868 [803; 947]	< 0.001
AST, U/L	98.5 [50; 145]	200 [153; 223]	380 [309; 422]	< 0.001
Total bilirubin, $\mu\text{mol/L}$	40.0 [23.3; 59.3]	50.0 [40.0; 69.5]	52.0 [38.7; 69.8]	0.049
Direct bilirubin, $\mu\text{mol/L}$	21.9 [14.5; 38.0]	30.0 [26.3; 40.2]	31.0 [23.0; 51.5]	0.048
Indirect bilirubin, $\mu\text{mol/L}$	16.0 [11.5; 22.3]	20.0 [15.2; 24.3]	20.0 [15.1; 24.0]	0.274
Total protein, g/L	60 [57; 64.8]	58.5 [57.3; 60.8]	60 [57; 64]	0.715
Glucose, mmol/L	4.10 [3.63; 4.30]	4.35 [4.13; 4.50]	4.15 [3.70; 4.30]	0.016
Urea, mmol/L	4.3 [3.6; 5.0]	4.4 [3.7; 5.0]	4.25 [3.8; 4.6]	0.929

Parameter	Mild (n = 30)	Moderate (n = 30)	Severe (n = 30)	p
Creatinine, $\mu\text{mol/L}$	54.0 [50; 58]	54.1 [48.3; 60]	56.0 [49; 60]	0.983
IL-6, pg/mL	7.65 [7.17; 8.17]	9.25 [9.03; 9.90]	16.6 [12.8; 18.7]	< 0.001
TNF- α , pg/mL	6.35 [2.40; 8.20]	6.30 [4.38; 8.70]	9.65 [5.13; 11.28]	0.013
IL-1 β , pg/mL	12.4 [11.2; 13.8]	12.45 [11.5; 16.7]	12.95 [11.65; 14.1]	0.639

Haemoglobin was reduced in all groups (median 100 g/L in groups 1 and 2 and 102 g/L in group 3) without differences between groups ($p = 0.773$). Erythrocyte count, colour index, leukocytes, segmented and band neutrophils and ESR also did not differ (Table 3). The relative lymphocyte count differed between groups ($p = 0.005$), with a lower value in the severe than in the moderate group (34% vs 36%; adjusted $p = 0.006$); the absolute difference was small.

Table 3. Haematological parameters by disease severity

Parameter	Mild (n = 30)	Moderate (n = 30)	Severe (n = 30)	p
Haemoglobin, g/L	100 [96; 108]	100 [96; 108]	102 [96; 108]	0.773
Erythrocytes, $\times 10^{12}/\text{L}$	3.0 [3.0; 3.3]	3.0 [2.9; 3.15]	3.0 [3.0; 3.0]	0.574
Leukocytes, $\times 10^9/\text{L}$	5.65 [4.95; 6.20]	5.75 [5.05; 6.65]	5.80 [4.65; 6.30]	0.855
Segmented neutrophils, %	63 [61; 65.5]	62 [60; 63]	63 [61; 65]	0.177
Band neutrophils, %	1 [1; 2]	1 [1; 2]	1 [1; 2]	0.516
Lymphocytes, %	35 [32; 37]	36 [36; 38]	34 [31; 35.8]	0.005
ESR, mm/h	9.5 [7.25; 13]	8 [8; 10]	8 [6.25; 10]	0.431

Across all 90 patients, the severity grade correlated very strongly with IL-6 ($\rho = 0.94$; $p < 0.001$), strongly with ALT ($\rho = 0.90$) and AST ($\rho = 0.84$), and only weakly with TNF- α ($\rho = 0.31$; $p = 0.003$), total bilirubin ($\rho = 0.22$; $p = 0.036$) and direct bilirubin ($\rho = 0.23$; $p = 0.031$). IL-6 correlated strongly with ALT ($\rho = 0.88$) and AST ($\rho = 0.81$; both $p < 0.001$) and weakly with total and direct bilirubin ($\rho = 0.21$; $p = 0.048$ and $p = 0.045$). TNF- α correlated weakly with ALT ($\rho = 0.29$; $p = 0.005$) and AST ($\rho = 0.32$; $p = 0.002$) and not with bilirubin. IL-1 β was not significantly correlated with any liver parameter (ALT $\rho = 0.09$, AST $\rho = 0.17$). IL-6 and TNF- α were moderately correlated with each other ($\rho = 0.34$). These pooled correlations partly reflect the differences between the severity groups.

For the distinction of severe from non-severe disease, the AUC was 1.00 for IL-6, 0.97 for AST, 0.96 for ALT, 0.67 for TNF- α , 0.58 for total bilirubin and 0.54 for IL-1 β . In this sample, IL-6 ranged from 5.9 to 8.6 pg/mL in the mild group, 8.6 to 11.3 pg/mL in the moderate group and 11.4 to 30.8 pg/mL in the severe group, i.e. the ranges did not overlap between severe and non-severe patients. Such perfect separation is unusual and should be interpreted with caution (see Limitations).

Conclusions

1. In acute hepatitis A, ALT, AST and serum IL-6 increased stepwise with disease severity, and IL-6 correlated strongly with aminotransferase activity.
2. Bilirubin, TNF- α , IL-1 β , protein, renal and routine haematological parameters differed little or not at all between severity groups.



3. Combined assessment of aminotransferases and IL-6 may help to characterise the intensity of the inflammatory process in hepatitis A, but the findings require prospective validation in larger independent cohorts before use in clinical decision-making.

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