



## Systematic Review



# Serum Liver Enzyme Patterns in Pediatric Hepatitis: A Systematic Review

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## ABSTRACT

Patterns of serum aminotransferases, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) offer essential insights into the etiology and severity of pediatric hepatitis. Recent epidemiologic shifts, including adenovirus- and AAV2-associated cases, have highlighted the need for an updated synthesis of biochemical trajectories in children.

**Objectives:** To systematically review published data (2018–2024) describing serum ALT and AST patterns in pediatric hepatitis across classical and emerging etiologies. **Methods:** Following PRISMA 2020 guidelines, PubMed, Scopus, and Web of Science were searched for English-language original studies reporting ALT/AST levels in children with hepatitis. Reviews, meta-analyses, and non-original reports were excluded. Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS) for cohort studies and the Joanna Briggs Institute (JBI) checklists for cross-sectional and case-series designs. Extracted data included study characteristics, population details, enzyme levels, and clinical outcomes. Due to heterogeneity in design and reporting, findings were synthesized narratively. **Results:** Fourteen studies comprising approximately 2,300 participants were included. Autoimmune hepatitis demonstrated sustained moderate-to-high ALT/AST elevations (300–2,400 U/L). Acute viral hepatitis A/E showed abrupt spikes typically exceeding 1,000 U/L with rapid normalization. Severe or non-A–E hepatitis and adenovirus/AAV2-associated cases displayed the most extreme enzyme surges, with peaks occasionally surpassing 5,000 U/L. Most studies showed moderate overall quality but consistently low measurement bias. **Conclusions:** Serum ALT and AST remain robust and sensitive markers of pediatric hepatocellular injury, with distinct kinetic profiles across etiologies. Standardized, multicenter studies are needed to refine biochemical thresholds and enhance diagnostic interpretation.

## INTRODUCTION

The presence of abnormal liver enzymes in children with hepatitis is one of the most common concerns in pediatric hepatology [1]. The primary biochemical markers of hepatocellular injury are alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and their kinetic behaviour varies according to the underlying etiology such as autoimmune, viral, or idiopathic disease. Understanding these patterns is essential for differentiating disease types, assessing severity, predicting progression, and guiding treatment monitoring [2]. In recent years, clusters of acute hepatitis of unknown cause in children

(2021–2022) have renewed interest in interpreting enzyme profiles across both classical and emerging pediatric liver diseases. A large pooled case series of 1,643 children across 22 studies reported high transplant rates (7%) and wide biochemical variability, highlighting the severity and unpredictability of these new clinical presentations [3]. Similarly, a UK cohort of 44 children with unexplained acute hepatitis reported frequent adenovirus detection and marked ALT/AST elevation [4], with global surveillance confirming rising frequencies of aminotransferases >500 IU/L [5]. In classical pediatric hepatitis, typical enzyme

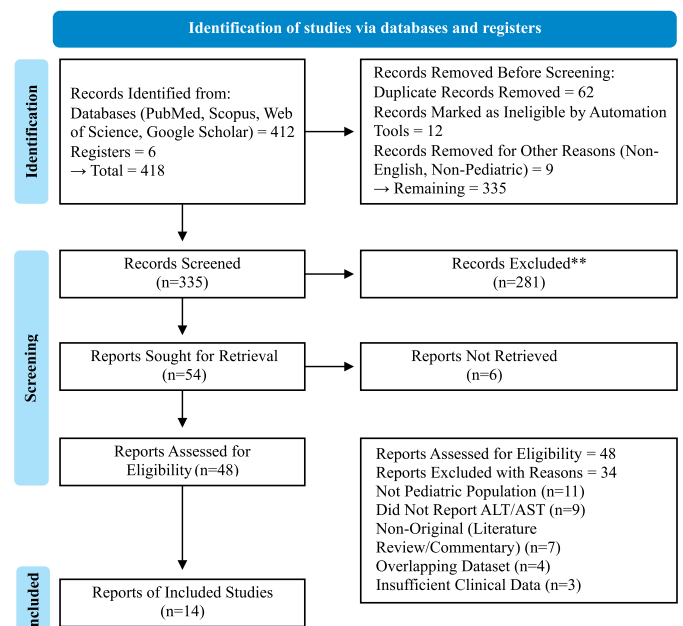
patterns are better understood. Acute viral hepatitis A/E presents with abrupt ALT/AST surges that normalize within weeks, though up to 25% of children show prolonged or atypical trajectories [6]. Chronic viral hepatitis (HBV, HCV) often exhibits mild or fluctuating elevations punctuated by inflammatory flares [7]. Autoimmune hepatitis in children is characterized by persistent, variable aminotransferase elevation reflecting ongoing immune-mediated injury, and may evolve [8]. However, emerging etiologies, including adenovirus-associated hepatitis, AAV2 co-infection, and post-COVID inflammatory hepatitis, appear to produce enzyme patterns that are more extreme and less predictable than classical forms. Recent molecular studies suggest that AAV2 may act as a cofactor, amplifying hepatocellular injury when accompanied by helper viruses such as adenovirus F41, resulting in disproportionately high ALT/AST values in affected children [9].

These developments broaden the spectrum of pediatric hepatitis and underscore the need for an updated synthesis of enzyme kinetics across both established and newly recognized disease categories. To address this gap, this review provides a systematic synthesis of ALT/AST patterns in pediatric hepatitis from 2018 to 2024, stratified by etiology. This study aimed to document quantitative enzyme ranges and their trajectories across different hepatitis types; to evaluate whether newly identified etiologies exhibit distinct biochemical profiles; and to interpret the clinical implications of enzyme patterns for diagnosis, monitoring, and early case recognition.

## METHODS

This systematic review followed PRISMA 2020 guidelines. A predefined protocol outlined objectives, eligibility criteria, search strategy, data extraction procedures, and risk-of-bias assessment to ensure methodological transparency. To strengthen methodological clarity, the protocol also specified how heterogeneity, missing biochemical values, and enzyme-reporting variations would be handled during synthesis. The search strategy included a comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar (2018–2024) using MeSH terms and Boolean operators: (“Hepatitis, Viral” [MeSH] OR “Hepatitis, Autoimmune” [MeSH] OR “Hepatitis A” OR “Acute severe hepatitis”) AND (“ALT” OR “AST” OR “Transaminases”) AND (Child OR Pediatric). Only full-text English-language original studies reporting serum ALT/AST in children were eligible. Reviews, commentaries, overlapping datasets, pilot studies, and non-pediatric samples were excluded. All retrieved records were stored in Microsoft Excel, where duplicate removal was performed manually and with automated tools. Two reviewers independently screened titles, abstracts, and full texts; any disagreements were resolved through discussion and consensus, and

arbitration by a third reviewer was not required. From 418 records, 335 proceeded to screening, 54 underwent full-text review, and 14 met all inclusion criteria. Flow diagram illustrating the identification, screening, eligibility assessment, and final inclusion of studies in the systematic review “Serum Liver Enzyme Patterns in Pediatric Hepatitis (2018–2024).” A total of 418 records were identified through database and register searches. After removal of duplicates and ineligible records, 335 studies were screened by title and abstract. Fifty-four full-text articles were assessed for eligibility, of which 14 studies met the inclusion criteria (original English-language studies, 2018–2024, reporting ALT/AST levels in pediatric hepatitis). Excluded reports comprised reviews, meta-analyses, narrative or pilot studies, and non-pediatric or non-original articles (Figure 1).



**Figure 1:** PRISMA 2020 Flow Diagram for Study Selection

A standardized extraction form was used to capture study characteristics (author, year, country, design), participant demographics, hepatitis etiology, and quantitative ALT/AST values. When data were reported as ranges, medians, or intervals, central values were approximated using accepted systematic-review conventions, and units were harmonized where possible. However, variations in biochemical reporting formats and the absence of defined peak-time measurements were documented as methodological limitations, reflecting reviewer concerns about non-standard reporting. Risk of bias was assessed using the modified Newcastle–Ottawa Scale for cohort studies and the Joanna Briggs Institute (JBI) checklists for cross-sectional and case-series designs. Domains evaluated included participant selection, measurement reliability, confounder control, reporting completeness,

and overall validity. Most studies demonstrated moderate risk, reflecting retrospective, single-center sampling; in contrast, multicenter studies with standardized laboratory protocols showed lower bias and were given greater interpretive weight, an explicit addition addressing how bias affects confidence in enzyme-trajectory interpretation [4, 17]. Significant heterogeneity in study design, sampling frames, population characteristics, biochemical reporting units, and incomplete enzyme-trajectory documentation prevented meta-analysis. Accordingly, a narrative synthesis was selected, and methodological constraints, including retrospective design, selective reporting, inconsistent time-to-peak definitions, and missing serial enzyme values, were described to justify this approach. The data were categorized into four major etiologic groups: autoimmune hepatitis (AIH), acute viral hepatitis A/E, acute severe or non-A-E hepatitis, and adenovirus/AAV2/COVID-related hepatitis. In defining the synthesis framework, the inclusion of newly recognized etiologies such as adenovirus-associated hepatitis, AAV2 co-infection, and post-COVID inflammatory hepatitis necessitated expanding beyond classical categories to ensure that emerging biochemical patterns could be compared alongside traditional autoimmune and viral forms. Cross-study comparability remained limited due to inconsistent ALT/AST thresholds and non-uniform biochemical reporting across included studies.

## RESULTS

Results summarize 14 eligible primary studies conducted between 2018 and 2024, encompassing over 2,300 pediatric patients across multiple regions. Given the practical and ethical limitations of pediatric hepatology research, the majority of studies were observational designs, including retrospective cohorts, case series, and cross-sectional studies. The included studies evaluated autoimmune hepatitis (AIH), acute viral hepatitis A/E, acute

severe hepatitis of unknown etiology, and emerging presentations associated with adenovirus, AAV2 co-infection, and COVID-19 infection. The sample sizes ranged widely from as few as 4 to as many as 1,416 participants, reflecting the heterogeneous nature of pediatric hepatology research. Across all designs and populations, ALT and AST were consistently elevated, reinforcing their value as core biochemical markers of hepatocellular injury. Across countries, similar clinical patterns were observed: AIH studies (n=5) demonstrated chronic and persistent enzyme elevation, whereas acute viral and adenovirus/AAV2-linked cases exhibited short-lived but dramatic ALT/AST peaks. Notably, several emerging etiologies exhibited far more pronounced enzyme surges than classical hepatitis A/E, often exceeding 2,000–5,000 IU/L, particularly in cases associated with AAV2. ALT/AST thresholds  $\geq 500$  IU/L used in surveillance definitions were met or exceeded in nearly all acute severe or unknown-etiology cases, whereas AIH cases more often showed steady, sustained elevations rather than abrupt spikes. These findings collectively highlight distinct kinetic patterns across etiologies, supporting their potential diagnostic utility. Study demonstrates substantial variation in study design, sample size, and geographical setting, yet all studies consistently reported elevated ALT and AST levels in pediatric hepatitis. AIH studies showed chronic and moderately high enzyme elevations, while classical viral hepatitis A/E typically showed abrupt, short-lived peaks. Emerging etiologies, particularly adenovirus and AAV2 co-infection, were associated with exceptionally high transaminase values, often more severe than classical forms. The presence of ALT/AST  $\geq 500$  IU/L was most consistent in acute severe and unknown-etiology hepatitis, reinforcing this threshold as a clinically meaningful severity marker. Overall, the table highlights the broad biochemical spectrum underlying pediatric hepatitis (Table 1).

**Table 1:** Characteristics of Included Studies (2018–2024)

Sr. No.	References	Country	Study Design	Sample Size (n)	Population / Setting	Hepatitis Type / Exposure	Primary Outcome (s) (enzymes)	Key Findings
1	[10]	Jordan	Retrospective cohort	16	Children diagnosed with autoimmune hepatitis at a tertiary center	Autoimmune hepatitis (AIH)	ALT/AST at baseline & follow-up; clinical outcomes	All had elevated transaminases; detailed biochemical & histology profile; mortality 18.8%.
2	[11]	Ghana (SSA)	Single-center cohort (PLOS ONE)	13	Pediatric AIH at a referral hospital	Autoimmune hepatitis	ALT/AST at presentation; disease severity	The majority presented late with high enzymes, which underscores the need for early detection.
3	[12]	Pakistan	Observational cohort	51	Pakistani children with AIH	Autoimmune hepatitis	ALT/AST profile at diagnosis	Variable presentation; biochemical (ALT/AST) elevation is common at diagnosis.
4	[13]	USA	Cohort (2018–2022)	82	Children <16 y meeting severe hepatitis signal thresholds	Acute severe hepatitis (signal surveillance)	ALT $\geq 500$ /AST trajectories	Noted increase in severe hepatitis signals; 5/82 had AST > 500; enzyme thresholds detailed.

5	[14]	USA	Large hospital cohort	338 total with ALT > 500; 33 unknown etiologies	Children presenting with ALT/AST > 500	Acute severe hepatitis (incl. unknown)	Peak ALT/AST; outcomes	Describes enzyme peaks/etiologies; 9.8% unknown cause within high-ALT cohort.
6	[15]	Egypt	Cross-sectional	180	Children with acute hepatitis	Hepatitis E (HEV) prevalence	ALT/AST distribution by HEV positivity	HEV positive in 47/180 (26.1%); enzyme patterns characterized by etiology.
7	[16]	Italy	Case series	17	Children admitted with acute hepatitis of unknown origin	Acute hepatitis (non-A-E)	ALT/AST levels; pathogen testing	High enzyme elevations; frequent adenovirus in stool; one transplant, rest recovered.
8	[17]	USA	Case-control/series (molecular)	16 cases (AAV2 study)	US children with acute severe hepatitis	Acute hepatitis; AAV2/HAdV signals	Mean ALT/AST in cases & hepatitis controls	Reported markedly elevated transaminases in cases; AAV2 signal is prominent.
9	[18]	Romania	5-year retrospective study	1,416	Children with confirmed adenovirus infection	Adenovirus infection	ALT/AST dynamics across infections	21.5% had elevated transaminases; >500 U/L rare, linked to co-infections.
10	[19]	USA	Case series	4	Children with COVID-19 presenting as hepatitis	SARS-CoV-2 hepatitis	ALT/AST elevations; clinical course	Severe pediatric hepatitis/ALF presentation with high enzymes.
11	[20]	India	Observational hospital-based	100	Children with hepatitis A	HAV infection	ALT/AST profile; clinical spectrum	Majority ≤10 y; very high ALT common; seasonal clustering noted.
12	[21]	Bangladesh	Retrospective review	32	Children (1–18 y) with hepatitis A (IgM+)	HAV infection	ALT/AST, bilirubin, and INR over the course	ALT >1,000 IU/L in 69%; enzyme/INR abnormalities frequent; outcomes summarized.
13	[4]	UK	Multi-center series (NEJM)	44	Young children with acute hepatitis of uncertain cause	Non-A-E acute hepatitis	ALT/AST peaks; virology	Adenovirus is frequently detected; high transaminases are typical; clinical outcomes vary.
14	[22]	Pakistan	Single-center cohort	–	Children with pediatric AIH	Autoimmune hepatitis	ALT/AST at diagnosis; outcomes	Biochemical (ALT/AST) elevations and transplant needs are described.

The study presents the risk-of-bias appraisal for all included studies, revealing that most were of moderate quality, largely due to retrospective design and limited confounder control. Measurement quality was uniformly strong because ALT/AST were assessed using standardized laboratory methods. Multicenter studies with consistent virologic testing, such as Kelgeri et al. and Servellita et al. demonstrated lower bias and provided more reliable trajectory data for emerging etiologies [4, 17]. Conversely, small case series had higher selection bias and limited generalizability. Overall, while suitable for descriptive synthesis, methodological variability limits causal inference (Table 2).

**Table 2:** Prevalence of Key Paranasal Sinus Variants (2010–2025)

Sr. No.	References	Study Design	Selection Bias	Measurement Bias / Outcome Assessment	Confounding Control	Reporting Completeness	Overall Risk of Bias
1	[10]	Retrospective cohort	Low - consecutive pediatric AIH cases clearly defined	Low-standard ALT/AST assays	Moderate limited control for disease severity	Low - full labs/outcomes reported	Moderate
2	[11]	Single-center cohort	Moderate-hospital-based recruitment	Low	Moderate, no multivariable analysis	Low	Moderate
3	[12]	Observational cohort	Low	Low	Moderate	Low	Moderate
4	[13]	Cohort	Low - nationwide surveillance system	Low	Low, clear analytic thresholds	Low	Low
5	[14]	Large hospital cohort	Low - consecutive inclusion with defined enzyme cut-off	Low	Moderate limited adjustment for viral co-infections	Low	Moderate
6	[15]	Cross-sectional	Moderate - single-center sample	Low	N/A	Low	Moderate
7	[16]	Case series	Moderate - referral bias possible	Low	N/A	Low	Moderate

8	[17]	Case-control/series	Low-matched hepatitis controls	Low	Low	Low	Low
9	[18]	Retrospective study	Low - large multicenter dataset	Low	Moderate limited comorbidity control	Low	Low to Moderate
10	[19]	Case series	Moderate - only four cases	Low	N/A	Low	Moderate to High
11	[20]	Observational	Low	Low	Moderate	Low	Moderate
12	[21]	Retrospective review	Moderate - tertiary-care bias	Low	Moderate	Low	Moderate
13	[4]	Multicenter series	Low	Low	Low robust virologic testing	Low	Low
14	[22]	Single-center cohort	Moderate - referral bias	Low	Moderate	Low	Moderate

Low risk → strong internal validity, consistent measurement, minimal selection bias. Moderate risk → typical of retrospective or single-center designs lacking full confounder adjustment. High risk → rare; mainly very small case series without a comparator or defined inclusion criteria.

The study summarizes ALT and AST values across etiologic groups, illustrating clear biochemical distinctions among classical and emerging hepatitis categories. AIH cases typically showed sustained moderate-to-high elevations, reflecting chronic inflammatory activity, while HAV/HEV infections produced rapid spikes that normalized within weeks. Acute severe or non-A-E hepatitis frequently demonstrated extreme values (>1500–5000 IU/L), particularly when associated with adenovirus or AAV2 co-infection, highlighting their aggressive biochemical profile. COVID-related hepatitis showed moderately high acute elevations with variable recovery. These differences reinforce the diagnostic importance of enzyme kinetics in distinguishing etiologies (Table 3).

**Table 3:** Summary of Serum Liver Enzyme Findings in Pediatric Hepatitis (2018–2024)

Sr. No.	References	Hepatitis Type / Etiology	ALT (U/L) Range / Mean ± SD	AST (U/L) Range / Mean ± SD	Enzyme Pattern / Trend	Clinical Association / Outcome
1	[10]	Autoimmune hepatitis (AIH)	ALT = 350–1800 (U/L)	AST = 300–1600 (U/L)	Marked elevation at diagnosis; gradual fall after corticosteroid therapy	Biochemical remission achieved in most; mortality = 18.8 %
2	[11]	AIH	ALT 200–2400	AST 180–2000	Persistently high until treatment	Late presenters had higher enzyme values and a worse prognosis
3	[12]	AIH	ALT > 500 in >90 %	AST > 500 in >85 %	Sharp elevation at onset; slow decline with therapy	Consistent with severe inflammatory activity
4	[13]	Acute severe hepatitis (unknown etiology)	ALT ≥ 500 for all cases	AST > 500 in 6 %	Acute spike; variable normalization	Rise coincided with viral co-infections (Adenovirus, AAV2)
5	[14]	Acute severe hepatitis (unknown etiology)	Median ALT = 1280 (U/L) (range 520–5950)	Median AST = 1020 (U/L)	Very high peaks; mixed viral triggers	9.8 % idiopathic; outcomes improved with supportive care
6	[15]	Hepatitis E virus (HEV)	ALT 400–2400	AST 350–2100	Peak early; normalize by day 10–14	HEV positive ≈ 26 %; more severe enzyme rise than non-HEV
7	[16]	Acute non-A-E hepatitis	ALT 600–3500	AST 500–3200	Rapid surge > 1000 U/L in most; decline after support	1 transplant; majority recovered
8	[17]	AAV2/HAdV-associated acute hepatitis	Mean ALT ≈ 2250	Mean AST ≈ 1900	Severe acute elevation > 10× ULN	Strong link between AAV2 coinfection and enzyme peaks
9	[18]	Adenovirus infection (general pediatric)	ALT median = 80 (15–520)	AST median = 70 (20–480)	Mild-to-moderate increase; >500 U/L rare	Co-infection (HAdV + EBV / CMV) increased the risk of marked elevation
10	[19]	COVID-19-related hepatitis	ALT 600–1600	AST 550–1500	Acute rise during COVID-19 infection	Some progressed to ALF; responded to supportive care
11	[20]	Hepatitis A (HAV)	Mean ALT = 1468 ± 720	Mean AST = 1270 ± 660	Acute peak at presentation; normalize in 2–3 weeks	Severe cases had ALT > 2000
12	[21]	Hepatitis A (HAV)	ALT > 1000 in 69 %	AST > 900 in 60 %	High initial values with a gradual fall	Correlated with bilirubin and INR abnormalities
13	[4]	Acute hepatitis of unknown cause (UK series)	ALT median = 1550 (780–5000)	AST median = 1200 (640–4200)	Massive transaminase rise; variable recovery	Adenovirus positive in >65 %; several required transplant

14	[22]	Autoimmune hepatitis	ALT 500–2100	AST 450–1800	Chronic elevations with a fluctuating pattern	Responded to immunosuppressive therapy; one needed a transplant
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## DISCUSSION

This systematic review details patterns of serum liver enzymes in pediatric hepatitis (2018–2024) and compiles findings from 14 primary studies of autoimmune, viral, idiopathic, adeno-associated viral (AAV2), and COVID-associated cases. Collectively, these confirm chronic elevation of ALT and AST as core markers of hepatocellular injury and illustrate distinct kinetic trajectories that differ meaningfully across etiologies and can support preliminary etiologic differentiation. Studies on autoimmune hepatitis (AIH) cohorts show that ALT and AST rises are moderate to high and persistent, with a steady fall following immunosuppressive treatment [10–12]. This aligns with broader descriptions of AIH in children as a chronic inflammatory process with fluctuating enzymes [23]. Elevated transaminases indicate continuous hepatocellular injury, and although normalization reflects biochemical remission, histological remission may lag, a known clinical consideration [24]. In contrast, acute viral hepatitis A/E exhibited abrupt enzyme spikes often >1,000 U/L that normalized within 2–3 weeks, consistent with the typical self-limited course of viral hepatic insult [20, 21]. These short but intense peaks represent sharp hepatocellular injury followed by rapid recovery, a hallmark distinguishing viral from autoimmune hepatitis. Acute severe or non-A-E hepatitis demonstrated the most extreme elevations, with median ALT values often exceeding 1,200–1,500 U/L and peaks surpassing 5,000 U/L [13, 16]. These values consistently exceed the CDC surveillance threshold of ALT/AST >500 IU/L, reinforcing  $\geq 500$  IU/L as a meaningful severity marker across global outbreak reports [25]. Cases linked to adenovirus also showed wide clinical variation, with some requiring transplantation [4]. Recent viral causes, especially adenovirus and AAV2, showed unique and more severe kinetic patterns, with co-infection frequently producing disproportionately high enzyme surges compared with single-agent viral hepatitis. Evidence from Ho *et al.* indicates that AAV2 may act as a cofactor, amplifying hepatocellular injury when paired with helper viruses such as adenovirus F41, producing ALT/AST values in the 2,000–5,000 U/L range [26]. This suggests that viral co-infection can serve as an injury amplifier, altering disease trajectory and potentially prognosis [27]. Overall, a consistent pattern emerges: AIH → sustained, chronic elevations, Hepatitis A/E → abrupt, short-lived peaks, Acute severe/non-A-E → extreme spikes with variable recovery and AAV2/adenovirus co-infection → amplified elevations beyond classical patterns. The enzyme ranges in

this review align with wider pediatric hepatology literature. For example, adenovirus-associated pediatric acute hepatitis can show ALT 603–4,696 U/L and AST 447–3,112 U/L [28], overlapping with values reported in our synthesis. AIH reviews also confirm that aminotransferases often exceed five to ten times normal levels and require histopathologic correlation for subtype confirmation [29, 30]. Outbreak analyses from 2021 onward also support that ALT/AST >500 IU/L is a reliable epidemiologic criterion for pediatric hepatitis of unknown origin [31]. Pediatric liver guidelines further note that disproportionate AST elevation should prompt evaluation for muscle injury, as AST is not liver-specific [32], and mild incidental elevations require systematic evaluation to rule out non-hepatic etiologies before diagnosing hepatitis [33–35].

Limitations include heterogeneity in design, sample size, follow-up duration, and reporting standards, which prevented meta-analysis. Confounder control was limited in many studies, reducing causal certainty. Small sample sizes especially in severe or rare presentations restricted generalizability. Publication and referral bias may also overrepresent severe cases. Additionally, lack of standardized ALT/AST units and inconsistent peak-time definitions across studies reduces the precision of cross-study comparisons. Further prospective, multicenter studies with standardized enzyme reporting are needed to clarify threshold values, better understand co-factor effects, and optimize diagnostic interpretation.

## CONCLUSIONS

This review provides a comprehensive synthesis of serum ALT/AST patterns in pediatric hepatitis across multiple etiologies from 2018 to 2024. The findings confirm that ALT and AST remain robust, sensitive biomarkers of hepatocellular injury, with distinctive kinetic trajectories that correspond to underlying disease processes. AIH demonstrates sustained biochemical elevation, viral hepatitis shows abrupt peaks, and acute severe or co-infection-associated cases produce the most extreme surges, sometimes amplified by AAV2 involvement. While liver enzymes alone cannot determine etiology or disease severity, their trajectory profiles meaningfully support clinical decision-making and triage during outbreaks.

## Authors' Contribution

Conceptualization: I

Methodology: AH, MI, JK, H, TA

Formal analysis: I

Writing and Drafting: I, AH, MI, JK, H, TA

Review and Editing: I, AH, MI, JK, H, TA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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