

Original Article

Immunoregulatory therapy restores T cell subset balance and reveals risk factors for liver injury in children with infectious mononucleosis

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Abstract: Objective: To investigate changes in T-cell subset profiles and factors associated with liver injury in patients with infectious mononucleosis (IM) before and after treatment. Methods: Clinical data of 152 children with IM treated at Xijing Hospital from August 2024 were retrospectively analyzed. They were divided into a group with liver injury (n = 78) and a group without liver injury (n = 74). All patients received ganciclovir and pidotimod. T-cell subsets were measured before and after treatment, and factors associated with liver injury were assessed. Results: After treatment, the proportions of CD3⁺ and CD8⁺ T cells were (72.44±6.52)% and (42.84±7.58)% respectively, significantly lower than the pretreatment values of (78.42±6.79)% and (54.49±8.42)% (P < 0.05). In contrast, the proportion of CD4⁺ T cells and the CD4⁺/CD8⁺ ratio increased to (24.38±7.62)% and (0.66±0.14)%, compared with (21.68±6.24)% and (0.43±0.09)% before treatment (P < 0.05). Univariate analysis indicated that age, season of onset, disease duration, fever duration, and disease severity were associated with liver injury in children with IM. Multivariate analysis revealed that older age, onset in spring or autumn, prolonged disease course, longer fever duration, moderate to severe disease, and elevated CD8⁺ percentage were independent risk factors for liver injury, whereas higher CD4⁺ percentage and increased CD4⁺/CD8⁺ ratio were protective factors (P < 0.05). Conclusion: Immunoregulatory therapy can effectively improve T-cell subset profiles and promote immune recovery in children with IM. Liver injury in IM is associated with age, season of onset, disease duration, fever duration, and disease severity.

Keywords: Immunoregulatory therapy, infectious mononucleosis, T cell subsets, liver injury, risk factors

Introduction

Infectious mononucleosis (IM) is an acute lymphoproliferative disorder predominantly affecting children and adolescents, with Epstein-Barr virus (EBV) identified as its principal etiologic agent [1-3]. EBV, a double-stranded DNA virus of the Herpesviridae family, infects hosts and elicits robust immune responses, particularly through the proliferation of B lymphocytes [4, 5]. Transmission typically occurs via saliva, and following an incubation period of 4-8 weeks, the virus can establish lifelong latency within the host [3]. Clinically, IM presents with fever, pharyngitis, lymphadenopathy, and hepatosplenomegaly. The symptom spectrum varies by age: younger children often exhibit upper respiratory manifestations such as nasal con-

gestion, whereas older children are more prone to hepatic dysfunction [3].

The pathogenesis of IM is closely linked to EBV-induced immune dysregulation [6]. The virus encodes numerous immune-modulatory proteins and microRNAs that interfere with host immunity, particularly by altering B-cell proliferation and T-cell function, thereby disrupting immune homeostasis [6, 7]. During acute infection, EBV-infected B cells may become aberrantly activated and disseminate to peripheral tissues, including the central nervous system, triggering localized inflammatory responses that explain the multi-organ involvement occasionally observed in IM [6, 7]. Moreover, mechanisms such as molecular mimicry and epitope spreading may connect EBV infection to autoim-

mune diseases, wherein cross-reactive immune responses against self-antigens exacerbate tissue injury [8-10].

Liver involvement is among the most frequent complications of IM and is primarily immune-mediated [11, 12]. EBV may directly injure hepatocytes or promote immune-cell infiltration - particularly by cytotoxic T cells and macrophages - resulting in elevated liver enzymes and hepatic inflammation [12, 13]. The risk and severity of liver injury may be influenced by factors such as age, gender, and splenomegaly, though the precise mechanisms remain unclear [11]. Findings from studies on immune-related hepatotoxicity, including those involving immune checkpoint inhibitors, suggest that dysregulated T-cell responses, especially excessive CD8⁺ T-cell activation - play a key role in immune-mediated hepatic injury [14, 15]. These insights provide a useful framework for understanding liver injury secondary to IM.

Although previous studies have identified immune dysregulation in IM, the dynamic alterations of T-cell subsets following specific antiviral and immunomodulatory treatments remain insufficiently characterized. Furthermore, the risk factors underlying IM-associated liver injury, a common and clinically significant complication, have not been clearly defined. Therefore, this study aimed to evaluate the effects of ganciclovir and pidotimod on T-cell subset restoration and to identify independent risk and protective factors associated with liver injury in pediatric IM patients. These findings may offer valuable clinical evidence for early intervention and improved management of IM-related complications.

Materials and methods

Clinical data of 152 children diagnosed with IM and treated at Xijing Hospital between August 2021 and August 2024 were retrospectively analyzed.

They were divided into a group with liver injury (n = 78) and a group without liver injury (n = 74).

Inclusion criteria: (1) Children meeting the diagnostic criteria for IM and presenting with typical clinical manifestations such as sore throat, fever, abnormal liver function [alanine aminotransferase (ALT) > 40 U/L and/or aspartate aminotransferase (AST) > 40 U/L], and hepato-

splenomegaly confirmed by abdominal ultrasonography [16]; (2) Laboratory findings showing atypical lymphocytes > 10% and lymphocytes > 50% in peripheral blood; (3) Serological evidence of EBV infection, indicated by anti-viral capsid antigen IgM positivity or EBV-DNA positivity; (4) Ultrasonographic confirmation of hepatosplenomegaly; (5) Complete clinical and laboratory data available.

Exclusion criteria: (1) EBV-positive patients not fulfilling full diagnostic criteria for IM; (2) Patients with other causes of hepatitis (e.g., viral hepatitis, breast milk jaundice); (3) Elevated transaminases secondary to non-hepatic diseases (e.g., skeletal muscle or myocardial disorders); (4) Coinfection with hepatitis B virus or hepatitis A virus; (5) Use of immunomodulators or corticosteroids within four weeks prior to admission.

This study was approved by the Institutional Review Board (IRB) of Xijing Hospital. The study protocol complied with the ethical principles outlined in the Declaration of Helsinki. Given its retrospective nature and exclusive use of anonymized data, the requirement for informed consent was waived by the IRB and Ethics Committee.

Treatment methods

Upon admission, all patients received antiviral and immunomodulatory therapy.

Ganciclovir (SFDA approval no. H10980187; China Meheco Keyi Pharma Co., Ltd., specification: 0.25 g) was administered intravenously at 5-10 mg/kg/day diluted in 100 mL of 10% glucose solution for five consecutive days.

Simultaneously, pidotimod oral solution (SFDA approval no. H20150635; Doppel Farmaceutici S.R.L., specification: 7 mL × 10 bottles) was administered at 0.4 g (one bottle) twice daily for two consecutive weeks.

Data collection and laboratory measurements

Demographic, clinical, and laboratory data were retrospectively extracted from the hospital's electronic medical record system. Variables included age, gender, onset season, disease duration, fever duration, peak body temperature, disease severity, and T-cell subset percentages.

Table 1. Comparison of age and liver injury in children with IM (n, %)

Age group/year old	n	Liver Damage (cases, %)	X ²	p
≤ 3	52	11 (21.54%) ¹	13.226	< 0.001 ^a
4-7	61	34 (55.74%) ²	36.723	< 0.001 ^b
> 7	39	33 (84.62%) ³	10.909	0.001 ^c

Note: Inter-group comparisons were performed using the Chi-square test with Bonferroni correction for post-hoc pairwise comparisons. Superscript numbers (1, 2, 3) denote the specific group being compared. a: comparison between group 1 (≤ 3 years) and group 2 (4-7 years); b: comparison between group 1 (≤ 3 years) and group 3 (> 7 years); c: comparison between group 2 (4-7 years) and group 3 (> 7 years).

Criteria for liver function injury: Liver function injury was defined as ALT > 40 U/L and/or AST > 40 U/L, total bilirubin (TBil) > 20.5 μmol/L, or direct bilirubin (Dbil) > 6.8 μmol/L [17].

Detection of T-cell subsets: Peripheral venous blood samples (1-2 mL) were collected into EDTA-K₂ anticoagulant tubes. Within two hours of collection, samples were processed by flow cytometry (Beckman CytoFLEX, Beckman Coulter, USA). Fluorescently labeled monoclonal antibodies - anti-CD3-FITC, anti-CD4-PE, and anti-CD8-APC (Beckman Coulter, USA) - were used. The gating strategy identified CD3⁺ T cells, followed by CD4⁺ and CD8⁺ subsets within the lymphocyte population. The CD4/CD8 ratio was automatically calculated by the instrument software. All procedures followed the manufacturer's instructions.

Assessment of disease severity: Based on the number of organs involved (including spleen, lungs, kidneys, heart, and lymph nodes), IM severity was classified into: Mild: ≤ 2 organs involved, n = 63; Moderate: 3 organs involved, n = 55; Severe: > 3 organs involved, n = 34.

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). A two-tailed *p* value < 0.05 was considered statistically significant.

Categorical variables were expressed as numbers and percentages (n, %) and compared using the chi-square (χ²) test. For comparisons involving more than two groups, overall differences were first evaluated with the chi-square test, and post hoc pairwise comparisons were performed using the Bonferroni-adjusted significance level (*P* < 0.017).

Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm SD$). Differences between two independent groups were analyzed using the independent-samples *t*-test. For comparisons among multiple groups, one-way ANOVA was applied for normally distributed data, and the Kruskal-Wallis test was used for non-normally

distributed data. When overall differences were significant, Bonferroni-corrected pairwise tests (*P* < 0.017) were conducted.

Variables showing statistical significance in univariate analyses - including age group, onset season, disease duration, fever duration, disease severity, CD3%, CD4%, CD8%, and CD4/CD8 ratio - were entered into a multivariate logistic regression model to identify independent predictors of liver injury.

Categorical variables were dummy coded for regression analysis, with reference categories defined as follows: Age group: ≤ 3 years; Onset season: Winter; Disease severity: Mild.

Continuous variables (disease duration, fever duration, CD3%, CD4%, CD8%, and CD4/CD8 ratio) were entered as continuous predictors. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated.

Results

Comparison of age and liver injury in children with IM

The incidence of liver injury in children older than 7 years was significantly higher than that in those aged 4-7 years and ≤ 3 years. Moreover, the incidence in the 4-7-year group was also significantly higher than that in the ≤ 3-year group (*P* < 0.05), as shown in **Table 1**.

Comparison of gender and liver injury in children with IM

Although liver injury occurred more frequently in female than in male IM patients, the difference was not statistically significant (*P* > 0.05), as shown in **Table 2**.

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Table 2. Comparison of Gender and Liver Injury in Children with IM (n, %)

Gender	n	Liver Damage (Cases, %)
Male	78	40 (51.28%)
Female	74	38 (51.35%)
χ^2		0.000
p		0.993

Comparison of T-cell subsets before and after treatment in children

As shown in **Figure 1B**, the proportion of CD3⁺ T cells decreased significantly from (78.42±6.79)% before treatment to (72.44±6.52)% after treatment (t = 7.832, P < 0.001).

The proportion of CD4⁺ T cells increased from (21.68±6.24)% to (24.38±7.62)% (t = 3.380, P < 0.001), whereas CD8⁺ T cells decreased markedly from (54.49±8.42)% to (42.84±7.58)% (t = 12.678, P < 0.001).

Correspondingly, the CD4⁺/CD8⁺ ratio rose from (0.43±0.09)% to (0.66±0.14)% (t = 17.038, P < 0.001).

These findings indicate substantial improvement in T-cell subset balance following treatment. Representative flow-cytometric plots are shown in **Figure 1A**.

Comparison of onset seasons and liver injury in children with IM

The incidence of liver injury was highest in autumn, followed by spring, and significantly greater than that in winter or summer (P < 0.05), as shown in **Table 3**.

Comparison of disease course, fever duration, and peak temperature in relation to liver injury

Children without liver injury had significantly shorter disease courses and fever durations compared with those with liver injury (both P < 0.05). Interestingly, the peak body temperature in the liver-injury group was significantly lower than that in the non-injury group (P < 0.05), as shown in **Table 4**.

Comparison of disease severity and liver injury in children with IM

The incidence of liver injury in the mild group was significantly lower than in the moderate

and severe groups (P < 0.05). However, there was no significant difference between the moderate and severe groups (P > 0.05), as shown in **Table 5**.

Multivariate analysis of risk factors for liver injury in children with IM

Multivariate logistic regression identified several independent predictors of liver injury (**Table 6**).

Significant risk factors included: Age > 7 years (aOR = 25.027, 95% CI: 8.502-73.532, P < 0.001); Age 4-7 years (aOR = 4.532, 95% CI: 1.807-11.252, P = 0.001); Severe disease (aOR = 4.034, 95% CI: 1.502-10.656, P = 0.006); Moderate disease (aOR = 3.057, 95% CI: 1.209-7.507, P = 0.018); Spring onset (aOR = 12.011, 95% CI: 3.209-45.059, P < 0.001); Autumn onset (aOR = 15.094, 95% CI: 4.001-56.249, P < 0.001); Longer disease course (aOR = 1.221, 95% CI: 1.052-1.371, P = 0.007); Longer fever duration (aOR = 1.346, 95% CI: 1.106-1.536, P = 0.002); Increased CD8% (aOR = 1.155, 95% CI: 1.082-1.223, P < 0.001).

Protective factors included: Higher CD4% (aOR = 0.854, 95% CI: 0.780-0.926, P < 0.001); Elevated CD4/CD8 ratio (aOR = 0.649 per 0.1-unit increase, 95% CI: 0.503-0.727, P < 0.001).

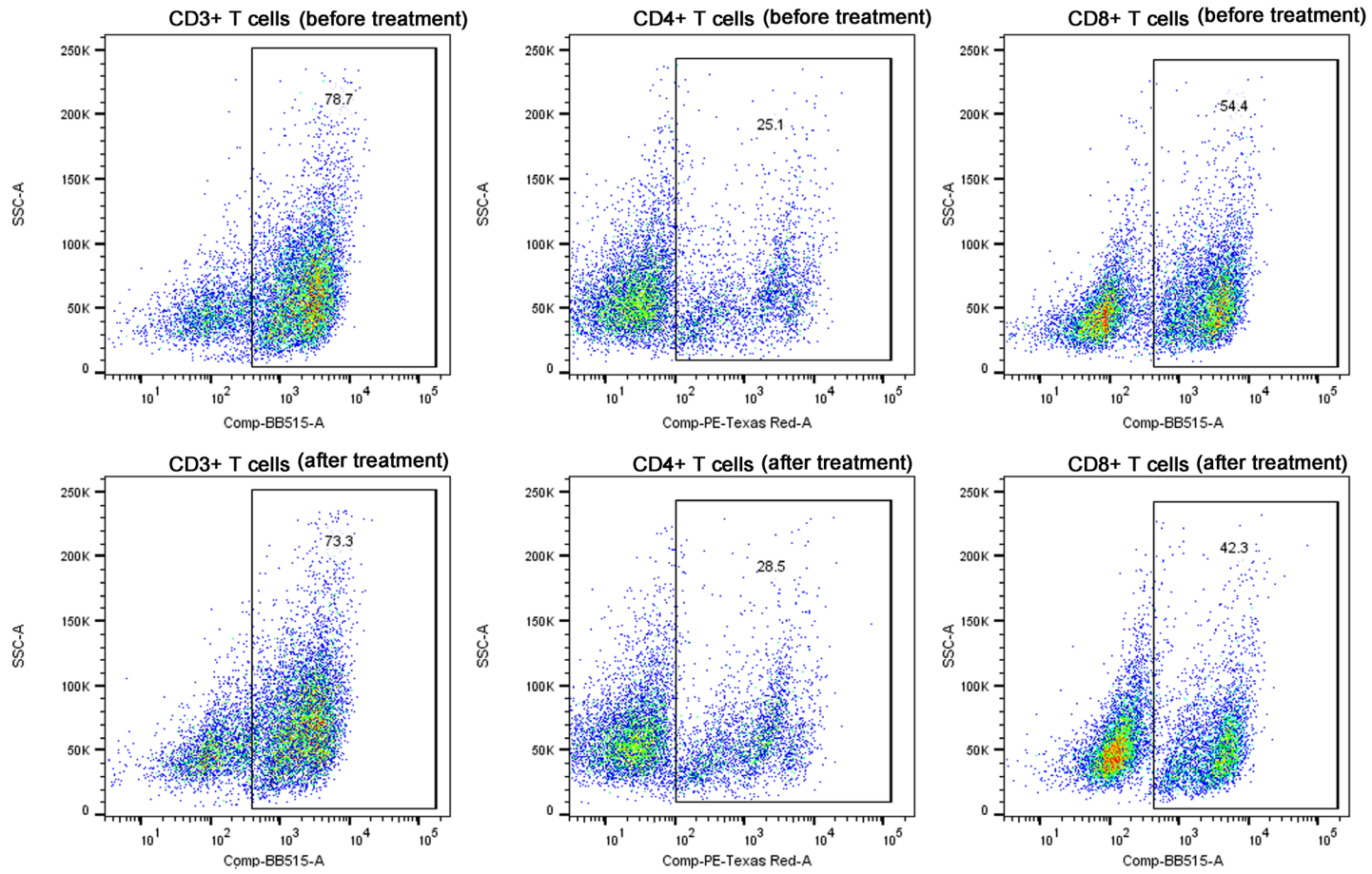
Discussion

IM, primarily caused by EBV, is a common lymphoproliferative disorder in children, characterized by fever, pharyngitis, lymphadenopathy, and potential multi-organ involvement, including hepatic dysfunction [18, 19]. EBV exhibits strong tropism for B lymphocytes, inducing their proliferation and triggering an intense, often dysregulated, cytotoxic T-cell response [20]. While this immune activation is essential for viral control, it also contributes to the clinical manifestations and complications of IM, particularly liver injury [21-23]. The present study demonstrates that combined immunomodulatory therapy with ganciclovir and pidotimod effectively restores T-cell subset balance and identifies key demographic, clinical, and immunological risk factors for liver injury in pediatric IM.

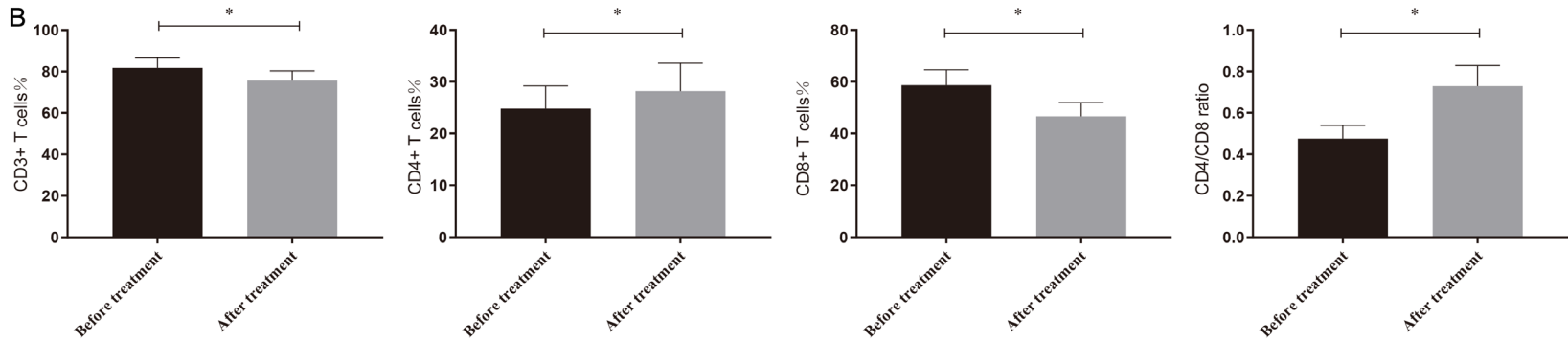
The immunopathological findings of this study align with current knowledge of EBV-associated immune dynamics. The observed post-treat-

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A



B



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Figure 1. Representative flow cytometry profiles and quantitative analysis of T cell subsets in children with infectious mononucleosis before and after treatment. A. Flow cytometry dot plots gated on lymphocytes show the expression of CD4 and CD8 in a representative patient at baseline and post-treatment. B. Bar graphs (mean \pm SD) demonstrate the percentages of CD3⁺, CD4⁺, CD8⁺ T lymphocytes and the CD4/CD8 ratio in patients before and after treatment (*P < 0.05).

Table 3. Comparison of onset season and liver injury in children with IM (n, %)

Onset Seasons	n	Liver Damage (Cases, %)	X ²	p
Spring	38	28 (73.68%) ¹	20.098	< 0.001 ^a
			0.221	0.638 ^b
Summer	28	5 (17.86%) ²	26.403	< 0.001 ^c
			0.016	0.900 ^d
Autumn	50	39 (78.00%) ³	31.562	< 0.001 ^e
Winter	36	6 (16.67%) ⁴	24.199	< 0.001 ^f

Note: Inter-group comparisons were performed using the Chi-square test with Bonferroni correction for post-hoc pairwise comparisons. Superscript numbers (1, 2, 3, 4) denote the specific group being compared. a: comparison between group 1 (Spring) and group 2 (Summer); b: comparison between group 1 (Spring) and group 3 (Autumn); c: comparison between group 2 (Summer) and group 3 (Autumn); d: comparison between group 2 (Summer) and group 4 (Winter); e: comparison between group 3 (Autumn) and group 4 (Winter); f: comparison between group 1 (Spring) and group 4 (Winter).

Table 4. Comparison of disease course, fever duration and peak temperature in relation to liver injury ($\bar{x} \pm s$)

Factors	Group with liver damage (n = 78)	Group without liver damage (n = 74)	t	p
Disease Duration (d)	11.36 \pm 2.78	9.54 \pm 2.64	4.134	< 0.001
Fever Time (d)	8.16 \pm 2.39	5.26 \pm 2.27	7.662	< 0.001
Peak Temperature ($^{\circ}$ C)	38.38 \pm 0.31	40.15 \pm 0.14	44.954	< 0.001

Note: Independent samples t-test used for group comparisons.

Table 5. Comparison of disease severity and liver injury in children with IM (n, %)

Disease Severity	n	Liver Damage (Cases, %)	X ²	p
Mild	63	21 (33.33%) ¹	9.574	0.002 ^a
Moderate	55	34 (61.82%) ²	10.491	0.001 ^b
Severe	34	23 (67.65%) ³	0.310	0.578 ^c

Note: Inter-group comparisons were performed using the Chi-square test with Bonferroni correction for post-hoc pairwise comparisons. Superscript numbers (1, 2, 3) denote the specific group being compared. a: comparison between group 1 (Mild) and group 2 (Moderate); b: comparison between group 1 (Mild) and group 3 (Severe); c: comparison between group 2 (Moderate) and group 3 (Severe).

ment reduction in CD8⁺ T cells, together with the increase in CD4⁺ T cells and a higher CD4⁺/CD8⁺ ratio, indicates successful modulation of the initially exaggerated immune response. Correction of this CD4⁺/CD8⁺ inversion repre-

sents an important marker of immune reconstitution, consistent with prior studies reporting similar improvements in IM patients treated with ganciclovir or interferon- α [20, 24].

During acute EBV infection, clonal expansion of CD8⁺ T cells is critical for eliminating infected B cells and controlling viral replication [20]. However, excessive or persistent CD8⁺ activity may lead to collateral tissue injury - particularly in the liver, a frequent target of EBV-related inflammation [2, 25]. Our findings reinforce this dual role: elevated CD8⁺ percentages independently predicted liver injury, while a higher CD4⁺/CD8⁺ ratio was protective. These results suggest that hepatic complications are driven not merely by the magnitude of immune activation but by the imbalance between effector and regulatory T-cell responses.

Age was another major determinant of liver injury. The risk was markedly higher in children aged 4-7 years and was greatest in those older than 7 years, consistent with previous reports [26, 27]. Xiao et al. [2] similarly observed higher hepatic involvement in older children, proposing that their more mature immune

systems mount stronger but potentially more injurious cytotoxic responses compared with the relatively tolerogenic immunity of younger children. This aligns with the epidemiological pattern of EBV infection: asymptomatic in early

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Table 6. Multivariate logistic regression analysis of risk factors for liver injury in children with IM

Variable	aOR	95% CI (Lower)	95% CI (Upper)	P
Age group (ref: ≤ 3 years)				
4-7 years	4.532	1.807	11.252	0.001
> 7 years	25.027	8.502	73.532	< 0.001
Onset season (ref: winter)				
Spring	12.011	3.209	45.059	< 0.001
Summer	1.206	0.328	4.806	0.800
Autumn	15.094	4.001	56.249	< 0.001
Disease course				
Fever duration	1.346	1.106	1.536	0.002
Disease severity (ref: mild)				
Moderate	3.057	1.209	7.507	0.018
Severe	4.034	1.502	10.656	0.006
CD3%	0.952	0.904	1.003	0.067
CD4%	0.854	0.780	0.926	< 0.001
CD8%	1.155	1.082	1.223	< 0.001
CD4/CD8	0.649	0.503	0.727	< 0.001

Note: ref: reference category; aOR: adjusted Odds Ratio; CI: Confidence Interval.

childhood but more often manifesting as classic IM - with complications - in older children and adolescents [28, 29].

A noteworthy observation was the seasonal variation in liver injury, with incidence peaking in autumn and spring. Although seasonal trends in IM incidence have been documented, their relationship to complications has received limited attention [20]. Co-circulation of other respiratory viruses during these periods in Northern China may enhance immune activation or inflammatory synergy, aggravating EBV-induced hepatic injury. Environmental and host factors associated with these seasons may also modulate immune function [25, 30]. Further epidemiological investigations are needed to confirm and clarify these seasonal effects.

Disease severity, prolonged clinical course, and extended fever duration also emerged as independent risk factors for liver injury. This is consistent with the concept that more severe or protracted disease reflects higher viral load and more intense immune activation, increasing the likelihood of organ injury [31-33]. The classification of disease severity based on multi-organ involvement effectively captures IM's systemic nature. The strong association

between disease severity and hepatic injury supports the view that liver dysfunction is part of a broader systemic inflammatory process rather than an isolated manifestation [34-36].

The present study has several strengths, including a well-defined pediatric cohort, standardized therapeutic and laboratory protocols, and comprehensive multivariate analysis controlling for potential confounders. Nonetheless, certain limitations should be acknowledged. First, its retrospective design introduces risks of selection bias and unmeasured confounding. Second, being a single-center study, external generalizability may be limited. Third, T-cell

subsets were assessed only at two discrete time points; serial monitoring would better illustrate the temporal evolution of immune recovery. Finally, the absence of long-term follow-up precludes assessment of persistent hepatic dysfunction or chronic sequelae.

In conclusion, this study provides clinical evidence that immune-regulatory therapy with ganciclovir and pidotimod effectively normalizes T-cell subsets in children with IM. Older age, onset in spring or autumn, prolonged disease and fever duration, higher disease severity, and elevated CD8⁺ T-cell levels were identified as independent risk factors for liver injury, while an increased CD4⁺/CD8⁺ ratio was protective. These findings emphasize the central role of T-cell imbalance in the pathogenesis of IM-associated complications. Future prospective multi-center studies should validate these predictors and clarify the mechanisms through which CD8⁺ T cells mediate hepatic injury. Developing targeted immunomodulatory strategies to mitigate immune-mediated hepatotoxicity while preserving antiviral defense represents an important direction for improving outcomes. Clinicians should maintain vigilance for liver dysfunction in children with these risk profiles to enable early intervention and prevent serious hepatic complications.

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Disclosure of conflict of interest

None.

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