Original Article **Open Access**

Clinical Characteristics, Prognostic Factors and Outcomes of Paediatric Patients with Haemophagocytic Lymphohistiocytosis

Sehar Aslam, Nadeem Sadiq, Tariq Nadeem, Awais Arshed, Imrana Atta, Kiran Minhas

ABSTRACT

Objective: Haemophagocytic lymphohistiocytosis (HLH) is a multi-system autoimmune disorder. The objective of this study was to find out the clinical characteristics and prognosis of paediatric patients with Haemophagocytic Lymphohistiocytosis.

Study Design and setting: Cross sectional study conducted at Pak Emirates Military Hospital, Rawalpindi from July 2021 to June 2023.

Methodology: Children with diagnosis of HLH were assessed by including patients who were aged = 13 years during hospitalization. All the patients who had not been diagnosed by using the HLH-2004 criteria were disqualified. Relevant findings were noted by evaluating records pertinent to physical examination, radiology and laboratory markers. Prognosis was assessed by determining the underlying clinical aetiology and whether patient-related factors modulated the overall life expectancy.

Results: A total of 32 patient records were evaluated. Mean age at diagnosis was 44.3 ± 39.1 months (Range: 1-132 months) with majority being males [n=23 (71.9%)]. The common clinical characteristics included fever [n=29 (90.6%)], lymphadenopathy [n=27 (84.4%)], splenomegaly [n=23 (71.9%)] and hepatomegaly [n=23 (71.9%)]. Serum ferritin, bilirubin, ALT, AST, and LDH were also raised. All patients were followed for a mean period of 12 months and 18 (56.3%) children failed to survive. Negative prognostic indicators included severe anaemia (p=0.001), neutropenia (p=0.007), thrombocytopenia (p=0.033), and hyperferritinemia (p<0.001). Elevation of liver enzymes (ALT: p<0.001; AST: p=0.031), serum bilirubin (p=0.037), and LDH (p<0.001) also indicated worse disease prognosis.

Conclusion: HLH in childhood is a potentially life-threatening disease and carries a significant association with deranged liver function.

Keywords: HLH, Liver enzymes; Prognosis; Clinical characteristics

How to cite this Article:
Aslam S, Sadiq N, Nadeem T, Arshed A, Atta I, Minhas K. Clinical Characteristics, Prognostic Factors and Outcomes of Paediatric Patients with Haemophagocytic Lymphohistiocytosis. J Bahria Uni Med Dental Coll. 2024;14(2):139-43 DOI: https://doi.org/10.51985/JBUMDC2024320

Sehar Aslam *(Corresponding Author)*
Registrar, Department of Paediatrics
PEMH Rwalpindi / PNS SHIFA, Karachi
Email: seharaslam126@gmail.com

Nadeem Sadiq
Associate Professor, Department of Paediatrics
PNS SHIFA, Karachi
Email: drnadeemsadiq@yahoo.com

Tariq Nadeem
Associate Professor, Department of Paediatrics
CMH Rawalpindi, Karachi
Email: nadeemchauhan31@gmail.com

Awais Arshed
Assistant Professor, Department of Paediatrics
CMH Rawalpindi, Karachi
Email: awaisarshed@hotmail.com

Imrana Atta
Consultant, Department of Paediatrics
PNS SHIFA, Karachi
Email: imranaatta.dr@gmail.com

Kiran Minhas
Consultant, Department of Paediatrics
PNS SHIFA, Karachi
Email: kirandmc@gmail.com

Received: 30-01-2024
Accepted: 04-04-2024
1st Revision: 19-02-2024
2nd Revision:23-03-2024
3rd Revision: 26-03-2024

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is characterized as an autoimmune, multisystem disorder, the pathogenesis of which is mediated by a myriad of cytokines including interferon-gamma (IFN-ã), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-á), that eventually leads to hyper activation of immune system.[1] Persistent and abnormal activation of CD8+ T-lymphoctytes and resulting mediators of inflammation are the key mechanism of pathogenesis. Paediatric HLH can either be genetic (due to familial or immunodeficiency related syndromes resulting from diverse range of genetic pathologies) or acquired. In addition to the role of genetic mutations in mediating the pathogenesis of familial HLH variants i.e., Perforin (PRF1), Munc13-14 (UNC13D), Syntaxin 11 (STX11) and Syntaxin binding protein 2 (STXBP2)[2], genetic alterations can also be associated with secondary HLH that is seen in Chediak-Higashi syndrome (CHS), Griscelli syndrome and X-linked lymphoproliferative disorders. Infections such as Epstein-Barr virus (EBV) and other herpesviruses, Bacterial, fungal and protozoan infections have also been attributed to the pathogenesis of Secondary HLH.[3,4] Secondary HLH can

also rarely secondary to inborn error of metabolism and drugs such as phenytoin. It is also noteworthy that up to 40% cases of paediatric HLH can arise secondary to systemic infections.[5]

Although paediatric HLH can be manifested at any point during childhood, the condition predominantly impacts children during the initial 18 months of life. Paediatric HLH is marked by a diverse spectrum of clinical manifestations. Depending upon the age at the time of diagnosis, a child may encounter a febrile illness and hepato-splenic enlargement. Characteristic haematological findings include bicytopenia, or even pancytopenia. The reduction in cell counts arises due to the classical feature of haemophagocytosis which potentiates hepatospleenomegaly and widespread lymphadenopathy.[6,7] A few notable biochemical abnormalities include markedly raised triglyceride and ferritin levels associated with significant hypoproteinaemia.[7] Clinical and laboratory criteria have been formulated which includes fever, splenomegaly, cytopenias in two or more lineages (ANC $<1x10^9$ /L, Hb <9g/dl or <12g/dl if age is less then 4weeks and pletelets $<100x10^9$ /L), Hypertriglyceridemia and/ hypofibrinogenaemia (TG> 3mmol/L, Fibrinogen < 1.5g/dl), Ferritin above 500 ug/L, sCD25 >2400/ml, decreased or absent NK cell activity and evidence of Haemophagocytosis in BM, CSF or LN. Of these 5 out of 8 criterias are required to make diagnosis of HLH.[8] Zhou et al., (2022) have identified a high mortality rate among children, with up to 30% patients dying during the 30-day period following disease onset.[9] Although patient outcomes can be substantially improved through timely diagnosis and provision of critical care, a lot of factors can potentially modulate the overall prognosis of paediatric HLH. In adults, these novel factors include haematological markers, biochemical indicators and background of malignancy-associated HLH. Nonetheless, prognostic data regarding paediatric HLH is rather inadequate.[10]

Given the diminished survival rates observed in HLH[11], it is imperative to generate a better know-how pertaining to prognostic markers of the disease. In turn, this data can allow clinicians to carry out an efficient prediction of adverse outcomes in childhood HLH and initiate timely treatment. In line with this, the current study was designed to assess the clinical manifestations, prognostic factors, and clinical outcomes of paediatric patients with HLH.

METHODOLOGY:

The study was organised as a cross-sectional analysis of paediatric cases of HLH and was conducted at Pak Emirates Military Hospital, Rawalpindi. The authors analysed paediatric HLH patients spanning over a period 02 years from July 2021 to June 2023. Data collection, statistical analysis, and report writing were carried out for a period of 03 months from Sep 2023 to Dec 2023. Patients were incorporated into the study by using convenience sampling.

Inclusion Criteria: Diagnosed patients of HLH who were aged = 13 years at the time of hospital admission, and had been diagnosed with haemophagocytosis using the HLH-2004 criteria were included in the study. As per HLH-2004, patients had to meet the following diagnostic parameters for HLH: (A) HLH confirmation by genetic analysis or (B) Five out of the following eight criteria have to be fulfilled: (1) Temperature = 38.5°C; (2) Splenomegaly; (3) Anemia / Neutropenia / Thrombocytopenia; (4) Hypertriglyceridemia >3mmol/L and/or hypofibrinogenemia ; (5) Histological evidence of haemophagocytosis in bone marrow, lymph nodes, spleen, or liver; (6) Low or absent natural killer cell activity; (7) Serum ferritin raised above 500 ng/mL; (8) Elevated soluble CD25 (soluble IL-2 receptor alpha) = 2,400 U/mL.[12]

Exclusion Criteria: Those paediatric patients whose clinical records indicated only a marked clinical suspicion for HLH without implementing the HLH-2004 criteria, were excluded from the study. Moreover, the patients who could not be contacted to evaluate clinical outcomes were eliminated from the study.

Two separate authors investigated the eligible clinical records for extracting information pertinent to the clinical characteristics, prognostic indicators, and outcomes associated with HLH. With regard to clinical characteristics, patient findings confirmed by physical examination, diagnostic imaging, and laboratory markers were noted. Prognosis was assessed by determining the underlying aetiology of HLH (malignant vs. non-malignant) and whether factors including laboratory markers or childhood malignancy significantly modulated the overall outcome. In addition, clinical outcomes were evaluated by estimating the cumulative mortality rate. Patient survival time was defined as the interval from the point of first admission to the point of subsequent contact during data analysis.

The authors in-charge of data entry and analysis strictly followed the ethical charter set by the Helsinki protocol while the study was also conducted after approval from the institutional review board (ERC no: A/29/EC/414/2022). Statistical analysis was conducted by utilizing IBM Statistical Package for Social Sciences (SPSS) 23.0. The mean ± SD values were calculated for quantitative variables including patient age, follow-up intervals, and laboratory values. The independent t-test and the chi-square (÷2) test were applied to evaluate the statistical correlation of data. A p-value < 0.05 was considered significant.

RESULTS:

A total of 32 eligible cases were accessed and incorporated into the study. Mean age of the participants was 44.3 ± 39.1 months [Range: 1-132 months]. The majority of children were males [n=23 (71.9%)]. The most prevalent clinical characteristics included fever [n=29 (90.6%)], lymphadenopathy [n=27 (84.4%)], splenomegaly [n=23

(71.9%)], and hepatomegaly [n=23 (71.9%)] (Table-2). In terms of haematological parameters, mean haemoglobin levels were 8.7 ± 2.4 g/dL, mean neutrophil count was 0.6 ± 0.2 x 10^3/mm^3, and mean platelet count was equivalent to 89 ± 63.0 x 10^3/mm^3. Serum ferritin levels were significantly elevated at 3910 ± 3018 ng/mL. Serum albumin levels were found in the lower range i.e., 2.8 ± 0.6 g/dL. As a marker of coagulopathy, mean patient INR was estimated to be 1.3 ± 0.4. In addition to liver function, liver biochemistry was also found to be deranged with significantly elevated bilirubin

Table-1. Demographic, Clinical, and Aetiological Parameters of Paediatric HLH

Patient-related parameters (n = 32)			Statistical Value
Demographic variables	Age in months (Mean ± SD)		44.3 ± 39.1
	Gender	Male [n (%)]	23 (71.9%)
		Female [n (%)]	9 (28.1%)
Clinical characteristics	Fever [n (%)]		29 (90.6%)
	Splenomegaly [n (%)]		23 (71.9%)
	Hepatomegaly [n (%)]		23 (71.9%)
	Jaundice [n (%)]		18 (56.3%)
	Lymphadenopathy [n (%)]		27 (84.4%)
Clinical aetiology of HLH	EBV infection [n (%)]		12 (37.5%)
	Non-EBV infection [n (%)]		14 (43.8%)
	Malignancy [n (%)]		6 (18.8%)

EBV: Epstein-Barr Virus

Table-2. Laboratory-based Parameters of children with HLH

HLH Laboratory Markers	Statistical Value (Mean ± SD)
Haemoglobin (g/dL)	8.7 ± 2.4
Neutrophil Count (x10^3/mm^3)	0.6 ± 0.2
Platelet Count (x10^3/mm^3)	89 ± 63.0
Ferritin (ng/mL)	3910 ± 3018
International Normalized Ratio (INR)	1.3 ± 0.4
Albumin (g/dL)	2.8 ± 0.6
Bilirubin (mg/dL)	3.5 ± 3.4
Alanine transaminase (ALT; IU/L)	186.0 ± 170.7
Aspartate transaminase (AST; IU/L)	136.9 ± 108.3
Lactate dehydrogenase (LDH; IU/L)	434.2 ± 329.1

Table-*3*. Determinants of Clinical Prognosis in Paediatric HLH

Prognostic Indicators			Mortality (n=18)	No mortality (n=14)	p-value
Demographic variables	Age in months (Mean ± SD)		47.4 ± 43.4	40.2 ± 33.8	0.612
	Gender	Male [n (%)]	12 (37.5%)	11 (34.3%)	0.457
		Female [n (%)]	6 (18.8%)	3 (9.3%)	
Clinical characteristics	Fever [n (%)]		16 (50%)	13 (40.6%)	0.702
	Splenomegaly [n (%)]		13 (40.6%)	10 (31.3%)	0.960
	Hepatomegaly [n (%)]		13 (40.6%)	10 (31.3%)	0.960
	Jaundice [n (%)]		9 (28.1%)	9 (28.1%)	0.419
	Lymphadenopathy [n (%)]		15 (46.9%)	12 (37.5%)	0.854
Clinical aetiology	EBV infection [n (%)]		6 (18.8%)	6 (18.8%)	0.581
	Non-EBV infection [n (%)]		7 (21.9%)	7 (21.9%)	0.530
	Malignancy [n (%)]		5 (15.6%)	1 (3.1%)	0.138
Laboratory markers (Mean ± SD)	Haemoglobin (g/dL)		7.6 ± 2.0	10.2 ± 2.1	0.001*
	Neutrophil Count (x10^3/mm^3)		0.5 ± 0.2	0.7 ± 0.2	0.007*
	Platelet Count (x10^3/mm^3)		65.6 ± 26.6	119.1 ± 82.3	0.033*
	INR		1.3 ± 0.3	1.4 ± 0.4	0.392
	Ferritin (ng/mL)		6010.6 ± 2211.8	1210.1 ± 1171.1	<0.001*
	Albumin (g/dL)		2.7 ± 0.6	2.9 ± 0.5	0.384
	Bilirubin (mg/dL)		4.6 ± 4.1	2.2 ± 2.0	0.037*
	Alanine transaminase (ALT; IU/L)		273.7 ± 175.1	73.4 ± 71.4	<0.001*
	Aspartate transaminase (AST; IU/L)		172.9 ± 111.0	90.6 ± 88.2	0.031*
	Lactate dehydrogenase (LDH; IU/L)		640.9 ± 299.2	168.3 ± 77.1	<0.001*

Significant determinants of mortality
EBV: Epstein-Barr Virus; INR: International Normalized Ratio

(3.5 ± 3.4 mg/dL), ALT (186.0 ± 170.7 IU/L) and AST (136.9 ± 108.3 IU/L) levels (Table-2). High LDH levels (434.2 ± 329.1 IU/L) were also noted (Table-2).

The HLH patients were categorized on the basis of their clinical aetiology. EBV infection was found to be associated with a total of 12 (37.5%) cases. A total of 14 (43.8%) cases were attributed to non-EBV systemic infections. Moreover, malignancy was the main underlying etiology for up to 6 (18.8%) patients (Table-1). Following their preliminary admission, paediatric patients were subsequently followed for a mean duration of 10 months. Up to 18 (56.3%) children had failed to survive upon follow-up evaluation while a survival period of more than 12 months was estimated only in up to 12 (37.5%) HLH patients. Regarding the clinical prognosis, the severity of anaemia (p=0.001), neutropenia (p=0.007), thrombocytopenia (p=0.033), and hyperferritinemia (p<0.001) was significantly associated with poor clinical progression in HLH. Moreover, elevation of liver enzymes (ALT: p<0.001; AST: p=0.031), serum bilirubin (p=0.037), and LDH (p<0.001) levels also indicated a poor disease prognosis (Table-3).

DISCUSSION:

Our study has assessed the clinical correlation of paediatric patients with haemophagocytic lymphohistiocytosis, most prevalent clinical characteristics included fever, lymphadenopathy and hepatosplenomegaly. Lab findings included cytopenias, elevated ferritin, deranged liver enzymes and raised LDH. A significantly poor long-term prognosis was identified in the sample cohort. Regarding the clinical prognosis, the severity of anaemia, neutropenia, thrombocytopenia, and hyperferritinemia was significantly associated with poor clinical progression in HLH. This is one of the preliminary studies exploring the clinical outcome of paediatric HLH within the developing tertiary healthcare sector of Pakistan.

Similar to our findings, the commonest clinical manifestations in HLH were reported by Zhang et al., (2016) as fever, elevated ferritin, and low platelet count. Compared to adults, paediatric HLH is more likely to potentiate the enlargement of liver and spleen. In line with previous studies, our findings showed that ferritin and/or LDH levels were significantly decreased after 2-3 weeks of treatment, suggesting that serum ferritin and/or LDH may function as sensitive markers reflecting the early treatment response. Deranged liver biochemistry, anaemia, and elevated LDH have also been reported in the literature by Benevenuta et al., (2023). Leucocytosis is not typical of HLH, except in HLH-associated with defined rheumatological conditions/macrophage activation syndrome-HLH (MAS-HLH)[11] Impaired liver function can precipitate Acute liver failure, therebyresulting in a substantially high risk of in-hospital mortality.[13] Although active HLH disease has been considered a relative contraindication to liver transplantation, the latter has been shown to potentially improve patient prognosis with overall graft and patient survival were 60%at 24 months median age after liver transplantation.[15]

A major etiological condition contributing to childhood HLH is EBV infection. In contrast to adult HLH, paediatric variant of HLH has been shown to be more frequently associated with EBV.[16] Thisunique vulnerability, as reported by Koh et al., to EBV infection in Asian patients with HLH suggests that different genetic backgrounds can contribute to the development of the disease, even in cases of secondary HLH. Although Zhou et al., (2022) have identified age >28 months as a protective factor in the pathophysiology of HLH.[8] our study has highlighted a non-significant role of increasing age in preventing child mortality where patients experiencing mortality were, on average, 7 months older than the surviving children. Besides, a significant transaminase elevation coupled with coagulopathy has been associated with a markedly poorer clinical prognosis in HLH.[16] Although the authors could not find any significant association between HLH secondary to malignancy and mortality, it has been previously documented that malignancy is a poor prognostic marker of the disease.[9,15]

Our study indicated a poor long-term prognosis among paediatric HLH patients where up to 56.3% of patients had failed to survive when assessed at a mean follow-up duration of 10 months after initial admission. In a broad systematic review and Cochrane meta-analysis, reported by Tan et al., which included a total of 36 studies involving clinical data of up to 493 HLH paediatric patients, a lower mortality rate of approximately 33% was noted.[18] This difference from our findings can be potentially explained by our study being restricted to a single referral hospital where many complicated cases were referred from peripheral hospitals. Nonetheless, early diagnosis and treatment in HLH can drastically reduce the risk of adverse outcomes.[8] In concordance, a study by Xu et al., (2017) up to two-third of HLH cases can undergo remission following 8 weeks of treatment.[19] To boost life expectancy, supportive care is also implicated in HLH since it can effectively reduce the risk of opportunistic infections and other comorbidities in the immunocompromised patients.[20]

A major strength of our study was follow up on patients for assessment of prognosis and clinical outcome. Limitations of this study include the incompleteness of testing for*STXBP2,SH2D1A, XIAP/BIRC4 ,UNC13D, PRF1, STX11,* and *ITK* mutations, which was why we adopted the term 'presumed' secondary HLH. This leaves the possibility of causation due to genetic mutation in the patients designated as having non-familial HLH.

CONCLUSION

Paediatric haemophagocytic lymphohistiocytosis is a rare and potentially fatal, multisystem disorder. Derangement of liver function and other serum biomarkers is significantly

associated with a poorer clinical prognosis. A multicentre, prospective trial that builds on the present results is warranted to identify subgroups of patients with a poor prognosis and identify optimal treatments.

Authors Contributions:
Sehar Aslam: Topic selection, study design, data collection, manuscript writing
Nadeem Sadiq: Study design, manuscript writing proof reading
Tariq Nadeem: Sample collection, study design, methodology
Awais Arshed: Sample collection, study design, methodology
Imrana Atta: Biostatistics
Kiran Minhas: Discussion, conclusion

REFERENCES

1. Griffin G, Shenoi S, Hughes GC. Hemophagocytic lymphohistiocytosis: An update on pathogenesis, diagnosis, and therapy. Best Pract Res Clin Rheumatol. 2020;34(4):101515. https://pubmed.ncbi.nlm.nih.gov/32387063/
2. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. Blood. 2020 ;135(16):1332–43. https://ashpublications.org/blood/article/135/16/1332/452577/Pediatric-hemophagocytic-lymphohistiocytosis
3. Chen X, Wang F, Zhang Y, Teng W, Wang M, Nie D, et al. Genetic variant spectrum in 265 Chinese patients with hemophagocytic lymphohistiocytosis: Molecular analyses of PRF1, UNC13D, STX11, STXBP2, SH2D1A, and XIAP. Clin Genet. 2018;94(2):200–12. https://pubmed. ncbi.nlm.nih.gov/29665027/
4. Chesshyre E, Ramanan AV, Roderick MR. Hemophagocytic lymphohistiocytosis and infections: An update. Pediatr Infec tDis J. 2019 38(3):e546. https://pubmed.ncbi.nlm. nih.gov/30461573/
5. Li J, Gao C, Zhu X, Yang D, Mao W, Yao H, et al. Hemophagocytic lymphohistiocytosis secondary to virus infection and followed by lupus nephritis recurrence in a renal transplantation pediatric recipient: a case report. BMC Nephrol. 2023;24(1). http://dx.doi.org/10.1186/s12882-023-03249-4
6. Nandhakumar D, Loganatha A, Sivasankaran M, Sivabalan S, Munirathnam D. Hemophagocytic lymphohistiocytosis in children. Indian J Pediatr. 2020 ;87(7):526–31. https://pubmed.ncbi.nlm.nih.gov/32056194/
7. Qiu K-Y, Guo S-Y, Zeng Y-H, Liao X-Y, Lin S-F, Fang J-P, et al. Analysis of clinical characteristics and prognostic factors associated with EBV-associated HLH in children. Hematology. 2022 ;27(1):874–80. https://pubmed.ncbi.nlm. nih.gov/35950974/
8. Kwak A, Jung N, Shim YJ, Kim HS, Lim HJ, Lee JM, et al. A retrospective analysis of etiology and outcomes of hemophagocytic lymphohistiocytosis in children and adults. Yeungnam Univ J Med. 2021 ;38(3):208–18. https://pubmed.ncbi.nlm. nih.gov/33242384/
9. Zhou Y-H, Han X-R, Xia F-Q, Poonit N-D, Liu L. Clinical features and prognostic factors of early outcome in pediatric hemophagocytic lymphohistiocytosis: A retrospective analysis of 227 cases. J Pediatr Hematol Oncol. 2022 ;44(1):e217–22. https://pubmed.ncbi.nlm.nih.gov/34986134/
10. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol. 2015;90(3):220–4. https://pubmed.ncbi.nlm.nih.gov/25469675/
11. Benevenuta C, Mussinatto I, Orsi C, Timeus F. Secondary hemophagocytic lymphohistiocytosis in children (Review). Exp Ther Med. 2023;26(3). http://dx.doi.org/1 0.3892/etm .2023.1212
12. Kim YR, Kim D-Y. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. Blood Res. 2021;56(S1):S17–25. https://pubmed. ncbi.nlm.nih.gov/33935031/
13. Zhang Z, Wang J, Ji B, von Bahr Greenwood T, Zhang Y, Wang Y, et al. Clinical presentation of hemophagocytic lymphohistiocytosis in adults is less typical than in children. Clinics (Sao Paulo). 2016;71(4):205–9. http://dx.doi.org /10.6061/clinics/2016(04)05
14. Abdullatif H, Mohsen N, El-Sayed R, El-Mougy F, El-Karaksy H. Haemophagocytic lymphohistiocytosis presenting as neonatal liver failure: A case series. Arab J Gastroenterol, 2016;17(2):105–9. https://pubmed.ncbi.nlm.nih.gov/27397412/
15. Amir AZ, Ling SC, Naqvi A, Weitzman S, Fecteau A, Grant D, et al. Liver transplantation for children with acute liver failure associated with secondary hemophagocytic lymphohistiocytosis. Liver Transpl. 2016 ;22(9):1245–53. https://pubmed.ncbi.nlm.nih.gov/27216884/
16. Koh K-N, Im HJ, Chung N-G, Cho B, Kang HJ, Shin HY, et al. Clinical features, genetics, and outcome of pediatric patients with hemophagocytic lymphohistiocytosis in Korea: report of a nationwide survey from Korea Histiocytosis Working Party. Eur J Haematol. 2015;94(1):51–9. https://pubmed .ncbi.nlm.nih.gov/24935083/
17. Huang Z, Jia Y, Zuo Y, Wu J, Lu A, Zhang L. Malignancy-associated hemophagocytic lymphohistiocytosis in children: a 10-year experience of a single pediatric hematology center. Hematology. 2020;25(1):389–99. https://pubmed.ncbi .nlm.nih.gov/33161882/
18. Tan CJ-W, Ng ZQ, Bhattacharyya R, Sultana R, Lee JH. Treatment and mortality of hemophagocytic lymphohistiocytosis in critically ill children: A systematic review and meta-analysis. Pediatr Blood Cancer. 2023;70(3). https://pubmed. ncbi.nlm.nih.gov/36579732/
19. Xu X-J, Wang H-S, Ju X-L, Xiao P-F, Xiao Y, Xue H-M, et al. Clinical presentation and outcome of pediatric patients with hemophagocytic lymphohistiocytosis in China: A retrospective multicenter study: XU ET AL. Pediatr Blood Cancer. 2017;64(4):e26264. https://pubmed.ncbi. nlm.nih.gov/27781387/
20. Ishii E. Hemophagocytic Lymphohistiocytosis in Children: Pathogenesis and Treatment. Front Pediatr. 2016 https://pubmed.ncbi.nlm.nih.gov/27242976/