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Hemophagocytic lymphohistiocytosis: pediatric hepatic perspective

Manal Hamdy El-Sayed[1], Salwa Mostafa Abd El Kader[1*], Fatma Soliman Elsayed Ebeid[1], Fatma Mohamed El-Shorbagy[1] and Iman Ahmed Ragab[1,2]

Abstract

Background Hepatic manifestations of hemophagocytic lymphohistiocytosis (HLH), an underrecognized primary presentation in pediatric age group, mandate high levels of suspicion for early diagnosis.

Aim This is to study the frequencies of clinical and laboratory hepatic involvement in patients with familial/primary or secondary/acquired HLH in relation to disease reactivation and outcome.

Methods A 6-month retrospective cohort study recruited 35 patients with HLH. Detailed clinical, laboratory, and genetic characteristics of HLH were collected. Hepatic transaminases and synthetic liver functions were collected at presentation, weeks 2 and 8 after starting treatment, and at time of reactivation. Biochemical liver involvement was considered when alanine aminotransferase (ALT) lived three-times more than the upper normal level. Overall (OS) and reactivation free survival were analyzed according to liver involvement.

Results Twenty patients (57%) had genetically confirmed HLH, 12 (34.3%) had MUNC13D mutations, 3 (8.5%) had STXBP2 mutations, and 5 (14.3%) had RAB27A mutations, while 9 (25.7%) had no genetic mutations with 4 of them had secondary HLH. Six patients (17.2%) patients had unknown genetics status. Median (IQR) age of the whole group was 18 months (6–36) with an age range of 2–108 months. Liver enlargement was detected at diagnosis in 29 (82.9%) and at reactivation in 18 (51.4%) patients. Eight (22.86%) patients had biochemical hepatic involvement at presentation with no significant difference in their demographic, initial clinical presentation, survival, or the type of mutant gene according to liver involvement.

Conclusion Variable hepatic biochemical involvement might be the presenting manifestation of HLH at diagnosis and upon reactivation, yet it did not impact disease outcome.

Keywords Hemophagocytic lymphohistiocytosis, HLH, Children, Pediatric, Liver

Introduction

Classically, hemophagocytic lymphohistiocytosis (HLH) has been divided into two types primary HLH which is attributed to germline mutations implicated in the cytotoxic dysfunction of the NK cell/CTL, presenting mainly in infancy and early childhood and acquired HLH which occurs in elder population [1]. The clinical findings of pediatric HLH are usually non-specific, and the eight important criteria to diagnose initially as HLH as proposed by the HLH-2004 study include persistent fever that is resistant to antibiotics and splenomegaly with or without hepatomegaly [2].

While hepatobiliary disorders in HLH are being increasingly described in both pediatric and adults; the characteristics of hepatic affection are variable [3]. Organomegaly with elevated liver enzymes, biphasic hyperbilirubinemia, and coagulopathy can occur early in the

*Correspondence:
Salwa Mostafa Abd El Kader
salwamostafa33@live.com
[1] Pediatrics Hematology Oncology and BMT Department, Faculty of Medicine, Ain Shams University, Cairo 11566, Egypt
[2] Ibn Sina National College of Medical Science, Jeddah, Saudi Arabia

disease, presenting a challenging diagnosis of hepatobiliary HLH [3]. In rare instances, acute hepatic failure may dominate the clinical picture, which in combination with hyperferritinemia may mimic neonatal hemochromatosis [4].

Cytokine-mediated hepatic damage includes wide range of biochemical changes such as hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, disseminated intravascular coagulation (DIC), and multi organ dysfunction (MOD), which if not treated early may lead to death in virtually all the patients [5].

We aimed to study the clinical and laboratory features of hepatic involvement in children with HLH, their frequencies, and the hepatic flares in relation to disease reactivation and disease outcome.

Patients and methods

This retrospective cohort study recruited 35 children diagnosed clinically as HLH including genetically confirmed primary HLH as well as patients with secondary HL. Patients with confirmed other liver diseases by genetic testing as inborn errors of metabolism with primary hepatic affection were excluded.

Patients were recruited from Pediatric Hematology oncology Clinic, Children's Hospital, Ain Shams University during the period 1 April 2021 to 30 September 2021. The study was approved by the institutional Regulatory Board of Pediatrics Department, Faculty of Medicine, Ain Shams University as well as the Research Ethics Committee, Faculty of Medicine, Ain Shams University (FMASU M S 284/2021) with Assurance No. FWA00017585 in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans (2013).

Revising the records for included patients was performed with emphasis on detailed history including demographic data, perinatal history, consanguinity, family history of any similar conditions or related conditions, sibling death or abortions, disease presentation including age of disease presentation, presenting symptoms of the disease, HLH criteria, disease progression, and disease response to treatment. A detailed revision of the hepatic presenting symptoms or developing hepatic symptoms within the course of the disease at time of initial presentation and at each scheduled visit was recorded.

Laboratory investigations were recorded at different time points initially at time of presentation, at weeks 2 and 8 after treatment start, and at time of reactivation. Parameters included in HLH–2004 criteria including complete blood counts (CBC) (Sysmex XP300, Sysmex, Germany), ferritin (Cobas E 411, Roche, Germany), fibrinogen (Stago, Stago, France), and triglycerides (AU480, Beckman coulter, American) were recorded. Full liver function tests including hepatic transaminases; alanine aminotransferase (ALT), aspartate aminotransferase (AST) (AU 480, Beckman coulter, USA), synthetic prothrombin time (PT), partial thromboplastin time (PTT) (Stago, Stago, France), serum albumin, serum total bilirubin, serum direct bilirubin (AU480, Beckman coulter, USA), viral screen (Cobas E411, Roche, Germany), and results of molecular analysis for known mutations for familial HLH together with bone marrow aspirate and biopsy when applicable were recorded.

Pelviabdominal ultrasound comparing sonographic hepatic size to age adjusted normal size [6] and/or computerized tomography results was recorded, and liver biopsy with detailed description of histopathology was collected from patient's files.

Hepatic involvement was considered if elevated hepatic transaminase (ALT and/or AST) were more than three folds the upper limit for normal with the minimum of grade 1 toxicity according to CTCAE [7].

Method of genetic analysis

For FHL genetic screening, segregation analysis of polymorphic markers at perforin encoding gene (*PRF1*), Munc13-4 encoding gene (*UNC13D*), syntaxin11 encoding gene (*STX11*), and Munc18-2 encoding gene (*STXBP2*) was first performed in consanguineous families followed by Sanger sequencing of the suspected gene. In non-consanguineous families, a dedicated next generation sequencing panel was more recently used, and the identified mutations were confirmed by Sanger sequencing.

Patients were treated at first presentation according to the HLH-2004 protocol [8]. Reactivation was considered when had achieved remission and develop at least 3 of the initial diagnostic criteria for HLH or new CNS symptom.

Statistical analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as numbers and percentages, while quantitative data were presented as mean and standard deviations when their distribution found parametric. Interquartile ranges and minimum maximum were added when non-parametric data are presented. The comparison between two groups with qualitative data were done by using Chi-square test, and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found less than 5. The comparison between two independent groups with quantitative data was done by using Mann–Whitney if non-parametric. Overall survival was the time from start of treatment to death from any cause. Reactivation free

survival and OS were estimated using the Kaplan–Meier survival analysis, and comparisons between the different prognostic factors were made using the log-rank test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the *p* value was considered significant if < 0.05.

Results

Out of 35 recruited patients, 20 patients (57%) had genetically confirmed HLH, 12 of them (34.3%) had MUNC13D mutations, 3 (8.6%) had STXBP2 mutation, and 5 (14.3%) had RAB27A mutation (Fig. 1). Nine (25.7%) patients had no genetic mutation with 4 of them having secondary HLH with underlying disease systemic onset juvenile idiopathic arthritis, Langerhans cell histiocytosis, selective IgA, and acute EBV infection in those patients respectively, while 6 (11.4%) patients had not undergo molecular studies, so their genetic status is unknown. The median (IQR) age of the studied patients at enrolment to the study was 18 months (6–36) and at initial presentation was 6 months (3–18); 57.1% ($n=20$) were males and 42.9% ($n=15$) females, 60.0% ($n=21$) had first cousin consanguineous parents, 37.1% ($n=13$) showed positive family history of similar condition, and 40.0% ($n=14$) had history of sibling death.

Comparison of initial parameters according to hepatic involvement

Recruited patients were sub-grouped according to whether they had biochemical hepatic involvement or not at time of presentation into 2 groups, group A without hepatic involvement which included 27 (77.14%) and group B patients with hepatic involvement which included 8 (22.86%) patients. By comparison of both, there was no difference as regards demographic data, age at presentation, their clinical presentation, the type of HLH either primary or secondary, the type of mutant gene, or the survival of both groups as illustrated in Tables 1 and 2.

The main presenting symptoms of the total group were fever in 29 (82.9%) patients with HLH, pallor 13 (37.1%); 29 (82.9%) had liver enlargement, 30 (85.7%) had splenomegaly, and 17 (48.6%) had neurological symptoms. There was no significant difference in presenting symptoms comparing groups A and B.

As regards the radiological findings, the standard deviation score of the sonographic liver size for age was as follows:

- Patients age from 0 to < 3 m maximum size 80 mm, minimum size 20 mm, mean 51 mm, − 0.9 SD
- Patients age from 3 to < 6 m maximum size 125 mm, minimum size 30 mm, mean 66 mm, − 0.4 SD
- Patients age from 6 to < 12 m maximum size 100 mm, minimum size 30mm, mean 62 mm, − 1.7 SD
- Patients age from 12 to < 2 years maximum size 100 mm, minimum size 20mm, mean 54 mm, − 2.8 SD
- Patients age from 2 to < 4 years maximum size 120 mm, minimum size 40 mm, mean 66 mm, − 2.3 SD
- Only one patient age > 4 years size 110 mm, + 0.6 SD

Only two of patients (5.7%) with HLH underwent liver biopsy to exclude other causes of hepatic diseases because of the poor response of liver size to HLH treatment. Biopsy revealed bile duct pathology in both patients, while as regards hepatocellular pathology, one had storage liver disease, and the other patient had intact liver architecture; diagnostic workup for liver storage disease was negative for the first patient.

Comparison of follow-up-parameters according to hepatic involvement

Re-activation was reported in 32 (91.4%) patients with 3 patients (8.6%) had CNS reactivation; while systemic reactivation showed hepatic manifestations in 18 (51.4%) patients and hematologic manifestations in 11 (31.4%) with the median (IQR) duration until reactivation was 3 (1–5) months with a range 1–33. When comparing the

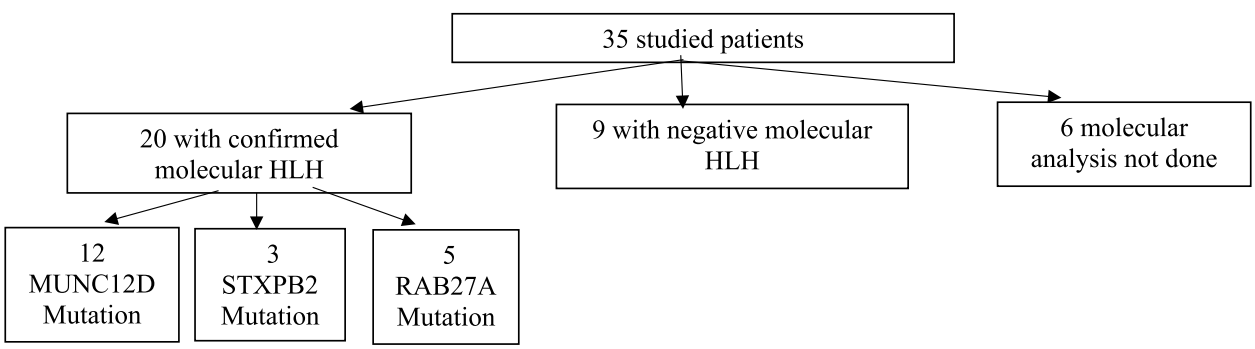

Fig. 1 Distribution of the studied patients according to molecular analysis

Table 1 Demographic and clinical characteristics of children with hemophagocytic lymphohistiocytosis without (group A) and with (group B) hepatic involvement

	Hepatic involvement at presentation		*P* value
	Group A (without) *N* = 27	Group B (with) *N* = 8	
Demographic characteristics			
Age of enrollment (months) Median (IQR) Min–max	18 (6–36) 2–108	18 (12.5–30) 5–66	0.649‡
Sex (female, male); *n* (%)	11 (40.7%), 16 (59.3%)	4 (50.0%), 4 (50.0%)	0.642^
Positive consanguineous parents; *n* (%)	17 (63.0%)	4 (50.0%)	0.511^
Positive family history; *n* (%)	11 (40.7%)	2 (25.0%)	0.418^
Sibling death	11 (40.7%)	3 (37.5%)	0.869^
Age at time of presentation (months); median (IQR) Min–max	6 (3–18) 1–84	6 (5–24) 1–66	0.549‡
Genetic profile; *n* (%)			
Genetic mutation confirmed	16 (59.3%)	4 (50.0%)	0.132^
MUNC13D STXBP2 RAB27A	10 (37.0%) 1 (2.7%) 5 (18.5%)	2 (25.0%) 2 (25.0%) 0 (0.0%)	
Genetic mutation excluded	7 (25.9%)	2 (25.0%)	
Unknown	4 (14.8%)	2 (25.0%)	
Secondary HLH	2 (7.4%)	2 (25.0%)	0.245^
Type of reactivation; *n* (%)			
No	2 (7.4%)	1 (12.5%)	0.614^
Central nervous system	2 (7.4%)	1 (12.5%)	
Hepatic involvement	13 (48.1%)	5 (62.5%)	
Hematologic involvement	10 (37.0%)	1 (12.5%)	
Outcome; *n* (%)			
Died	15 (55.6%)	5 (62.5%)	0.833^
Survived	11 (40.7%)	3 (37.5%)	
Unknown	1 (3.7%)	0 (0.0%)	
Duration until reactivation (months); median (IQR), range	3 (1–5), 1–33	2.5 (1.5–4.5), 1–8	0.779‡
OS (months); median (IQR), range	7.5 (4–12), 2–51	7 (3–9), 2–14	0.427‡

^ Fisher exact; ‡Mann–Whitney test, *IQR* interquartile range

initial laboratory results at presentation and during HLH reactivation, there was significantly higher platelets and WBCs count at reactivation compared to initial presentation ($p=0.005$, 0.24 respectively). By comparing the biochemical liver tests at initial presentation to those at reactivation, there was no difference in median (IQR) ALT 30.5 (17.5 – 100) IU/L, range 3 – 3287, total bilirubin 1.5 (0.7 – 3), range 0.3 – 13.8 mg/dl, direct bilirubin 0.8 (0.2 – 2.3), range 0.1 – 9.5 mg/dl at initial presentation while at to reactivation setting, 60.5 (19 – 162), range IU/L; 1.85 (0.7 – 2.1), range 0.1 – 23 and 0.9 (0.4 – 1.9) mg/dl, range 0.1 – 11 mg/dl, respectively P>0.05.

Laboratory results of patients with HLH illustrate the course from presentation to different time points; hemoglobin, platelets, and WBCs were significantly increased ($p<0.001, <0.001$, and 0.005 respectively), while changes in other laboratory results were not clinically significant. As regards CMV and EBV affection as assessed by IgG and IgM of patients with HLH according to hepatic involvement, there was a significant higher number of patients with EBV IgG positive in those with hepatic involvement ($n=8$; 100%) compared to those without ($n=14$; 51.9%) ($p=0.047$) as depicted in Table 3.

As regards the outcome of included patients; the 1-year survival was 40.0% (n=14) with a median overall survival rate of 7.5 months (2–51), 17.1% (n=6) underwent HSCT, five of them had no hepatic involvement at presentation. The comparison between the two groups as regards OS and reactivation-free survival is illustrated in Fig. 2.

Discussion

HLH is a hyper-inflammatory disorder caused by systemic overgrowth of macrophages in the reticulo-endothelial system leading to cytokine storm, presented

Table 2 Comparison of laboratory results of children with hemophagocytic lymphohistiocytosis according to hepatic involvement

	Hepatic involvement at presentation		***P* value**
	Group A (without) ***N*** **= 27**	**Group B (with)** ***N*** **= 8**	
TAG (mg/dl); median (IQR), range			*P* value‡
Initial	293 (183–387), 97–1380	343 (184.5–746.5), 82–1049	0.644
2 weeks	196 (163–348), 59–920	175 (104–257), 89–304	0.464
8 weeks	188 (92–411), 44–604	177.5 (123–257.5), 121–285	0.960
Reactivation	298.5 (172–426), 105–670	319.5 (186.5–412), 73–485	0.865
Fibrinogen (mg/dl); mean ± SD (range)			P-value•
Initial	1.51 ± 0.75 (0.5–3.3)	1.33 ± 0.83 (0.6–3.2)	0.566
2 weeks	2.55 ± 1.46 (0.7–6)	1.96 ± 0.97 (0.1–3.2)	0.330
8 weeks	2.61 ± 0.79 (1.2–4.1)	2.77 ± 1.46 (1.2–4.1)	0.787
At end of therapy	3.53 ± 2.60 (1–9.8)	3.20 ± 1.13 (2.4–4)	0.867
Reactivation	2.21 ± 1.03 (0.6–4)	1.67 ± 0.67 (1.1–2.4)	0.398
Ferritin (ng/ml) median (IQR), range			*P* value‡
Initial	1315 (66–4244), 132–130,000	951.25 (102–2077), 12.25–15,910	0.239
2 weeks	805 (398–2061), 86–11,250	781 (615–800), 61.7–1720	0.445
8 weeks	673 (40–1896), 254–13,000	1245 (957–1754.5), 933–2000	0.347
At end of therapy	462 (244–2000), 116–3258	987.5 (112–1863), 112–1863	0.553
Reactivation	1839 (600–2045), 212–48,280	1730 (831–2629), 831–2629	0.810
ALT (IU/L); median (IQR), range			*P* value‡
Initial	28 (14.5–41.5), 3–586	159.5 (30.5–301.5), 5–3287	0.047
2 weeks	34 (21–50), 12–166	73 (16.5–134.5), 10–146	0.858
8 weeks	22 (20–47), 11–75	23 (22–27), 11–119	0.777
At end of therapy	31 (23–40), 10–47	88.5 (29–148), 29–148	0.380
Reactivation	47.5 (19–162), 15–284	101.5 (29–158.5), 6–166	1.000
AST (IU/L); median (IQR), range			*P* value‡
Initial	31 (20–50), 8–318	103 (25.5–183), 7–1373	0.193
2 weeks	35 (30–43), 11–185	33.5 (13.5–58.5), 12–65	0.858
8 weeks	21 (20–30), 20–33	28 (19–33), 10–51	1.000
At end of therapy	26 (18–43), 15–47	32 (28–36), 28–36	0.558
Reactivation	40 (20–142), 12–654	110 (56–222), 56–222	0.173
PT (sec); mean ± SD (range)			*P* value•
Initial	25.10 ± 15.96 (11.5–60)	21.70 ± 9.37 (13.5–34.1)	0.710
2 weeks	15.30 ± 6.92 (11.5– 30.8)	14.10 ± 0.79 (13.5–15)	0.779
PTT (sec); mean ± SD (range)			P value•
Initial	50.38 ± 27.89 (33.7–120)	45.92 ± 15.66 (26.5–60)	0.750
2 weeks	38.02 ± 14.64 (24.6–54.5)	34.05 ± 9.83 (27.1–41)	0.745
Total bilirubin (mg/dl); median (IQR), range			*P* value‡
Initial	1.5 (0.8–3), 0.5–13.4	0.7 (0.6–6.5), 0.3–13.8	0.525
2 weeks	1.05 (0.4–1.8), 0.1–8.1	1.9 (1.1–3.7), 1.1–3.7	0.271
Reactivation	1.8 (0.7–2.1), 0.5–8.9	2 (0.1–23), 0.1–23	0.732
Direct bilirubin (mg/dl); median (IQR), range			*P* value‡
Initial	0.99 (0.2–2.3), 0.2–9.5	0.8 (0.2–5.3), 0.1–7.4	0.678
2 weeks	0.3 (0.1–1.1), 0.1–5.2	0.7 (0.4–2), 0.4–2	0.351
Reactivation	1.1 (0.4–1.9), 0.1–5.7	0.9 (0.6–11), 0.6–11	0.437
Albumin (g/dl); mean ± SD (range)			*P* value•
Initial	3.03 ± 0.96 (2.1–4.5)	2.92 ± 0.75 (2–3.8)	0.823
2 weeks	3.33 ± 0.99 (2.5–4.5)	3.50 ± 0.56 (2.9–4)	0.798
Reactivation	2.70 ± 0.77 (1.7–3.8)	2.78 ± 1.26 (1.5–4)	0.904

•Independent t-test; ‡Mann–Whitney test

Table 3 Comparison of CMV and EBV affection of patients with HLH according to hepatic involvement

		Hepatic involvement				*P* value
		Group A (negative)		Group B (positive)		
		No	%	No	%	
CMV IgM	Negative	16	59.3%	6	75.0%	0.619
	Positive	3	11.1%	1	12.5%	
	Unknown	8	29.6%	1	12.5%	
CMV IGG	Negative	14	51.9%	7	87.5%	0.174
	Positive	5	18.5%	0	0.0%	
	Unknown	8	29.6%	1	12.5%	
EBV IGM	Negative	12	44.4%	7	87.5%	0.084
	Positive	7	25.9%	1	12.5%	
	Unknown	8	29.6%	0	0.0%	
EBV IGG	Negative	14	51.9%	8	100.0%	0.047
	Positive	5	18.5%	0	0.0%	
	Unknown	8	29.6%	0	0.0%	

P value > 0.05: non-significant (NS). *P* value < 0.05: significant (S). *P* value < 0.01: highly significant (HS)

* Chi-square test

Group A = HLH patients without hepatic involvement

Group B = HLH patients with hepatic involvement

mainly with fever, splenomegaly, bi/pancytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia, which can progress early to multiorgan dysfunction with dismal outcome [9]. Hepatic manifestations are not a well-recognized primary presentation in pediatric patients with HLH, thus mandating high levels of suspicion for early diagnosis [10].

In the current study, 82.7% of patients had hepatomegaly, and 22.8% had biochemical hepatic involvement. HLH can present with wide range of hepatic dysfunction ranging from mild elevation of transaminases to liver failure. This percent of biochemical alteration in the current study is lower than that reported in a Turkish study of 57 patients with HLH, where they found that hepatic involvement was defined as elevated bilirubin, transaminases, low albumin levels, and coagulopathy in 46% of their cohort [11], and a Saudi study, where 83% had abnormal liver function tests [12]. In another Iranian study, liver transaminases were abnormal in 41.7% of the whole group of children with HLH and in 52% of primary HLH [13]. In the Italian registry, 12 out of 500 patients presenting with HLH had liver failure at presentation [14]. Due to the pathogenesis of HLH, the macrophage that derived IL-2, IFN-γ, and TNF-α mediated inflammation is predominantly porto-sinusoidal without any significant alteration in lobular architecture, which in turn produces raised transaminases, hepatocyte hemosiderosis, sinusoidal dilatation and congestion, Kupffer cell hyperplasia, and hypertrophy producing hemosiderosis and hemophagocytosis. Furthermore, lymphocytes- or lymphohistiocyte-mediated biliary ductular injury and cytokine (IL 1, IL 6, and TNF-α) mediated impaired lipoprotein lipase activity causes cholestasis, hyperbilirubinemia, and hypertriglyceridemia [15].

In a trial to find any etiologic difference in patients with or without hepatic involvement, there was no difference in age, gender, or distribution of molecular subtypes between both groups. In the Turkish study, the majority of patients with hepatic involvement were less than 2 years of age [11]. Regarding the molecular results, in a study of 78 children with acute liver failure, 30 fulfilled HLH criteria; of those, the most common mutation had PRF mutation [16].

We could not find a difference in EBV or CMV status according to hepatic alteration; yet, we did not study other viral etiologies. In some case series, they had reported that LCF and HLH presentation had high possibility of underlying viral infection [17].

In our study, only two of patients with HLH had liver biopsy that revealed bile duct pathology, storage liver disease, and mild steatosis. Liver histology is very variable in patients with HLH; bile duct pathology has been previously reported up to vanishing bile duct [18]. In a study examining different liver histology in patients with HLH, portal/sinusoidal infiltrate with lymphocytes and histiocytes exhibited hemophagocytosis was observed. Four histopathologic patterns were observed, chronic hepatitis-like, leukemia-like, histiocytic storage disorders-like,

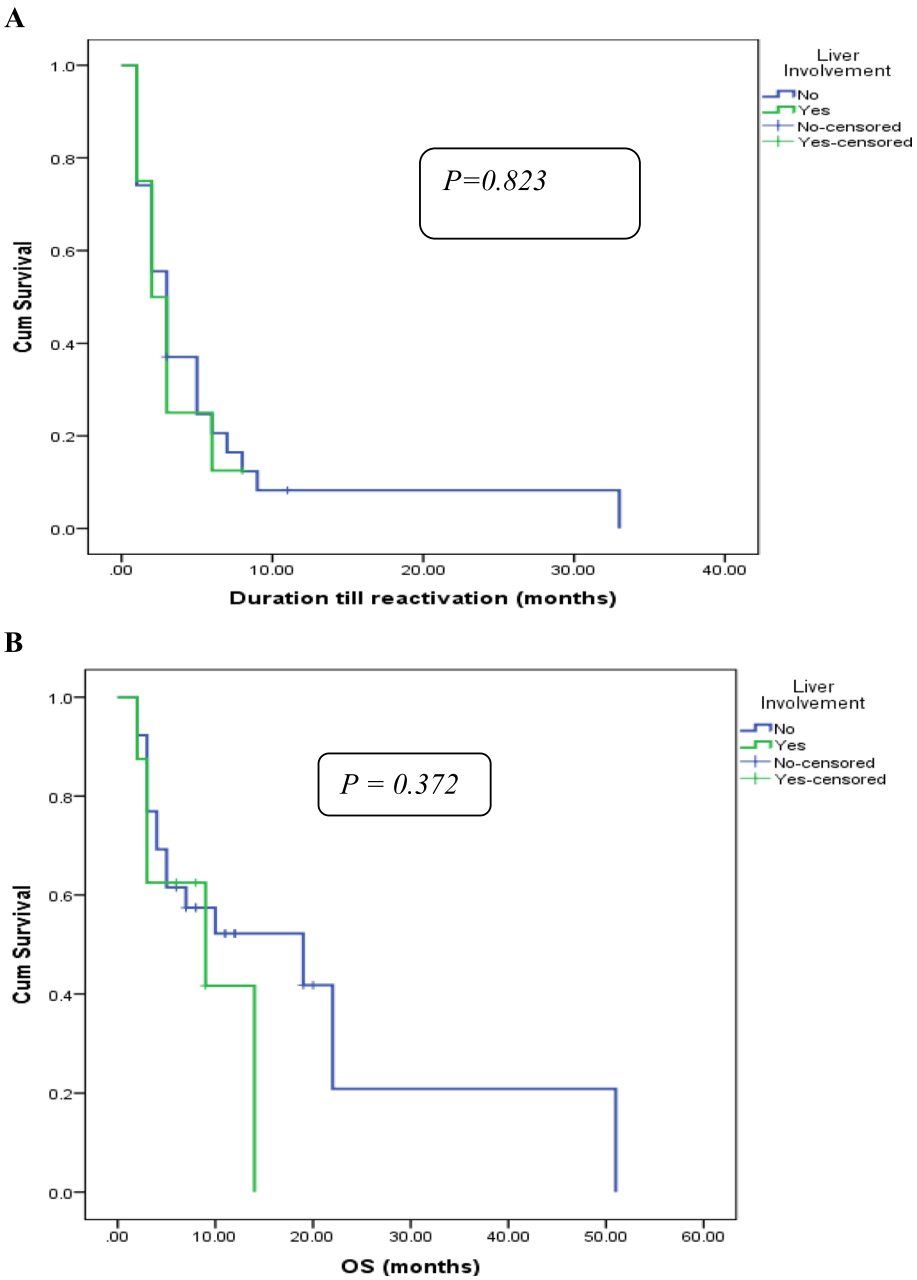

Fig. 2 Kaplan–Meier survival curve for the cumulative (cum) overall survival according to the log rank test of children with hemophagocytic lymphohistiocytosis. **A** Duration till reactivation (months) and **B** Overall survival between patients with and without hepatic involvement

and neonatal giant hepatitis-like [19]. On the other hand, according to a the study done in academic liver transplant center liver biopsies showing diffuse lobular necro inflammation, HLH can present as acute liver failure (ALF), early diagnosis is critical, and high degree of suspicion should be exercised in patients with unexplained ALF [19].

Regarding the impact of initial hepatic involvement on reactivation and survival, there is no significant difference according to hepatic involvement in the current study; furthermore, there was impact on survival. These findings were similar to the Turkish study, where a 5-year survival did not differ according to hepatic involvement [11]; yet in studying, in patients less than 2 years of age, the 5-year survival rate of the patients with hepatic involvement was significantly lower than those

without hepatic involvement. The impact is mostly related to the severity of hepatic involvement. In a retrospective study of 11 patients with liver cell failure to HLH, 54% of patients died [20].

Conclusion

Hepatic manifestations including variable transaminitis are an underrecognized presentation of HLH at diagnosis and upon reactivation in pediatric age group. There is no clear association between age, CMV, EBV status, and molecular subtype with biochemical hepatic affection in HLH. There is no difference in outcome according to hepatitis; yet due to small number patients with liver cell failure, further analysis of those severe cases needs to be considered in larger series.

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None

Authors' contributions
The corresponding author, on behalf of all authors, hereby states that all authors have contributed to the manuscript in significant ways, have reviewed, and have agreed upon the manuscript content.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
The study was approved by the institutional Regulatory Board of Pediatrics Department, Faculty of Medicine, Ain Shams University as well as the Research Ethics Committee, Faculty of Medicine, Ain Shams University (FMASU M S 284/2021) with Assurance No. FWA00017585. This is a retrospective cohort study; informed consent was obtained whenever applicable.

Consent for publication
We did not include any identifying images or other personal details of participants that may compromise anonymity.

Competing interests
The authors declare no conflict of interest. They do not have a commercial or other association that might pose a conflict of interest (e.g., pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding).

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