Clinical and Experimental Medicine (2025) 25:58
https://doi.org/10.1007/s10238-025-01570-w

RESEARCH

Assessing the effectiveness of etoposide treatment in adult haemophagocytic lymphohistiocytosis: a systematic review and meta-analysis

Tiankuo Gao[1] · Dina Suolitiken[1] · Chun Yang[1] · Chaofan Wu[2] · Lingbo He[3] · Yini Wang[1]

Received: 3 October 2024 / Accepted: 17 January 2025

Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a serious condition characterised by uncontrolled hyperinflammation. Etoposide has been used as a treatment option in paediatric HLH; however, its effectiveness and the necessity for adult induction therapy remain unclear. This systematic review and meta-analysis aimed to assess the effectiveness of etoposide-based induction therapy in adult HLH, focusing on overall response (OR). A systematic literature search was conducted to identify relevant studies on 11 December 2023, resulting in the inclusion of seven studies in the analysis. The pooled data demonstrated a significant improvement in OR with etoposide-based therapy in adult patients with HLH (1.95, 95% CI 1.51–2.53), compared with non-etoposide-treated patients. Furthermore, overall survival improved with etoposide treatment (1.25, 95% CI 1.03–1.52). Our analysis revealed the potential benefit of etoposide-based therapy in adult patients with HLH. Therefore, etoposide should be considered as a timely and early therapeutic option for the management of adult HLH.

Keywords Haemophagocytic lymphohistiocytosis · Etoposide · Systematic review · Meta-analysis

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is an uncommon and potentially fatal condition characterised by an overactive immune system, leading to excessive inflammation and tissue damage. This disorder can be caused by genetic mutations that typically affect the function of cytotoxic cells, most often occurring in children, whereas various non-Mendelian triggers such as infections, autoimmune disorders, and malignancies are the most common causes of HLH in adults. HLH occurring alongside autoimmune diseases is also referred to as macrophage activation syndrome (MAS), and its recognition is increasing in adults [1]. Malignancy-triggered HLH, especially lymphoma-associated HLH (LAHS), together with infection-associated HLH, is the most common cause of secondary HLH [2, 3]. Without appropriate treatment, the prognosis in HLH is poor and for such patients a median survival time of between 1 and 2 months and a survival rate of below 5% have been reported [4]. However, survival rates have increased markedly over the last decades, and with etoposide-based first-line therapy, a 3-year survival of 77% has recently been reported [5]. The overall mortality rate of adult HLH has been estimated to about 40% [3]. Paediatric patients with HLH are typically treated with a combination of chemotherapy, steroids, and immunosuppressants. Aggressive immunosuppression and supportive care are important components of treatment to alleviate symptoms and improve survival. The HLH-94 protocol, which includes etoposide, has been widely used to improve the survival rates of paediatric patients [6]. Supported by expert opinions, etoposide has been widely adopted as the preferred medication for managing severe adult HLH in clinical practice, primarily based on paediatric experience [7]. A previous meta-analysis suggested that etoposide did not improve overall survival (OS) in adult patients with HLH. However, as the authors stated, these results are highly susceptible to bias because OS

✉ Yini Wang
wangyini@ccmu.edu.cn

1 Department of Hematology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing 100029, China

2 Department of Hematology, Capital Medical University Affiliated Beijing Friendship Hospital, Beijing 100050, China

3 Department of General Medicine, Capital Medical University Affiliated Beijing Friendship Hospital, Beijing 100050, China

Published online: 15 February 2025

is related to multiple factors [8]. Overall response (OR) is an important factor that affects OS and can be used to measure the effectiveness of treatment. Currently, a meta-analysis of adult HLH and etoposide in relation to OR is lacking. Therefore, in this study, we aimed to evaluate the effectiveness of etoposide in adult patients with HLH, using OR as the primary endpoint. We also selected OS as the secondary endpoint to investigate the relationship between OR and OS. Based on the available evidence, we aimed to determine whether etoposide has been effective in adult HLH.

Material and methods

Search strategy

Under the PRISMA guidelines [9], a comprehensive literature search was performed across four online databases (PubMed, Embase, Web of Science, and Cochrane) covering the period from database establishment to 11 December 2023. Search terms included: hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, HLH, haemophagocytic lymphohistiocytosis, hemophagocytic syndrome, HPS, Haemophagocytic syndrome, macrophage activation syndrome, MAS, erythrophagocytosis, hypercytokinaemia, hemophagocytic activation syndrome, lymphoma-associated hemophagocytic syndrome, LAHS, etoposide, etoposide derivative, riboposid, citodox, celltop, epsidox, etomedec, eposin, nexvep, etophos, etomedac, etopol, etopos, etopoxan, etoposido, etosid, vp-tec, vp-16, vp16, vp-16213, vp16-213, vp16213, lastet, lastet-s, nsc-141540, nsc141540, posid, toposar, topresid, vepesid, vepeside, and vespid.

Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were: (1) studies involving patients aged ≥ 18 years or studies with separately reported adult data; (2) studies that reported treatment response; and (3) studies including patients diagnosed with HLH.

The exclusion criteria were: (1) non-English articles; (2) studies including conferences, case reports, meta-analyses, and review literature; (3) studies with fewer than three patients treated with etoposide or fewer than three patients treated without etoposide; and (4) duplicate studies from the same population, with only most recent studies included.

Two reviewers independently screened the titles and abstracts of the selected studies. Full-text articles were acquired from the relevant studies. Any differences between the reviewers were resolved through discussion or consultation with a third reviewer, if required.

Data extraction

To extract the necessary details from each study, two investigators collected the following information: study name, first author, year of publication, country of publication, sample size, definition of response, potential triggers linked to HLH, treatment response, and survival status at the end of the study. In this study, the OR was defined as a combination of complete response and partial response.

Risk of bias assessment

Two reviewers independently used the Newcastle–Ottawa Scale (NOS) to conduct a quality assessment of the non-randomised trials included in the study. Scores falling between 7–9, 4–6, and 0–4 were categorised as a low, moderate, and high risk of bias, respectively.

Statistical analysis

For this meta-analysis, statistical analyses and forest diagrams were constructed using *R* software version 4.3.1. Binary data were evaluated using the relative risk (RR) with a 95% confidence interval (95% CI). The I^2 statistic was used to assess heterogeneity among the studies, and a common-effects model was applied when I^2 was < 50%. Funnel plots were used to evaluate publication bias. To investigate the impact of the results in various directions on the final outcomes, subgroups were analysed based on the different etiological triggers of HLH. A sensitivity analysis was used to assess the influence of each study on the overall findings. Values were considered statistically significant at $P < 0.05$.

Result

Literature search

A total of 4002 studies potentially meeting our criteria were identified across the selected databases. After removing duplicates, 3345 relevant studies remained. After screening the titles and abstracts of these studies, 3241 of them were excluded after further consideration. Of the remaining 104 records, seven met the inclusion criteria. The literature search and screening processes are summarised in Fig. 1.

This meta-analysis included seven studies that satisfied the selection criteria. All the studies were retrospective in nature. Across these studies, 238 evaluable patients were enrolled. Four studies included patients with LAHS, two included patients with MAS, and one focused on pregnant

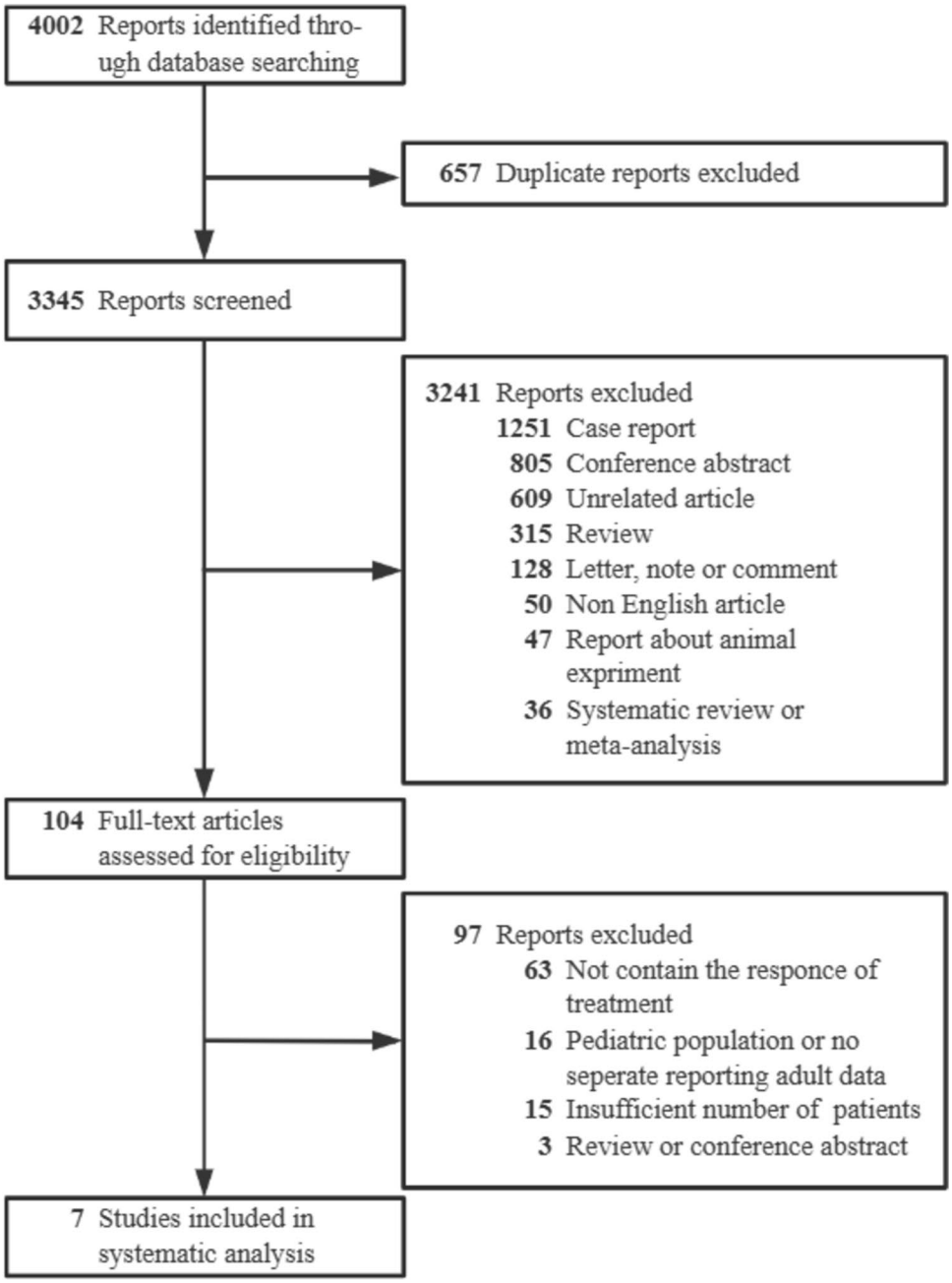


Fig. 1 Flowchart of the literature search and screening

women. Quality assessment using the NOS classified six studies as low risk, while one report was classified as having an intermediate risk. These findings indicated that the overall quality of the included articles was high. Table 1 presents the characteristics of all the included studies.

Meta-analysis results

All seven studies provided data on OR. Owing to the low heterogeneity between studies ($I^2 = 9\%$), we chose the common-effects model. The pooled analysis of OR was 1.95 (95% CI 1.51–2.53), indicating statistical significance between etoposide-treated patients and non-etoposide-treated patients (Fig. 2). A symmetrical forest plot, illustrating the RRs of individual study, indicated that no publication bias existed (Fig. 3). Sensitivity analysis was conducted to assess the impact of each individual study on the OR outcomes. The results fluctuated around 1.95, suggesting that the data were relatively stable and credible (Fig. 4).

All studies were stratified into subgroups according to the trigger type. In the MAS and LAHS groups, the pooled proportion of OR was 2.08 (95% CI 1.56–2.79) and 1.90 (95% CI 0.78–4.65), respectively, and low heterogeneity was found in both groups (Fig. 5).

Table 1 Characteristics and quality evaluation results of the seven studies

No.	Author	Year	Country	Trigger	Sample size		Supporting the effect of etoposide	Risk of bias according to NOS	Reference
					OR	OS			
1	He et al.	2022	China	Autoimmune diseases	118	118	Yes	Low risk	[10]
2	Wang et al.	2022	China	AOSD	28	28	Yes	Low risk	[11]
3	Song et al.	2019	China	Pregnancy	13	13	Yes	Intermediate risk	[12]
4	Jia et al.	2016	China	ENKTL	22	22	NS	Low risk	[13]
5	Han et al.	2014	China	T-cell lymphoma	18	22	NS	Low risk	[14]
6	Li et al.	2014	China	Lymphoma	10	16	NS	Low risk	[15]
7	Han et al.	2007	Korea	Lymphoma	12	19	NS	Low risk	[16]

AOSD, Adult-onset Still's disease; ENKTL, extranodal NK/T-cell lymphoma; OR, overall response rate; OS, overall survival; NS, not state

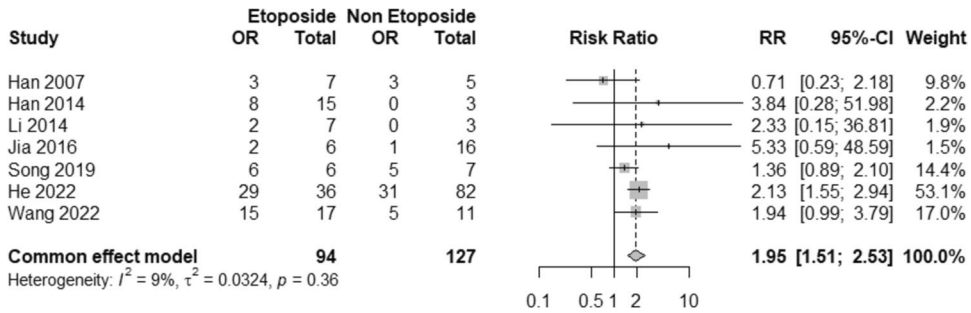


Fig. 2 Forest plot comparing overall response (OR) between etoposide-treated and non-etoposide-treated patients

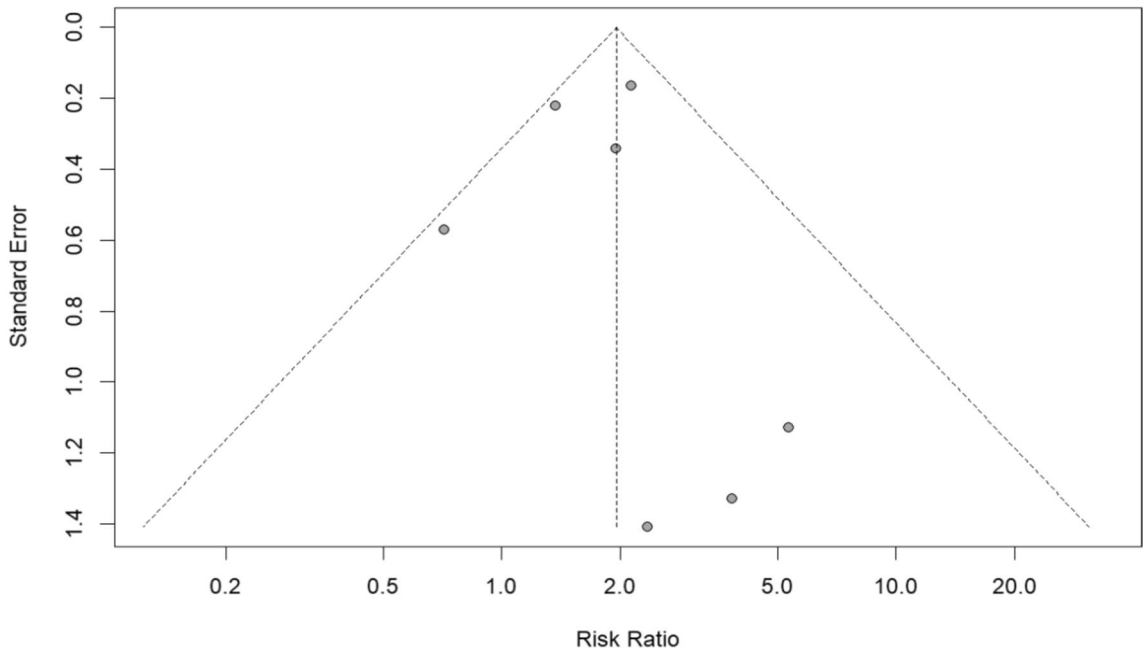


Fig. 3 Funnel plot for OR

Data on OS were also extracted. One article did not provide survival outcomes directly; therefore, alive patients at the end of follow-up were considered as survival [16]. Low heterogeneity was observed among these seven studies ($I^2 = 9\%$). The pooled proportion of OS was 1.25 (95% CI 1.03–1.52) (Fig. 6). The funnel plot remained symmetrical, indicating a lack of publication bias (Fig. 7). The results of the sensitivity test of the OS fluctuate around 1.25 stably (Fig. 8).

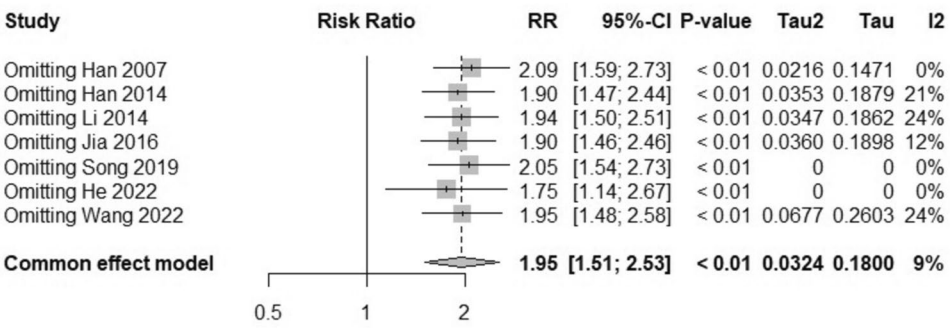


Fig. 4 Sensitivity analysis of OR

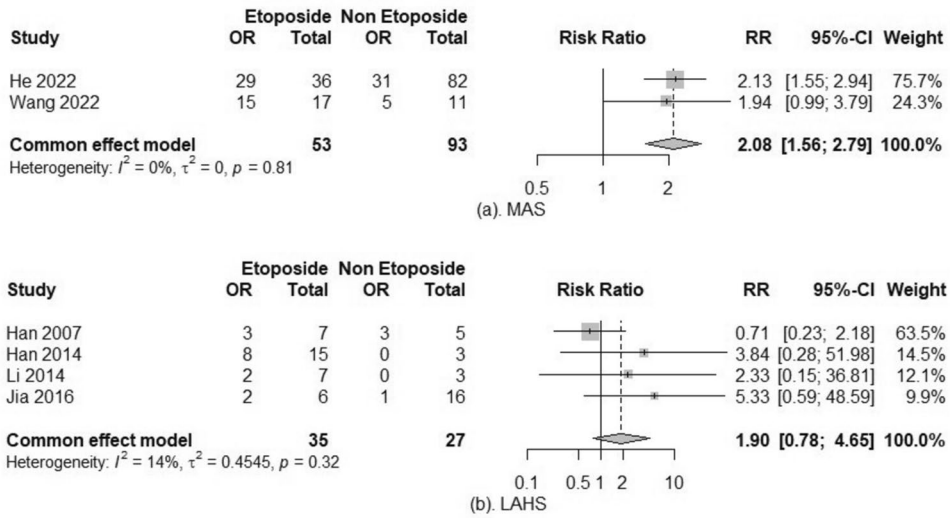


Fig. 5 Forest plot of OR in the **a** MAS and **b** LAHS groups

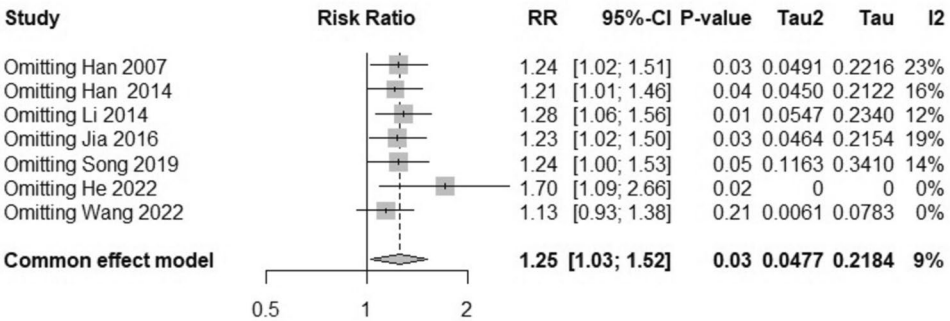


Fig. 6 Forest plots comparing overall survival (OS) between etoposide-treated and non-etoposide-treated patients

Discussion

The effectiveness of etoposide-based therapy (HLH-94 protocol) in the treatment of paediatric HLH is widely recognised and supported by the results of two rigorous clinical trials [17, 18]. The development of HLH is attributed to heightened activation of natural killer (NK) cells and cytotoxic T lymphocytes. The therapeutic mechanism of etoposide has been identified in a mouse model of T-cell proliferation and cytokine secretion [19]. Early use of etoposide has also been found to effectively improve outcomes in young adult patients with EBV-HLH [20]. In our study, a significantly higher response probability was observed in the etoposide-treated patients. In a study by He et al. [10], not only patients who were initially treated with etoposide but also those who switched to etoposide-based treatment after the glucocorticoid regimen showed a better response than patients not receiving etoposide during the entire therapy process. A retrospective cohort study on Epstein–Barr virus-associated HLH indicated that the inclusion of etoposide in the initial treatment can

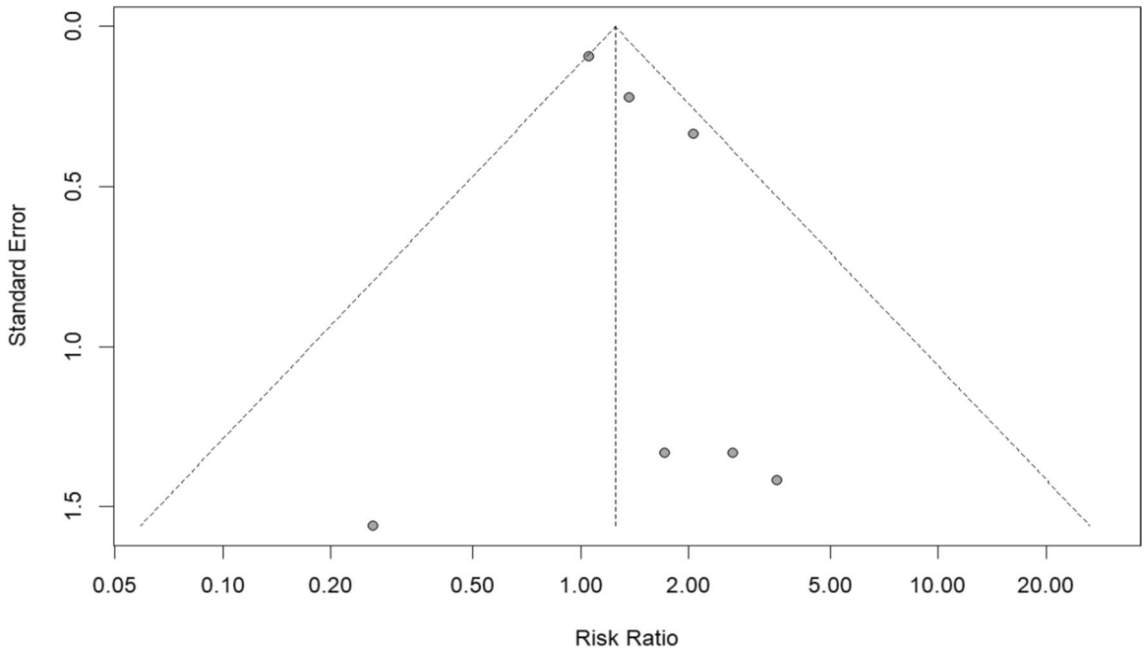
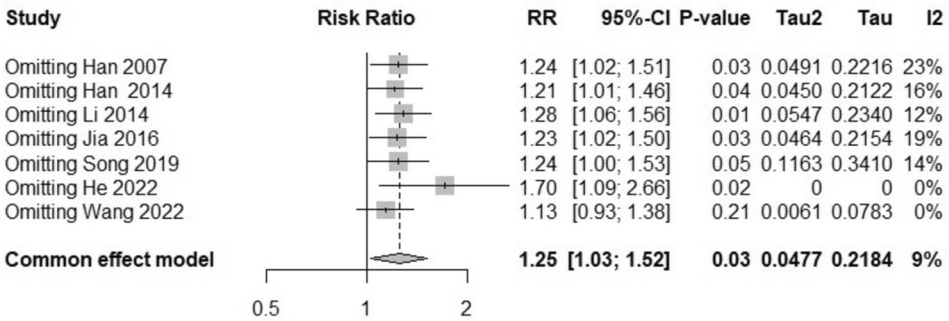


Fig. 7 Funnel plot for OS

Fig. 8 Sensitivity analysis of OS



improve prognosis, particularly in adult patients [21]. In conclusion, current studies support that the OR of adult patients with HLH can benefit from etoposide induction treatment. Thus, etoposide should be considered as an early and timely treatment option for these patients.

The treatment strategy for HLH comprises two main aspects. The short-term strategy is to control excessive inflammation and reduce early mortality, whereas the long-term goal is to control the primary disease and achieve long-term survival. The role of etoposide has been widely debated in previous studies, but the conclusions have varied. In a retrospective cohort study of 162 adult patients over 6 years of age, the use of etoposide as a first-line treatment tended to have a survival advantage in multivariable analysis [22]. Conversely, a multicentre study of 90 adult patients with various triggers did not demonstrate a significant benefit for etoposide [23]. A previous meta-analysis that focused on adult patients with HLH and selected survival as the outcome variable did not support the beneficial effects of etoposide [8]. However, that meta-analysis, like ours, noted that various factors have an impact on survival, making OS susceptible to bias. Thus, OS does not reflect the role of etoposide in induction therapy. For example, in the treatment of HLH with diverse aetiologies, the effectiveness of etoposide may vary owing to different prior mortality risks. In our meta-analysis, the pooled analysis of OS supported the beneficial effects of etoposide, which differs from previous meta-analyses. A possible reason for this is that, compared with our study, patients with a wider variety of etiological HLH triggers were included in the previous meta-analysis. The impact of different diseases on survival led to a negative conclusion regarding the use of etoposide in the previous meta-analysis. Besides the underlying triggers, other factors may have an impact on survival. Some etoposide-treated patients received other HLH-directed therapies, which may have an impact on their long-term prognosis. In addition,

the severity of the disease may affect whether doctors use etoposide; therefore, the etoposide group probably had a more severe clinical disease than the non-etoposide group, leading to a negative result for the etoposide effect.

Compared to OS, OR evaluates short-term efficacy; therefore, it is less affected by confounders. As a widely used standard for efficacy evaluation, OR directly indicates the effectiveness of treatment. Although OR cannot replace OS in evaluating the long-term prognosis, the response to first-line treatment significantly affects the rate of early mortality during the induction period [24]. According to the results of the HLH-94 and HLH-04 clinical trials, most deaths in patients with HLH occur within the initial 2 months of induction therapy [6, 17]. Consequently, OR is a crucial factor influencing OS and can serve as an outcome measure reflecting the effects of etoposide.

In the subgroup analysis, etoposide had a positive effect on OR in patients with MAS, whereas no relationship was found between OR and etoposide administration in the patients with LAHS. We believe this is primarily due to the different characteristics of the two diseases. Glucocorticoid pulse therapy is the primary treatment for MAS, with etoposide considered a more powerful drug when the initial treatment is ineffective. Compared with the reported mortality rates ranging from 20 to 30% in MAS, the prognosis for patients with LAHS is lower, with an early mortality rate of approximately 50% [2]. Additionally, the treatment of LAHS requires a careful balance between HLH- and tumour-specific therapies. In those conditions, a 2-step approach has been suggested which (1) targets the cytokine storm and T-cell proliferation using etoposide (75–100 mg/m2, corticosteroids, and polyvalent immunoglobulins and (2) targets neoplastic disease by specific treatment as soon as organ function is re-established or, at the least, has improved to an acceptable degree. In cases of highly active HLH or imminent severe organ damage, etoposide can be incorporated into treatment protocols for lymphoma [25]. Thus, the relationship between etoposide and the prognosis of LAHS is complicated. Meanwhile, all included LAHS studies had a small sample size, which can lead to overestimation of the effect size and low reproducibility of the results [26]. Although our study did not provide positive evidence between etoposide and LAHS, a recent study that included patients over 15 years of age found that compared to chemotherapy without etoposide, initial treatment of LAHS including etoposide can provide a higher response rate, lower mortality rate, and better survival [27]. In multivariate analysis of a large French cohort, etoposide treatment correlated with better OS in patients with LAHS [28]. Therefore, the role of etoposide in adult HLH should not be underestimated.

In this study, we analysed the role of etoposide in the treatment of adult HLH, confirming its potential benefits. Our conclusion is more persuasive than the results reported in a single study and can provide guidance for clinical treatment. However, this study has some limitations. Firstly, the lack of a consistent definition of response across all seven studies and the absence of baseline comparisons between the etoposide and non-etoposide groups in some studies compromised the reliability of the findings. Secondly, the underlying triggers included in this study were not comprehensive. There was a lack of samples with common aetiologies such as infections. Therefore, we cannot conclude whether the entire population of adult patients with HLH can benefit from etoposide regimen. Additionally, it is important to highlight that all the studies included in this analysis were conducted retrospectively, which has inherent limitations. Therefore, it is crucial to conduct large-scale prospective randomised clinical trials to provide further insight and guide clinical treatment.

Conclusion

Overall, based on our meta-analysis of seven studies, etoposide has shown positive effects in the treatment of adult HLH from the perspective of OR. Thus, the early and timely use of etoposide-containing regimens should be considered for adult patients with HLH.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10238-025-01570-w.

Author contribution Tiankuo Gao did writing—original draft, formal analysis, investigation. Dina Suolitiken done formal analysis, conceptualisation, and visualisation. Chun Yangwas involved in investigation and data curation. Chaofan Wu performed investigation and formal analysis. Lingbo He done supervision and writing—review & editing. Yini Wang contributed to writing—review & editing and conceptualisation.

Funding National Natural Science Foundation of China, 82170122, High-Level Discipline Construction Project of Beijing Anzhen Hospital Affiliated to Capital Medical University, 2024AZC4001, Beijing Natural Science Foundation, 7252035.

Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Conflicts of interest The authors declare no competing interests.

References

1. La Rosée P, Horne A, Hines M, von Bahr GT, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133:2465–77. https://doi.org/10.1182/blood.2018894618.
2. Zhang Q, Zhu L, Zhou Li L, Xie W, Tan Y, et al. Risk factors and prognosis of early death in secondary hemophagocytic lymphohistiocytosis. Ann Hematol. 2023;102:2301–8. https://doi.org/10.1007/s00277-023-05153-1.
3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383:1503–16.
4. Janka GE. Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr. 1983;140:221–30. https://doi.org/10.1007/bf00443367.
5. Böhm S, Wustrau K, Pachlopnik Schmid J, Prader S, Ahlmann M, Yacobovich J, et al. Survival in primary hemophagocytic lymphohistiocytosis, 2016 to 2021: etoposide is better than its reputation. Blood. 2024;143:872–81. https://doi.org/10.1182/blood.2023022281.
6. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 2011;118:4577–84. https://doi.org/10.1182/blood-2011-06-356261.
7. Ehl S, Astigarraga I, von Bahr GT, Hines M, Horne A, Ishii E, et al. Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: consensus statements by the HLH steering committee of the histiocyte society. J Allergy Clin Immunol-In Pract. 2018;6:1508–17. https://doi.org/10.1016/j.jaip.2018.05.031.
8. Zondag TCE, Lika A, van Laar JAM. The role of etoposide in the treatment of adult patients with hemophagocytic lymphohistiocytosis. Exp Hematol Oncol. 2023;12:2. https://doi.org/10.1186/s40164-022-00362-2.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71. https://doi.org/10.1136/bmj.n71.
10. He L, Yao S, Zhang R, Liu M, Hua Z, Zou H, et al. Macrophage activation syndrome in adults: characteristics, outcomes, and therapeutic effectiveness of etoposide-based regimen. Front Immunol. 2022;13: 955523. https://doi.org/10.3389/fimmu.2022.955523.
11. Wang R, Li T, Ye S, Lv L, Chen S, Wang X, et al. Short-term, low-dose etoposide in refractory adult-onset still's disease-associated macrophage activation syndrome. Clin Rheumatol. 2022;41:2817–23. https://doi.org/10.1007/s10067-022-06184-1.
12. Song Y, Wang Z, Hao Z, Li L, Lu J, Kang H, et al. Requirement for etoposide in the treatment of pregnancy related hemophagocytic lymphohistiocytosis: a multicenter retrospective study. Orphanet J Rare Dis. 2019;14:50. https://doi.org/10.1186/s13023-019-1033-5.
13. Jia J, Song Y, Lin N, Liu W, Ping L, Zheng W, et al. Clinical features and survival of extranodal natural killer/T cell lymphoma with and without hemophagocytic syndrome. Ann Hematol. 2016;95:2023–31. https://doi.org/10.1007/s00277-016-2805-9.
14. Han L, Li L, Wu J, Li X, Zhang L, Wang X, et al. Clinical features and treatment of natural killer/T cell lymphoma associated with hemophagocytic syndrome: comparison with other T cell lymphoma associated with hemophagocytic syndrome. Leuk Lymphoma. 2014;55:2048–55. https://doi.org/10.3109/10428194.2013.876629.
15. Li F, Li P, Zhang R, Yang G, Ji D, Huang X, et al. Identification of clinical features of lymphoma-associated hemophagocytic syndrome (LAHS): an analysis of 69 patients with hemophagocytic syndrome from a single-center in central region of China. Med Oncol. 2014;31:902. https://doi.org/10.1007/s12032-014-0902-y.
16. Han AR, Lee HR, Park BB, Hwang IG, Park S, Lee SC, et al. Lymphoma-associated hemophagocytic syndrome: clinical features and treatment outcome. Ann Hematol. 2007;86:493–8. https://doi.org/10.1007/s00277-007-0278-6.
17. Bergsten E, Horne A, Aricó M, Astigarraga I, Egeler RM, Filipovich AH, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017;130:2728–38. https://doi.org/10.1182/blood-2017-06-788349.
18. Henter JI, Samuelsson-Horne A, Aricò M, Egeler RM, Elinder G, Filipovich AH, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood. 2002;100:2367–73. https://doi.org/10.1182/blood-2002-01-0172.
19. Johnson TS, Terrell CE, Millen SH, Katz JD, Hildeman DA, Jordan MB. Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. J Immunol. 2014;192:84–91. https://doi.org/10.4049/jimmunol.1302282.
20. Imashuku S, Kuriyama K, Sakai R, Nakao Y, Masuda S, Yasuda N, et al. Treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in young adults: a report from the HLH study center. Med Pediatr Oncol. 2003;41:103–9. https://doi.org/10.1002/mpo.10314.
21. Song Y, Wang Y, Wang Z. Requirement for etoposide in the initial treatment of Epstein-Barr virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol. 2019;186:717–23. https://doi.org/10.1111/bjh.15988.
22. Arca M, Fardet L, Galicier L, Rivière S, Marzac C, Aumont C, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. Br J Haematol. 2015;168:63–8. https://doi.org/10.1111/bjh.13102.
23. Naymagon L, Tremblay D, Mascarenhas J. The efficacy of etoposide-based therapy in adult secondary hemophagocytic lymphohistiocytosis. Acta Haematol. 2021;144:560–8. https://doi.org/10.1159/000514920.
24. Zhang R, Cui T, He L, Liu M, Hua Z, Wang Z, et al. A study on early death prognosis model in adult patients with secondary hemophagocytic lymphohistiocytosis. J Healthcare Eng. 2022;2022:6704859. https://doi.org/10.1155/2022/6704859.
25. Daver N, McClain K, Allen CE, Parikh SA, Otrock Z, Rojas-Hernandez C, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. Cancer. 2017;123:3229–40. https://doi.org/10.1002/cncr.30826.
26. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14:365–76. https://doi.org/10.1038/nrn3475.
27. Song Y, Wang Y, Wang J, Wang ZJB. Etoposide plays an important role in treatment of lymphoma associated hemophagocytic lymphohistiocytosis. 2019;134:5341. https://doi.org/10.1182/blood-2019-132119

28. Bigenwald C, Fardet L, Coppo P, Meignin V, Lazure T, Fabiani B, et al. A comprehensive analysis of Lymphoma-associated haemophagocytic syndrome in a large French multicentre cohort detects some clues to improve prognosis. British J Haematol. 2018;183:68–75. https://doi.org/10.1111/bjh.15506.