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Comprehensive insights into tuberculosis-associated hemophagocytic lymphohistiocytosis: a systematic review

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Abstract

Background Tuberculosis-associated hemophagocytic lymphohistiocytosis (TB-HLH) presents significant challenges in diagnosis and treatment due to its complex interplay between TB and HLH. This systematic review aims to provide comprehensive insights into the epidemiology, clinical characteristics, and treatment outcomes of TB-HLH patients.

Methods We performed a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, searching PubMed, Scopus, Web of Science, and Embase up to May 16, 2023, without language restrictions. We included case reports and cases series on patients with both TB and HLH with documented treatment outcomes. Data were analyzed using descriptive statistics, chi-square or Fisher's exact tests, t-tests, and mortality rates. Significant variables ($p < 0.05$) from univariate analysis and clinically relevant factors were used in binary logistic regression to determine odds ratios, 95% confidence intervals, and p-values.

Results A total of 185 articles involving 213 patients were included. The overall mortality rate was 39%. Age ≥ 44 years and comorbidities were identified as independent risk factors for increased mortality ($p = 0.005$). Anti-tuberculosis treatment (ATT) combined with HLH-specific therapies, was associated with reduced mortality compared to ATT alone ($p < 0.05$), especially IVIG ($p = 0.04$).

Conclusion Integrating ATT with HLH-specific therapies significantly enhances survival in TB-HLH patients. Additionally, IVIG plays a key role in improving outcomes. Age ≥ 44 years and comorbidities are critical risk factors for increased mortality. Early and high suspicion of TB-HLH is essential, especially in high TB burden regions or recent travel contexts. Future research should focus on prospective multicenter studies to validate our findings and develop standardized treatment strategies on TB-HLH.

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Keywords Hemophagocytic lymphohistiocytosis, HLH, Tuberculosis, TB-HLH, Intravenous immunoglobulin

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening syndrome with an incidence of about 1 case per 2,000 patients in tertiary referral centers [1–4]. Its diagnosis is complex due to the wide range of symptoms and triggers, including genetic mutations, infections, malignancies, and autoimmune disorders [1, 2, 5]. HLH has traditionally been classified as "primary" (genetic) or "secondary" (acquired), but recent classifications have introduced categories such as syndromic HLH, disease-specific HLH, HLH mimics, and Macrophage Activation Syndrome [2–4].

Central to the pathophysiology of HLH is a hyperinflammatory state driven by an overproduction of proinflammatory cytokines, which can be triggered by various infections, including tuberculosis (TB). Also, disseminated TB (DTB) can mimic HLH and contribute to the immune dysregulation seen in the syndrome [5–9]. (Fig. 1) Additionally, genetic mutations (e.g., PRF1, UNC13D, STX11) play a role in immune dysfunction, highlighting the complex interaction between genetic and environmental factors [2].

Infections are recognized as a major trigger for HLH, with studies reporting rates of infection-triggered HLH ranging from 36 to 74% in pediatric population. A review of adult HLH cases found that approximately 50% were triggered by infections, with bacterial infections contributing to 9% of the cases, and tuberculosis (TB) being the cause in 38% of infection-related HLH cases [2–4, 10–12]. These figures, however, are drawn from literature and not systematically collected registry data, which introduces potential biases, particularly in cases where previous antibiotic treatment may have hindered the identification of bacterial species. This emphasizes the importance of thoroughly investigating underlying infections, especially in cases where HLH mimics infectious processes rather than being a direct consequence of immune dysregulation [2].

In patients with fever, hepatosplenomegaly, coagulopathy, cytopenias, and high ferritin, HLH should be considered. The HLH-2004 criteria were originally designed for diagnosing primary HLH in pediatric populations and may have limitations when applied to adult-acquired or secondary HLH cases [1]. In contrast, the H-score was specifically developed for use in adults with secondary HLH, providing a more tailored diagnostic approach by incorporating factors relevant to adult patients. (Table S1) [13–15].

The treatment of HLH, particularly in adults, requires an individualized approach due to the heterogeneity of the condition and the wide variety of underlying triggers. For stable patients, identifying and addressing the underlying cause is crucial. For instance, in cases of infection-induced HLH, it is necessary to treat the underlying infection using appropriate antibiotics, antivirals, antifungals, or antiparasitic agents. In intracellular infection-triggered HLH, it is often advised to avoid using the HLH-94 treatment protocol due to the risk of exacerbating immunosuppression. In contrast, for unstable patients, corticosteroids, with or without intravenous immunoglobulin (IVIG), are recommended as a first-line treatment. In some infection-induced HLH cases, such as those triggered by Epstein-Barr virus (EBV), a modified HLH-94 protocol may be recommended. For refractory or relapsed cases, newer salvage regimens such as ruxolitinib, emapalumab, and alemtuzumab are proving effective and are being increasingly incorporated into treatment protocols [4, 16, 17].

Standard anti-tuberculosis treatment (ATT) employs a regimen of isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE). For drug-resistant TB or those with adverse reactions, WHO-endorsed salvage therapy is utilized, comprising groups A (levofloxacin or moxifloxacin, bedaquiline, linezolid), B (clofazimine, cycloserine or trizidone), and C (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin or streptomycin, ethionamide or protonamide, p-aminosalicylic acid) [18, 19].

Limited patient numbers and lack of multi-language report analysis in existing reviews on tuberculosis-associated HLH (TB-HLH) have resulted in inadequate epidemiological and treatment insights. A global, comprehensive systematic review could mitigate this issue. Our study aims to address these gaps by systematically analyzing worldwide data on TB-HLH, focusing on demographics, clinical manifestations, laboratory findings, pathology, and treatment outcomes. This approach is designed to improve understanding, management, and care for TB-HLH patients.

Materials and methods

Our study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022364180) [21].

Data source and search strategy

We conducted a comprehensive search of PubMed, Scopus, Web of Science, and Embase databases using

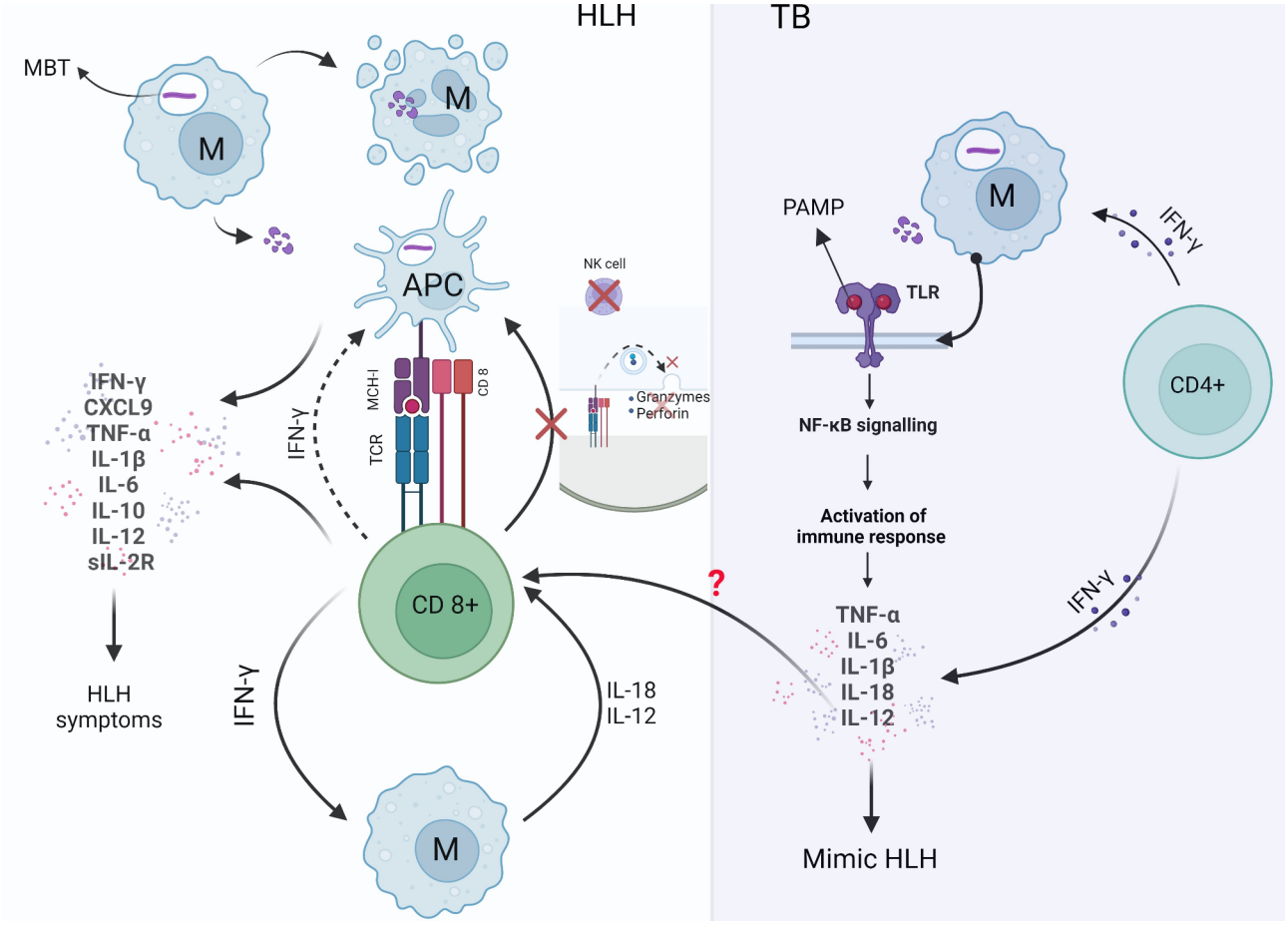

Fig. 1 Immunopathological interactions in tuberculosis-associated hemophagocytic lymphohistiocytosis (TB-HLH). *Mycobacterium tuberculosis* (MBT) infects macrophages (M), leading to an antigen presentation to CD8 + T cells via Major Histocompatibility Complex Class I (MHC-I). This interaction stimulates CD8 + T cells to produce interferon-gamma (IFN-γ), which further activates macrophages. These activated immune cells release a range of cytokines including IFN-γ, CXCL9, TNF-α, interleukin-1β (IL-1β), IL-6, IL-10, IL-12, and soluble IL-2 receptor (sIL-2R), contributing to the clinical symptoms of HLH. Natural killer cells and/ or CD8 +, which are typically involved in the clearance of infected or activated cells, are shown to be dysfunctional, as indicated by the cross symbol. This dysfunction, and a lack of granzyme and perforin, exacerbates the ongoing inflammatory response. Of particular note is the role of IL-18 and IL-12, which are thought to enhance the production of IFN- γ by CD8 + T cells, feeding into a self-amplifying cycle of immune activation [2, 51–54]. In disseminated TB infection, pathogen-associated molecular patterns (PAMPs) are recognized by toll-like receptors (TLRs) on macrophages, initiating the NF-κB signaling pathway and augmenting the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, IL-18, and IL-12. This cascade leads to the activation of CD4 + T cells, which contribute to the pool of IFN-γ and further perpetuates the inflammatory cycle [5–8, 55]. The convergence of these pathways may precipitate a cytokine storm integral to the pathogenesis of both disseminated TB and HLH. This hyperinflammatory state can resemble HLH, complicating the distinction between primary HLH and TB-induced HLH. Consequently, the application of anti-tuberculosis treatment emerges as a critical therapeutic measure. The question mark (?) depicted in the schematic indicates the potential involvement of IL-12 and IL-18 in activating HLH via the NF-κB signaling pathway. This hypothesis remains to be fully elucidated, pointing to a gap in our current understanding and necessitating further research

keywords related to "Mycobacterium tuberculosis" and "Hemophagocytic lymphohistiocytosis" from inception until May 16, 2023, without language limits. Reference lists of relevant articles were also reviewed. (Table S2)

Study selection

We included studies on patients with both TB and HLH that reported treatment outcomes, specifically recovery or death. For the purposes of this study, TB-HLH refers to cases where HLH is triggered by active tuberculosis infection. However, it is important to note that TB may also coexist with HLH as a contributing or co-occurring condition. Given this complexity, we considered all patients diagnosed with both HLH and TB simultaneously to account for both scenarios, as it is often difficult to definitively determine which condition triggered the other. Studies with unclear outcomes or diagnoses were excluded. (Table 1)

Data extraction and quality assessment

Retrieved articles were uploaded to Rayyan QCRI for screening, with duplicates removed by three reviewers (S.A., A.E., H.A.). Titles and abstracts were evaluated by five reviewers (S.A., A.E., R.A., S.Kh., H.A.),

Table 1 Inclusion and exclusion criteria, using PICOS framework

	Inclusion criteria	Exclusion criteria
Population	All patients who diagnosed with HLH and TB simultaneously	Patients who did not diagnose with HLH and TB simultaneously
Intervention	NA	NA
Control	NA	NA
Outcome	Survival/Death	Did not report survival/death
Study design	Case report studies, case series, letters, correspondence	Conference papers/Abstract/Poster
Others	All Languages	NA

NA: not applicable

and final oversight was provided by three experts (I.A., D.M., K.A.). Full texts were independently reviewed by five reviewers (S.A., A.E., R.A., S.Kh., H.A.), with consensus reached on any disagreements. Data on patient characteristics, laboratory details, treatments, outcomes, and diagnoses were collected using a standardized Excel template.

Risk of bias was assessed using the Joanna Briggs Institute (JBI) criteria [22] by four researchers (S.A., A.E., R.A., S.Kh.). Any discrepancies were resolved by consensus or by consulting a fifth expert (I.A.).

Treatment classification

For the purpose of this study, we categorized patients into four treatment groups based on the therapies they received:

1. **No Treatment**: Patients who did not receive any specific treatment for HLH or TB.
2. **HLH-only**: Patients who received specific treatment for HLH but did not receive ATT.
3. **ATT-only**: Patients who received ATT but no specific HLH treatment.
4. **ATT + HLH**: Patients who received both ATT and specific HLH treatment.

Anti-tuberculosis treatment (ATT) regimens

For patients receiving ATT, we further divided the treatments into following categories [18, 19]:

- **HRZE-based regimen**: The standard first-line ATT regimen consisting of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E).
- **Classic Non-HRZE regimens**: Alternative first-line ATT regimens that do not contain the full HRZE combination. These may include HRE (Isoniazid, Rifampicin, and Ethambutol) or other variations based on clinical factors such as drug intolerance or resistance.
- **Salvage therapy**: we categorized patients under salvage therapy, as per WHO recommendations:
  - **Group A**: Levofloxacin or Moxifloxacin, Bedaquiline, Linezolid.
  - **Group B**: Clofazimine, Cycloserine or Terizidone.
  - **Group C**: Ethambutol, Delamanid, Pyrazinamide, Imipenem-Cilastatin or Meropenem, Amikacin or Streptomycin, Ethionamide or Prothionamide, p-Aminosalicylic Acid.

HLH-specific treatment regimens

HLH-specific treatments included Corticosteroids (CS), IVIG, Etoposide (VP-16), Cyclosporine A (CSA), and other immunosuppressive agents. We also analyzed the impact of monotherapies (e.g., CS or IVIG alone) and combination therapies (e.g., CS+IVIG, CS+VP-16) on outcomes.

Statistical analysis

Data analysis was conducted using SPSS version 27 by A.K. We performed descriptive statistics to summarize patient demographics, treatments, and outcomes. To compare categorical variables, we used the Chi-square test or Fisher's exact test where appropriate. Continuous variables were compared using t-tests. We calculated the mortality rate (MR) across treatment groups and performed subgroup analyses based on ATT and HLH-specific treatments.

We also conducted a binary logistic regression analysis to identify factors associated with mortality. Variables with a p-value <0.05 in univariate analysis, along with clinically relevant factors (e.g., age, comorbidities, type of treatment), were included in the multivariate model. The model outputs were presented as odds ratios (OR) with 95% confidence intervals (CI) and corresponding p-values.

Results

Study selection and characteristics

Our search across major databases initially returned 1,440 records, which were narrowed down to 741 after deduplication. Following the title and abstract screening, 316 articles were selected for full-text review. Ultimately, 177 studies met the criteria for inclusion. Reference searches and our case report added 8 more records, resulting in a total of 185 studies encompassing 213 reports (Fig. 2). (Tables S3, S4) Of the 213 cases, 173 (81.22%) were single case reports, and 40 (18.78%) were part of 13 case series.

Of the patients, 61.6% were male (130/211), with an average age of 39.62 years (SD: 22.55; median: 40; IQR: 22–59). Geographically, 20.7% of the reports originated

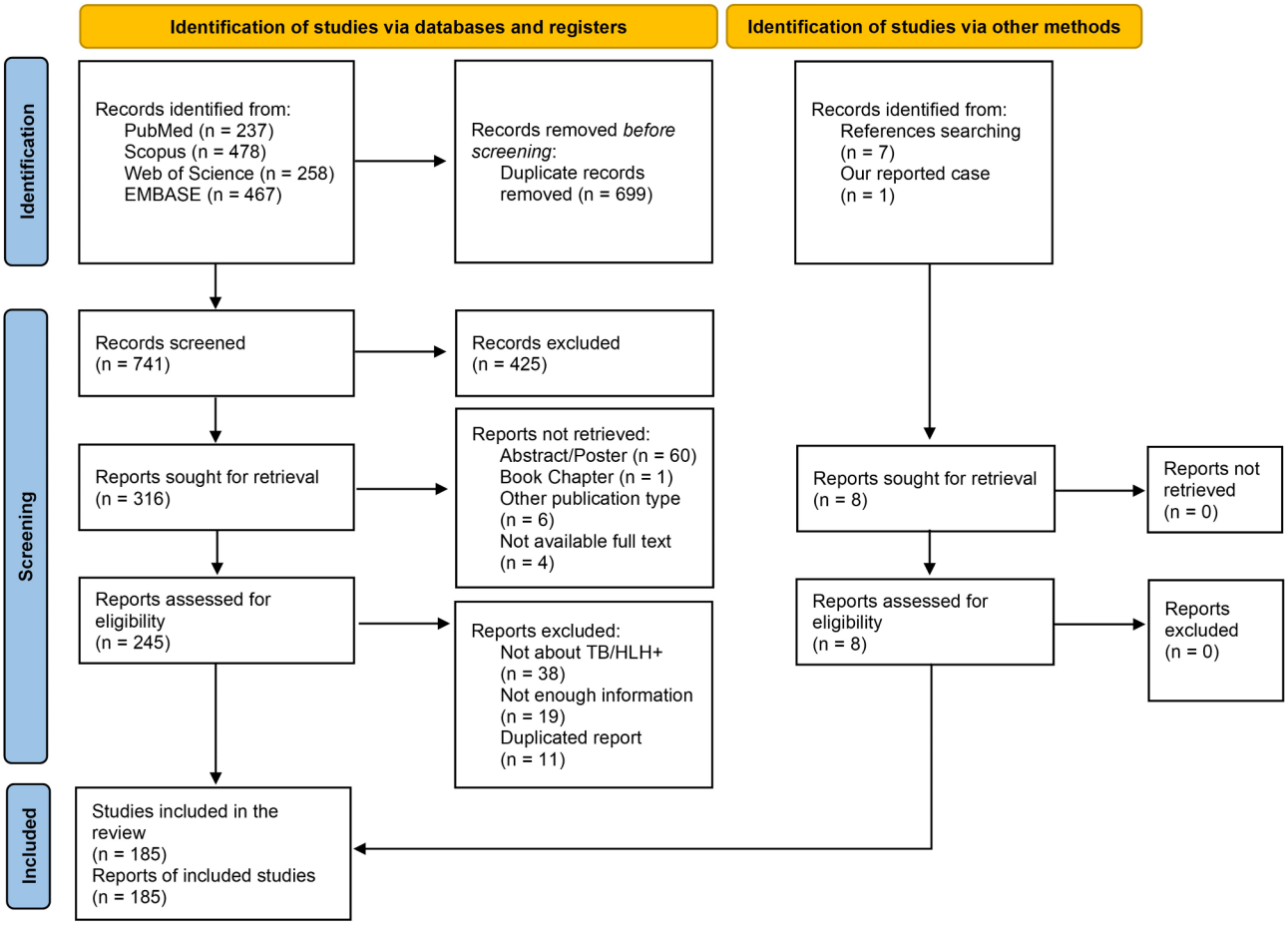

Fig. 2 Prisma flow diagram

from India, with an additional 23.34% involving patients of Indian descent. Furthermore, 10.3% of the reports came from the United States, of which 36.2% were non-US nationals. Additionally, 9.4% of the patients were from Japan, and a notable number of cases from England, France, and Spain involved immigrants (Fig. 3). (Tables S4, S5)

Previous infectious diseases

A history of previous infectious diseases was reported in 34 patients (17.43%). Documented TB prior to the current disease course was noted in 7.2% of cases. EBV infection was suspected in 15 cases (7.7%) based on EBV IgG, detectable viral loads, EBV DNA by PCR, EBV IgM, and the presence of EBV nuclear antigen (EBNA). Cytomegalovirus (CMV) infection was suspected in eight patients (4.1%) based on IgG or IgM positivity, with five patients showing concurrent positive IgG or IgM for both EBV and CMV. Additionally, 8.7% had a history of HIV, and 6.7% had other infections, including COVID-19 and fungal infections.

Comorbidities

Immunodeficiency was present in 28.2% of cases, primarily due to immunosuppressive treatments or inherent disorders. About 20% of patients were on immunomodulatory drugs, including DMARDs, JAK inhibitors, TNF-alpha inhibitors, and corticosteroids. Cancer was noted in 8.2%, hematological disorders in 3.1%, and rheumatologic diseases in 9.2% of the cohort. Cardiovascular diseases affected 11.3% of patients, pulmonary diseases 3.1%, diabetes mellitus 10.8%, and renal disease 13.3% (Table S6).

Signs and symptoms at presentation

Fever was present in 97% of cases (195/201), with an average temperature of 39.06 °C (SD: 0.8 °C) and a median of 39 °C (IQR: 38.5 –39.65 °C). Respiratory symptoms appeared in 29.1% of patients, lymphadenopathy in 25.4%, and Central nervous system (CNS) symptoms in 13.6%. Other symptoms included icterus (14.1%), skin rash (11.3%), edema (8.7%), and bleeding (12.7%). Skin lesions varied, ranging from non-specific rashes to malar, hyperemic, hemorrhagic, purpuric, papulovesicular, and papulonodular erythema. Among 178 patients, 21.9%

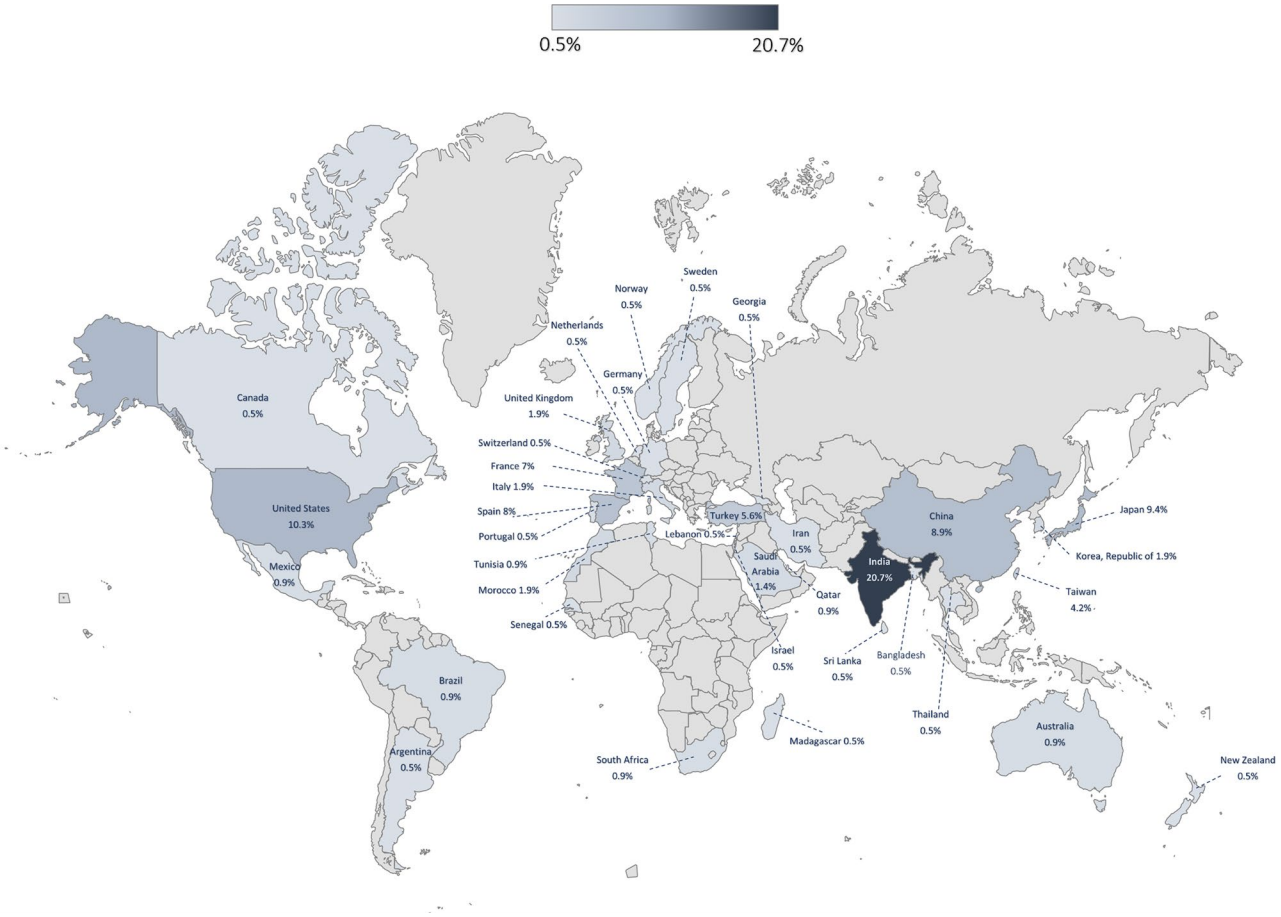

Fig. 3 Global Distribution of TB-HLH Cases by Country. Countries in gray indicate no reported cases of TB-HLH

had no hepatomegaly or splenomegaly, while 15.2% had splenomegaly alone, 7.9% had hepatomegaly alone, and 55.1% had both hepatosplenomegaly (Table 2).

HLH diagnosis

Diagnosis of HLH in most studies relied on clinical evidence and identification of hemophagocytes in bone marrow, lymph nodes, or other tissues. Of the 207 cases, 135 (65.2%) met the HLH 2004 criteria with a score of five or higher. (Table 2) Of the 213 cases reviewed, only 31 (14.6%) explicitly reported all the criteria required for calculating the H-score. However, by using the available data, we were able to estimate the H-score for the remaining cases. As a result, 98 cases (46%) had an H-score above 169, which is diagnostic for HLH. This indicates that while the H-score is underreported in the literature, a significant proportion of cases still meet the diagnostic threshold when the criteria are reconstructed from the available information. It is important to note, however, that these numbers may be subject to bias due to inconsistent reporting of criteria across studies. Genetic analyses revealed IFN-γ receptor deficiency, GZMB mutation, and PRF1 mutations in some cases. Additionally, biomarkers like soluble CD163, CXCL9, and IL-18 were noted in a few patients.

TB diagnosis

Tuberculosis was diagnosed using histology, molecular tests, acid-fast staining, and other methods. However, the diagnostic method was unidentified in 17 patients. Among 179 patients, 22.3% had lung involvement only, 28.5% had exclusive extrapulmonary TB, and 46.4% had both lung and extrapulmonary TB. Miliary tuberculosis was present in 155 cases (82%). (Fig. S1) Fundoscopic exams found signs of disseminated TB in 9 out of 12 cases.

Time and priority

For the 42 surviving patients, the median hospitalization duration was 38.5 days (IQR: 23.5–60). For the 44 patients who died, the median time from admission to death was 21 days (IQR: 10-36.5). Specifically, among these cases, 12.7% (27 patients) were diagnosed postmortem with TB, 1.9% (four patients) with HLH, and 0.5% (one patient) had postmortem diagnoses of both conditions.

Table 2 HLH-2004 criteria

			Deceased	Survived	Total Cases	*p*-Value
Temperature	Fever	Yes	75 38.5%	120 61.5%	195	**0.03**
		No	5 83.3%	1 16.7%	6	
	Temperature, °C	below 38.5 °C	10 43.5%	13 56.5%	23	0.06
		above 38.5 °C	27 34.6%	51 65.4%	78	
peripheral blood cell	Cytopenia (affecting ≥ 2 of 3 lineages in the peripheral blood)	Yes	76 41.3%	108 58.7%	184	0.56
		No	4 30.8%	9 69.02%	13	
	Hemoglobin, g/dL	Number of cases Mean ± SD Median IQR Range	59 8.22 ± 2.07 8.2 7.4–9.7 2.40–13	101 8 ± 2 8 6.7-9 3.10–15.4	160	0.50
	Absolute Neutrophil Count, $\times 10^3/\mu L$	Number of cases Median IQR Range	36 1.27 0.718–4.114 0-15.895	53 2.13 0.796–5.452 0-13.4	89	0.26
	Thrombocyte $\times 10^3/\mu L$	Number of cases Median IQR Range	64 32 19.25–75.75 2.5–157	101 57 23.5–111 1-545	165	**0.009**
Spleen	Splenomegaly	Yes	47 37.6%	78 62.4%	125	0.50
		No	19 38.8%	30 61.2%	49	
Triglyceride and/or fibrinogen	Hypertriglyceridemia (≥ 265 mg/dl) and/or hypofibrinogenemia (≤ 150 mg/dL)	Yes	36 36%	64 64%	100	0.57
		No	17 41.5%	24 58.5%	41	
	Triglyceride (mg/dL)	Number of cases Mean ± SD Median IQR Range	32 330.42 ± 164.22 305.37 187.8–462 117–696	70 315.27 ± 162.53 283.10 218.09-398.97 63–811	102	0.66
	Plasma fibrinogen (mg/dL)	Number of cases Mean ± SD Median IQR Range	30 207.48 ± 149.54 161.45 113.22-286.25 0-642	55 195.25 ± 171.51 137.20 100–240 0.8–861	85	0.74
Ferritin	Elevated Ferritin ≥ 500 (ng/mL)	Yes	55 35.3%	101 64.7%	156	0.71
		No	2 25.0%	6 75.0%	8	
	Serum ferritin (ng/mL)	Number of cases Median IQR Range	45 5001 1942.5-11500 369.65- 395,644	94 4393.5 1189-12200.75 20.4-375554	139	0.88
NK-cell activity	Low or absent NK-cell activity (according to local laboratory reference)	Yes	8 42.1%	11 57.9%	19	0.25
		No	0 0%	4 100%	4	

Table 2 (continued)

			Deceased	Survived	Total Cases	*p*-Value
Soluble IL-2r	Elevated Soluble IL-2r ≥ 2400(U/mL)	Yes	12 33.3%	24 66.7%	36	0.67
		No	0 0%	1 100%	1	
Hemophagocytosis	Hemophagocytosis in bone marrow or spleen or lymph nodes	Yes	78 43.%	102 56.6%	180	0.07
		No	2 16.7%	10 83.3%	12	

IQR: Interquartile range

Mortality

The overall MR was 39% (83/213), with single case reports having a MR of 36.99% (64/173) and case series showing a slightly higher rate of 47.5% (19/40). A Chi-square test comparing MR between single case reports and case series revealed no statistically significant difference ($p=0.23$).

There was a significant age difference between survivors and deceased patients, with a mean age gap of 16.43 years (SE:2.98, 95% CI:10.561–22.312), indicating higher mortality among older patients ($p<0.001$).

Platelet counts were significantly lower in deceased patients, with medians of 32×10^3/μL compared to 57×10^3/μL in survivors, showing a mean difference of $31{,}026.99\times10^3$/μL ($p=0.009$). LDH levels were also significantly higher in deceased patients, with a median of 1623.00 U/L versus 876.50 U/L in survivors ($p<0.001$). No other parameters showed significant differences between groups. (Table S7)

Patients with cardiac diseases (MR: 61.9%, $p=0.016$), diabetes mellitus (MR: 71.4%, $p=0.001$), and renal disease (MR: 65.4%, $p=0.002$) exhibited significantly higher mortality rates. The MRs for patients with previous TB, suspected EBV, suspected CMV, and HIV were 57.1%, 80%, 25%, and 27.8%, respectively. Additionally, MRs were noted for patients with immunodeficiency (46.7%), immunomodulatory drug use (48.7%), cancer (43.8%), hematological diseases (28.6%), rheumatologic diseases (55%), pulmonary diseases (27.2%), and other conditions, though these did not show statistically significant higher mortality.

Treatment approaches

No treatment received

All 11 patients who did not receive HLH-specific treatment and/or ATT did not survive. Post-mortem diagnoses revealed tuberculosis in seven patients and both tuberculosis and HLH in one patient. (Fig. 4)

Only HLH treatment received

Among the 11 patients treated exclusively for HLH, the MR was 90.9%. Post-mortem diagnoses showed tuberculosis in 10 of these patients. Notably, 90.9% were treated with corticosteroids, either alone or combined with other HLH therapies, resulting in a 90% MR. Only one patient, treated with Mycophenolate Mofetil (MMF), Cyclosporine A (CSA), and corticosteroids, survived. In this case, the patient was diagnosed with abdominal tuberculosis and was treated for 18 months. After remaining clinically asymptomatic for 6 months following the completion of ATT, the patient developed HLH. While it is unclear whether TB was the direct cause of HLH, there was speculation that a combination of a severe infection (due to X-linked chronic granulomatous disease) and a heterozygous PRF1 gene mutation may have contributed to the development of late-onset familial HLH-2. Given these underlying factors, the role of TB as a trigger for HLH remains uncertain [23]. (Table 3) (Fig. 4).

Only ATT received

In the ATT-only subgroup of 41 patients, the MR was 43.9%. Of these, 68.6% received classic ATT with a MR of 41.7%, while 31.4% had combined classic and salvage ATT, showing a MR of 45.5% ($p=0.56$). The HRZE regimen, used in 62.9% of cases, notably reduced the MR to 22.7%, compared to 76.9% for non-HRZE treatments ($p=0.004$). (Table 3) It is important to note that none of these patients had CNS involvement, and therefore, corticosteroid use—commonly used in cases with CNS involvement—did not influence the course of HLH in this group.

ATT + HLH treatment received

In 142 patients receiving both ATT and HLH therapy, the MR was 26.8%. Within this group, 68.1% received classic ATT (MR 28.4%), and 31.9% had combined classic and salvage therapy (MR 28.9%) ($p=0.55$). HRZE treatment (83 patients) led to a 26.5% MR, while non-HRZE regimens (36 patients) resulted in a 30.3% MR ($p=0.51$). Salvage therapy included regimen A in 25.6% of cases, regimen C in 33.3%, a combination of B and C in 2.6%, and A and C in 38.5%. For HLH-specific treatments, 71 patients received monotherapy (26.8% MR), while 70

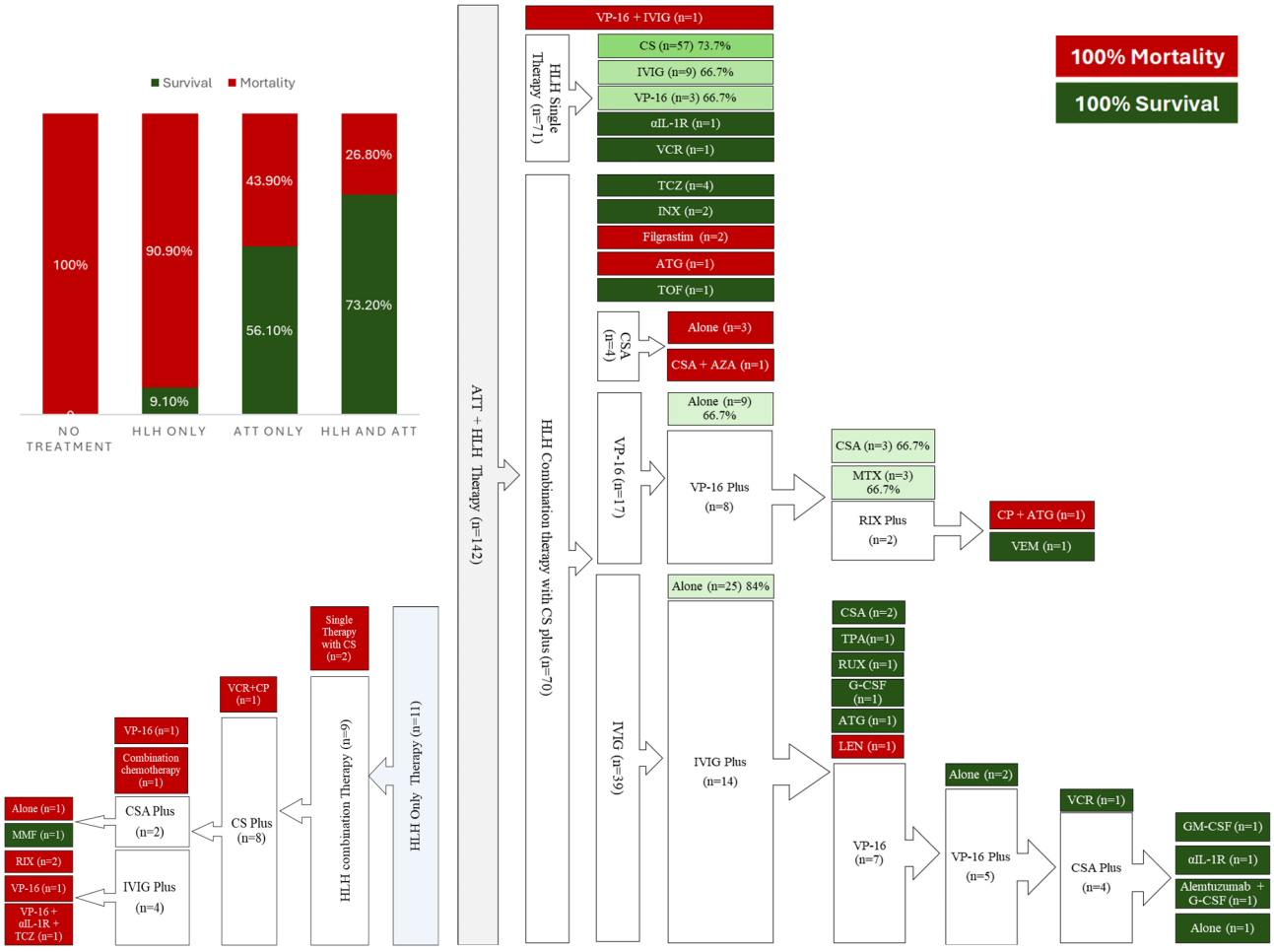

Fig. 4 Treatment Approaches and Outcomes. This figure illustrates a comprehensive range of treatments for patients with HLH-TB. The left graph compares survival rates for those receiving no treatment, HLH-only therapy, ATT-only, or a combination of ATT and HLH-specific therapies. The left panel details outcomes for patients receiving only HLH-specific treatment, while the right panel focuses on those treated with both ATT and HLH therapies. Dark green indicates 100% survival, red denotes 0% survival, and light green represents partial survival rates, with lighter shades corresponding to lower survival percentages, as indicated within each box. ATG: Antithymocyte Globulin, AZA: Azathioprine, CP: Cyclophosphamide, CSA: Cyclosporine, CS: Corticosteroids, INX: Infliximab, IVIG: Intravenous Immunoglobulin, LEN: Lenograstim, MMF: Mycophenolate Mofetil, MTX: Methotrexate, RIX: Rituximab, RUX: Ruxolitinib, TCZ: Tocilizumab, TPA: Thymic Peptide A, TPE: Therapeutic Plasma Exchange, TOF: Tofacitinib, VCR: Vincristine, VEM: Vemurafenib, VP-16: Etoposide, αIL-1R: Anakinra

underwent combination treatments (25.71% MR), primarily involving corticosteroids plus IVIG, etoposide, and CSA. MRs varied by therapy: corticosteroids (26% MR), IVIG (18.4% MR), etoposide (28.6% MR), CSA (38.5% MR), and Anakinra (0% MR). (Table 3, S8) (Fig. 4).

Plasma exchange

Therapeutic plasma exchange (TPE) was employed in six patients, resulting in an 83.3% survival rate. TPE was successfully used for resistant cytopenia in one patient, acute liver failure in another, and disseminated intravascular coagulation (DIC), hypotension, and resistant acute kidney injury (alongside hemodialysis) in a third. Additionally, TPE was administered to a patient with rapidly worsening acute respiratory distress syndrome and pancytopenia, achieving success.

Splenectomy as a supportive treatment

Splenectomy was performed in five patients, achieving an 80% survival rate. Indications included suspected lymphoma or splenic abscess, lack of response to ATT, persistent thrombocytopenia, and persistent splenomegaly due to hemorrhagic infarction.

Treatment in pregnancy

In two TB-HLH pregnancy cases, both mothers and newborns survived. One mother underwent a cesarean at 29 weeks, receiving ATT, IVIG, etoposide, CSA, and corticosteroids, with the newborn also treated with ATT. The other mother delivered at 28 weeks and was treated with ATT and corticosteroids.

Table 3 Treatments

			Deceased	Survived	Total	*p*-value
ATT	Classic	HRZE	27 (25.7%)	78 (74.3%)	105	**0.02**
		Non HRZE	22 (44.9%)	27 (55.1%)	49	
	Classic + Salvage	A	2 (15.4%)	11 (84.6%)	13	0.19
		C	8 (44.4%)	10 (55.6%)	18	
		A + C	6 (33.3%)	12 (66.7%)	18	
		B + C	1 (100%)	0 (0%)	1	
HLH		Corticosteroid	42 (30.7%)	95 (69.3%)	137	**0.004**
		IVIG	13 (24.5%)	40 (75.5%)	53	**0.03**
		Etoposide	11 (35.5%)	20 (64.5%)	31	0.84
		CSA	6 (40%)	9 (60%)	15	0.52
		Rituximab	3 (75%)	1 (25%)	4	0.15
		Anakinra	1 (33.3%)	2 (66.7%)	3	0.68
		Tocilizumab	1 (20%)	4 (80%)	5	0.65
		G-CSF	2 (40%)	3 (60%)	5	0.62
		Methotrexate	1 (33.3%)	2 (66.7%)	3	0.68
		Infliximab	1 (33.3%)	2 (66.7%)	3	0.68

ATT: Anti-tuberculosis treatment; CSA: Cyclosporine A; HLH: Hemophagocytic lymphohistiocytosis; IVIG: Intravenous immunoglobulin; HRZE: isoniazid, rifampin, pyrazinamide, and ethambutol; A: levofloxacin or moxifloxacin, bedaquiline, linezolid; B: clofazimine, cycloserine or trizidone; and C: ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin or streptomycin, ethionamide or protonamide, p-aminosalicylic acid

Table 4 Results of the binary logistic regression model

		Univariate			Multivariate		
	Variables	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**
Analysis within all patients	Age (y) ≥ 44	< 0.001	0.235	0.130–0.422	**0.04**	**0.408**	**0.176–0.950**
	Platelet < 79×10^3/μL	0.04	0.464	0.227–0.950	0.37	0.657	0.263–1.642
	Presence of comorbidity	< 0.001	0.139	0.065–0.297	**0.005**	**0.256**	**0.100-0.656**
	ATT use	< 0.001	48.00	6.301-365.665	**0.004**	**23.152**	**2.745-195.287**
	Corticosteroid use	0.003	2.468	1.360–4.477	0.17	1.798	0.773–4.181
	IVIG Use	0.02	2.238	1.107–4.523	**0.04**	**2.979**	**1.049–8.457**
Subgroup Analysis model A	Age (y) ≥ 44	< 0.001	0.274	0.141–0.531	**0.02**	**0.395**	**0.183–0.853**
	Presence of comorbidity	< 0.001	0.167	0.072–0.386	**0.001**	**0.231**	**0.095–0.563**
	ATT + HLH	0.04	2.142	1.043–4.401	**0.03**	**2.491**	**1.094–5.669**
Subgroup Analysis model B	Age (y) ≥ 44	< 0.001	0.274	0.141–0.531	**0.02**	**0.406**	**0.187–0.878**
	Presence of comorbidity	< 0.001	0.167	0.072–0.386	**< 0.001**	**0.213**	**0.087–0.521**
	Corticosteroid	0.04	1.985	1.022–3.856	0.19	1.685	0.766–3.710
	IVIG	0.03	2.401	1.073–5.373	**0.02**	**3.318**	**1.205–9.141**

ATT: Anti-tuberculosis treatment; CI: Confidence Interval, IVIG: Intravenous immunoglobulin; OR: Odd Ratio; y: years

Binary logistic regression model

The binary logistic regression model identified age ≥ 44, platelet count < 79×10^3/μL, comorbidities, and the use of ATT, corticosteroids, and IVIG as significant factors ($p<0.05$) for inclusion in the multivariate analysis. Significant independent associations with survival were found for IVIG (OR = 2.979, 95% CI:1.049–8.457, $p=0.040$), ATT (OR = 23.152, 95% CI:2.745-195.287, $p=0.004$), presence of comorbidities (OR = 0.256, 95% CI: 0.100-0.656, $p=0.005$), and age ≥ 44 years (OR = 0.408, 95% CI: 0.176–0.95, $p=0.038$). (Table 4)

In a subgroup analysis of TB-HLH patients receiving ATT, age ≥ 44, presence of comorbidities, and combined ATT and HLH-specific therapy were significant in the univariate model ($p<0.05$) and included in the multivariate model. Older patients (age ≥ 44) had a lower survival chance (OR = 0.395, 95% CI: 0.183–0.853, $p=0.018$). Adding HLH-specific therapy to ATT significantly reduced mortality, with an OR of 2.491 ($p=0.030$), indicating a 59.85% decrease in mortality compared to ATT alone. (Table 4, Model A)

Another subgroup analysis of TB-HLH patients receiving ATT, assessed the impact of IVIG and corticosteroids. IVIG, when used in addition to ATT, significantly reduced mortality (OR = 3.318, 95% CI:1.205–9.141, $p=0.020$), underscoring the potential benefit of incorporating IVIG into the treatment regimen alongside ATT. (Table 4, Model B)

Disease progression

End-organ damage was reported in 76 patients. Of these, 32 experienced respiratory failure alone, with a 34.4% mortality rate. Four patients had renal failure alone, with a 50% survival rate, and one patient with liver failure alone survived. Among 39 patients with multiple organ dysfunction, the mortality rate was 69.2%. Nineteen patients experienced DIC, with a 47.4% mortality rate. Of the 43 patients admitted to the Intensive Care Unit, 55.8% successfully recovered.

Risk of bias assessment result

Using the JBI checklist [22], an eight-point scale for evaluating case report quality, we assessed individual reports and 13 multi-case studies not qualifying as case series. The majority of cases exhibited moderate to good quality, with 14.55% achieving a score of eight, 23.47% attaining a score of seven, and 33.80% securing a score of six. Conversely, the remaining cases demonstrated lower quality, with 12.20% scoring five, 7.98% scoring four, 3.28% scoring three, 4.22% scoring two, and 0.46% scoring one. (Table S9)

Discussion

This systematic review addresses critical gaps in understanding TB-HLH, offering insights into its epidemiology, clinical characteristics, and treatment outcomes globally. We found that ATT is crucial for managing TB-HLH. Combining ATT with HLH-specific therapies significantly enhances treatment efficacy, emphasizing the need for an integrated therapeutic approach. Adjunctive therapy with IVIG may further improve outcomes, though additional research is needed. Age≥44 years and the presence of comorbidities were identified as independent risk factors for increased mortality, highlighting the need for comprehensive management strategies considering both age and comorbid conditions.

Geographical distribution

Our findings show that TB-HLH is a global condition, with notable concentrations in high TB burden countries like India and China [24], indicating a strong correlation between TB prevalence and TB-HLH incidence. Additionally, TB-HLH cases in countries with lower TB prevalence, such as France, Spain, and the United States, highlight the impact of global migration and travel. This pattern underscores the need for heightened clinical awareness and consideration of a patient's geographic origin and travel history in diagnosing TB-HLH. However, the data may be subject to reporting bias, as not all cases of HLH-TB may be identified or reported.

Diagnosis

In our review, fever was the most common symptom, followed by respiratory complaints, and lymphadenopathy. Hepatosplenomegaly was also observed in a significant number of patients. These findings are consistent with prior TB-HLH review, underscoring the importance of these symptoms and signs in the diagnosis of TB-HLH [25–27].

However, establishing precise diagnostic criteria for TB-HLH is challenging due to the overlapping and nonspecific features of both conditions. Patients often present with prolonged symptoms such as persistent fever, hepatosplenomegaly, and cytopenias (particularly thrombocytopenia), which typically prompt clinicians to investigate more common diagnoses like malignancies, infections, metabolic disorders, or rheumatologic conditions. However, when patients present with acute liver failure, hepatitis, coagulopathy, or sepsis with multi-organ failure, HLH should be considered a key differential diagnosis. Similarly, in acute disseminated TB, symptoms like multi-organ failure, septic shock, and ARDS, along with fever, can be the initial indicators [2, 28–32]. In patients where HLH is suspected, especially those from high TB-burden areas, it is essential to consider TB as a potential trigger. If disseminated TB is diagnosed but the patient's condition deteriorates despite receiving ATT, coexisting HLH should be strongly considered. Further diagnostic evaluations, such as bone marrow biopsy and sCD25 levels, are necessary to confirm the HLH diagnosis [17].

Our analysis showed that most patients who did not receive treatment for either TB or HLH remained undiagnosed until death. Conversely, nearly all patients treated solely for HLH were not diagnosed with TB during their lives. Postmortem TB diagnoses were found only in patients from non-high TB-burden countries, underscoring the need for vigilance in diagnosing TB even in low-prevalence regions.

In four patients, despite a history of TB, the diagnosis was achieved only post-mortem. Additionally, three patients did not receive ATT during their clinical course. These cases, although few, highlight the need for clinicians to be vigilant for TB reactivation or reinfection in patients with a history of TB, even if they have completed treatment. This is especially critical in endemic regions where reinfection is more likely or where patients may have been re-exposed to TB in high-transmission environments. An example is the case of an immigrant in the UK who was reinfected during a trip to Africa, which subsequently triggered HLH [33]. In patients with a history of TB who present with suspicious symptoms of HLH—symptoms that often overlap with those of disseminated TB—it is essential to consider TB as a possible underlying infection that could either initiate the HLH

process or mimic HLH itself. This highlights the need for further studies to determine whether empiric TB treatment in HLH patients with a prior infection history of TB—particularly in critically ill patients with recent TB exposure in endemic regions or high-risk environments—can be lifesaving.

Treatment

Our study provides important insights into the management of TB-HLH, a condition for which standardized treatment protocols have been lacking [25, 26]. Both ATT and IVIG were found to independently reduce mortality rates, and combining ATT with HLH-specific therapies further improved outcomes. In contrast, corticosteroids did not show a significant impact on mortality, possibly because of the unique complexities of TB-HLH. The immunosuppression caused by treatments like corticosteroids, etoposide, and cyclosporine A can lead to secondary infections, which are a major cause of mortality and can be mistaken for HLH relapse [17]. Moreover, immunosuppressive therapies may worsen underlying infections such as TB, which is especially concerning in TB-HLH cases. Given these risks, alternative treatments like IVIG or biologic agents may be more suitable in TB-HLH cases, as they help regulate the immune response without significantly worsening infections [34]. Additionally, it is important to note that IVIG is not exclusive to HLH treatment and was used in TB management itself in limited studies [35–37]. Therefore, the benefits of IVIG observed in our review may not be entirely due to its role in treating HLH.

Recent consensus recommends considering treatments such as TPE and splenectomy in cases of refractory or relapsed HLH [17]. In addition to the mentioned situations, these two treatments may offer greater effectiveness. Some reports have shown that for critically ill patients or those with rapidly deteriorating symptoms, TPE can be lifesaving [38–40]. Furthermore, splenectomy may be beneficial, particularly in cases with splenic infarction [41] or persistent thrombocytopenia unresponsive to conventional therapy [42, 43]. Although the number of such cases is limited, further research is needed to establish their efficacy.

In patients treated with classic ATT, compared to those who received salvage therapy, mortality was slightly lower, with the HRZE regimen also showing a significant reduction in MR. However, interpreting this data must be done cautiously, as salvage therapies are typically administered to critically ill patients or those with antibiotic resistance, inherently skewing the outcomes. Due to the heterogeneity of the data and the lack of a standardized severity score for TB-HLH cases, our study was unable to account for disease severity as a confounding factor.

Prognosis

Previous HLH studies reported MRs between 40% and 88% [4, 44, 45]. TB-HLH research indicated MRs of approximately 40–50% [25–27]. Consistently, our study observed a MR of 39%.

Recent HLH studies have identified key mortality factors, including CNS issues, high creatinine, age over 50, low platelets, elevated AST or LDH, and malignancies [44, 46–49]. HLH-TB research links higher mortality to age over 30, comorbidities, ferritin above 1000, and bone marrow hemophagocytosis [26]. The latest TB-HLH review also show comorbidities and MTB presence in bone marrow as critical indicators of increased mortality [27].

Our review, which includes nearly double the cases of prior TB-HLH studies and comprehensive global data, provides new and likely more accurate insights. We found that age≥44 and the presence of comorbidities independently and significantly increased MRs. Although LDH levels were not significant in the regression, they were higher in deceased patients compared to survivors ($p=0.002$). Additionally, renal disease, diabetes mellitus, and cardiovascular disease were linked to higher MRs.

Strengths and limitations

This study's strengths lie in its comprehensive, multilingual analysis of 213 patients, nearly double the number included in previous studies. The diverse geographic representation adds to the robustness and reliability of our findings. We underscore the potential efficacy of combining ATT with IVIG, which may be suggested as a possible standard treatment approach for TB-HLH. Additionally, identifying age≥44 years and the presence of comorbidities as significant mortality risk factors supports the need for tailored treatment strategies and comprehensive management protocols. Prospective, multicenter studies are essential to validate these findings and refine future treatment protocols.

However, the study also has limitations. There is considerable variability in diagnostics, treatments, and outcomes among the included studies, which impacts data reliability. This underscores the need for standardized diagnostic and treatment criteria in future research. Additionally, reporting bias may have influenced the generalizability of findings, especially as most studies were retrospective, which inherently limits data accuracy. Furthermore, the presence of comorbidities like malignancy and immunosuppression could introduce bias in determining whether TB was the primary cause of HLH. These conditions likely influenced clinical outcomes, complicating the interpretation of the results. Additionally, our study did not find a significant correlation between HLH severity and prognosis in TB-HLH, which contrasts with previous studies that have demonstrated such

a relationship. This discrepancy may be due to the heterogeneity in reporting HLH severity across the included cases, with many lacking standardized severity scores. Moreover, TB may act as the primary driver of mortality in TB-HLH cases, overshadowing the impact of HLH severity. Due to the retrospective nature of most included studies, standardized assessment of HLH severity was often missing. Moving forward, prospective studies should include standardized severity scoring systems to better assess the relationship between HLH severity and prognosis in TB-HLH.

Implications for clinical practice

Clinicians should maintain a high index of suspicion for TB-HLH, particularly in patients presenting with fever, hepatosplenomegaly, cytopenia, and elevated ferritin levels, especially those from TB-endemic regions or with a history of TB exposure. Early diagnosis is critical, as delayed identification of coexisting TB and HLH can result in poor outcomes. Patients aged ≥ 44 and those with comorbidities are at higher risk of mortality. Tailored treatment protocols considering age and comorbid conditions are essential for optimizing patient survival.

Our study supports the integration of ATT as a fundamental component of TB-HLH management. When combined with HLH-specific therapies, this approach has been shown to significantly reduce mortality rates. Notably, IVIG, as an immunomodulatory agent, plays a crucial role in improving outcomes by either controlling HLH or assisting in the management of disseminated TB infection.

Future research directions

This systematic review underscores the need for future research to refine and optimize the management of TB-HLH. Prospective, multicenter studies are essential to validate the effectiveness of combining ATT with HLH-specific therapies. Additionally, while our findings suggest a significant role for IVIG in reducing mortality, more research is needed to differentiate its effects specifically in treating HLH versus its benefits in managing tuberculosis itself.

Most of the studies we reviewed did not consistently report the timeline between TB symptom onset and HLH diagnosis, making it difficult to assess whether early TB treatment could help prevent the progression to HLH. Understanding this relationship could lead to earlier interventions and potentially improved patient outcomes. Future prospective research should focus on gathering this data to clarify the impact of early TB treatment in preventing HLH development.

Given the rarity of TB-HLH, it is essential that future case reports include comprehensive patient details, such as past medical history, exposure history, initial symptoms, and severity assessments. Detailed timelines from symptom onset to long-term follow-up, along with step-by-step management details, are critical for advancing our understanding of TB-HLH and developing more effective treatment strategies.

Conclusion

This systematic review supports integrating ATT as a core component in managing TB-HLH. When combined with HLH-specific therapies, this approach significantly reduces mortality. Notably, IVIG, as an immunomodulatory agent, plays a key role in improving outcomes, either by controlling HLH or helping manage disseminated TB infection. It identifies age ≥ 44 and the presence of comorbidities as significant risk factors for increased mortality. The study recommends maintaining a high suspicion for TB-HLH in patients from high TB burden areas or with relevant travel histories. Future prospective multicenter studies are necessary to establish standardized treatment guidelines and optimize protocols for managing TB-HLH.

Abbreviations

ANC	Absolute neutrophil count
ATT	Anti-tuberculosis treatment
CMV	Cytomegalovirus
CNS	Central nervous system
CSA	Cyclosporine A
CTLs	Cytotoxic T lymphocytes
DIC	Disseminated intravascular coagulation
DM	Diabetes Mellitus
DTB	Disseminated hematogenous tuberculosis
EBNA	Epstein Barr virus nuclear antigen
EBV	Epstein-Barr virus
HLH	Hemophagocytic lymphohistiocytosis
HRZE	Isoniazid, rifampicin, pyrazinamide, and ethambutol
IFN-γ	Interferon-gamma
IL	Interleukin
IQR	Interquartile range
IVIG	Intravenous immune globulin
JBI	Joanna Briggs Institute
MFM	Mycophenolate Mofetil
MHC-I	Major Histocompatibility Complex Class I
MR	Mortality rate
MTB	Mycobacterium tuberculosis
NK	Natural killer cell
P	p-value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
sIL-2R	Soluble interleukin 2 receptor alpha
SD	Standard deviation
SE	Standard error difference
TB	Tuberculosis
TB-HLH	Tuberculosis-associated hemophagocytic lymphohistiocytosis
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TPE	Therapeutic plasma exchange

Supplementary Information

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Supplementary Material 1: Include: S1 Table. HLH diagnostic criteria: HLH-2004 vs. H-score.; S2 Table. Full search terms.; S3 Table. Reasons for studies not being included.; S4 and S5 Tables. Characteristics of included studies.; S6 Table. Summary of comorbidities.; Fig. S1. Distribution of tuberculosis isolation sites by diagnostic method.; S7 Table. Other laboratory findings.; S8. Table. Treatment in ATT + HLH therapy group; S9 Table. Reported cases and their risk of bias according to the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports.; and Supplementary material references

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Author contributions
Conceptualization: A.E., S.A., and I.A. conceived the idea for this review and developed the study protocol. Data Curation and Investigation: A.E., S.A., S.Kh., H.A., and R.A. conducted the searches, screening, and data extraction, with validation and support from I.A., D.M., and K.A. Formal Analysis: A.K. performed the statistical analysis of the data. Methodology: A.E. and S.A. developed the study protocol, with feedback from I.A. and K.A. Project Administration: A.E. and S.A. coordinated the review process. Resources: Data sources and tools were managed by A.E. and S.A. Software: Data synthesis was performed using SPSS version 27 by A.K. Supervision: I.A. and K.A. provided oversight and guidance throughout the study. Validation: I.A., D.M., and K.A. supported the data extraction process. Visualization: A.E. performed data visualization. Writing – Original Draft: A.E. and S.A. drafted the initial manuscript, incorporating suggestions from I.A., D.M., and K.A. Writing – Review and Editing: All authors discussed the results and contributed to the final manuscript's review and editing. All authors had full access to all the data in the study and took responsibility for the decision to submit for publication. A.E., S.A., and I.A. directly accessed and verified the underlying data reported in the manuscript, fulfilling the requirement for data verification by more than one author.

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Data availability
Data extracted from published articles, which were utilized in our analysis, will be made available upon reasonable request to the corresponding author. Additionally, data that was provided directly by the authors of the studies included in our analysis will be available for sharing only after the investigators, who request such data, obtain explicit permission from the authors of the original studies.

Declarations

Ethics approval and consent to participate
Not applicable.

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