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MAJOR ARTICLE

Tuberculosis-Associated Hemophagocytic Lymphohistiocytosis: Diagnostic Challenges and Determinants of Outcome

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Background. Tuberculosis (TB) can induce secondary hemophagocytic lymphohistiocytosis (HLH), a severe inflammatory syndrome with high mortality. We integrated all published reports of adult HIV-negative TB-associated HLH (TB-HLH) to define clinical characteristics, diagnostic strategies, and therapeutic approaches associated with improved survival.

Methods. PubMed, Embase, and Global Index Medicus were searched for eligible records. TB-HLH cases were categorized into (1) patients with a confirmed TB diagnosis receiving antituberculosis treatment while developing HLH and (2) patients presenting with HLH of unknown cause later diagnosed with TB. We used a logistic regression model to define clinical and diagnostic parameters associated with survival.

Results. We identified 115 individual cases, 45 (39.1%) from countries with low TB incidence (<10/100 000 per year). When compared with patients with HLH and known TB (n = 21), patients with HLH of unknown cause (n = 94) more often had extrapulmonary TB (66.7% vs 88.3%), while the opposite was true for pulmonary disease (91.5% vs 59.6%). Overall, *Mycobacterium tuberculosis* was identified in the bone marrow in 78.4% of patients for whom examination was reported (n = 74). Only 10.5% (4/38) of patients tested had a positive result upon a tuberculin skin test or interferon-γ release assay. In-hospital mortality was 28.1% (27/96) in those treated for TB and 100% (18/18) in those who did not receive antituberculosis treatment ($P < .001$).

Conclusions. Tuberculosis should be considered a cause of unexplained HLH. TB-HLH is likely underreported, and the diagnostic workup of patients with HLH should include bone marrow investigations for evidence of *Mycobacerium tuberculosis*. Prompt initiation of antituberculosis treatment likely improves survival in TB-HLH.

Keywords. anergy; bone marrow; hemophagocytic lymphohistiocytosis; mortality; tuberculosis.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome characterized by elevated proinflammatory cytokine production, excessive macrophage activation, and phagocytosis of mature blood elements [1, 2]. Contrary to primary HLH, which is driven by known genetic mutations, secondary HLH is caused by malignancies, autoimmune and autoinflammatory disorders (formerly termed macrophage activation syndrome), or infections, including tuberculosis (TB) [3]. Overall, HLH is associated with high mortality [4]. Immunomodulation with corticosteroids, interleukin-1 receptor antagonists, or T cell-directed chemotherapy may be necessary to curb inflammation. However, in the case of secondary HLH of infectious origin, pathogen-directed treatment is crucial [5, 6].

Diagnosis of TB disease relies on microbiological identification of *Mycobacterium tuberculosis* (*M tuberculosis*) by culture, microscopy, or molecular testing, and can be supported by histopathologic evidence of granulomatous inflammation. Low suspicion for TB may preclude use of appropriate TB diagnostics in low TB-endemic settings, while in high TB-endemic settings, diagnosing HLH may be difficult if bone marrow examination and other tests for HLH are unavailable. T cell–based assays for immune memory to *M tuberculosis*, such as the tuberculin skin test (TST) or interferon-γ release assay (IGRA), are sometimes used to exclude TB, but their diagnostic accuracy might be affected by the concurrent immune dysregulation associated with HLH.

Currently, understanding of optimal diagnostic strategies and therapeutic approaches in TB-HLH is limited because

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data are largely confined to case reports and small case series. A recent review on clinical characteristics of TB-HLH included a heterogenous patient population including children and lacked predefined patient categorization or multivariate assessment of the determinates of outcomes [7]. This limits the ability to draw firm conclusions on how to best identify patients with TB-HLH, the investigations with greatest diagnostic yield, and the interventions that most affect survival. To address these unanswered research questions, we undertook a systematic review of all TB-HLH cases described to date according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[8], performing a patient-level meta-analysis of all reported clinical parameters. We specified 2 categories of patients with TB-HLH: patients who had a confirmed TB diagnosis and were already receiving antituberculosis treatment at the time of HLH diagnosis and patients who presented with HLH of unknown etiology, in whom TB was later diagnosed. The standardized collection of information from the TB-HLH cases allowed us to integrate findings on the clinical presentation, diagnosis, treatment, and outcomes in TB-HLH.

METHODS

Search Strategy and Selection Criteria

We defined and followed a prespecified strategy according to the PRISMA guidelines [8] registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42022349077 [9]). We searched PubMed, Embase, and Global Index Medicus for records indexed before 23 October 2022, without any language or publication restrictions in our search strategy: "tuberculosis" AND "hemophagocytic lymphohistiocytosis" OR "macrophage activation syndrome", and their synonyms and abbreviations (Supplementary Table 1). Duplicate records were removed with Endnote and Rayyan [10]. First, 1 reviewer (L. K.) screened all titles and abstracts using the exclusion criteria: (1) the described patient was not diagnosed with TB; (2) the record contained no primary data of at least 1 patient; or (3) all described patients were HIV coinfected, as in-between patient differences in immune status (CD4+ T-cell count) would cause more heterogeneity and create an overlap with HIV-associated immune reconstitution inflammatory syndrome. Next, 2 reviewers (G. P. and A. v. L.) screened the remaining titles and abstracts using the inclusion criteria. Specifically, records were included if they described at least 1 patient meeting both the following criteria: TB and HLH. Disagreements were resolved through discussion and mutual agreement by all 3 reviewers.

Data Extraction, Eligibility, and Bias Assessment

Full-text records were assessed for eligibility by 1 reviewer (L. K. or T. S.) during data extraction using a standardized form. For each record, we collected data relating to record characteristics, patient characteristics, TB disease features and therapy, HLH characteristics and therapy, TST/IGRA test results, and patient outcomes. A detailed description of the collected data is provided in Supplementary Table 2. We assessed the risk of bias using the Joanna Briggs Institute critical appraisal tool for case reports [11]. We assessed the risk of bias on 8 domains: demographic characteristics, medical history, clinical condition, diagnostics, intervention and treatment, postintervention clinical condition, adverse events, and takeaway lesson. Reports with missing data on any 1 the following key variables were excluded by the first reviewer: sex, age, TB localization, use of antituberculosis treatment at the onset of HLH, and outcome. A second reviewer (1 of S. v. D., R. v. C., G. P., A. v. L.) reviewed all coded data for accuracy so that all eligible studies received independent assessment from 2 reviewers. Disagreements were resolved through discussion and mutual agreement by both reviewers for each record in question.

Missing blood biochemical test results (continuous variables) were coded as missing. Comorbidities were assumed to be absent if not reported, except for *M tuberculosis* bone marrow examination, which was scored as follows: "present" when evidence of *M tuberculosis* was reported, whether microbiological (culture, staining for acid-fast bacilli, or polymerase chain reaction) or histologic; "absent" when the absence of microbiological or histologic evidence was reported; or otherwise "not tested," as we did not assume that all bone marrow examinations included *M tuberculosis* diagnostics. Continuous values were converted to standard units when necessary.

Case Definitions and Classifications

Identified patients were categorized into 2 groups: (1) patients with known TB developing HLH as a paradoxical reaction while receiving antituberculosis treatment and (2) patients presenting with HLH of unknown cause who were later diagnosed with TB and therefore were not receiving antituberculosis treatment at the onset of HLH. Of note, our prespecified systematic review protocol had considered 2 subgroups within this latter category: (1) patients diagnosed with HLH in which retrospective assessment considered this the unmasking event for a TB diagnosis and (2) patients who presented at a health care facility with fever or inflammation of unknown origin, in which the HLH diagnosis and the TB diagnosis were confirmed at a later stage (PROSPERO, CRD42022349077 [9]). In practice, these 2 groups proved indistinguishable; therefore, we combined them into a single category of patients presenting with HLH of unknown cause.

Data Analysis and Visualization

Data were analyzed with SPSS (version 27; IBM) [12]. Mann-Whitney *U* tests (continuous variables) and χ^2 tests (nominal variables) were used to assess differences between groups. To determine associations with TB-HLH mortality, we built a logistic regression model. First, we explored the association of mortality with sex, variables reported to influence HLH mortality (age, presence of comorbidities, hepatomegaly,

hemoglobin and ferritin levels) [13–15], as well as steroid therapy [16], supplemented by covariates relevant to TB-HLH: TB localization, evidence of *M tuberculosis* in the bone marrow, and receipt of antituberculosis treatment during the disease episode. Covariates univariately associated with survival were tested in a multivariable regression model. Data were visualized with Prism (version 10.0.2; GraphPad) [17] and R 4.1.3 [18] via the R packages *xlsx* [19], *maps* [20], and *ggplot2* [21].

RESULTS

We identified 641 records from the database search (Figure 1). After deduplication, screening of titles and abstracts (417

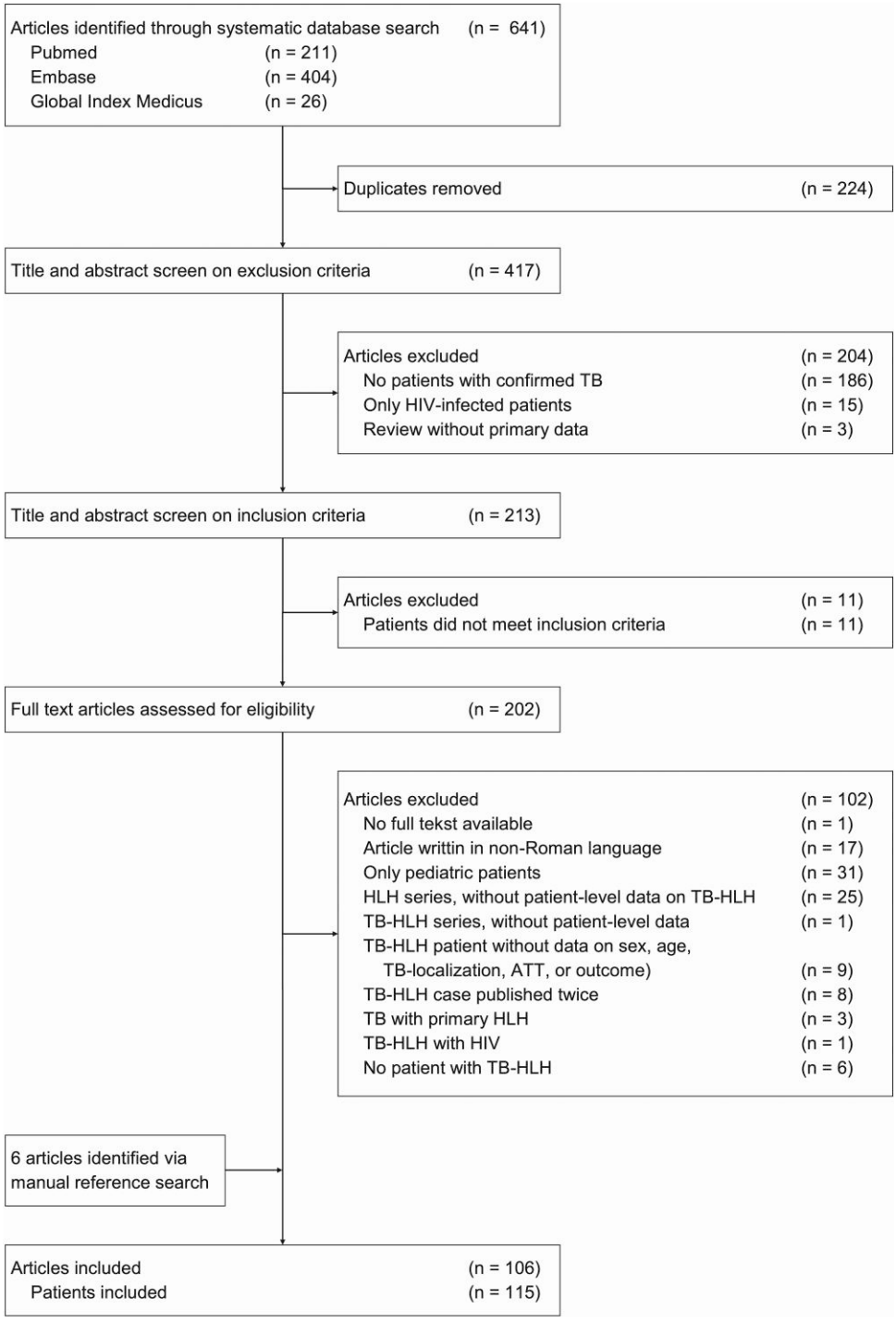

Figure 1. PRISMA diagram of articles reporting ≥1 cases of TB-HLH. ATT, antituberculosis treatment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; TB, tuberculosis; TB-HLH, tuberculosis-associated hemophagocytic lymphohistiocytosis.

records), and full-text screening (202 records), 100 publications were included. An additional 6 records that had not been picked up by our search criteria were identified via manual reference searches of reference lists of identified articles. As missing data for our key variables were an exclusion criterion, the risk of bias was uniformly assessed as low (Supplementary Table 3). The 106 records described 115 patients from 34 countries across all continents except Antarctica (Figure 2). Reports from the 20 World Health Organization–defined high TB-burden countries for 2021 to 2025, which account for 84% of the global TB burden [22], contributed only 35.6% (41/115) of cases in our analysis. In contrast, reports from low TB incidence (<10/100 000 [23]) comprised 39.1% (45/115) of cases, and just one-third (15/45) of these patients had previously lived in a moderate to high incidence country (≥10/100 000).

Patients were mostly male (69.6%) with a median age of 43 years (IQR, 30–63), and approximately half had ≥1 comorbidities (Table 1). HLH criteria were incompletely assessed, with limited availability of natural killer cell activity and soluble interleukin-2 receptor levels (recorded in 5.2% and 11.3% of cases, respectively). Consequently, out of the 8 HLH-2004 criteria [16] for secondary HLH, a median of 5 (IQR, 4–6) were assessed, and 66.1% cases fulfilled ≥5 criteria required to make a diagnosis of HLH (Supplementary Figure 1). The minority of patients with TB-HLH developed HLH while already receiving antituberculosis treatment for a confirmed TB diagnosis (n = 21) at a median 14 days (IQR, 7–36 days) after start of antituberculosis treatment. Most patients with TB-HLH initially presented with HLH of unknown etiology, and a TB diagnosis was made later (n = 94). These 2 groups were similar in sex, age, presence of fever, splenomegaly, hemophagocytosis (ie, in bone marrow, spleen, and/or lymph nodes), hyperferritinemia, and other HLH criteria, as well as underlying comorbidities, except for renal disease (Table 1, Supplementary Table 4). Notably, the diagnosis of TB-HLH could not be ruled out by ferritin alone, as hyperferritinemia (≥500 μg/L, HLH-2004 cutoff [16]) was reported in 71.3% and ferritin levels ≥2000 μg/L (H-score minimum [24]) in only 38.3%.

Pulmonary disease was present in 90.5% (19/21) of patients with TB-HLH and a known TB diagnosis but in just 59.6% (56/96) of patients first presenting with HLH of unknown cause ($P = .007$; Table 2). Pulmonary TB followed a miliary pattern in around half of patients in both groups. Most TB-HLH cases showed extrapulmonary TB involvement: 66.7% (14/21) of those with a confirmed TB diagnosis vs 88.3% (83/94, $P = .014$) in those presenting with HLH of unknown cause. The distinction between the groups was even more pronounced by evidence of *M tuberculosis* in the bone marrow, present in 14.3% (3/21)

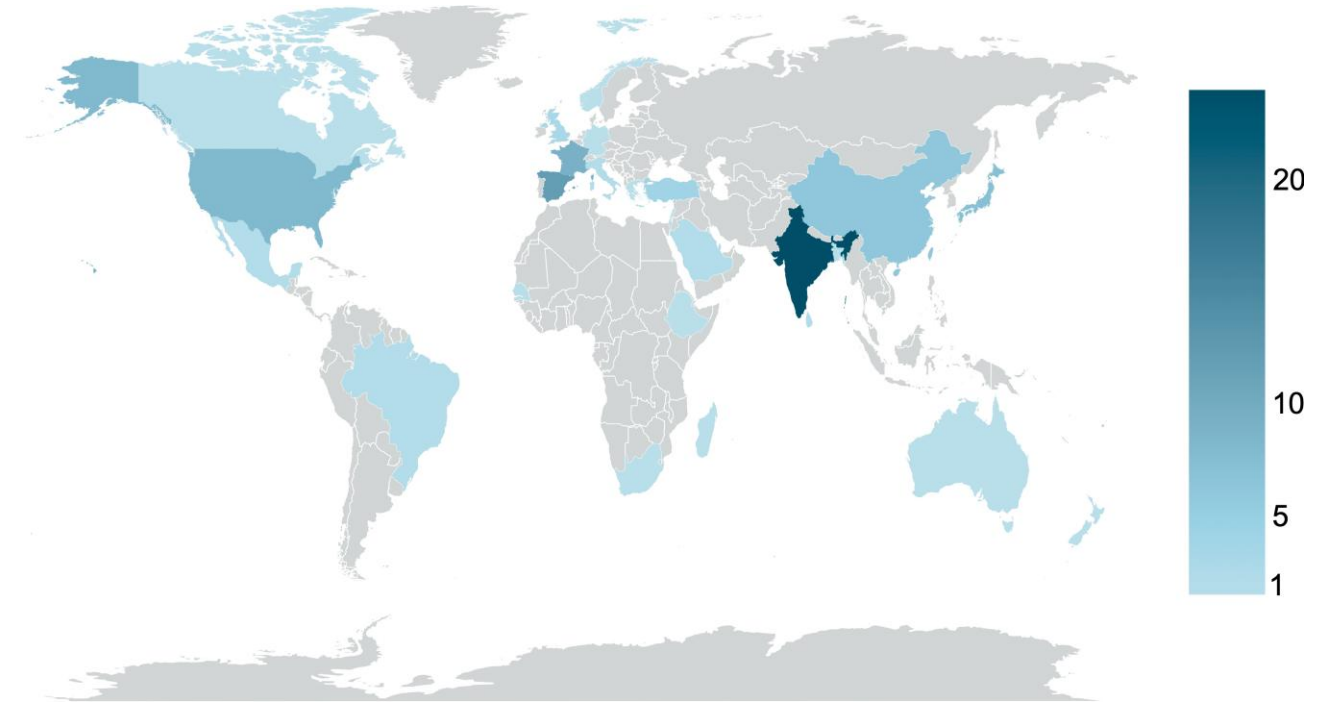

Figure 2. Geographic distribution of TB-HLH cases: number of reported TB-HLH cases according to country of origin for published report. Gray, no TB-HLH cases reported. TB-HLH, tuberculosis-associated hemophagocytic lymphohistiocytosis.

Table 1. Patient Characteristics and Disease Characteristics at the Time of HLH Presentation

	ATT at HLH Onset, n (%) or Median (IQR)		
	Yes (n = 21)	No (n = 94)	*P* Value
Patient characteristics			
Female	6 (28.6)	29 (30.9)	.84
Age, y	37.0 (28.5–59.0)	45.0 (30.8–63.0)	.66
Comorbidities	9 (42.9)	49 (52.1)	.44
Immunocompromised host[a]	4 (19.0)	15 (16.0)	.73
Diabetes mellitus	2 (9.5)	15 (16.0)	.45
Malignancy	0 (0.0)	8 (8.5)	.17
Autoimmune disorder	4 (19.0)	11 (11.7)	.37
Renal disease	0 (0.0)	15 (16.0)	<.05
Cardiovascular disease	4 (19.0)	10 (10.6)	.29
Other comorbidities	3 (14.3)	15 (16.0)	.85
HLH-2004 criteria [16][b]			
Fever	20 (95.2)	91 (96.8)	.72
Splenomegaly[c]	9 (42.9)	57 (60.6)	.14
Bicytopenia or pancytopenia	19 (90.5)	83 (88.3)	.78
Hypertriglyceridemia and/or hypofibrinogenemia[d]	9 (42.9)	51 (54.3)	.34
Hemophagocytosis [e]	19 (90.5)	87 (92.6)	.75
Hyperferritinemia[f]	16 (76.2)	66 (70.2)	.58
HLH score ≥5[g]	13 (61.9)	63 (67.0)	.65

For categorical variables, *P* values were calculated with χ^2 tests, and differences in age were assessed with the Mann-Whitney *U* test.

Abbreviations: ATT, antituberculosis treatment; HLH, hemophagocytic lymphohistiocytosis.

[a]All 4 patients who were immunocompromised and undergoing ATT at HLH onset received immunomodulatory medication due to an underlying autoimmune disorder. Of the patients who were immunocompromised and not undergoing ATT at HLH onset, 8 received immunomodulatory medication because of an underlying autoimmune disorder and 7 because of the presence of malignancy or previous transplantation. Steroids and tumor necrosis factor inhibitors were the most commonly used immunomodulatory medication.

[b]Natural killer cell activity and soluble CD25 were measured in 6 and 13 patients, respectively, and are therefore not mentioned in the table.

[c]Splenomegaly was assessed clinically or via imaging.

[d]Triglycerides ≥265 mg/dL or reported as hypertriglyceridemia and/or fibrinogen ≤1.5 g/L or reported as hypofibrinogenemia.

[e]Hemophagocytosis in bone marrow, spleen, and/or lymph nodes.

[f]Ferritin ≥500 µg/L or reported as hyperferritinemia.

[g]Calculation of HLH score was based on available data, including natural killer cell activity and soluble CD25 levels.

Table 2. Localization of Tuberculosis Disease in Patients With TB-HLH

	On ATT at HLH Onset (n = 21)			Not on ATT at HLH Onset (n = 94)		
	No *Mtb* in BM, n (%)	*Mtb* in BM, n (%)	Total, n (%)	No *Mtb* in BM, n (%)	*M.tb* in BM, n (%)	Total, n (%)
No pulmonary involvement			2 (9.5)			38 (40.4)
Solitary lymph node disease	2	NA		3	NA	
Extrapulmonary disease	0	0		15	9	
Solitary bone marrow disease	NA	0		NA	11	
Pulmonary involvement			19 (90.5)			56 (59.6)
Parenchymal disease only	2	2		7	7	
Parenchymal disease with extrapulmonary localization	4	0		5	11	
Miliary pattern only	5	0		4	12	
Miliary pattern with extrapulmonary localization	5	1		5	5	
Total, No (%)	**18 (85.7)**	**3 (14.3)**	**21 (100)**	**39 (41.5)**	**55 (58.5)**	**94 (100)**

For 11 and 21 patients undergoing and not undergoing ATT at HLH onset, respectively, bone marrow investigations for the evidence of *M tuberculosis* were not reported. These patients are reported as "no evidence of *M tuberculosis* in bone marrow" in the table.

Abbreviations: ATT, antituberculosis treatment; BM, bone marrow, HLH, hemophagocytic lymphohistiocytosis; *Mtb, Mycobacterium tuberculosis*; TB, tuberculosis.

and 58.5% (55/94) patients, respectively ($P < .001$). Notably, this difference was unlikely to be confounded by the frequency of bone marrow testing for *M tuberculosis* infection, as positivity rates of bone marrow investigations for *M tuberculosis* were lower in patients with a confirmed TB diagnosis vs those presenting with HLH of unknown cause (30% [3/10] vs 85.9% [54/64], $P < .001$; Supplementary Figure 2). T cell–based assays, TST, and/or IGRA, conducted in one-third of patients, yielded

positive results in only 10.5% (4/38) of those tested. Of the IGRA tests performed, 46.7% (7/15) were indeterminate (Figure 3).

At the time of HLH diagnosis, antituberculosis treatment was already started for all 21 patients with a known TB diagnosis, while 80.9% (76/94) of patients with TB-HLH presenting with HLH of unknown etiology received antituberculosis treatment at some point during their hospital stay. Corticosteroids were initiated in 65.2% (75/115). In-hospital mortality was 40.0% and did not significantly differ between those with and without known TB at time of HLH diagnosis (23.8% vs 43.6%, $P = .094$). Older age, presence of comorbidities, hepatomegaly, evidence of *M tuberculosis* in the bone marrow, no steroid therapy, and no receipt of antituberculosis treatment during the disease episode were individually associated with in-hospital mortality. All patients (18/18) not receiving antituberculosis treatment died, while in-hospital mortality was only 27.8% (28/97) in patients who started antituberculosis treatment ($P < .001$). Median time from hospital admission to death was 13 days (IQR, 7–22) in patients who did not receive antituberculosis treatment (14/18) and 31 days (IQR, 13–42; $P = .007$) for those who did receive antituberculosis treatment (22/28). Additionally, in 12 of 18 patients who did not receive antituberculosis treatment, the diagnosis of TB was made postmortem.

Multivariable regression analysis demonstrated a trend toward the presence of comorbidities and *M tuberculosis* in the bone marrow to be independently associated with increased mortality in TB-HLH (Table 3). The clear association between

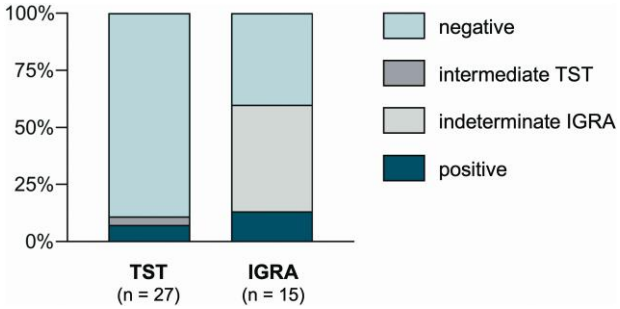

Figure 3. T cell–based immunoassay results in TB-HLH. Test results: TST (left) and IGRA (right). Results are presented as the proportion of all patients with TB-HLH in which test results were reported. Four patients had both TST and IGRA results. IGRA, interferon-γ release assay; TB-HLH, tuberculosis-associated hemophagocytic lymphohistiocytosis; TST, tuberculin skin test.

Table 3. Disease Outcomes

	No. (%) or Median (IQR)		Analysis	
	Discharged Alive (n = 69)	Deceased (n = 46)	Univariate, *P* Value[a]	Multivariate, OR (95% CI), *P* Value[b]
Sex			.41	NA
Female	23 (33.3)	12 (26.1)		
Male	46 (66.6)	34 (73.9)		
Age, y	38.0 (24.0–55.0)	58.0 (38.0–67.0)	<.001	1.01 (.98–1.04), .60
Comorbidities			<.001	
Absent	45 (69.6)	12 (26.1)		1 [Reference]
Present (any)	24 (34.8)	34 (73.9)		2.47 (.78–7.77), .12
Tuberculosis localization			.42	NA
No pulmonary involvement	22 (31.9)	18 (39.1)		
Pulmonary involvement	47 (68.1)	28 (60.9)		
Evidence of *M tuberculosis* in bone marrow			.003	
Absent	42 (60.9)	15 (32.6)		1 [Reference]
Present	27 (39.1)	31 (67.4)		2.38 (.90–6.28), .08
Hepatomegaly			.047	
Absent	32 (46.4)	30 (65.2)		1 [Reference]
Present	37 (53.6)	16 (34.8)		0.51 (.18–1.42), .20
Hemoglobin, mmol/L	4.8 (4.3–5.5)	5.2 (4.7–6.3)	.54	NA
Ferritin, µg/L	6432 (1298–17 052)	6000 (1705–17 105)	.22	NA
Steroids			.027	
Not initiated	26 (37.7)	27 (58.7)		1 [Reference]
Initiated	43 (62.3)	19 (41.3)		0.73 (.27–2.00), .48
Antituberculosis treatment			<.001	[c]
Not initiated	0 (0.0)	18 (39.1)		
Initiated	69 (100.0)	28 (60.9)		

Abbreviations: ATT, antituberculosis treatment; *M tuberculosis*, *Mycobacterium tuberculosis*; OR, odds ratio.

[a]Univariate associations with tuberculosis-associated hemophagocytic lymphohistiocytosis survival were performed with χ^2 tests, except for age, hemoglobin, and ferritin, where a Mann-Whitney *U* test was used.

[b]Multivariable regression model analysis on variables associated with outcome in univariate analyses.

[c]Exact OR and *P* value could not be calculated due to quasi-complete separation (Hauck-Donner effect) between mortality and antituberculosis treatment, as all patients who did not receive antituberculosis treatment died.

mortality and not receiving antituberculosis treatment - specifically, 100% (18/18) mortality in patients not receiving antituberculosis treatment - generated a Hauck-Donner effect [25] for antituberculosis treatment as a variable in multivariate analyses, precluding accurate estimate of the β coefficient and its associated *P* value. Of note, multivariable analysis did not show an independent effect of steroid treatment, the other key modifiable factor apart from initiation of antituberculosis treatment. This is exemplified in the 97 patients who received antituberculosis treatment, of whom 59 received steroids that had a mortality rate of 27.1% (16/59) as compared with 31.5% (12/38) in those who did not receive steroids ($P = .65$). All of the patients who did not receive antituberculosis treatment died, regardless of receiving steroids (3/18) or not (15/18).

DISCUSSION

In this patient-level meta-analysis, we identified 115 adults who were HIV negative with TB-HLH. As compared with the general TB population, a much larger proportion of patients with TB-HLH showed disseminated disease, manifested by extrapulmonary TB, miliary lung disease, or bone marrow involvement. T cell–based assays mostly yielded negative anergic results, and commencement of antituberculosis treatment was associated with a lower risk of death. Overall, our findings emphasize the importance of considering TB a cause of HLH, using appropriate diagnostics, and promptly initiating TB therapy.

HLH is associated with high mortality [4], and we found TB-HLH to be no different. In the cases that we identified, 40% of patients died. Antituberculosis treatment was associated with survival, independent of steroid therapy. Therefore, starting treatment for underlying TB disease was the only modifiable factor associated with lower mortality. This supports guidance to identify and treat underlying infectious drivers of secondary HLH, as recommended for viruses (EBV or CMV) and parasites (*Leishmania* spp) [5]. This also underlines the importance of diagnosing TB-HLH early. Given the geographic distribution of published TB-HLH cases, we infer that there are likely many undiagnosed cases of TB-HLH in countries with high TB burden.

Extrapulmonary TB, particularly bone marrow involvement, was reported in the majority of TB-HLH cases, whereas extrapulmonary TB was less frequent in non–HLH-TB case series [26–28]. TB should therefore be considered in patients with unexplained HLH [29], and the diagnostic workup for TB in suspected or confirmed HLH should include bone marrow histology and microbiological testing for *M tuberculosis*. If bone marrow sampling is not possible, mycobacterial blood cultures may provide additional diagnostic benefit, but their slow turnaround time means that molecular and antigen tests that detect *M tuberculosis*, which are currently limited to research, may become useful in this setting [30, 31].

When TB is diagnosed first, confirming secondary HLH can be challenging, as TB disease alone can lead to fever, cytopenias, and other characteristics of HLH [27]. Hyperferritinemia is often considered specific for HLH, but this has been refuted for adults with HLH [32, 33]; furthermore, we corroborated that a ferritin level <2.000 μg/L or even a normal ferritin level does not exclude TB-HLH. In clinical practice, soluble interleukin 2 receptor concentration and especially natural killer cell activity are not routinely measured, as demonstrated in the identified cases, being measured in just 11.3% and 5.2%, respectively. Still, the majority of patients met ≥5 HLH criteria. Of note, while anemia is almost universally seen in TB, even in miliary TB, it is rare to see leukopenia (<20%) or thrombocytopenia (<25%) [34]. The high proportion of patients (>85%) with at least bicytopenia, with hemophagocytosis in >90% of patients, is the best attainable proof of a high likelihood of true HLH in these patients. Our data suggest that an unusual severe presentation of TB (particularly when disseminated) or an unexplained clinical deterioration during antituberculosis treatment warrants further testing for HLH.

We found a strikingly high incidence of anergy, defined by the absence of interferon-γ–mediated T-cell memory. A lack of response to *M tuberculosis* antigens [35] and mitogen stimulation [36] is associated with miliary TB, and in keeping with this, we found very few cases of TB-HLH contained to lungs or lymph nodes [37]. Defective adaptive immune responses to *M tuberculosis* may facilitate persistence and dissemination of *M tuberculosis* to the bone marrow, a scenario that may further impair protective host defense [38]. Central to HLH pathophysiology is a positive feedback loop between proinflammatory cytokines produced by macrophages and overstimulation but impaired lysis by lymphocytes [2], as evidenced by defective natural killer and CD8+ T-cell cytolytic function in influenza- and dengue-associated HLH [39, 40]. The exact pathophysiology of TB-HLH needs further investigation, but our data indicate that removal of mycobacterial antigen drivers through initiation of antituberculosis treatment may be a key step in attenuating pathologic hyperinflammation in TB-HLH.

Our study is the first PRISMA-compliant, individual patient–level meta-analysis bringing together all reported adult cases of HIV-negative TB-HLH. We overlap 73 adult cases but have added an additional 42 to those in the most recent review that comprised 116 cases, including 43 that we excluded because they were pediatric or HIV positive or they had missing data [7]. This allowed a priori–specified subgroup comparisons and multivariate outcome analyses. Limitations include publication bias and geographic selection inherent to all series of case reports. Further limitations include heterogeneity and selectivity in outcome reporting and the lack of non-TB secondary HLH groups for comparison. Genetic testing for mutations associated with primary HLH was performed in few cases, and assessments of

immune function were limited to TSTs and IGRAs. For indeterminate IGRA results, individual tube results were lacking, precluding separation of global anergy (negative mitogen tube) vs systemically circulating interferon-γ yielding nil values above the quality control, which can occur in non–TB-HLH [41] and TB-HLH [42]. Lymphocyte counts were available too infrequently to explore their effects on indeterminate IGRA results. More detailed immunophenotyping, such as quantifying interferon-γ signaling activity and genetic testing, is necessary to explore possible primary defects in macrophage or lymphocyte function, while assessing inflammasome function could better inform the pathophysiology underlying the observed hyperinflammation. The limited availability of IGRA results prevented testing for an association between indeterminate IGRA and mortality, as has been demonstrated in non–HLH-TB [43]. Focusing on individuals who were HIV negative prevented us extrapolating our conclusions to the setting of HIV coinfection, in which antiretroviral-associated immune reconstitution inflammatory syndrome reactions share features with HLH [42, 44]. Finally, our inference on the importance of prompt antituberculosis treatment commencement in TB-HLH could be prone to survivor bias, and given the absence of data and the low sample size, no firm conclusions can be made regarding a beneficial role for other HLH-targeting therapies used in TB-HLH.

CONCLUSIONS

Our meta-analysis demonstrates that TB should be considered and bone marrow tested for *M tuberculosis* in cases of HLH without a known driver, irrespective of patients' geographic origin or presentation. Moreover, our findings suggest that HLH should be considered in patients with TB who are developing clinical features of hyperinflammation. Mortality in TB-HLH is high, and a key modifiable factor in improving survival is prompt initiation of antituberculosis treatment.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. L. K., G. P., and A. v. L. conceptualized and designed the study. L. K., G. P., and A. v. L. screened the abstracts for relevance. L. K. and T. S. acquired primary data out of the included articles, reviewed for accuracy by S. v. D., R. v. C., G. P., and A. v. L. L. K. analyzed the data, followed by interpretation of the data by all authors. L. K. and T. S. drafted the article, which was reviewed and approved by all authors.

Patient consent statement. This study does not include factors necessitating patient consent. All data used in this systematic review and meta-analysis were derived from openly available published case reports and series.

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