Immune Checkpoint Inhibitor–Associated Hemophagocytic Lymphohistiocytosis: A Systematic Review

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome increasingly recognized as an immune-related adverse event with immune checkpoint inhibitors (ICIs). Because published experience is dispersed across case reports and small series, its clinical phenotype and optimal recognition remain incompletely characterized. This systematic review synthesized patient-level reports of ICI-associated HLH to define presentation, timing, diagnostic approaches, treatment, outcomes, and rechallenge experience.

METHOD

PubMed/MEDLINE, Scopus, and Web of Science were searched from inception to 10 March 2026 using a prior protocol. English-language case reports and case series describing ICI-associated HLH with extractable patient-level data were included. Data were pooled descriptively, including demographics, malignancy, ICI exposure, timing of HLH onset, diagnostic approach, clinical and laboratory findings, treatment, outcomes, and rechallenge.

CONCLUSIONS

ICI-associated HLH is an early-onset, severe, and diagnostically heterogeneous immune-related toxicity. HLH typically developed within the first few treatment cycles and showed a consistent hyperinflammatory phenotype despite variable application of formal diagnostic criteria. Corticosteroids were nearly universal and most reported patients improved or resolved, yet mortality remained substantial at more than one-quarter of cases. In ICI-treated patients, fever, cytopenias, and marked hyperferritinemia should prompt urgent consideration of HLH. Rechallenge was uncommon; recurrent HLH occurred in 3 of 7 rechallenged patients.

CLINICAL SIGNAL

Fever + cytopenias + marked hyperferritinemia in an ICI-treated patient should trigger evaluation for HLH.

CONTACT & KEYWORDS

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RESULTS

Ninety-six patients from 78 reports were included (65 case reports and 13 case series). Median age was 60.0 years, and 55.2% were male. The most common malignancies were melanoma (27.1%) and lung cancer (24.0%); PD-1 blockade was the most common ICI exposure (62.5%). HLH occurred after a median of 2 ICI cycles and 30 days from ICI initiation. Fever occurred in 97.9%, cytopenias in 97.8%, and median ferritin was 10,450 ng/mL. Corticosteroids were administered in 99.0%; clinical improvement or resolution occurred in 83.0%, and death occurred in 25.3%.

STUDY COHORT

96	78	60.0
patients	**reports**	**years**
patient-level data	65 case reports; 13 case series	median age; IQR 42.5-72.0; range 2-86

55.2%	2	30 d
male	**ICI cycles**	**from ICI start**
53/96 patients	median at HLH onset	median onset

CLINICAL PRESENTATION

97.9%	97.8%	10,450
Fever	**Cytopenias**	**Ferritin**
94/96 patients	91/93 patients	median ng/mL

TREATMENT & OUTCOMES

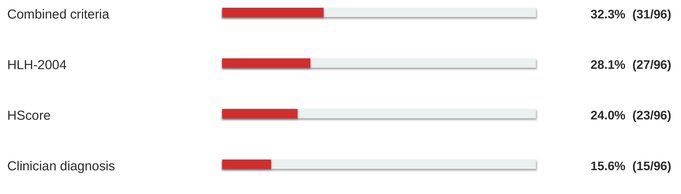
Therapies used

Clinical outcomes

83.0%	25.3%	3 / 7
Improvement / resolution	**Death**	**HLH recurrence**
78/94 patients	24/95 patients	after ICI rechallenge

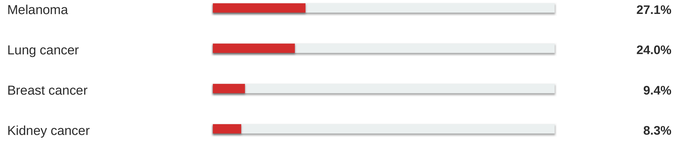
DIAGNOSTIC APPROACH

Heterogeneous ascertainment across reports



No single diagnostic approach predominated. Combined criteria were most common, followed by HLH-2004, HScore, and clinician diagnosis, underscoring substantial variation in reported diagnostic practice.

MALIGNANCIES & ICI EXPOSURE



62.5%	20.8%
PD-1 blockade	**Mixed-class**
60/96 patients	20/96 patients

TAKE-HOME MESSAGE

Early onset
Median onset after 2 ICI cycles and 30 days from treatment initiation.

Recognize the triad
Fever, cytopenias, and marked hyperferritinemia were dominant clinical signals.

Treatment
Corticosteroids were used in 99.0%; improvement/resolution occurred in 83.0%.

Risk remains substantial
Death occurred in 25.3% of reported patients.

Rechallenge
Only 7 patients were rechallenged; recurrent HLH occurred in 3.