

Table 3. Key HLH diagnostic criteria.

	HLH-2004 criteria²²	HLH-2024 criteria²⁸	H-score for secondary adult HLH (2014)⁸	EULAR/ACR/PRINTO (2016) MAS criteria²⁹
Diagnostic criteria	<p>Presence of either</p> <p>(A) Molecular diagnosis consistent with familial HLH; or</p> <p>(B) ≥ 4–5 of the following:</p> <ul style="list-style-type: none"> - Fever $\geq 38.5^{\circ}\text{C}$ - Splenomegaly (≥ 2 cm below the costal margin) - Cytopenias of ≥ 2 peripheral blood lineages (haemoglobin < 9 g/dL, platelets $< 100 \times 10^9/\text{L}$, neutrophils $< 1 \times 10^9/\text{L}$) - Fasting triglycerides ≥ 3 mmol/L and/or fibrinogen ≤ 1.5 g/L - Ferritin levels ≥ 500 $\mu\text{g/L}$ - Low/absent natural killer cell activity - Soluble CD25 levels ≥ 2400 U/mL - Haemophagocytosis in bone marrow, spleen, lymph node, or liver 	<p>Presence of either</p> <p>(A) Molecular diagnosis consistent with familial HLH in a patient with suggestive clinical symptoms/signs; or</p> <p>(B) Functional cellular findings consistent with familial HLH in a patient with suggestive clinical symptoms/signs; or</p> <p>(C) ≥ 4–5 of the following:</p> <ul style="list-style-type: none"> - Fever $\geq 38.5^{\circ}\text{C}$ - Splenomegaly (≥ 2 cm below the costal margin) - Cytopenias of ≥ 2 peripheral blood lineages (Hb < 9 g/dL, platelets $< 100 \times 10^9/\text{L}$, neutrophils $< 1 \times 10^9/\text{L}$) - Fasting triglycerides ≥ 3 mmol/L and/or fibrinogen ≤ 1.5 g/L - Ferritin levels ≥ 500 $\mu\text{g/L}$ - Soluble CD25 levels ≥ 2400 U/mL - Haemophagocytosis in bone marrow, spleen, lymph node, or liver <p>Removal of NK cell activity from HLH-2004 criteria</p>	<p>Calculate H-score (proposed cut-off value of 169) based on the following parameters:</p> <ul style="list-style-type: none"> - Underlying immunosuppressed state (e.g. HIV, or long-term immunosuppressant therapy such as glucocorticoid, cyclosporine, azathioprine): absent or present - Fever ($^{\circ}\text{C}$): < 38.4, 38.4–39.4, or > 39.4 - Organomegaly: none, hepatomegaly OR splenomegaly, or hepatomegaly and splenomegaly - Cytopenias: 1 lineage, 2 lineages, or 3 lineages - Ferritin ($\mu\text{g/L}$): < 2000, 2000–6000, or > 6000 - Fasting triglycerides (mmol/L): < 1.5, 1.5–4, > 4 - Fibrinogen (g/L): ≥ 2.5 or < 2.5 - Aspartate transaminase (IU/L): ≥ 30 or < 30 - Haemophagocytosis in bone marrow: absent or present 	<p>In a patient with known or suspected systemic juvenile idiopathic arthritis, diagnosis can be made if there is fever, ferritin level > 684 $\mu\text{g/L}$, and ≥ 2 of the following:</p> <ul style="list-style-type: none"> - Platelet $\leq 181 \times 10^9/\text{L}$ - Aspartate transaminase > 48 U/L - Fasting triglycerides > 1.76 mmol/L - Fibrinogen ≤ 3.6 g/L
Usage	Originally developed for use in patients with primary familial HLH, but with extended usage in secondary adult HLH based on external validation studies		Developed for use in adult patients with secondary HLH	Developed for use in MAS secondary to systemic juvenile idiopathic arthritis, but subsequently validated in MAS secondary to adult-onset Still's disease
Efficacy (in specific derivation cohorts)	<p>Familial HLH: 99% sensitivity, 97.1% specificity (for cut-off ≥ 5)²⁸</p> <p>Adult HLH: 91% sensitivity, 93% specificity (for cut-off ≥ 5)³¹</p> <p>Critically ill adult HLH: 73–93% sensitivity, 95–99% specificity (for cut-off ≥ 5)^{31,32}</p> <p>Secondary HLH patients (both adults and children): 87% sensitivity, 86% specificity (for cut-off ≥ 4)²⁵</p>	<p>Familial HLH: 96.2% sensitivity, 99.5% specificity (for cut-off ≥ 5)²⁸</p> <p>Critically ill HLH patients (both adults and children): 84% sensitivity, 88% specificity (for cut-off ≥ 4)²⁵</p>	<p>Adult HLH: 93–96% sensitivity, 71–86% specificity (for H-score ≥ 169)^{8,31}</p> <p>Critically ill adult HLH: 98% sensitivity, 83% specificity (for H-score ≥ 169)^{8,31}</p> <p>Secondary HLH patients (both adults and children): 82% sensitivity, 88% specificity (for H-score ≥ 169)²⁵</p>	<p>Systemic juvenile idiopathic arthritis (paediatric): 73% sensitivity, 99% specificity³⁰</p> <p>Adult-onset Still's disease: 100% sensitivity, 70% specificity⁴⁴</p>

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology;

HLH: haemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome; PRINTO: Paediatric Rheumatology International Trials Organisation

Performance figures for HLH-2004/HLH-2024 were derived from paediatric familial-HLH case-control databases tested against severe infection and systemic juvenile idiopathic arthritis; accuracy in adult secondary HLH is likely to be lower.