

Supplementary Information

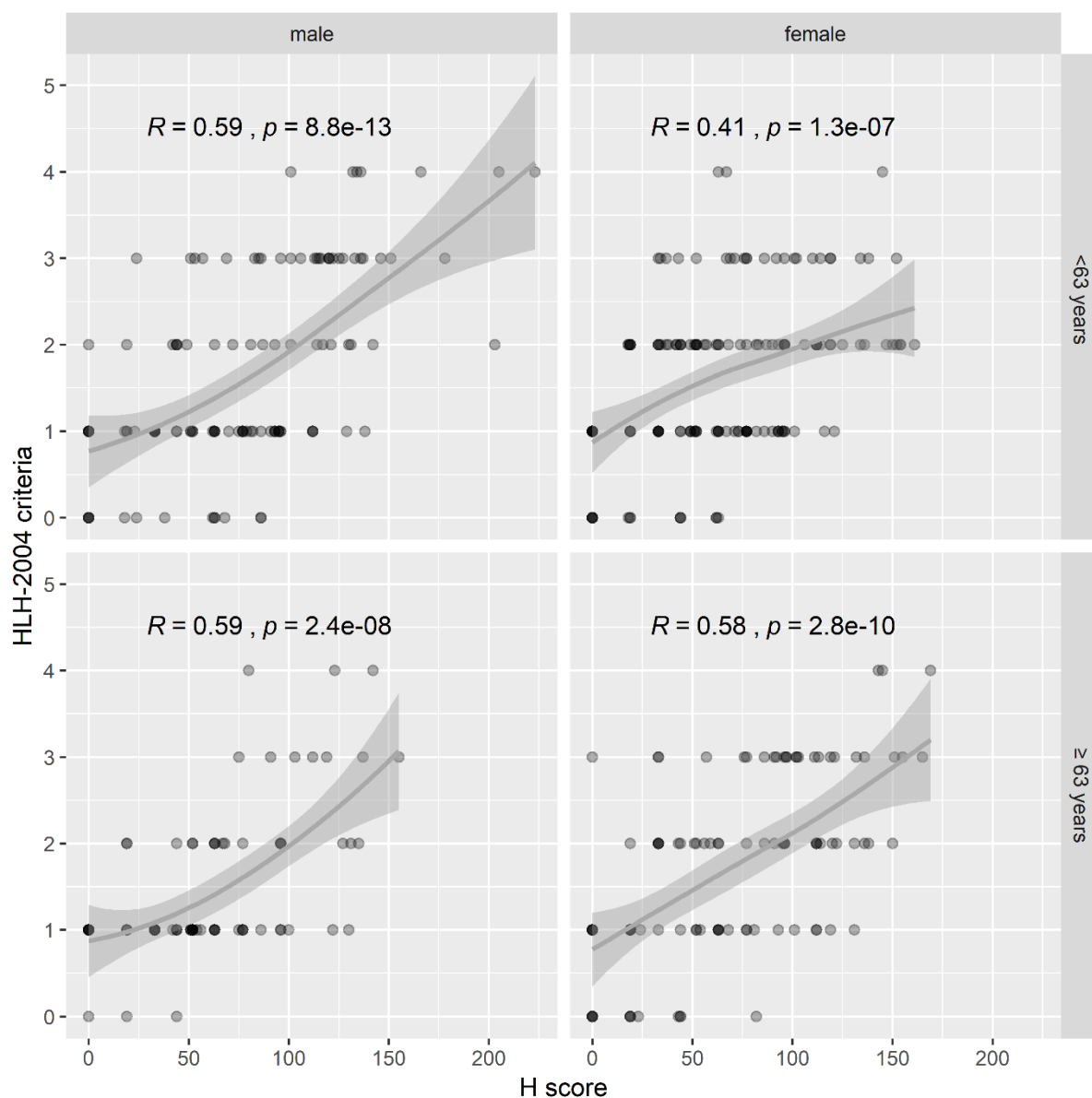


Figure S1. Age- and sex-dependent correlation between the Hscore and the HLH-2004 criteria.

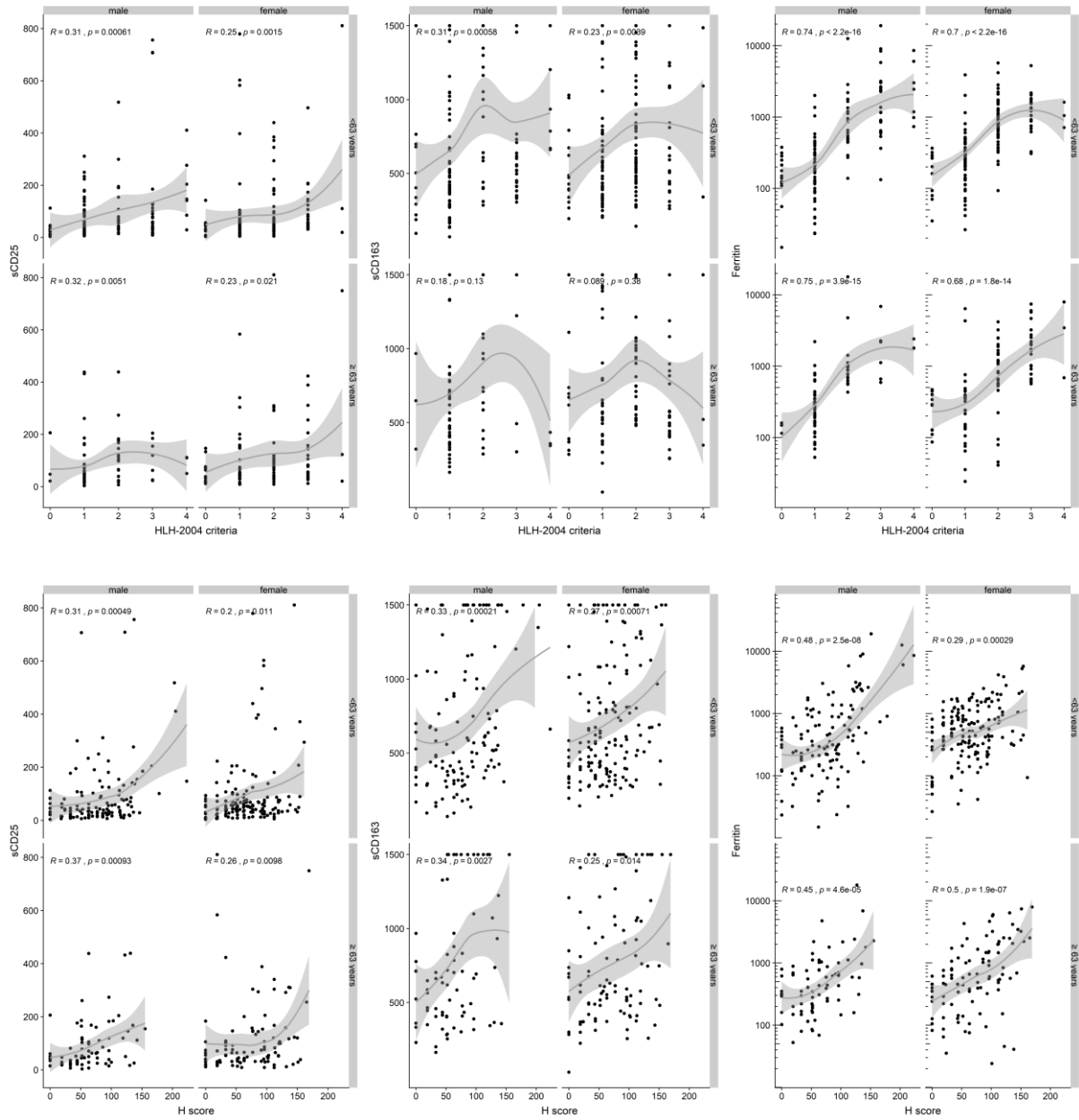


Figure S2. Age- and sex-dependent biomarker correlation to the studied scores.

Table S1. Overview of the HLH-2004 criteria¹ and the Hscore².

HLH-2004 criteria	H-Score
	Known underlying immune suppression
	0 (no) or 18 (yes)
	Temperature
	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
	Organomegaly
	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepato- and splenomegaly)
	Nr. of cytopenias
	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
	Hypertriglyceridemia (mmol/L)
	0 (<1.5), 44 (1.5–4), or 64 (>4)
	Hypofibrinogenemia (g/L)
	0 (>2.5) or 30 (≤ 2.5)
	Hemophagocytosis
	in bone marrow aspirate
	0 (no) or 35 (yes)
	Ferritin
	0 (<2000), 35 (2000–6000), or 50 (>6000)
	Serum glutamic oxaloacetic transaminase (IU/L)
	0 (<30) or 19 (>30)
Fever	
Splenomegaly	
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):	
hemoglobin <90 g/L	
Platelets <100 × 10 ⁹ /L	
Neutrophils <1.0 × 10 ⁹ /L	
Hypertriglyceridemia and/or hypofibrinogenemia:	
Fasting triglycerides ≥3.0 mmol/L (i.e., ≥265 mg/dL)	
Fibrinogen ≤1.5 g/L	
Hemophagocytosis	
in bone marrow or spleen or lymph nodes	
Low or absent NK-cell activity	
Ferritin ≥500 mg/L	
Soluble CD25 ≥2400 U/mL	

Table S2. Distribution of infections according to ECDC classification criteria modified ECDC class according to ³.

Type	ECDC Class	n	%
Bloodstream infection¹	C-CVC ³ (n = 20), S-DIG ⁴ (n = 20), S-PUL ⁵ (n = 11), S-SSI ⁶ (n = 9), S-SST ⁷ (n = 3) S-UTI ⁸ (n = 12), S-OTH ⁹ (n = 18), S-UO ¹⁰ (n = 33)	126	39.7%
Respiratory tract infection²	PN1 ¹¹ (n = 3), PN3 ¹² (n = 6), PN4 ¹³ (n = 5), PN5 ¹⁴ (n = 62), LRI-Bron ¹⁵ (n = 3), LRI-Lung ¹⁶ (n = 2)	81	25.6%
Gastrointestinal system infection²	GI-CDI ¹⁷ (n = 4), GI-GE ¹⁸ (n = 4), GI-GIT ¹⁹ (n = 7), GI-IAB ²⁰ (n = 13), EENT-ORAL ²¹ (n = 2)	30	9.5%
Urinary tract infection²	UTI-A ²² (n = 19), UTI-B ²³ (n = 20)	39	12.3%
Others²	SYS-CESP ²⁴ (n = 6), SYS-DI ²⁵ (n = 7), SSI-S ²⁶ (n = 9), SSI-D ²⁷ (n = 1), CVS-Card ²⁸ (n = 2), CVS-Vasc ²⁹ (n = 1), CVS-Endo ³⁰ (n = 2), SST-Skin ³¹ (n = 4), SST-ST ³² (n = 3), REPR-OREP ³³ (n = 2), CRI-CVC ³⁴ (n = 3), CNS-IC ³⁵ (n = 1)	41	12.9%
Total		317	100%

Type = type of infection, ¹= blood culture positive; ²= blood culture negative; ³= blood stream infection (BSI), related to central vascular catheter; ⁴= BSI, secondary digestive tract infection; ⁵= BSI, secondary to pulmonary infection; ⁶= BSI, secondary to surgical site infection; ⁷= BSI, secondary to skin and soft tissue infection; ⁸= BSI, secondary to urinary tract infection; ⁹= BSI, secondary to another infection; ¹⁰= BSI, (confirmed) unknown origin; ¹¹= pneumonia, positive quantitative culture from minimally contaminated lower respiratory tract specimen; ¹²= pneumonia, microbiological diagnosis by alternative microbiology methods, ¹³= pneumonia, positive sputum culture or non-quantitative culture from lower respiratory tract specimen; ¹⁴= pneumonia, clinical signs of pneumonia without positive microbiology; bronchitis, tracheobronchitis, bronchiolitis, tracheitis, without evidence of pneumonia; ¹⁵= LRI, other infections of the lower respiratory tract, bronchitis, tracheobronchitis, bronchiolitis, tracheitis; ¹⁶= lower respiratory tract infection, other than pneumonia; ¹⁷= gastrointestinal system infections (GI) *clostridium difficile* infection; ¹⁸= GI, gastroenteritis (excluding CDI); ¹⁹= Gastrointestinal tract (oesophagus, stomach, small and large bowel, and rectum), excluding GE, CDI; ²⁰= GI, intra-abdominal infection, not specified elsewhere; ²¹= eye, ear, nose or mouth infection (EENT), oral cavity (mouth, tongue, or gums); ²²= urinary tract infection (UTI), microbiologically confirmed symptomatic UTI; ²³= UTI, not microbiologically confirmed symptomatic UTI; ²⁴= systemic infections (SYS), clinical sepsis in adults and children; ²⁵= SYS, disseminated infection; ²⁶= surgical site infection (SSI), superficial incisional; ²⁷= surgical site infection (SSI), deep incisional; ²⁸= cardiovascular system infection (CVS), myocarditis or pericarditis; ²⁹= CVS, arterial or venous infection; ³⁰= endocarditis, ³¹= skin and soft tissue infections (SST), skin; ³²= SST, soft tissue (necrotizing fasciitis, infectious gangrene, necrotizing cellulitis, infectious myositis, lymphadenitis, or lymphangitis); ³³= reproductive tract infections (REPR)-other infections of the male or female reproductive tract (OREP), ³⁴= central vascular catheter-related infection (CRI), general CVC-related infection (no positive blood culture); ³⁵= central nervous system infection (CNS), intracranial infection.

Supplementary Methods

Bacteremia was defined by a positive BC result or real-time multiplex polymerase chain reaction (PCR) analysis result for a recognized bacterial species. Bacterial contaminants were specified as described in ³. Coagulase-negative staphylococci (CNS) were recognized as causative pathogens only when found in two blood samples taken in separate occasions. Blood specimens were cultured in a set of FA Plus (aerobic) and FN Plus (anaerobic) bottles using the BacT/ALERT 3D automated blood culture system (bioMérieux, Marcy l'Etoile, France). Bacterial pathogens were identified by matrix-assisted laser desorption ionization (MALDI) time of flight (TOF) mass spectroscopy (MS) using

Microflex LT with the Biotyper database (Bruker Daltonik GmbH, Bremen, Germany). In the event of *Streptococcus pneumoniae* detection, the test result was further verified by optochin disc tests. In 220 patients, the occurrence of microbial DNA was additionally tested by the SeptiFast MGRADE assay, as described in 4. Further, the occurrence of infection was assessed retrospectively by applying the definition criteria for hospital-acquired infections, established by the European Centre of Disease Control 3.

The following blood variables were analyzed on the first day after blood culture taking as standard laboratory parameters in an ISO 9001 certified and ISO 15189 accredited environment: procalcitonin (PCT, ng/ml, Hoffmann-La Roche Ltd, Basel, Switzerland), C-reactive protein (CRP, mg/dl, Latex test; Beckman Coulter, Brea, CA, USA), fibrinogen according to Clauss (Fib, mg/dl, Hoffmann-La Roche Ltd, Basel, Switzerland), aspartate transaminase (ASAT, U/L, Beckman Coulter), triglycerides (mg/dl, Beckman Coulter), and ferritin (ng/ml, Beckman Coulter). Variables of the complete blood count including white blood cell counts (WBC, G/l), hemoglobin (Hb, g/dl), platelets (G/l), and relative proportion of neutrophils (NeuR, %) were analyzed using a Stromatolyser-4DS (Sysmex, Norderstedt, Germany).

References

1. Henter, J.-I.; Horne, A.; Aricó, M.; Egeler, R.M.; Filipovich, A.H.; Imashuku, S.; Ladisch, S.; McClain, K.; Webb, D.; Winiarski, J.; et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr. Blood Cancer* **2007**, *48*, 124–131.
2. Fardet, L.; Galicier, L.; Lambotte, O.; Marzac, C.; Aumont, C.; Chahwan, D.; Coppo, P.; Hejblum, G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol Hoboken NJ* **2014**, *66*, 2613–2620.
3. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals protocol version 4.3, full-scale survey and codebook. Stockholm: ECDC; 2012.
4. Ratzinger, F.; Tsirkinidou, I.; Haslacher, H.; Perkmann, T.; Schmetterer, K.G.; Mitteregger, D.; Makristathis, A.; Burgmann, H. Evaluation of the Septifast MGrade Test on Standard Care Wards-A Cohort Study. *PLoS One* **2016**, *11*, e0151108.