Supplementary Information

Malignancy-associated hemophagocytic lymphohistiocytosis in Sweden: Incidence, clinical characteristics and survival

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Supplementary Methods: Information on the Swedish National Patient Register, the Swedish National Cause of Death Register, and the Swedish National Cancer Register

The Swedish National Patient Register (NPR) is a population-based register of in-patient care within the National Board of Health and Welfare in Sweden (NBHWS; 'Socialstyrelsen'). The register was established in 1964 and is now updated monthly. The register contains in-patient visits in specialized care, categorized by ICD-codes. From 1987 and onwards, the register has a nationwide coverage of more than 99%.[1]

The *National Cause of Death Register* (CoDR; 'Dödsorsaksregistret') is also a register within NBHWS. This register was established in 1961 and contains all deaths occurring in Sweden. The register is virtually complete regarding the deaths reported, only in a small subset of patients (<1%) the underlying cause of death or personal identification number (PIN) is missing. In around 3% the cause of death is insufficiently specified, but at least 96% of all individuals have a specified cause of death.[2]

The Swedish National Cancer Register (SCR; 'Cancerregistret') compiles data on all invasive cancers in Sweden, with data back to 1958 when the register was established. SCR is also held by NBHWS. It is mandatory for treating physicians to report all newly diagnosed cancers (primary tumors) to SCR, and for pathologists to report cancer diagnoses based on pathological specimens. Relapses are not registered. The completeness is high, only around 4% of diagnoses are missing when compared to the virtually complete NPR. The degree of missing data depends on cancer subtype and age of patient. Around 98% of the cancers in the register are confirmed morphologically.[3]

References

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Supplementary Table 1: A list of all histiocytosis-related diagnoses included in the study.

ICD 10 diagnosis code	Description
D76.0	Other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue
D76.1	Hemophagocytic lymphohistiocytosis
D76.2	Hemophagocytic syndrome, infection-associated
D76.3	Other histiocytosis syndromes
D76.3A	Giant cell reticulohistiocytoma
D76.3B	Rosai-Dorfman, sinushistiocytosis with massive lymphadenopathy
D76.3C	Juvenile xantogranuloma
D76.3D	Necrobiotic xantogranuloma
D76.3E	Benign cephalic histiocytosis
D76.3W	Other histiocytosis syndromes
C96.0	Multifocal and multisystemic Langerhans-cell histiocytosis
C96.5	Langerhans-cell histiocytosis, multifocal
C96.6	Langerhans-cell histiocytosis, unifocal, or not otherwise specified

Supplementary Table 2: Clinical characteristics and laboratory parameters in the patients with both a malignancy and HLH from 1997 to 2011.

	Confirmed Malignancy-triggered HLH n=15	**Confirmed HLH during chemotherapy n=20**	**Confirmed allo-HSCT-associated HLH n=4**	**Assumed HLH but < 4 criteria fulfilled n=14**	**Total n=53**
Age (years, median)	57.3	53.8	34	63.8	56.3
Sex (Male/Female)	7/8	15/5	3/1	7/5	32/19
HLH criteria: #					
- Fulfilled criteria	4.8	5.2	5.3	2.4	4.3
- Fever	15/15 (100%)	20/20 (100%)	4/4 (100%)	8/11 (73%)	47/50 (94%)
- Splenomegaly	10/11 (91%)	9/11 (82%)	4/4 (100%)	1/3 (33%)	24/29 (83%)
- Bicytopenia [§]	12/15 (80%)	19/20 (95%)	3/4 (75%)	5/9 (56%)	39/48 (81%)
- Fibrinogen (≤1.5 g/L)	5/10 (50%)	2/10 (20%)	1/1 (100%)	1/1 (100%)	9/22 (41%)
- Triglycerides ((≥3.0 mmol/L)	7/7 (100%)	5/8 (63%)	1/2 (50%)	0	13/17 (76%)
- Hemophagocytosis	10/12 (83%)	17/18 (94%)	3/4 (75%)	8/11 (73%)	38/45 (84%)
- Ferritin (≥500 µg/L)	11/11 (100%)	19/19 (100%)	3/3 (100%)	4/4 (100%)	37/37 (100%)
- Soluble CD25 (≥2400 U/mL)	4/4 (100%)	7/7 (100%)	1/2 (50%)	2/2 (100%)	14/15 (93%)
HScore * (range)	194 (n=15; 124-288)	174 (n=20;113-242)	175.5 (n=4; 109-272)	102.5 (n=14; 51-159)	160 (n=53; 51-288)
OH-index positive **	4/4 (100%)	3/6 (50%)	1/2 (50%)	-	8/12 (67%)
Lab values (median; range):					
- Ferritin (µg/L)	16,500 (n=12; 1,515-210,770)	25,654 (n=15; 1,860-95,000)	108,000 (n=3; 38,000-645,291)	7,610 (n=4; 4,500-15,500)	16,750 (n=34; 1,517-645,291)
- Soluble CD25 (U/mL)	7,500 (n=4; 7,500-20,781)	5,256 (n=8; 1-30,000)	2,973 (n=2; 603-5,344)	17,396 (n=2; 13,000-21,793)	7,500 (n=16; 1-30,000)
- Aspartate transaminase (U/L)	227 (n=11; 44-1,596)	223 (n=10; 18-622)	4410 (n=2; 180-8,640)	78 (n=5; 16-270)	192 (n=28; 16-8,640)
- Alanine transaminase (U/L)	159 (n=12; 17-571)	90 (n=11; 22-360)	167 (n=2; 149-186)	102 (n=7; 40-254)	108 (n=32; 17-571)
- Lactate dehydrogenase (U/L)	1,260 (n=13; 312-4,320)	549 (n=6; 192-4,266)	720 (n=3; 600-11,340)	558 (n=8; 168-6,180)	675 (n=30; 168-11,340)
- Bilirubin (µmol/L)	32 (n=9; 2-182)	90 (n=12; 15-495)	27.5 (n=2; 24-31)	96 (n=7; 10-565)	49 (n=30; 2-565)

Abbreviations and clarifications: # Fibrinogen and triglycerides are a combined criterion. No data on NK-cell activity was available. [§] Bicytopenia is defined as ≥ 2 of 3 lineages in the peripheral blood affecting hemoglobin (<90 g/L), platelets (<100 x 10^9/L), and/or neutrophils (<1.0 x 10^9/L). *HScore cut-off 169 points defines 90% of patients with HLH accurately[7]. **OH-index positive = Ferritin >1000 µg/L and soluble CD25 >3,900 U/mL. HSCT = hematopoietic stem cell transplant.

Supplementary Table 3: Frequency of different types of malignancies in patients with confirmed malignancy-associated HLH 1997 to 2011.

	Confirmed Malignancy-triggered HLH n=15	**Confirmed HLH during chemotherapy n=20**
	Number (%)	Number (%)
B cell lymphomas	4 (27%)	7 (35%)
NK/T cell lymphomas	8 (53%)	4 (20%)
Hodgkin's lymphomas	2 (13.5%)	1 (5%)
Myeloid leukemias	-	4 (20%)
Lymphocytic leukemias	1 (6.5%)	3 (15%)
Solid malignancies	-	1 (5%)

Supplementary Figure 1: Regional variation of incidence of diagnosis code-based malignancy-associated HLH in Sweden 2012-2018. The numbers refer to the incidence per 100,000 individuals (children and adults) annually.