

Table S1 The CCHG-LCH-2019 treatment regimen used for the children with LCH in our study

First-line treatment courses	CCHG-LCH-2019
Initial treatment course 1 (Week 1-6)	Pred: 40mg/m ² /day, orally, full dose for 4 weeks and then reduced dose for 2 weeks. VDS: 3mg/m ² , i.v., Once a week, for 6 times.
Initial treatment course 2 (Week 7-12)	Pred: 40mg/m ² /day, for 3 days, orally taking on the day of injecting the VDS every week, for 6 weeks. VDS: 3mg/m ² /time, i.v. Once a week, for 6 times.
Maintenance treatment	The SS (included the CNS-risk bone involvements) and MSRO ⁻ groups: Prednisone and Vindesine, for 1 year. These patients were divided into two groups, with or without adding 6-MP randomly. Patients with other single-system involvements maintained for half a year. MSRO ⁺ group: Prednisone, Vindesine and 6-MP, for 1 year. Pred: 40mg/m ² /day, for 5 days, orally taking on the day of injecting the VDS. VDS: 3mg/m ² /time, i.v., Q3W. 6-MP: 50 mg/m ² /day, orally, QN.
Stratified treatment (Disease state at week 6, week 12)	1) Patients with NAD were directly admitted to maintenance treatment. 2) RO ⁻ group: Patients with AD-B, AD-S or AD-I were admitted to Initial treatment course 2. Patients with AD-W were transferred to the second-line treatment (Week 6). Patients with AD-B or AD-S were admitted to maintenance treatment. Patients with AD-I or AD-W were transferred to the second-line treatment (Week 12). 3) RO ⁺ group: Patient with AD-B or AD-S was admitted to Initial treatment course 2 (Week 6) or maintenance treatment (Week 12). All the patients with AD-I and AD-W, or no improvement at the risk organ, or developing abnormal organ function were transferred to second-line treatment. 4) No improvements in pituitary or lung were moved to Second-line treatment at week 6 and week 12.
Second-line Treatment courses	CCHG-LCH-2019
Intensification treatment	Patients were divided into 2 groups: A: Cladribine group, every 4 weeks for a course 2CDA, Ara-c, VDS and DEX 2CDA, intravenous injection before Ara-c, from day 2. 1) RO ⁻ group: 9mg/m ² /day, for 3 days; 2) RO ⁺ group: 9mg/m ² /day, for 3 days; Ara-c: 150 mg/m ² /day, 5 days, I.V. or subcutaneous injection for 2 hours, day 1-5. VDS: 3 mg/m ² , i.v., day 1. DEX: 6 mg/m ² /day, orally or i.v., day 1-5. B: Ara-c group, every 3 weeks for a course, Ara-c, VDS and DEX. Ara-c: 150 mg/m ² /day, 5 days, i.v. or subcutaneous injection for 2 hours, day 1-5; VDS: 3 mg/m ² , i.v., day 1; DEX 6 mg/m ² /day, orally or i.v., day 1-5.
Maintenance treatment	A total course of 1 year including intensive treatment. 6-MP: 50mg/m ² /time, orally, once for every night; VDS: 3mg/m ² /time, intravenous injection, once for every 3 weeks. Prednisone: 40mg/ m ² /day, orally for 5 days, every 3 weeks from the day intravenously injection of the VDS. Follow-up time points (assessments of therapeutic efficacy) Included six, 12, 25 and 52 weeks after first-line treatment; every four courses after the second-line treatment; after one, three, six, nine and 12 months of targeted therapy; every three months during maintenance treatment; and three months, six months, one year, two years, three years and five years after drug withdrawal. Dose titration 1) When the weight of patients is less than 10 kg, the dosages will be adjusted. 2CDA: 0.3 mg/kg, VCR: 0.05 mg/kg, every time. 6-MP: 1.7 mg/kg, every time. 2) VCR could be replaced by VDS or VBL. 3) The maximum daily dosage: VCR 2mg, VDS 4.5mg, Pred 60mg.

CCHG, Chinese Children's Histiocytic Group; LCH, Langerhans cell histiocytosis; Pred: Prednisone, 40mg/m²/day, orally, in two divided doses every day. SS: Patients with single-system involvement. MS: patients with multiple system involvement. Q3W: once every 3 weeks. 6-MP, 6-mercaptopurine. The specific dose of 6-MP was adjusted according to the blood routine examination, and the neutrophils were maintained above 0.5×10⁹/L. QN: every night before sleeping. RO⁺, patients with risk organ involvement. RO⁻, Patients without risk organ involvement. 2-CDA, cladribine; AD-B, AD-better; AD-I, AD-intermediate; AD-S, AD-stable; AD-W, AD-worse; Ara-c, cytarabine; Dex, dexamethasone; i.v., intravenous injection; MTX, methotrexate; VCR, vincristine; VDS, vindesine.

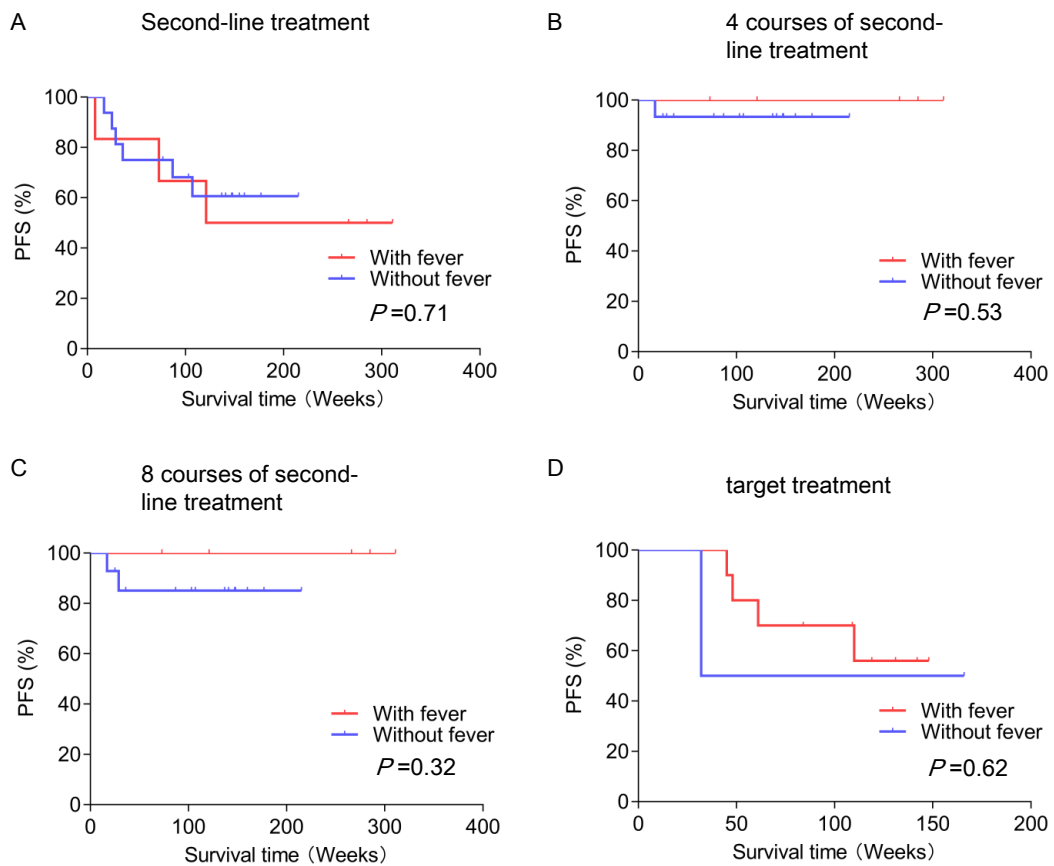


Figure S1 The 3-year PFS rates of pediatric patients with LCH after second-line treatment and target treatment (groups of patients with and without fever). (A) The 3-year PFS rates of second-line treatment in pediatric LCH patients with and without fever. (B,C) The 3-year PFS rates of second-line treatment at different courses. (D) The 3-year PFS rates of target treatment in pediatric LCH patients with and without fever. LCH, Langerhans cell histiocytosis; PFS, progression-free survival.

Table S2 Gene mutations and therapeutic regimens of 52 children with fever in LCH (including 23 patients accompanied with a hemophagocytic syndrome)

Children with fever	Gene mutation (Tissue/Peripheral Blood)	Therapeutic regimens	Hemophagocytic syndrome (More than five)	Duration time (Days)
P1	MAP2K1 (14.07%, c.170_184del)/ None	V	/	22
P2	None/ None	II	/	121
P3	None/ None	I, II	a, b, c, d, g, h	20
P4	None/None	I, II, V	a, b, c, e, h	120
P5	None/None	II	a, b, c, d, e, h	7
P6	None/ <i>BRAF</i> ^{V600E} -	I, II, V	a, b, c, e, f, h	15
P7	<i>BRAF</i> ^{V600E} -/None	I	/	15
P8	<i>BRAF</i> ^{V600E} -/ <i>BRAF</i> ^{V600E} -	I	/	31
P9	None/ <i>BRAF</i> ^{V600E} -	I, II, V	/	93
P10	None/ <i>BRAF</i> ^{V600E} -	II	/	28
P11	None/ <i>BRAF</i> ^{V600E} -	I, II	/	31
P12	None/ <i>BRAF</i> ^{V600E} 3.10%	I, II	/	31
P13	None/ <i>BRAF</i> ^{V600E} 1.53%	II, V	a, b, c, d, g, h	93
P14	None/ <i>BRAF</i> ^{V600E} -	I, II	/	31
P15	None/ <i>BRAF</i> ^{V600E} 1.24%	I, II, V	/	31
P16	<i>BRAF</i> ^{V600E} 24.05%/ <i>BRAF</i> ^{V600E} 0.91%	I, II, V	/	21
P17	ROS1 3.10%/None	I, II	/	62
P19	None/ <i>BRAF</i> ^{V600E} 3.46%	I, II, V, Dabrafenib, trametinib prednisone, and vindesine	a, b, c, d, e, f, h	21
P21	<i>BRAF</i> ^{V600E} 29.52%/ <i>BRAF</i> ^{V600E} 22.52%	I, V	a, b, c, d, e, h	31
P22	<i>BRAF</i> ^{V600E} 6.00%/ <i>BRAF</i> ^{V600E} -	I, II, V	/	124
P23	None/ <i>BRAF</i> ^{V600E} 26.62%	I, V	/	31
P24	<i>BRAF</i> ^{V600E} 9.00%/ <i>BRAF</i> ^{V600E} 2.12%	I, II, V	a, b, c, d, h	19
P25	<i>BRAF</i> ^{V600E} -, ALK 2%/ <i>BRAF</i> ^{V600E} -	I, II	/	62
P26	<i>BRAF</i> ^{V600E} 7.00%/ <i>BRAF</i> ^{V600E} 1.172%	V, Dabrafenib and trametinib, Dabrafenib and cytarabine	a, b, c, e, h	24
P27	<i>BRAF</i> ^{V600E} -/ <i>BRAF</i> ^{V600E} -	III, IV	/	31
P28	<i>BRAF</i> ^{V600E} 2.00%/ <i>BRAF</i> ^{V600E} 24.49%	III, V	a, b, c, d, h	31

Table S2 (continued)

Table S2 (continued)

Children with fever	Gene mutation (Tissue/Peripheral Blood)	Therapeutic regimens	Hemophagocytic syndrome (More than five)	Duration time (Days)
P29	<i>BRAF</i> ^{V600E} 17%, MAP2K1 p.Q354H 47.4%/ <i>BRAF</i> ^{V600E} 24.49%	III, IV	/	124
P30	<i>BRAF</i> ^{V600E} 12.00%/ <i>BRAF</i> ^{V600E} 5.15%	V	/	7
P31	<i>BRAF</i> ^{V600E} -, <i>BRAF</i> ^{V600D} 10.00%/ <i>BRAF</i> ^{V600E} -	III, V	/	10
P32	<i>BRAF</i> ^{V600E} -/ <i>BRAF</i> ^{V600E} -	III, IV	/	31
P33	<i>BRAF</i> ^{V600E} 1.00%/ <i>BRAF</i> ^{V600E} 12.97%	V, IV	a, b, c, d, e, g, h	9
P34	<i>BRAF</i> ^{V600E} 4.00%/ <i>BRAF</i> ^{V600E} -	Observation	/	155
P35	<i>BRAF</i> ^{V600E} -/ <i>BRAF</i> ^{V600E} -	III, IV, V	a, b, d, f, g, h	31
P36	None/ <i>BRAF</i> ^{V600E} 0.51%	I, V	/	8
P37	<i>BRAF</i> ^{V600E} -, MAP2K1 c.172_186delCAGAAGGTGGGAGAA, p.58_62delQKVGE 1.30% / <i>BRAF</i> ^{V600E} -	III, V, IV	a, b, d, h, f	31
P38	<i>BRAF</i> ^{V600E} 11.00%/ <i>BRAF</i> ^{V600E} 12.68%	V	a, b, c, d, h	14
P39	<i>BRAF</i> ^{V600E} 2.00%/ <i>BRAF</i> ^{V600E} 15.25%	V	a, b, e, f, h	29
P40	<i>BRAF</i> ^{V600E} 3.00%/ <i>BRAF</i> ^{V600E} 7.98%	V, Dabrafenib and trametinib	a, b, c, e, f, h	9
P41	None/ <i>BRAF</i> ^{V600E} -	III	/	62
P42	None/ <i>BRAF</i> ^{V600E} 3.78%	V	/	8
P43	None/ <i>BRAF</i> ^{V600E} 0.35%	I, II, III	a, b, c, d, e, h	31
P46	<i>BRAF</i> ^{V600E} 3.38%/ <i>BRAF</i> ^{V600E} 1.80%	I, V, III, V	a, b, c, d, e, f, h	12
P47	<i>BRAF</i> ^{V600E} 3%/ <i>BRAF</i> ^{V600E} 1.92%	III, IV	/	77
P49	None/ <i>BRAF</i> ^{V600E} 3.29%	V, Dabrafenib and trametinib	a, b, c, d, e, h	8
P50	<i>BRAF</i> ^{V600E} 2.42%/ <i>BRAF</i> ^{V600E} 9.31%	I	a, b, c, d, e, h	17
P51	<i>BRAF</i> ^{V600E} 3.56%/ <i>BRAF</i> ^{V600E} 7.90%	I	/	14

Table S2 (continued)

Table S2 (continued)

Children with fever	Gene mutation (Tissue/Peripheral Blood)	Therapeutic regimens	Hemophagocytic syndrome (More than five)	Duration time (Days)
P52	None/None	I, II	a, b, c, d, h	12
P53	<i>BRAF</i> ^{V600E} -/None	I, II	a, b, c, d, f, h	10
P54	<i>BRAF</i> ^{V600E} 23.94%/ <i>BRAF</i> ^{V600E} 3.2%	I, II, V	/	14
P56	None/ <i>BRAF</i> ^{V600E} -	II, V	/	20
P59	<i>BRAF</i> ^{V600E} 14.00%/ <i>BRAF</i> ^{V600E} -	III, IV	/	30
P60	<i>BRAF</i> ^{V600E} 3.60%/ <i>BRAF</i> ^{V600E} 2.80%	V, IV	a, b, c, d, f, g, h	15

BRAF^{V600E} mutations were sequenced by MyGenostics Inc., Beijing, China. None: no additional sequencing data. "-": negative. Therapeutic regimens: I: first-line treatment of BCH-LCH-2014; II: second-line treatment of BCH-LCH-2014; III: first-line treatment of CCHG-LCH-2019; IV: second-line treatment of CCHG-LCH-2019; V: target therapy. Hemophagocytic syndrome: a. fever ≥ 38.5 °C; b. splenomegaly; c. Cytopenias (affecting 2 of 3 lineages in the peripheral blood, hemoglobin < 90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L), Platelets $< 100 \times 10^9/L$, Neutrophils $< 1 \times 10^9/L$); d. Hypertriglyceridemia and/or hypofibrinogenemia (Fasting triglycerides ≥ 265 mg/dL or 3 mmol/L; Fibrinogen ≤ 1.5 g/L); e. Hemophagocytosis in bone marrow or spleen or lymph nodes; f. lower or absent activity of NK cells. g. Ferritin > 500 $\mu\text{g/L}$; h. Soluble CD25 level ($\geq 6,400$ pg/mL).

Table S3 Differences in various laboratory indicators between children with fever and children without fever in LCH disease

Clinical characteristics or laboratory indicators	Children with fever	Children without fever	P value
Age (years)	1.17 (0.17, 9.00)	3.17 (0.04, 17.00)	<0.001
sCD25 (pg/mL)	12974.00 (1982.00, 44000.00)	2771.00 (115.00, 44000.00)	<0.001
<i>BRAF</i> ^{V600E} in tissue (%)	2.42 (0.00, 29.52)	1.48 (0.00, 36.00)	0.18
<i>BRAF</i> ^{V600E} in blood (%)	1.39 (0.00, 26.62)	0.00 (0, 24.05)	<0.001
CD4:CD8	1.46 (0.26, 5.58)	1.54 (0.32, 6.91)	0.17
Total T cells (%)	61.60 (34.30, 87.40)	65.20 (23.10, 84.30)	0.01
Total B cells (%)	24.70 (2.60, 54.30)	20.30 (5.40, 61.70)	0.02
T helper cells (%)	34.20 (13.70, 64.00)	34.90 (7.40, 62.30)	0.16
T suppression cells (%)	25.30 (5.60, 52.70)	22.60 (6.50, 48.10)	0.11
NK (%)	11.40 (2.30, 34.40)	12.30 (1.40, 51.40)	0.97
IgA (g/L)	0.44 (0.06, 3.03)	0.76 (0.06, 5.97)	0.001
CRP (mg/L)	40.00 (1.31, 170.31)	5.00 (0.00, 96.80)	<0.001
Red blood cell ($\times 10^9/L$)	3.70 (1.55, 5.45)	4.66 (2.27, 7.39)	<0.001
Hemoglobin (g/L)	89.00 (53.00, 125.00)	121.00 (57.00, 167.00)	<0.001
Platelet ($\times 10^9/L$)	225.00 (14.00, 598.00)	354.50 (36.00, 959.00)	<0.001
Absolute value of lymphocyte ($\times 10^9/L$)	2.81 (0.71, 6.33)	3.33 (0.96, 14.58)	0.11
Percentage of eosinophils (%)	0.50 (0.00, 10.20)	1.70 (0.00, 11.10)	<0.001
Albumin (g/L)	32.10 (21.70, 66.10)	42.60 (24.40, 69.20)	<0.001
Total bilirubin ($\mu\text{mol/L}$)	9.25 (2.93, 104.34)	6.76 (2.00, 122.66)	<0.001
Direct bilirubin ($\mu\text{mol/L}$)	1.52 (0.28, 69.97)	0.99 (0.00, 94.24)	<0.001
Indirect bilirubin ($\mu\text{mol/L}$)	7.57 (2.50, 34.58)	5.78 (1.50, 43.18)	<0.001
Serum total bile acid ($\mu\text{mol/L}$)	7.27 (0.98, 119.99)	4.68 (0.41, 113.07)	0.001
Triglyceride (mmol/L)	1.53 (0.45, 8.00)	1.13 (0.38, 6.59)	<0.001
creatine kinase (U/L)	28.00 (9.00, 171.00)	80.00 (11.00, 525.00)	<0.001
Lactate dehydrogenase (U/L)	305.50 (106.00, 988.00)	271.00 (146.00, 1150.00)	0.008
α -hydroxybutyrate dehydrogenase (U/L)	235.00 (84.00, 789.00)	214.00 (98.00, 957.00)	0.07
HDLC (mmol/L)	0.70 (0.14, 3.30)	1.28 (0.34, 3.20)	<0.001
Cholinesterase (U/L)	3506.00 (1024.00, 10221.00)	8325.00 (59.00, 16622.00)	<0.001
Prealbumin (mg/L)	75.00 (0.22, 316.00)	156.00 (2.114, 344.00)	<0.001
Unsaturated iron binding force ($\mu\text{mol/L}$)	39.60 (1.70, 80.80)	50.25 (19.90, 85.20)	<0.001
Total iron binding capacity ($\mu\text{mol/L}$)	48.30 (16.30, 84.20)	58.55 (2.78, 92.50)	<0.001
Transferrin (g/L)	2.00 (0.67, 3.36)	2.41 (1.26, 3.80)	<0.001
Dynamic ESR (mm/h)	12.00 (2.00, 115.00)	12.00 (2.00, 120.00)	0.70
D-dimer (mg/L)	0.40 (0.05, 8.99)	0.15 (0.00, 19.08)	<0.001
Procalcitonin (ng/mL)	0.40 (0.05, 11.63)	0.05 (0.05, 3.48)	<0.001

Table S3 (continued)

Table S3 (continued)

Clinical characteristics or laboratory indicators	Children with fever	Children without fever	P value
Ferritin (ng/mL)	88.40 (5.00, 1949.00)	39.90 (0.00, 562.00)	<0.001
IFN- γ (pg/mL)	1.59 (0.00, 141.71)	0.61 (0.00, 204.55)	<0.001
IL-10 (pg/mL)	7.50 (1.25, 77.62)	3.44 (0.00, 79.23)	<0.001
TNF- α (pg/mL)	1.83 (0.00, 143.72)	2.13 (0.00, 521.76)	0.68
IL-6 (pg/mL)	61.36 (2.21, 2500)	19.00 (0.00, 2500.00)	0.007
IL-4 (pg/mL)	0.00 (0.00, 3.21)	0.00 (0.00, 5.37)	0.75
IL-2 (pg/mL)	0.00 (0.00, 81.27)	0.00 (0.00, 59.94)	0.48

Data are presented as mean/median (range). P value stands for the asymptotic significant value (2-tailed) of Mann-Whitney *U* test or significant value (2-tailed) of independent-samples *t*-tests.

Table S4 Univariate analyses of important clinical characteristics and laboratory indicators affecting the prognosis of first-line treatment in the 386 children with LCH

Clinical characteristics or laboratory indicators	Total number (events)	PFS rate (%), 95% CI	Standard error	P (Log Rank)
Fever				
+	35 (25)	5.22 (6.46, 13.54)	5.01	<0.001
-	351 (123)	64.23 (272.29, 301.71)	2.71	
Age				
0-2 years	141 (69)	45.67 (0.00, 234.27)	4.54	<0.001
>2 years	245 (79)	68.03 (269.36, 304.64)	3.14	
Hemophagocytic syndrome				
+	14 (12)	0.00 (1.58, 4.42)	0.00	<0.001
-	372 (136)	61.98 (269.92, 304.08)	2.68	
Plasma cfBRAF^{V600E}				
+	92 (46)	42.94 (34.78, 185.22)	5.82	<0.001
-	178 (51)	71.02	3.50	
Risk organ involvement				
+	65 (35)	33.41 (0.00, 33.27)	7.05	<0.001
-	321 (113)	64.48 (274.73, 329.27)	2.80	
Pituitary involvement				
+	23 (9)	34.00 (0.00, 72.21)	14.70	0.006
-	363 (139)	61.04 (269.86, 304.14)	2.69	
Skin involvement				
+	84 (45)	36.97 (0.00, 129.67)	6.11	<0.001
-	302 (103)	65.60 (275.23, 328.78)	2.86	
Total T cells				
55-82%	302 (111)	63.21 (212.24, 292.70)	2.92	0.02
<55% or >82%	80 (35)	47.77 (126.05, 190.89)	6.23	
NK cells				
7-40%	309 (111)	62.65 (210.97, 292.06)	2.94	0.05
<7% or >40%	75 (37)	49.41 (132.71, 194.16)	6.01	
CRP				
0-8 mg/L	224 (63)	73.92 (275.11, 328.89)	3.01	<0.001
>8 mg/L	158 (84)	36.24 (30.92, 99.08)	4.43	
Red blood cell				
$3.5 \times 10^{12}/L - 5.5 \times 10^{12}/L$	364 (132)	61.91 (270.06, 303.94)	2.71	<0.001
$<3.5 \times 10^{12}/L$ or $>5.5 \times 10^{12}/L$	20 (14)	27.64 (7.57, 14.43)	11.48	

Table S4 (continued)

Table S4 (continued)

Clinical characteristics or laboratory indicators	Total number (events)	PFS rate (%), 95% CI	Standard error	P (Log Rank)
Hemoglobin				
100–160 g/L	270 (87)	68.08 (263.83, 340.17)	2.93	<0.001
<100 g/L or >160 g/L	114 (59)	39.27 (24.57, 133.43)	5.28	
Eosinophils				
<0.5%	299 (106)	63.38	2.96	0.003
0.5–5.0%	84 (39)	49.58 (69.62, 168.38)	5.93	
Total bilirubin				
3.42–20.50 μ mol/L	370 (137)	61.15 (271.71, 302.30)	2.70	0.003
<3.42 μ mol/L or >20.50 μ mol/L	16 (11)	33.85 (0.00, 36.39)	12.26	
Dynamic ESR				
0–15 mm/h	210 (65)	69.95 (220.20, 326.78)	3.29	<0.001
>15 mm/h	162 (78)	45.85 (133.62, 179.33)	4.36	
D-dimer				
0–0.243 mg/L	225 (83)	63.41 (269.49, 292.51)	3.35	0.008
>0.243 mg/L	101 (47)	45.04 (8.22, 197.78)	5.62	
Procalcitonin				
0–0.25 ng/mL	333 (120)	63.13 (264.52, 339.48)	2.79	<0.001
>0.25 ng/mL	44 (23)	36.51 (0.00, 69.59)	8.74	
Ferritin				
28–397 ng/mL	344 (120)	63.14 (272.31, 301.69)	2.78	<0.001
<28 or >397 ng/mL	29 (24)	21.03 (7.45, 12.55)	7.86	
IFN-γ				
0–2.1 pg/mL	287 (104)	62.51 (246.38, 327.62)	3.04	0.03
>2.1 pg/mL	90 (41)	51.38 (3.55, 318.45)	5.65	

Table S5 Influence of fever on prognosis of children with risk organ involvement, single-system involvement, multiple-bone involvement and multiple-system involvement in LCH disease

First-line treatment	Total	Children with LCH		P
		With fever, n (%)	Without fever, n (%)	
Children with risk organ involvement				
Final prognosis				
With progression	35	16 (72.73)	19 (44.19)	0.04
Without progression	30	6 (27.27)	24 (55.81)	
Prognosis of Week 6				
With progression	24	13 (59.09)	11 (25.58)	0.01
Without progression	41	9 (40.91)	32 (74.42)	
Children with single-system involvement				
Final prognosis				
With progression	64	3 (75.00)	61 (28.64)	0.08
Without progression	153	1 (25.00)	152 (71.36)	
Prognosis of Week 6				
With progression	11	1 (25.00)	10 (4.69)	0.19
Without progression	206	3 (75.00)	203 (95.31)	
Children with multiple-system involvement				
Final prognosis				
With progression	84	22 (70.97)	62 (45.25)	0.02
Without progression	84	9 (29.03)	75 (54.74)	
Prognosis of Week 6				
With progression	41	13 (41.94)	23 (16.79)	0.006
Without progression	127	18 (58.06)	114 (83.21)	
Children with multiple-bone involvement				
Final prognosis				
With progression	106	17 (70.83)	89 (36.93)	0.002
Without progression	159	7 (29.17)	152 (63.07)	
Prognosis of Week 6				
With progression	32	9 (37.50)	23 (9.54)	0.001
Without progression	233	15 (62.50)	218 (90.46)	

“Progression” refers to current disease progression, reactivation, or death during treatment. Progression-free survival (PFS) was evaluated during all the treatment strictly from the date of diagnosis until the date of AD-I, AD-W, reactivation or death due to any reason, whichever came first, or the last contact with the patients.