Additive Prognostic Impact of Gastrointestinal Involvement in Severe Multisystem Langerhans Cell Histiocytosis

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Objective To evaluate the prognostic impact of gastrointestinal involvement on the survival of children with Langerhans cell histiocytosis (GI-LCH) registered with the international clinical trials of the Histiocyte Society.

Study design This was a retrospective analysis of 2414 pediatric patients registered onto the consecutive trials DAL-HX 83, DAL-HX 90, LCH-I, LCH-II, and LCH-III.

Results Among the 1289 patients with single-system LCH, there was no single case confined to the GI tract; 114 of 1125 (10%) patients with multisystem LCH (MS-LCH) had GI-LCH at initial presentation. GI-LCH was significantly more common in children aged <2 years at diagnosis (13% vs 6% in those aged >2 years; $P < .001$) and in those with risk organ involvement (15% vs 6% in those without risk organ involvement; $P < .001$). The 5-year overall survival (OS) in patients without risk organ involvement was excellent irrespective of GI disease (98% vs 97% in patients with GI-LCH; $P = .789$). In patients with risk organ involvement, the 5-year OS was 51% in 70 patients with GI-LCH vs 72% in 394 patients without GI-LCH ($P < .001$).

Conclusions GI-LCH has an additive unfavorable prognostic impact in children with MS-LCH and risk organ involvement. The emerging need for more intensive or alternative treatments mandates prospective evaluation. *(J Pediatr 2021;237:65-70)*.

Langerhans cell histiocytosis (LCH) is a rare inflammatory myeloid neoplasia, affecting 4-9 children per million.[1-4] It is characterized by the accumulation of $CD1a^+/CD207^+$ dendritic cells with an inflammatory infiltrate in many organs, including bone, skin, lungs, liver, spleen, and pituitary gland. LCH encompasses an extremely heterogeneous spectrum of clinical presentations, with variable courses and outcomes.[5] The involvement of a single organ or system is generally associated with a favorable prognosis, whereas the clinical course of multisystem LCH (MS-LCH) varies from spontaneous remission to rapid deterioration with a potentially lethal outcome.[6,7]

Gastrointestinal (GI) involvement in LCH (GI-LCH) is infrequent, accounting for approximately 2%-3% of the pediatric series.[8-10] It can present clinically with protein-losing enteropathy, bloody diarrhea, malabsorption, and failure to thrive.[10] However, current international guidelines do not take GI-LCH into account in the pretreatment stratification.[11]

Since the first description of GI-LCH in autopsy specimens, 2 reviews have highlighted poor outcomes in children with GI-LCH, with >50% mortality.[9,12] A retrospective review of 43 pediatric cases identified GI-LCH as an independent poor prognostic factor, associated with an overall survival of 53.6% after excluding patients with risk organ involvement (risk organ–positive).[10] Therefore, we performed a retrospective data analysis of 2 cooperative group trials (DAL-HX and LCH I/II/III) to investigate the clinical features and outcomes of children with GI-LCH.

GI	Gastrointestinal
GI-LCH	Gastrointestinal involvement in Langerhans cell histiocytosis
LCH	Langerhans cell histiocytosis
MS-LCH	Multisystem Langerhans cell histiocytosis
pSU	Probability of survival

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Methods

From June 1983 to July 2009, 2414 patients with LCH were enrolled onto the consecutive studies DAL-HX 83, DAL-HX 90, LCH-I, LCH-II, and LCH-III.[13-16] Eligibility criteria for all these trials were biopsy-proven diagnosis of LCH, age <18 years at diagnosis, no prior treatment for LCH, and provision of written informed consent.

There was no single case of GI-LCH among the 1289 patients with single-system LCH. Thus, we confined this retrospective analysis to the 1125 patients with MS-LCH. Characteristics of the study cohort are summarized in **Table I** (available at www.jpeds.com).

Diagnostic Confirmation and Initial Patient Examination

Definitive diagnosis of LCH according to the criteria of the Histiocyte Society[17] was required for enrollment onto the DAL-HX 90, LCH-I, LCH-II, and LCH-III trials. In the DAL-HX 83 trial, which preceded the aforementioned criteria, diagnostic confirmation was ascertained by either central pathology review or additional investigations (eg, Birbeck granules on electron microscopy, positive immunostaining for S-100).

An obligatory diagnostic evaluation at diagnosis included complete physical examination, complete blood count, liver enzymes (alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transpeptidase), bilirubin, total protein, albumin, skeletal survey, chest radiography, and abdominal ultrasound. Additional laboratory tests, imaging, or invasive investigations were performed at the discretion of the treating physicians.

Definitions

According to the criteria of the Histiocyte Society,[18] MS-LCH is defined as involvement of 2 or more organ systems (eg, skeleton, skin, lungs, liver, spleen, hematopoiesis, brain). A skeletal lesion with involvement of adjacent soft tissue or regional lymph nodes is classified as single-system LCH.

In this analysis, the term "risk organ" is defined as involvement of at least 1 of the following organs: hematopoietic system, liver, or spleen. Hematopoietic involvement is defined as at least 1 of the following: anemia (hemoglobin <100 g/L, or <90 g/L in infants) not explained by another condition, leukopenia (white blood cell count $<4.0 \times 10^9$/L), or thrombocytopenia (platelet count $<100 \times 10^9$/L). Liver involvement is defined as organ enlargement of >3 cm below the costal margin in the midclavicular line or liver dysfunction (ie, hypoproteinemia, hypoalbuminemia, hyperbilirubinemia, or increased liver enzymes) or histopathological diagnosis. Spleen involvement is defined as organ enlargement >2 cm below the costal margin in the midclavicular line.

The original trials documented GI-LCH as reported by the study sites and considered it for the definition of disease extent. However, neither an explicit definition nor guidance for a uniform diagnostic approach was provided. For this retrospective analysis, we used GI-LCH as documented in the database, and thus its definition relies on the judgment of the treating physician or the local principal investigator (eg, based on the presence of diarrhea and/or bloody stools and/or failure to thrive, and/or biopsy findings, etc). The manifestations of GI-LCH were specified in 50 of the 114 patients, the most common being diarrhea (n = 22), failure to thrive (n = 6), and oral ulcers (n = 5). GI-LCH was biopsy-proven in 28 of the 114 cases.

Statistical Analyses

Data collected for the original clinical trials were derived from case report forms filled out by the participating sites. The data are stored in the protected environment of the clinical trials database of the Histiocyte Society.

The probability of survival was estimated by the Kaplan–Meier method, and the log-rank test was used for statistical significance.[19,20] Survivors were censored at the date of their last follow-up evaluation. The 5-year probability of survival (pSU) is given unless indicated otherwise. Cox regression was used to evaluate the impact of GI-LCH adjusted for other known risk factors (ie, risk organ involvement and age). Two separate models are used in the evaluation, one exploring the impact of GI-LCH at diagnosis and the other evaluating GI-LCH developing at any time during the course of disease. In the second model, GI-LCH is included as a time-dependent covariate. The cumulative incidence of developing risk organ involvement and GI-LCH during the course of the disease was calculated, taking into account the competing risk of death. The median duration of follow-up was estimated using the inverse Kaplan-Meier estimate. The chi-square test was used to evaluate the correlation of GI-LCH with age and involvment of risk organs at diagnosis of LCH.

Results

At LCH diagnosis, GI-LCH was documented in 114 (10%) of the patients with MS-LCH, including 64 males and 50 females. Their median age was 0.9 years (range, 0-14 years); 90 of the 114 patients (79%) with GI-LCH at initial diagnosis were aged <2 years.

Correlations Among GI-LCH, Age, and Risk Organ Involvement at LCH Diagnosis

GI-LCH at diagnosis correlated significantly with age, as well as with involvement of risk organs (**Figure 1**; available at www.jpeds.com). GI-LCH was present in 90 of 702 patients (13%) aged <2 years at diagnosis, vs 24 of 423 patients (6%) aged >2 years ($P < .001$). GI-LCH was observed in 44 of 661 risk organ–negative patients (6%), compared with 70 of 464 risk organ–positive patients (15%) ($P < .001$).

The disease course with respect to GI and risk organ involvement is summarized in a flow chart (**Figure 2**; available at www.jpeds.com).

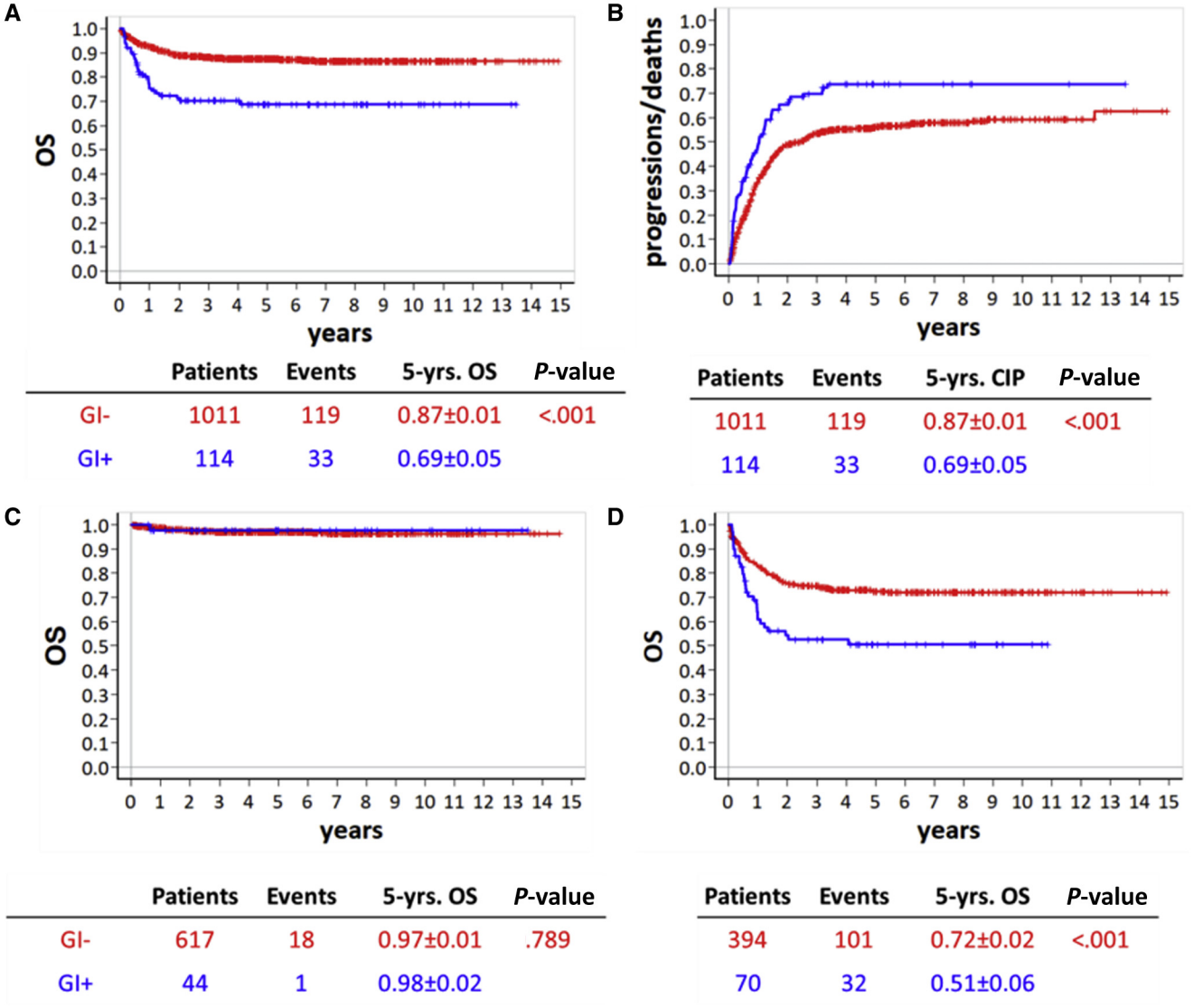
Risk for Developing GI-LCH During Disease Course

Of the 1011 patients without GI-LCH at diagnosis, 27 (2.6%) developed GI-LCH within a median of 6 months (range, 1 month to 2.5 years) after diagnosis of LCH. The cumulative risk of developing GI-LCH within 5 years after diagnosis was 3 ± 1%. The risk of developing GI-LCH after initial presentation was higher for risk organ–positive patients compared with those who were risk organ-negative at diagnosis (5-year cumulative incidence 4 ± 1% vs 2 ± 1%; $P = .077$, Gray's test).

GI-LCH at LCH Diagnosis and Survival

In univariate analysis, patients with GI-LCH at diagnosis had a significantly worse 5-year survival compared with those without GI-LCH (pSU, 69% vs 87%; $P < .001$, log-rank test) (Figure 3, A). The cumulative incidence of progression or death was higher in patients with GI-LCH (Figure 3, B). Among the 114 patients with GI-LCH, those with biopsy-proven involvement had a significantly inferior outcome compared with those without histologic verification. The 5-year pSU was 49 ± 10% vs 76 ± 5% ($P = .035$). The presence or absence of GI-LCH did not significantly influence survival among risk organ–negative patients (Figure 3, C), in contrast to those with risk organ–positive (Figure 3, D).

Multivariate analysis of the prognostic impact of GI-LCH was performed separately for organ involvement at diagnosis and organ involvement observed during the disease course (Table II). When adjusted for involvement of liver, hematopoietic system, spleen, and age, GI-LCH did not



	Patients	Events	5-yrs. OS	*P*-value
GI-	1011	119	0.87±0.01	<.001
GI+	114	33	0.69±0.05	

Patients	Events	5-yrs. CIP	*P*-value
1011	119	0.87±0.01	<.001
114	33	0.69±0.05	

	Patients	Events	5-yrs. OS	*P*-value
GI-	617	18	0.97±0.01	.789
GI+	44	1	0.98±0.02	

Patients	Events	5-yrs. OS	*P*-value
394	101	0.72±0.02	<.001
70	32	0.51±0.06	

Figure 3. GI involvement and outcome. **A,** Overall survival in the entire cohort. **B,** Cumulative incidence of progression or death. **C,** OS in patients without risk organ involvement. **D,** OS in patients with risk organ involvement. *CIP*, cumulative incidence of progression or death; *OS*, overall survival.

Table II. Cox survival analysis

	GI involvement at diagnosis			GI involvement at any time		
Risk factors*	*P* value	HR	95% CI	*P* value	HR	95% CI
GI	.014	1.6	1.1-2.4	<.001	2.2	1.5-3.1
Liver	<.001	5.0	3.0-8.3	<.001	5.0	3.0-8.2
Hematopoiesis	.003	1.8	1.2-2.7	.004	1.8	1.2-2.6
Spleen	.005	1.9	1.2-2.9	.004	1.9	1.2-2.9
Lung	.160	1.3	0.9-1.8	.113	1.3	0.9-1.9
Age <2 y	.145	1.4	0.9-2.3	.145	1.4	0.9-2.3

HR, hazard ratio.
*With the respective opposite (eg, organ involved vs not involved, age <2 y vs >2 y) as reference value.

significantly influence survival. An exploratory subgroup analysis revealed that the adverse impact of GI-LCH on survival is restricted to patients with risk organ involvement (**Figure 3**, D). Patients with risk organ involvement and GI-LCH had a worse outcome, with a 5-year pSU of 51 ± 6%, compared with 72 ± 2% in patients with risk organ involvement without GI-LCH. Thus, in patients with risk organ involvement, GI-LCH has an additive unfavorable prognostic impact.

Treatment and Outcome

The treatment regimens and the respective outcomes are listed in **Table III** (available at www.jpeds.com). Treatment modifications over time did not significantly reduce mortality in patients with risk organ involvement, and particularly failed in those with concomitant GI-LCH.

Discussion

GI involvement in LCH has long been an orphan research area, likely owing to its rarity and the lack of uniform diagnostic criteria. We analyzed the data of the clinical trial database of the Histiocyte Society, the largest cohort of patients with LCH ever collected through international cooperation. The GI tract is a rare site of LCH, and when affected, it is usually part of a multisystem disease.[9,10] Among the 1289 pediatric patients with single-system disease, there was no case of LCH confined to the GI tract. However, the existence of single-system GI-LCH has been supported by several anecdotal reports in adult patients.[21,22] A retrospective analysis of the French national LCH registry detected GI-LCH in 2% of patients, similar to the findings of other series.[12,23] Our database search revealed GI involvement in 4.7% of the entire cohort and in 10% of the patients with MS-LCH. Because neither a standardized diagnostic workup nor a uniform definition for GI-LCH was available, those numbers are likely biased by local practices and personal experiences of the investigators. In our cohort, the patients with biopsy-proven GI-LCH had a significantly inferior prognosis compared with those with GI-LCH diagnosed based on clinical findings (5-year pSU, 49 ± 10% vs 76 ± 5%; $P = .035$). Therefore, stringent diagnostic criteria and histologic verification may improve the prognostic value of GI-LCH.

A literature review suggests that the clinical manifestations of GI-LCH can vary depending on the affected gut segment. The small intestine, particularly the duodenum, seems to be the most commonly involved location, but all parts of the GI tract, from oral mucosa to perianal skin tags, can be affected.[24] Documented manifestations encompass vomiting, abdominal pain, failure to thrive, protein-losing enteropathy, anasarca, bloody or nonbloody diarrhea, hematochezia, and intestinal perforation.[9,10,12,25] A postmortem study of 12 deceased children with LCH suggested that clinically silent gut involvement may be more frequent than manifested GI-LCH.[24]

As shown by the few available case series and the numerous case reports and literature reviews, GI-LCH typically manifests in the setting of MS-LCH and affects predominantly infants and toddlers. GI-LCH in children is almost invariably associated with skin involvement.[9,10,12] The preceding or concomitant characteristic skin rash provides a clue as to the underlying LCH.

Reported endoscopic findings range from nonspecific inflammatory changes (mucosal redness, edema, and frailty) and erosion to deeper ulceration with or without bleeding. Histiocytic infiltration of the lamina propria is the common finding on microscopy, but other layers of the wall can be involved as well.[12,24] Villous atrophy is a possible but inconsistent finding. Staining for CD1a, CD207 (langerin), and S-100 aids the diagnosis in atypical cases. In the study by Geissmann et al, biopsy specimens from the skin and digestive tract of patients with GI-LCH revealed expression of the mucosal homing receptor integrin $\alpha 4\beta 7$ (LPAM-1) on the LCH cells in contrast to controls.[12] The authors concluded that cutaneous, mucosal, and digestive tract involvement in LCH characterizes a clinicopathologic entity.

The lack of detailed information on GI-LCH manifestations and of a consistent definition of GI-LCH are among the few limitations of our retrospective analysis. Owing to the retrospective character of the analysis and the changes in clinical practice over the time span of data collection, it is not possible to draw firm conclusions about the effectiveness of the individual treatment regimens used; however, in patients without involvement of risk organs, GI-LCH was not associated with increased mortality, which indicates that regimens based on the prednisone/vinblastine backbone have been effective in those patients.

GI-LCH is associated with increased mortality of up to 60%.[9,12,25] However, most reports to date have included only small case series, and the majority have involved individual cases and reviews. Thus, it is not possible to rule out a reporting bias. Furthermore, in most published cases, GI-LCH coincided with dysfunction of risk organs. Therefore, a sound assessment of the prognostic impact of GI-LCH requires a large cohort and a multivariate analysis to adjust for

Table IV. Diagnostic criteria for GI-LCH

GI-LCH should be defined as one of the following:
- Biopsy-proven GI-LCH and/or bloody stools (without biopsy)
- Two or more unexplained GI symptoms at LCH presentation or relapse:
  Abdominal pain
  Diarrhea
  Vomiting
- Chronic diarrhea and hypoalbuminemia (protein-losing enteropathy or malabsorption syndrome)
- GI symptoms with radiologic findings (ultrasound or positron emission tomography–computed tomography) suggestive of GI involvement

confounding factors, such as age and risk organ involvement. A recent small retrospective study found an unfavorable impact of GI-LCH on disease prognosis that appeared to be independent of risk organ involvement.[10] Our analysis validates the unfavorable impact of GI-LCH on disease outcome; however, we were able to find an additive negative prognostic effect in patients with risk organ involvement only.

Our findings call into question the independent prognostic value of GI-LCH. A definitive answer will require a prospective study in a large cohort of patients, such as the ongoing LCH-IV trial, with uniform workup and histologic confirmation of GI-LCH. In our view, a diagnostic workup toward GI-LCH is warranted in all patients with unexplained GI symptoms (eg, abdominal pain, diarrhea, vomiting) at LCH presentation or relapse, in patients with suspected protein-losing enteropathy (eg, protracted diarrhea, hypoalbuminemia, failure to thrive), and those with radiologic findings (on ultrasound or positron emission tomography–computed tomography) suggestive of gut involvement. The workup of the digestive tract may include abdominal imaging (computed tomography scan or magnetic resonance imaging) or even an endoscopic biopsy. However, it may be difficult to justify an invasive procedure (ie, endoscopy) in severely ill young children with LCH, especially if the results will not change the treatment approach. In view of the foregoing considerations, we propose a pragmatic definition of GI-LCH (**Table IV**). This proposal requires validation in a prospective study.

In summary, involvement of the GI tract has an additive unfavorable impact on the prognosis of patients with LCH and involvement of risk organs. We recommend considering an appropriate workup in the initial evaluation of patients with LCH showing signs and symptoms suggestive of GI tract involvement. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Pediatric Hyperthyroidism and Atrial Fibrillation: Lessons Learned

Perry LW, Hung W. Atrial fibrillation and hyperthyroidism in a 14-year old boy. J Pediatr 1971;79:668-71.

In 1971, Drs Perry and Hung described a 14-year-old patient with weight loss, tachycardia, and hypertension from long-standing hyperthyroidism, who was admitted for acute on chronic heart failure, likely secondary to atrial fibrillation. He was treated with digitalis, diuretics, and propylthiouracil with rhythm conversion after adding quinidine, and there was normalization of cardiac function without the need for long-term anti-arrhythmic therapy.

Improvements in understanding of pathophysiology and therapies have led to practice changes over 50 years. Pediatric patients most commonly have "lone" atrial fibrillation, without structural heart disease, with a reported prevalence of 7.5 in 100,000.[1] Additional arrhythmia substrates including atrial tachycardia, atrioventricular nodal re-entrant tachycardia, and accessory pathway mediated tachycardia are thought to trigger pediatric atrial fibrillation. Earlier recognition of irregular cardiac rhythm and availability of ambulatory cardiac monitoring has led to rapid diagnosis and treatment of pediatric atrial fibrillation.

Hyperthyroidism, most commonly due to Graves disease, affects 1 in 10 000 children in the US.[2] Automated radio immunoassays allow for rapid determination of thyroid function and diagnosis. In the hyperthyroid state, triiodothyronine (T3), acts on the myocardium and most commonly causes sinus tachycardia and systolic hypertension. Atrial fibrillation is a rare complication of pediatric hyperthyroidism[3] and is more common in male individuals over 60 years of age with pre-existing heart disease.

Although hyperthyroidism is a rare cause of pediatric atrial fibrillation, evaluation of thyroid stimulating hormone is recommended. Medical management of pediatric hyperthyroidism is primarily antithyroid medication and beta-blockers and methimazole replaced propylthiouracil as the preferred antithyroid agent because of the increased risk of liver failure.[2] Establishing a euthyroid state corrects atrial fibrillation without the need for cardioversion in more than one-half of adults and has been reported in a pediatric patient.[3] After initial atrial fibrillation control, electrophysiology study and ablation procedures allow for diagnosis and treatment of additional arrhythmic substrates, which may prevent recurrence of atrial fibrillation, regardless of thyroid status.

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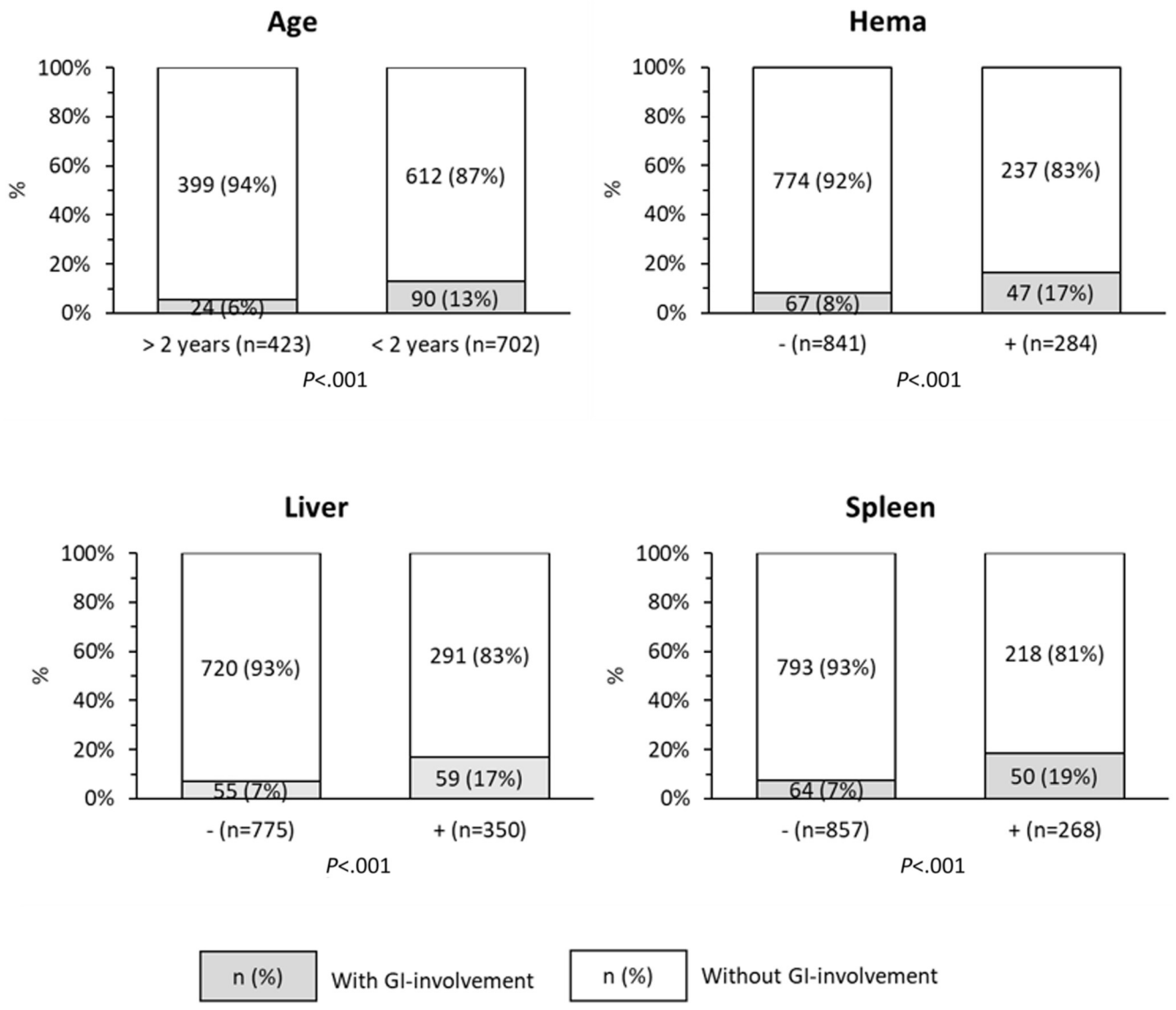

Figure 1. Correlation of GI involvement with age and involvement of risk organs at diagnosis of LCH.

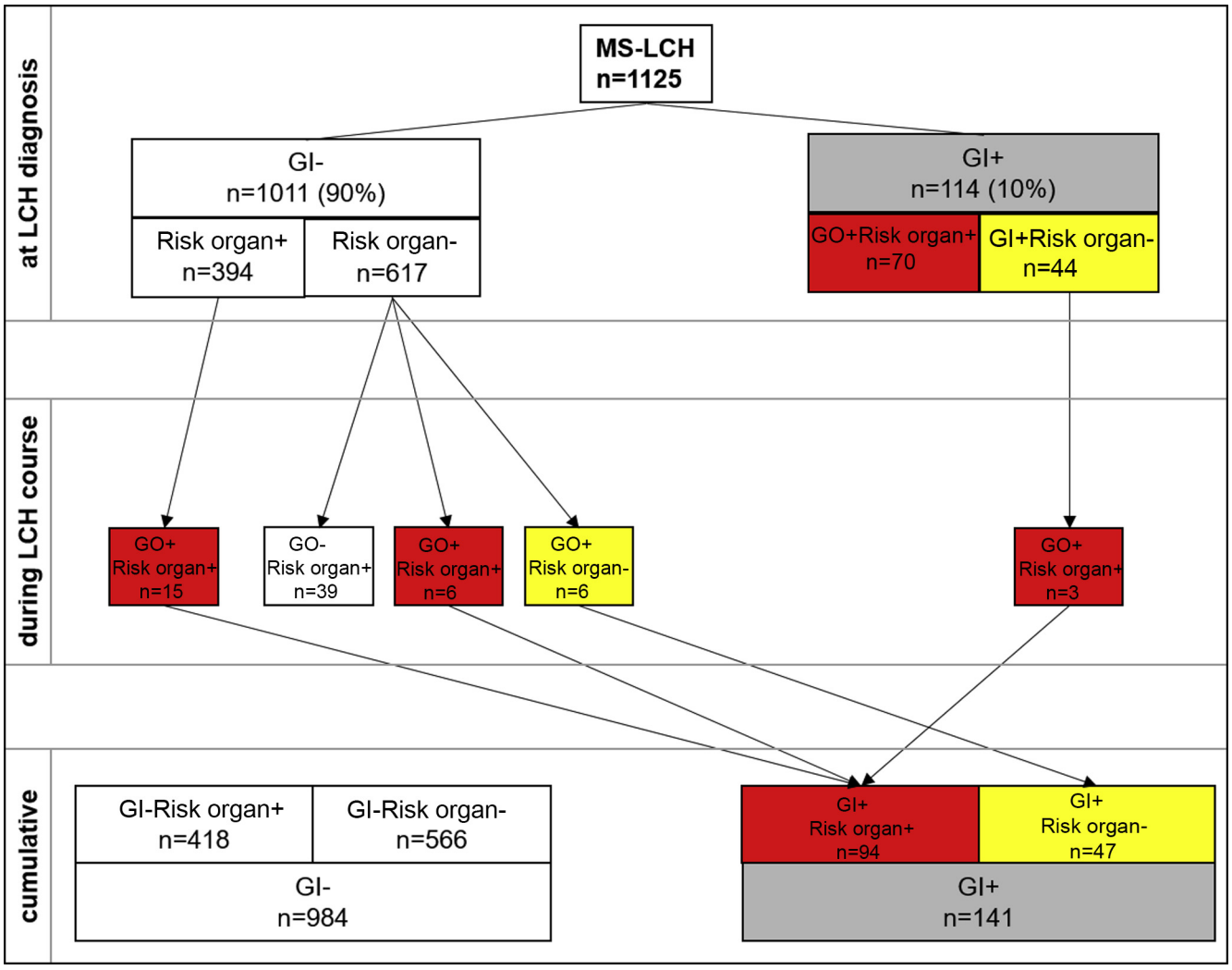

Figure 2. Flowchart of GI and risk organ involvement at diagnosis and throughout the disease course.

Table I. Characteristics of the patients with MS-LCH according to GI involvement status at presentation

Characteristics	GI⁻	GI⁺	Total
Number (%)	1011 (90)	114 (10)	1125
Age, y, n (%)			
<2	612 (87)	90 (13)	702
2-<5	247 (93)	19 (7)	266
5-<10	74 (96)	3 (4)	77
10-<15	40 (98)	1 (2)	41
≥15	38 (97)	1 (3)	39
Age, y, median (range)	1.5 (0-18)	0.9 (0-14)	1.5 (0-18)
Sex, male/female, n	547/764	64/50	611/514
Study cohort, n (%)			
DAL-HX83/90	82 (85)	14 (15)	96
LCH-I	169 (89)	21 (11)	190
LCH-II	303 (93)	22 (7)	325
LCH-III	457 (89)	57 (11)	514
Frequently involved organs at diagnosis, n (%)			
Hematopoiesis (cytopenia)	237 (83)	47 (17)	284
Liver	291 (83)	59 (17)	350
Spleen	218 (81)	50 (19)	268
Lung	238 (88)	33 (12)	271
Skin	657 (87)	99 (13)	756
Bone	749 (93)	59 (7)	808
Risk group, n (%)			
High risk (≥1 risk organ)	394 (85)	70 (15)	464
Low risk (no risk organ)	617 (93)	44 (7)	661
Observation time, y, median (IQR)			5.7 (3-5.6)

Table III. Treatment and 5-year survival

	Events/patients, 5-year overall survival			
Treatment regimen	GI⁻risk organ⁻	GI⁺risk organ⁻	GI⁻risk organ⁺	GI⁺risk organ⁺
DAL-HX	3/45, 0.93 ± 0.04	0/4, 1	10/37, 0.73 ± 0.07	5/10, 0.50 ± 0.16
LCH-I	5/88, 0.95 ± 0.02	1/8, 0.88 ± 0.12	24/81, 0.68 ± 0.05	10/13, 0*
LCH-II	2/185, 0.98 ± 0.01	0/6, 1	46/118, 0.60 ± 0.05	7/16, 0.51 ± 0.13
LCH-III	8/299, 0.97 ± 0.01	0/26, 1	21/158, 0.85 ± 0.03	10/31, 0.66 ± 0.09

*All 3 censored patients had a follow-up of <5 years.