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Review Article

Pediatric Hodgkin Lymphoma in Low- and Middle-Income Countries (LMICs). A Narrative Review

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Abstract. Pediatric Hodgkin lymphoma (HL) is a curable disease for more than 90% of children and adolescents in high-income countries. However, similar results cannot be achieved, particularly for advanced disease, in low- and middle-income countries (LMICs), where challenging socio-economic realities and the consequent scarcity of local resources heavily impact the treatment and patients' outcome. Information regarding the management and outcome of pediatric HL in LMICs is still limited. In this narrative review, we summarize the results reported in the literature so far and discuss the critical key points that have emerged from this overview.

Keywords: Children, Hodgkin lymphoma, Low- and middle-income countries.

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Introduction. In high-income countries (HICs), more than 90% of children and adolescents with Hodgkin lymphoma (HL) can be cured with combined chemo-radiotherapy adapted to the pediatric age.[1,2] During the last decade, multicenter pediatric studies aimed at modulating treatment according to well-defined risk groups and, in particular, at evaluating the reduction/omission of radiotherapy according to the early metabolic positron emission tomography (PET) response (ERA).[3-7] In low- and middle-income countries (LMICs), treatment strategies must find a balance between curative goals, toxicities, and local resources. The socio-economic, political, and cultural situation present in many LMICs leads to multiple problems that significantly impact pediatric HL treatment and outcomes. These issues include delays in referring patients to hospitals, the presence of comorbidities and malnutrition, high rates of abandonment, and a variety of other challenges that affect different countries to varying degrees. Owing to the lack of adequate supportive therapy, the more intensive schemes, successfully employed in HICs, are usually unsafe in the above setting. Radiotherapy is not always available, and HL treatment must often rely only on chemotherapy. Moreover, an accurate staging work-up at presentation and definition of response to treatment cannot be carried out in the absence of effective diagnostic/follow-up tools such as PET. It should also be recalled that information regarding the epidemiology and outcome of pediatric HL in LMICs is still limited, due to the lack of proper country registries and the paucity of updated reports and follow-up data also due to the increasing standards required for scientific papers and a preference for prospective multicenter studies that limit the publication of real-life reports from LMICs.

For this narrative review, we utilized PubMed to

search articles about pediatric HL management in LMICs. The search was narrowed to articles between 1990 and 2023, excluding sub-Saharan Africa, which has been the subject of a recent exhaustive report,[8] and far-East LMICs, for which data in the English literature are insufficient. A total of 33 articles were included. We summarized the results reported so far in these papers and discussed the lessons that have been derived from these different real-life experiences.

Epidemiology. The epidemiology of pediatric HL varies greatly among geographic areas with different socio-economic levels. In HICs, HL is the sixth most frequent childhood neoplasm, accounting for 5-6% of childhood cancers.[9] Data regarding the real incidence of pediatric HL in other parts of the world concern only some geographic areas and are often not updated. In developing countries, HL is more frequent, being the fourth most common neoplasm in childhood.[10] In Latin America, the incidence of childhood HL is particularly high, 1-1.5 per 100,000 children.[10]

In HICs, HL presents two peaks of age distribution in young adults (20-34 years) and older people (55-74 years).[11] In LMICs, the first peak occurs at a younger age in both children and adolescents, with 20% to 30% of childhood HL cases occurring before the age of 5, compared to about 5% in HICs.[12] Such patterns of occurrence are similar to those of Epstein-Barr virus (EBV) and other infections, suggesting an etiologic role of environmental exposure. In HICs, the incidence of EBV tumor cell positivity for HL ranges from 15% to 25% in adolescents and young adults.[13-15] It is significantly higher - between 70% and 100% - in LMICs where primary EBV infection occurs within a few months to years after birth. EBV-associated HL is more frequent in children below the age of 10, in males, and in the mixed cellularity (MC) subtype.[16,17] In India, EBV has been found in 78% of HL cases at all ages and in up to 98% of childhood HL.[18,19]

MC is the most common subtype of pediatric HL in LMICs (46-60%), and its association with EBV infection is well documented.

In LMICs, there is a male predominance in pediatric HL, particularly under the age of 10, with an M: F ratio between 2.5:1 and 5:1. The M: F ratio reaches 10.5:1 in Indian cases.[20,21] The reasons for this gender distribution are not fully understood. Increased male susceptibility to infection, as well as social-cultural factors leading to reduced attention to female children, have been suggested.[22]

Treatment

Therapeutic strategies and results in HICs. HL has been one of the most curable cancers since 1950, when the first successful protocols based on chemo and radiotherapy began to be used. In recent decades, the major focus, particularly in pediatric patients, has been to reduce the use of radiotherapy and chemotherapeutic agents such as anthracyclines and procarbazine, which are responsible for various severe long-term toxicities.[23] Nowadays, the survival rate of pediatric HL patients in HICs exceeds 90% with combined chemo-radiotherapy protocols adapted for younger patients.[1-3,5,6] In recent trials, staging, response assessment, and radiotherapy indications have been based on PET evaluations, and the number and intensity of cycles have been adjusted according to the risk group assignment. The 5-year event-free survival (EFS) ranges from 80% to 96% for children with low risk and from 79% to 90% for children with intermediate-high risk disease.[1,3-7,24-27] In the ongoing Children's Oncology Group (COG) and the European Network Pediatric Hodgkin Lymphoma (EuroNet-PHL) trials, the intensity and duration of chemotherapy, as well as the indication, doses, and fields of radiotherapy, are modulated according to two criteria: the risk category (mainly determined by stage, bulky disease and B symptoms) and the early metabolic response to treatment. Promising immuno-chemotherapy approaches,[28,29] including monoclonal antibodies and checkpoint inhibitors such as brentuximab[30-32] and pembrolizumab,[33] are under evaluation for first-line treatment in pediatric patients, with the aim of further reducing chemotherapy-related toxicity.

Reported results in LMICs. There are very little data in the literature on the treatment and outcome of pediatric HL in LMICs prior to the second decade of the 2000s. These studies are generally retrospective and mainly based on single-center experiences. Heterogeneous treatment approaches, including radiotherapy or not, as well as different modalities of data analysis, often censoring abandonment, make these studies difficult to interpret and compare. More recently, prospective cooperative studies have been implemented in Latin America[34] and in the Indian subcontinent.[35-37]

Papers on pediatric HL from LMICs, present in the literature from the 1990s, are summarized in **Tables 1-3**. These studies include patients up to the age of 14-21. In most studies, the median age is low, around 7 years, with many children less than 5 (from 8.3% up to 37%, median 16%).

The M: F ratio is high (median 3.8:1), ranging from values similar to Western countries (1.6-1.7:1) in Egypt,[38,39] Iran,[40] and Argentina,[41] and up to 10.5:1 in India[20,21] where very high rates are reported in all studies.

All the studies, except two excluding nodular lymphocyte predominance HL,[61,62] include all HL histologic subtypes. An MC histology is reported in more than 40% of cases, with this histologic subtype being even more represented (up to 86%) in Indian patients.[42] Many patients present with advanced stage (stage III-IV), with a median of 52% (range 26%-87%).

Abandonment, which was differently defined among the studies, was reported in 15 out of the 33 papers, with rates ranging from 1% to 17% (median 7.5%).

The most commonly used regimen was ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), alone or alternated with COPP (cyclophosphamide, oncovin, procarbazine, prednisone), with or without dacarbazine (COPP/ABV(D)). After the 2000s, other schemes derived from the European pediatric protocols, particularly OEPA (oncovin, etoposide, prednisone, adriamycin) and COPDAC (cyclophosphamide, oncovin, prednisone, dacarbazine), have been introduced.

The total number of cycles varied from 3 to 12 (median 6), generally depending on medical decisions according to stage, response to treatment, and availability of radiotherapy. In the absence of radiotherapy, more cycles of chemotherapy were administered (**Table 1**).

Table 1 describes the studies based on chemotherapy alone. Chemotherapy alone was delivered in six studies due to the unavailability of radiotherapy.[38,43-47] In four further studies, radiotherapy was sporadically delivered to a very small number of patients based on clinical decisions related to bulky disease at presentation or residual mass after chemotherapy.[20,21,42,48]

Table 2 (A, B, C) reports the studies based on a combined chemo-radiotherapy modality. In some studies, involved field (IF) radiotherapy was planned for patients with bulky or residual disease.[49-55] In other studies, radiotherapy, generally IF, was administered to all patients[34,41,56-58] or to patients selected according to risk.[39,40,59,60] Since 2010, in the most recent prospective protocols, radiotherapy (generally IF) was pre-planned based on ERA and in case of bulky disease (**Table 3**).[35-37,61-63]

Results according to therapeutic strategies. In the studies based on chemotherapy alone (generally COPP, COPP/ABV(D) or ABVD), the overall 5-year EFS and overall survival (OS) ranged from 69% to 87% (median 77.8%) and from 76.3% to 92.7% (median 91.5%), respectively, with good results (EFS up to 92% and OS up to 100%) in children presenting with localized disease. As previously mentioned, these patients received a high number of chemotherapeutic cycles, up to 10-12. Despite the high chemotherapy burden, the reported therapy-related deaths (TRD) are low (**Table 1**). However, little information on the long-term side effects is available. The median rate of abandonment is 12%. In the two studies in which abandonment was considered as an event, the 10- and 15-year EFS were 56.8% and 70.3%, respectively.[46,47]

When a chemo-radiotherapy combination was used, the chemotherapy regimens included mainly ABVD, COPP, and COPP/ABVD. Other schemes such as COPDAC and OEPA or OPPA (oncovin, procarbazine, prednisone, adriamycin), derived from pediatric European experiences, have been used in studies from Pakistan and South Africa since 2000. The overall 5-10-year EFS ranged from 60% to 91% (median 81.5%), and the OS ranged from 72% to 96.6% (median 91.6%), with EFS up to 91.7% and OS up to 100% in children with early-stage disease. The median rate of abandonment, reported only in a few papers, was 8%. In the two studies in which abandonment was considered as an event, the 5-year EFS was 46% and 70%, respectively.[34,64]

In the more recent studies, with different combined chemo-radiotherapy programs modulated according to the initial stage and ERA, the 3-5-year EFS and OS were 83.3% and 92.2%, respectively. Patients with localized disease reached a 3-year EFS and OS of 100%.[62,63]

No significant differences were observed among the three treatment strategies (**Tables 1-3**), with a median EFS of 72.8%, 81.5%, and 83.3% and OS of 91.5%, 91.6%, and 92%, respectively, for chemotherapy alone, chemo-radiotherapy, and ERA-based chemo-radiotherapy groups.

Discussion. Most children in the world live in LMICs, where over 80% of pediatric cancers occur.[65] Unfortunately, the good results of pediatric cancer treatment achieved in HICs are still not attained in the other parts of the world.[66] This is also true for a highly curable disease like HL. In LMICs, the survival rates reported in the published papers are acceptable, particularly for children with early-stage disease, though lower compared to those achieved in HICs and often at the cost of a high therapeutic burden. Moreover, we must consider that data on HL - and all pediatric cancers - are completely lacking for most LMICs. More data are recently emerging from Latin America with the implementation of cooperative studies and from the Indian subcontinent.

The data that emerge from this review confirm:

- Lower age and the high incidence of MC in the pediatric HL cohorts.
- The high incidence of MC is probably related to the high incidence of early EBV infection in LMICs.
- The high M: F ratio. Cultural reasons, with a lower interest in female children, are evident, particularly in the reports from India. The M: F ratio appears to be reducing, though remaining high also in the more recent studies.
- The advanced stage of disease presentation is often due to delayed referral and diagnosis for social and economic reasons.

In these countries, the most used therapeutic regimens were the well-known ABVD, COPP, or COPP/ABV regimens, which are less toxic and can be administered as outpatients. Radiotherapy was not always available, and the number of chemotherapy cycles administered was frequently high, with a risk of late side effects,

Table 1. Childhood/adolescent Hodgkin lymphoma in low-middle income countries. Treatment results I: Chemotherapy alone or sporadic radiotherapy.

Author, year	Country	Years	Type of study	Pts	Age y	<5y %	M/F	MC %	III-IV %	Treatment *	Cycles	Radio therapy	TRD/Rel (pts)	Aband.	EFS or RFS (years)	OS (years)
Lobo, 1994 [43]	CostaRica	1980-1992	Prosp.	86	<14	17	3.1:1	37	28	CVPP CVPP/EBO (IIIB-IV)	6, 12	no	na/14	na	I-IIIA 90 >IIIA 60 (5)	I-IIIA 100 >IIIA 81 (5)
Sripada, 1995 [44]	India	1989-1993	Retrosp.	53	<14	na	3.8:1	39.6	81	COPP/ABV	6	no	1/3	1	na	90 (5)
Baez, 1997 [45]	Nicaragua	1990-1995	Retrosp.	48	<15	na	2.4:1	52	58	COPP (I-IIA), COPP/ABV (>IIB)	6, 8, 10	no	na/na	4 (8%)	I-IIIA 83 >IIIA 74,9 (3)	na
Sagar, 2003 [48]	India	1989-1998	Retrosp.	134	<5	na	5.1:1	54.5	62	COPP/ABVD	6, 8	7 pts (Residual)	1/8	na	86.7 RFS (5)	92.5 (5)
Arya, 2006 [42]	India	1991-2001	Retrosp.	148	<15	14.9	9.6:1	86	63.5 (IIB-IV)	COPP/ABVD	8	5 pts (bulky)	2/5	22 (15%)	87.9 (5)	91.5 (5)
Chandra, 2008 [20]	India	1988-2004	Retrosp.	35	<18	37	10.5:1	50	83	COPP (29 pts), COPP/ABVD, ABVD	6	4 pts (bulky)	1/na	2 (6%)	80 (5)	na
Al Tombari, 2010 [38]	Egypt	2002-2006	Prosp.	119	<16	na	1.6:1	56	26	COMP or OAP (random)	na	no	na	na	62.3 (5) 69.8 COMP	68.1 (5) 76.3 COMP
Trehan, 2013 [21]	India	1990-2006	Retrosp.	206	<16	15.5	10.5:1	69.6	52.2	COPP/MOPP, VAEP, ABVD, ABVD/COPP (>1998)	4-10 (median 6)	3 pts	na/23	15 (7%)	77.7 (5) I II 90.2 III IV 73.2	92.7 (5) I II 97.7 III IV 87.2
Castellanos, 2014 [46]	Central America	1999-2004	Prosp. AHOPCA LH 1999	216	<18	20	3.7:1	35.2	41.7	COPP ±ABV(LR) COPP/ABV (HR)	6 (LR), 8	no	na/46	30 (14%)	71.4 (5) 67.6 (10) 60.8 (5) 56.8 (10) AS-EFS	not calculated
Testi, 2024 [47]	Iraq	2004-2019	Retrosp.	284	<14	16	2.4:1	60	52.8	ABVD 65%, COPP/ABV29%, other 6%	2-8 (median 6)	no	2/42	4	70.3 (15) AS-EFS	89.7 (15) AS-OS

Aband.= Abandonement; AHOPCA=Asociación de Hemato-Oncología Pediátrica de Centro América; AS= abandonment sensitive; EFS= event-free survival; HR=High Risk; LR=Low Risk; MC= mixed cellularity; M/F= Male / Female; na= not available; OS= overall survival; Prsop=Prospctive; Pts= patients; R=Random; Retrosp= Retrospective; RFS=relapse-free survival; Rx=Radiotherapy; TRD/Rel= therapy-related mortality/relapse; Y= years; *ABV (adriamycin, bleomycin, vinblastine); ABVD (adriamycin, bleomycin, vinblastine, dacarbazine); COMP (cyclophosphamide, oncovin, methotrexate, prednisone); COPP (cyclophosphamide, oncovin, procarbazine, prednisone); CVPP (cyclophosphamide, vinblastine, procarbazine, prednisone); EBO (epirubicine, bleomycin, oncovin); MOPP (mechlorethamine, oncovin, procarbazine, prednisone); OAP/OPA (oncovin, adriamycin, prednisone); VAEP (vincristine, adriamycin, etoposide, prednisone)

Table 2A. Children/adolescents Hodgkin lymphoma in Low-middle income countries. Treatment results II: Combined chemoradiotherapy

Author, year	Country	Years	Type of study	Pts	Age y	<5y %	M/F	MC %	III-IV %	Treatment * (pts)	Cycles	Radio therapy (pts)	TRD/ Rel (pts)	Aband.	EFS or RFS (years)	OS (years)
Kapoor, 1995 [56]	India	1985-1990	Retrosp.	147 ev.	<15	19	6:1	65	37	COPP, COPP/ABVD, ABVD	6	all IF	4/15	na	81 (7)	93 (7)
Sackmann, 1997 [41]	Argentina	1987-1994	Prosp. R	114	<17	20.2	1.7:1	51.7	40	CVPP, CVPP AOPE CCOPP/CAPte	3, 6	all IF	2/10	na	80 (7)	87 (7)
Muwakkit, 1999 [52]	Lebanon	1980-1996	Retrosp.	24	<13	na	na	50	37 (IIIB-IV)	COPP,ABVD, COPP/ABVD	6, 8, 12	9 pts	na	na	100 (+Rx) (5) 56 (no Rx)	100 (+Rx) (5) 79 (no Rx)
Alebouyeh, 2005 [40]	Iran	1988-2004	Prosp. DAL/G POH	40	<15	na	1.7:1	55	55	OPA, OPEA, OPPA, OPPA/COPP	2, 4, 6	IF, EF (29)	1/8	na	79.2 (5) 75.4 (16)	94.4 (5) 88.1 (16)
Belgaumi, 2008 [53]	Saudi Arabia	1975-2003	Retrosp.	69	<5	100	4.3:1	40.6	42	ABVD, MOPP, MOPP/ABVD, COPP/ABVD	4, 6	IF, EF (12)	2/8	na	81.5 (10)	90.4 (10)
El Badawi, 2008 [57]	Egypt	na	na	121	<18	na	na	na	na	female OPPA/COPP, male E-OPA/ COPP	2, 4, 6	all IF	na	na	86.1 (6)	95.3 (6)
Buyukpamukcu, 2009 [58]	Turchia	1971-2005	Retrosp.	614	<21	15	2.8:1	56	42	COPP, ABVD, COPP/ABVD	3, 6,	all EF, IF	na	na	60 (10)	83 (10)

Table 2B. Children/adolescents Hodgkin lymphoma in Low-middle income countries. Treatment results II: Combined chemoradiotherapy

Author, year	Country	Years	Type of study	Pts	Age y	<5y %	M/F	MC %	III-IV %	Treatment * (pts)	Cycles	Radio therapy (pts)	TRD/ Rel (pts)	Aband.	EFS or RFS (years)	OS (years)
Hessissen, 2013 [64]	Morocco	2004-2007	Prosp.	160	<20	12.5	2.0:1	41	87	VAMP (<IIB) OPPA/COPP	4 (<IIB), 6	all IF	5/14	20 (12.5%)	70 AS (5) <IIB 74 ≥IIB 69	88 (5)
Baharvand, 2014 [54]	Iran	ten years	Retrosp.	82	<14	12.2	2.7:1	45.1	47.5	na	na	56%	na	na	na	72% Survival rate
Radhakrisnan, 2016 [49]	India	2001-2010	Retrosp.	172	<18	15	2.8:1	45	40	ABVD or ABV/COPP	4, 6, 8 individual decision	IF + boost if residual (19%) bulky	2/27	14 (8%)	83.1 PFS (5) I 91.7 II 86.6 III 78.3 IV 57.1	92.9 (5) I 96 II 94.7 III 84 IV 69.8
Sherief, 2015 [39]	Egypt	2004-2012	Retrosp.	59	<18	22	1.7:1	50.8	55.9	ABVD	LR4, IR6, HR8	all LR IR IF (+boost)	2/7	na	84.7 (5)	96.6 (5)
Zubizzareta, 2017 [59]	Argentina	2000-2015	Prosp. LH-HPG 2000	165	<17	na	2.4:1	19.4	42 (LR 30, IR 30, HR 40)	ABVD	LR4, IR-HR6	IF + boost (47%) if residual LR IR all HR	1/17	na	84 (5) LR 88, IR 84, HR 82 (10)	95 (5) LR 100, IR 93, HR 85 (10)
Geel, 2017 [60]	South Africa	2000-2010	Retrosp.	294 (HIV 9.9%)	<20	17.3	3.3:1	40.8	54	ABVD (158) OPPA/OEPA-COPP (97) ABVcD-ChlVbPP (31)	4, 6	IF (83) all (OEPA-OPPA) or response/bulky	na/39	4.9%	na	79 (5) I 100 II 93 III 77 IV 56
Jain, 2016 [50]	India	1996-2013	Retrosp.	167	<18	13.7	9.4:1	49.8	31.8	ABVD	4, 5 , 6 (87%)	PR, bulky (51)	na/23	2	79 FFTF (5) I,II 93.9 III,IV 63.7	95.9 (5) I,II 97.2 III,IV 94.3

Table 2C. Children/adolescents Hodgkin lymphoma in Low-middle income countries. Treatment results II: Combined chemoradiotherapy

Author, year	Country	Years	Type of study	Pts	Age y	<5y %	M/F	MC %	III-IV %	Treatment * (pts)	Cycles	Radio therapy (pts)	TRD/ Rel (pts)	Aband.	EFS or RFS (years)	OS (years)
Mehereen, 2019 [55]	Pakistan	2009-2015	Retrosp.	748	ped	na	4.0:1	na	65	COPDAC/ ABVD (412) ChlVPP/ ABVD (176) OEPA/ COPP or COPDAC(125) various (33)	na	yes (17%)	na/6%	3%	91 (5)	94 (5)
Ashraf, 2019 [51]	Pakistan	2000-2012	Retrosp.	212	<20	20.8	4.7:1	65.1	49	ABVD/ COPDAC	≤ 4(23%), 6 (59%), 8(12%)	IF residual (10%)	6/20	na	82.1 (5) (LFU incl.70.8)	89.6 (5) (LFU incl. 77) I 100 II 95 III 85.5 IV82
Luna, 2023 [34]	Central America	2004-2009	AHOPCA HRHL 2004	181	<18	na	4.1:1	44	100 (IIB,IIIB,IV)	Stanford modified	12 weeks	IF (137)	8/30	31 (17%)	46 AS-EFS (5)	56 AS-EFS (5)

Aband.= Abandonement; AHOPCA=Asociación de Hemato-Oncología Pediátrica de Centro América; AS= abandonment sensitive; EF= extended field; EFS-RFS= event-free survival-relapse-free survival; FFTF= freedom from treatment failure IF= involved field; incl= included; LFU=Lost to Follow-up; LR, IR, HR=Low-risk, intermediate-risk, high-risk; MC= mixed cellularity; M/F= Male / Female; na= not available; OS= overall survival; PFS= progression free survival; Prosp=Prospective; PR= partial response; Pts=patients; Retrosp.= Retrospective; Rx= radiotherapy; TRD/Rel= therapy-related-death/relapse; y= years; *ABV (adriamycin, bleomycin, vinblastine); ABVD (adriamycin, bleomycin, vinblastine, dacarbazine); ABVcD (adriamycin, bleomycin, vincristine, dacarbazine); CAPte (cyclophosphamide, adriamycin, prednisone, teniposide); CCOPP (ccnu, oncovin, procarbazine, prednisone); COPDAC (cyclophosphamide, oncovin, prednisone, dacarbazine); COPP (cyclophosphamide, oncovin, procarbazine, prednisone); ChlVbPP (chlorambucil, vinblastine, procarbazine, prednisone); CVPP (cyclophosphamide, vinblastine, procarbazine, prednisone); MOPP (mechlorethamine, oncovin, procarbazine, prednisone); OPA (oncovin, adriamycin, prednisone); OEPA/OPEA/E-OPA/AOPE(oncovin, etoposide, prednisone , adriamycin); OPPA (oncovin, procarbazine, prednisone , adriamycin); VAMP (vinblastine, adriamycin, methotrexate, prednisone)

Table 3. Children/adolescents Hodgkin lymphoma in Low-middle income countries. Treatment results II: ERA based Combined chemoradiotherapy

Author, year	Country	Years	Type of study	Pts	Age years	<5 y %	M/F	MC %	III-IV %	Treatment*	Cycles	Radio therapy	TRD/ Rel (pts)	Aband.	EFS or RFS (years)	OS (years)
Ghafoor, 2019 [61]	Pakistan	2012-2018	Retrosp. Euronet PHL	106	<15	22.6	3.8:1	72.6	57.6 (TG1 27, TG2 31, TG3 42)	OEPA-COPDAC	TG1 2 TG2 4 TG3 6	Inadequate ERA IF +/- boost (19 pts)	8/13	na	80.2 (na) TG1 81.8 TG2 82.1 TG3 75.6	91.5 (na) TG1 95.5 TG2 94.9 TG3 86.7
Parambil, 2019 [62]	India	2013-2016	Retrosp.	126	<15	8.3	4.7:1	27.2	(LR 10, IR 16, HR 84)	LR: ABVD, IR,HR: OEPA-COPDAC	LR 4 IR 4 HR 6	Inadequate ERA IF, bulky (96 pts)	5/na	na	LR 100, IR 94.4, HR 90.3 (3)	LR 100, IR 94.4, HR 92.6 (3)
Mahajan, 2021 [35]	India	2015-2018	Prosp. InPOG-HL 15-01	134	<18	na	5.7:1	59.4	none	ABVD	4	Inadequate ERA sites, bulky (54 pts)	1/3	1	94 (5)	95.5 (5)
Jain, 2022 [36]	India	2015-2018	Prosp. InPOG-HL 15-01	262	<18	na	na	na	100 IIB-IV	ABVD	6	Inadequate ERA, bulky (111 pts)	4/28	na	81.1 (5)	90.8 (5)
Palayulla kandi, 2022 [37]	India	2010-2019	Prosp. Euronet PHLC1	143	<18	na	na	na	na	OEPA-COPDAC	LR 3 IR 4 HR 6	Inadequate ERA	7/9	13	86.2 (4)	93.5 (4)
Geel, 2024 [63]	South Africa	2016-2022	Prosp.	132 (HIV 17%)	<18	na	na	29	66 (LR 7, IR 27, HR 66)	LR, IR: ABVD HR : ABVD-COPDAC	LR 4 IR 6 HR 6	Inadequate ERA IF, bulky (36 pts)	6/6	4%	83 (2) PFS LR 100 IR 90 HR 79	92.6 (2) LR 100 IR 94 HR 91

Aband.= Abandonement; EFS-RFS= event-free survival-relapse-free survival; ERA= early response assessment; IF= involved field; LR, IR, HR= low-risk, intermediate-risk, high-risk; MC= mixed cellularity; M/F= Male / Female OS= overall survival; PFS= progression free survival; Prosp.=Prospective; Pts=patients; Retrosp.=Retrospective; TG=Therapy group; TRD/Rel= therapy-related death-relapse; Y= years; *ABVD (adriamycin, bleomycin, vinblastine, dacarbazine); COPDAC (cyclophosphamide, oncovin, prednisone, dacarbazine); OEPA (oncovin, etoposide, prednisone, adriamycin)

usually not reported in the published papers. In more recent years, treatment has also been modulated according to ERA with a consequent decrease in the chemo/radiotherapy burden. Based on the ERA evaluation, PET-CT should be the optimal choice, but unfortunately, it is not always available in LMICs where contrast-enhanced CT may be a valid option.[67] With the ERA-based strategies, good results were achieved in India with the ABVD protocol.[35,36] More aggressive schemes (OEPA/COPDAC), according to the European protocols, gave good results but increased the TRD due to the absence of appropriate supportive therapy.[37,61,62] In a very interesting study from South Africa, in high-risk patients, the more toxic OEPA scheme was replaced by ABVD[63] according to a EuroNet-CHL-inspired protocol. This was associated with a 2-year OS of 92.6% and very good results also in high-risk patients (OS 91%).

Key Points.

Unavailability of radiological facilities. Proper staging and response evaluation with PET is often not possible, limiting therapy modulation and potentially leading to overtreatment.

Inconsistent Availability of Chemotherapy Drugs. Treatment cycles are sometimes inadequate due to the omission or substitution of unavailable drugs.

Inadequate supportive treatment. Intensive treatments used in advanced stages in HICs can cause excessive toxicity without proper patient compliance and supportive measures.

Inconsistent Quality of Radiotherapy. Radiotherapy in LMICs, even when available, may not always meet the quality requirements necessary for safe delivery.

Difficulties in solving the Problem of gonadal toxicity. Implementing fertility preservation measures, now widely adopted in HICs, can be difficult or impossible in LMICs.[68,69]

Difficulties in long-term follow-up. Without long-term follow-up, obtaining information on the rate and severity of late treatment effects is particularly challenging in LMICs, making it difficult to modulate HL treatment effectively while maintaining good outcomes.

Which Strategy for LMICs? The Aria Guidelines. The St. Jude Global and the International Society of Pediatric Oncology (SIOP) created the adapted Resource and Implementation Application (ARIA) guidelines to provide pediatric oncologists worldwide with safe and evidence-based guidelines for diagnosing and treating pediatric cancers. The Aria guidelines for childhood HL identify three categories of centers according to resource availability, detailing the minimal requirements for diagnosis, staging, and treatment for each category. Treatment recommendations are tailored according to patient risk groups (low-risk, intermediate-risk, or high-risk) and center resource categories, with more intensive treatments reserved for high-resource centers. Caution is advised in radiotherapy indications, requiring precise quality assessment for safe delivery. Adapted radiotherapy guidelines for LMICs were recently implemented by the Pediatric Oncology in Developing Countries (PODC) committee of SIOP in collaboration with the Pediatric Radiation Oncology Society (PROS).[70]

The novel immunotherapeutic drugs could play an important role in LMICs, especially for high-risk and non-responding patients, offering more effective treatments without increasing chemotherapy-related TRD. However, the primary obstacles remain the costs and availability of these approaches in LMICs.

Conclusions. The so-far reported survival data obtained in LMICs for childhood HL may be considered satisfactory, particularly in early-stage patients. However, these results are obtained in most studies at the cost of a high chemotherapy or radiotherapy burden. The lack of long-term follow-up data means insufficient information on the late effects of these extensive treatments. To improve these results, contrarily to what has been described for aggressive non-Hodgkin lymphoma,[66] the main issue is not to deliver aggressive treatment to all patients, but rather a timely hospital referral and the modulation of treatment based on an accurate evaluation of the extension of the disease and, subsequently, on the response to treatment over time. This "modulation strategy" will need to be adapted to the different realities within LMICs. The availability of diagnostic tools such as PET or only CT, the possibility of safely delivering aggressive treatment for high-risk/not-responding patients, and finally, the availability of affordable radiotherapy may be different between countries and between hospitals in the same country. For these reasons, it is important to implement practical guidelines for the treatment of pediatric HL in LMICs that take into account the heterogeneity of the different realities. The ARIA guidelines for pediatric HL give harmonized, evidence-based general indications that will help pediatric oncologists worldwide. However, only local pediatricians, with their profound knowledge and experience of their specific local contexts, can correctly adapt these guidelines to each unique situation.

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All authors revised and approved the final version of the manuscript.

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