Treatment Outcome and Prognostic Factors in Children and Adolescents with Relapsed and Refractory Classic Hodgkin Lymphoma

Ali N[1], Moussa E[2], Hany Abdelrahman H[1], Hafez H[1], Zaghloul MS[3], Khorshed E[4], Elwakeel M[5], Mehesen M[6], Hammad M[1]

[1] 1Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
2 Department of Clinical Oncology, Elmenofya University, Egypt and Children Cancer Hospital Egypt (57357).
3 Department of Radiation Therapy, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
4 Department of Pathology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
5 Department of Radiodiagnosis, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
6 Department of Nuclear Medicine, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).

Received: 12 November 2023
Accepted: 10 March 2024

Abstract:

Background: Children with Hodgkin lymphoma (HL) achieve high cure rate around 80%, while 20% will ultimately relapse. Identifying reliable risk factors to guide treatment plans at relapse is essential. The purpose of this study is to evaluate the outcome and prognostic factors that affect the outcome of pediatric patients with relapsed and refractory classic HL.

Methods: A retrospective descriptive cohort study included all patients with relapsed and refractory classic HL at the Children's Cancer Hospital of Egypt (CCHE-57357) from July 2007 to December 2018.

Results: One hundred twenty-nine patients were eligible for the study. Male to female ratio was 1.9:1. The median age at relapse was 10.5 years. Time to relapse, stage at relapse, and response to salvage chemotherapy, all had a significant impact on survival outcomes. Overall survival (OS) and event-free survival (EFS) were 38.3% and 25% for those with refractory disease, while for early relapse were 68.0% and 49.6%, and 91.2% and 58.3% for those with late relapse, with p values of 0.001 and 0.001, respectively. At relapse, stage I patients had 100% OS and EFS and declined to 80% and 59.3%, respectively for stage II and 81.7% and 42.3% for stage III. The lowest OS and ES was observed in stage IV disease standing for 68% and 34.5%, respectively, with statistically significant differences for both OS and EFS (P values of 0.001). Patients who achieved negative positron emission tomography-computed tomography (PET-CT) after 2 cycles had OS and EFS of 91% and 70.1%, compared to 70% and 29.3% for those with positive PET-CT (p = 0.001 for both). Multivariate analysis identified two predictors of lower EFS: time to relapse and PET-CT response after salvage therapy. The 5-year OS and EFS rates for the cohort were 76% and 48.1%, respectively

Conclusions: The prognostic factors that have the most significant impact on the survival outcome of pediatric patients with relapsed and refractory classic HL are the time to relapse, and PET CT response after 2 cycles.

Keywords: Hodgkin lymphoma, relapsed, refractory, outcome, prognostic factors.

Authors Information:

Nesreen Ali
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: nesreenalinci@hotmail.com

Emad Moussa
Department of Clinical Oncology, Elmenofya University, Egypt and Children Cancer Hospital Egypt (57357).
email: emad.moussa@57357.org

Hany Abdelrahman
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: hanyrahman@hotmail.com

Hanafy Hafez
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: hanafy.hafez@57357.org

Mohamed S Zaghloul
Department of Radiation Therapy, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: mohamed.zaghloul@57357.org

Eman Khorshed
Department of Pathology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: Eman.Khorshed@57357.org

Madiha Elwakeel
Department of Radiodiagnosis, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: Madeeha.Elwakeel@57357.org

Maha Mehesen
Department of Nuclear Medicine, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: dr.maha_mehesen@yahoo.com

Mahmoud Hammad
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: mahmoud.hammad@nci.cu.edu.eg

Corresponding Author:
Nesreen Ali
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: nesreenalinci@hotmail.com

Introduction:

Since the early 1990s, salvage chemotherapy followed by autologous stem cell transplantation (ASCT) has been the treatment of choice for patients with primary refractory or recurrent classic HL [1, 2]. This treatment strategy can achieve sustained remission in the majority of patients; however, the optimal salvage treatment has yet to be defined in children [3,4,5,6,7].

There have been no randomized studies conducted in children to evaluate the outcomes of those who received salvage chemotherapy followed by a transplant versus those who had salvage chemotherapy followed by consolidation radiation without a transplant [8].

It is still hard to determine if intensive approaches will be advantageous for all patients with relapsed or refractory classic HL or if there is a group of patients who can be treated with a less intensive approach or without a transplant to avoid the side effects that come with intensive approaches. Despite the extensive research on the subject, most studies conducted in this field have included small samples and diverse groups of patients, including those with refractory disease and multiple relapses, making it difficult to determine the optimal plan of care [8].

The European pediatric national data set, which was published in refractory and relapsed HL, showed that a group of patients with late relapse who had non-transplant salvage chemotherapy and radiotherapy had a high rate of survival outcome [8].

Other studies showed that the survival outcome for primary refractory HL patients was inferior, and these patients should receive intensive treatment approaches, including transplants. Research conducted by Saint Jude showed that the initial response to salvage chemotherapy was significant. Children with an incomplete response had a significantly lower survival rate than those with complete responses [9,10].

Therefore, prognostic factors at the time of relapse, including the length of the first remission, the extent of the disease, the previous chemotherapy treatment, the existence of B symptoms, the number of previous chemotherapy cycles, and the response to salvage treatment, have a substantial impact on the survival outcome. Based on these factors, we can classify patients at relapse into risk groups that determine treatment intensity. [8, 11,12].

Therefore, we looked to study the management of pediatric patients with relapsed and refractory classic HL and to evaluate the outcome of this group of patients and all prognostic factors affecting the outcome.

Methods:

This is a retrospective cohort study that included pediatric patients with relapsed and refractory classic HL, treated at CCHE-57357 during the period from July 2007 to December 2018. Approvals from the institutional review board and the Children's Cancer Hospital Egypt Scientific Medical Advisory Committee have been obtained and the study was conducted in accordance with the Good Clinical Practice Guidelines.

Initial disease risk stratification and treatment details:

All data at initial presentation was collected from file records, including patient's characteristics, histopathology, disease stage, risk stratification, B symptoms, bulky disease, and the treatment received including the number of cycles and radiotherapy.

Patients were initially stratified as (1) low risk (LR) if they do not have bulky sites with stage IA or IIA disease. (2) Intermediate risk (IR) for patients with stages IB, IIB, bulky stage IA or IIA, and stage IIIA. (3) High-risk (HR) for patients with stages IIIB and IV [13].

All patients received Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) regimen as front-line chemotherapy; the number of cycles was based on the disease risk stratification as follows: four cycles for LR disease, six cycles for IR disease and eight cycles for HR disease. In 2012, an update was made to the protocol with the aim of minimizing cumulative chemotherapy toxicity to HR patients; thus, the number of cycles was reduced to six cycles.

Combined-modality treatment was the standard of care for patients except in few cases where radiotherapy was omitted. Radiotherapy was given as involved site radiotherapy at a dose of 19.8 grays for initial lymph node sites and 25 grays as a boost for nodes with persistently positive PET CT at the end of treatment.

Risk stratification and treatment details at relapse:

All data at the time of relapse were collected, including patient's characteristics pathology, time to relapse, stage of disease, B symptoms and signs, bulky disease, and response to salvage treatment.

Relapse was categorized as primarily refractory if it occurred within three months of the end of treatment or during therapy, early if it occurred between three and twelve months after therapy ended, or late if it occurred more than twelve months after therapy had ended [8].

Upon relapse, Ifosfamide, Carboplatin, and Etoposide (ICE) or was administered as the first-line of salvage treatment for the majority of our patients. Protocol modification was done in the first line of salvage to the Gemcitabine/Vinorelbine regimen due to the toxicity of the ICE regimen. Individuals who did not respond to the initial line of salvage treatment were administered the second line, depending on the regimen prescribed in the initial line of salvage.

Dexamethasone, high-dose Ara-C, and Platinol (DHAP) was administered as third-line salvage therapy to all patients except a few who received and brentuximab vedotin and Bendamustin. Regarding response assessment upon relapse, all patients underwent PET-CT scans for staging and response assessment. Patients with a Deauville score of 1, 2, or 3 on a PET-CT scan following two cycles of salvage treatment are considered complete responders, and all patients should have achieved a complete response before ASCT.

All patients who experienced a relapse were eligible to receive salvage chemotherapy followed by ASCT and consolidation radiotherapy at a dose of 19.8 Gy for

all relapsed sites. That was the standard of care at our hospital without any risk stratification.

The Euronet pediatric HL group recently published a risk stratification approach for relapsed and refractory classic HL patients considering prognostic factors at relapse and response to salvage chemotherapy (Table 1). According to their findings, patients meeting LR criteria exhibit a reduced likelihood of relapse and may benefit from less intensive chemotherapy, potentially avoiding ASCT. [8] Our objective is to validate this risk stratification model with our patient cohort and assess the outcomes of this LR group with a secondary objective of validating the Euronet risk stratification on our study group.

Table 1: Risk stratification of patients at the time of relapse according to Euronet recommendations [8]

Low Risk	Standard Risk
1-Early relapse after a maximum of 4 cycles of first-line chemotherapy 2-Late relapse after a maximum of 6 cycles of first-line chemotherapy **And all of the following:** 1-Stage at relapse is I-III 2-No previous radiotherapy or relapse only outside the previous radiotherapy field 3-No excessive radiotherapy fields required in salvage 4-Complete response after two cycles of salvage treatment with DS 1,2,3	1-Primary refractory HL 2-Early Relapse after more than four cycles of first-line chemotherapy 3-Stage IV at relapse 4-Relapse in a previous radiotherapy field 5-Relapse that requires radiotherapy in salvage that is considered as having severe toxicity 6- Patients with Low-risk criteria who failed to achieve an adequate response after two cycles of salvage treatment

DS: Deauville score, HL: Hodgkin lymphoma

Statistics:

Estimates of EFS and OS were calculated using the Kaplan-Meier test, and comparisons between groups were made using the log-rank test. P value is generated for every possible combination of factors. OS is the duration from the initiation of treatment until the patient dies of any cause. At the same time, EFS will be computed from the date of achieving remission to the date of progression, relapse, or death, whichever comes first. A P-value of 0.05 or less is deemed statistically significant

Results:

Patients and disease characteristics at initial presentation:

One-hundred twenty-nine pediatric patients with relapsed and refractory classic HL were included. Table 2 includes detailed patient and initial disease characteristics. The median age for patients at diagnosis was 10.5 years (range; 1 to 17.5 years), and the male-to-female ratio was 1.9:1. Two (1.6 %) patients presented with stage I disease, 31 (24%) with stage II, 48 (37.2%) with stage III, and 48 (37.2 %) with stage IV. One hundred and eight patients (84%) received six or more cycles of chemotherapy as first line. The Majority of patients (59.7%) presented with HR disease, 23.3% had IR disease and 17% of patients were LR. Of the whole cohort 76 (59%) underwent combined modality treatment, while 53 (41%) did not receive radiation therapy. Radiotherapy was skipped in 21 patients to avoid added toxicity as they already received a total of 8 cycles of chemotherapy, another 10 female patients had their radiotherapy omitted to avoid late side effects including secondary breast cancer and 22 patients had refractory disease and/or relapsed before they were eligible for irradiation.

Patients and disease characteristics at relapse:

The median age at relapse was 16 years (range 5 to 21 years). All patients had recurrence with the same histopathological diagnosis. Worth noting, the majority (80%) of patients had relapsed at sites that had been previously irradiated. Fifty-seven of patients had late relapse more than a year after the end of treatment (range: 12 to 105 months), 25% had an early relapse (range: 3.2 to 11.5 months), and 18% were primary refractory and had a relapse during treatment or within three months. Fifty percent of patients who experienced relapse had stage IV disease to distant sites including bone marrow, bone, liver and lungs. Only 18% of patients who developed relapse had B symptoms, and 11.6% had bulky disease. First salvage protocol was ICE and gemcitabine/vinorelbine in 67.5% and 32.5% of patients, respectively. All disease characteristics at relapse are presented in Table 3.

The standard treatment following relapse consisted of standard-dose chemotherapy, followed by high-dose chemotherapy, and autologous stem cell transplant (ASCT). Eighty-three (64.5%) patients underwent BMT, whereas 46 (35.5%) did not undergo stem cell transplant; of whom 27 patients had progressive diseases after salvage therapy and were considered palliative, 3 patients declined; and 2 patients failed to collect the required number of Cd34+ stem cells. Lastly, another 14 patients were treated with chemotherapy and radiotherapy due to the localized nature of the disease at relapse.

Table 2: Disease characteristics of the whole cohort at diagnosis

Characteristics	N	Percentage
All	129	100%
Gender		
Male	85	65.9%
Female	44	34.1%
Age Groups		
0 - ≤5 years	10	8%
>5 - ≤10 years	45	35%
>10 - ≤15 years	44	34%
>15 years	30	23%
Bulky disease		
No	91	70.5%
Yes	35	27%
Not applicable	3	2.5%
Pathology		
Lymphocyte depleted	5	3.9 %
Lymphocyte rich	5	3.9 %
Mixed cellularity	43	33.3 %
Nodular sclerosis	71	55 %
Unknown	5	3.9%
Stage of disease		
Stage I	2	1.6%
Stage II	31	24%
Stage III	48	37.2%
Stage IV	48	37.2%
B-Symptoms		
No	54	41.9%
Yes	75	58.1%
Initial risk classification		
HR	77	59.7%
IR	30	23.3%
LR	22	17%
Patients received radiotherapy on upfront treatment		
No	53	41%
Yes	76	59%
Number of cycles of chemotherapy given on upfront treatment		
4 cycles	21	16%
6 cycles	84	65%
8 cycles	24	19

HR: high risk, IR: intermediate risk, LR: low risk

Table 3: Disease characteristics at relapse

Characteristics	N	Percentage
All	129	100%
Time to relapse		
Refractory	24	18.6 %
Early	32	24.8 %
Late	73	56.6 %
PET-CT, after two cycles, salvage		
Negative	71	55.0 %
Positive	51	39.6 %
NA	7	5.4%
Stage at relapse		
Stage I	12	9.3%
Stage II	25	19.4%
Stage III	28	21.7%
Stage IV	64	49.6%
B- Symptoms at relapse		
No	106	82%
Yes	23	18%
Bulky disease at relapse		
No	114	88.4%
Yes	15	11.6%
1st line salvage regimen		
ICE	87	67.5%
Gemcitabin/Vinorelbine	42	32.5%
Number of salvage lines		
One salvage line	65	50%
Two salvage lines	49	38%
Three salvage lines	15	12%
BMT		
Yes	83	64.5%
No	46	35.5%
Risk stratification at relapse as per Euronet pediatric HL group		
LR	28	22%
SR	101	78%

PET-CT: Positron emission tomography–computed tomography, ICE: (Ifosfamide, Carboplatin, Etoposide), NA: not applicable, BMT: bone marrow transplantation, LR: low risk, SR: standard risk.

Table 4: OS and EFS in correlation to different prognostic factors at time of relapse

Prognostic factors	5 years EFS	P value	5 years OS	P value
Time to relapse				
Refractory	25%		38,3%	
Early relapse	49.6%	**0.001**	68%	**0.001**
Late relapse	58.3%		91.2%	
PET CT response after 2 cycles of salvage line				
Negative	70.1%	**0.001**	91%	**0.001**
Positive	29.3%		70%	
Stage at relapse				
Stage I	100%		100%	
Stage II	59.3%	**0.001**	80%	**0.001**
Stage III	42.3%		81,7 %	
Stage IV	34.5%		68%	
The previous burden of chemotherapy				
patients received 4 cycles	68.9%		90%	
patients received 6 cycles	43.8%	0.18	73.5%	**0.04**
patients received 8 cycles	45.8%		75%	
Bulky disease at the time of relapse				
No	49.6%		77.7%	
Yes	18.2%	0.1	63.6%	0.09
B symptoms at the time of relapse				
No	49.6%	0.45	79%	0.59
Yes	44.7%		66.1%	

OS: overall survival, EFS: event-free survival

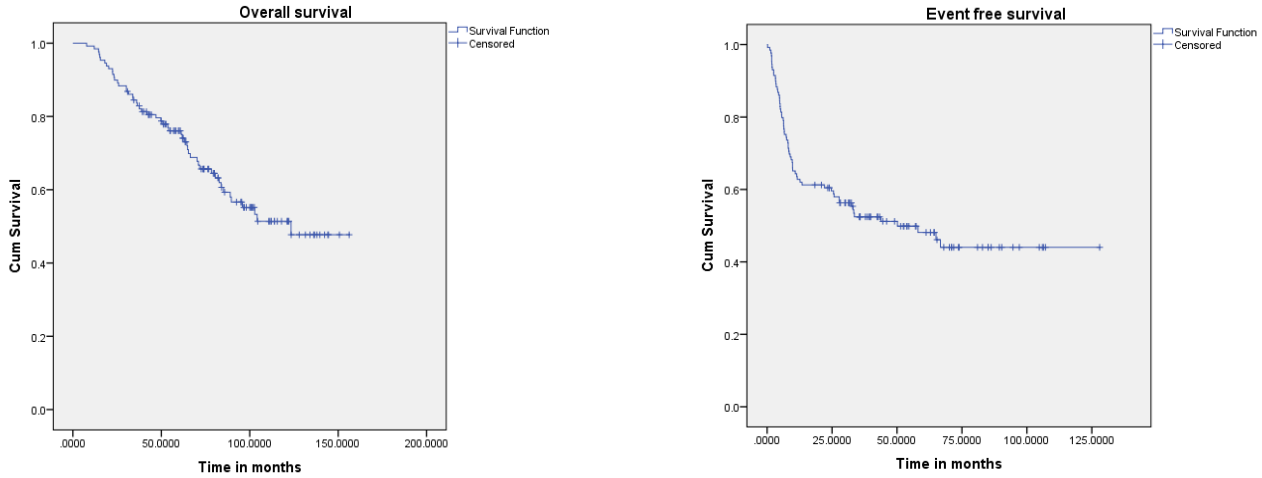

Figure 1
A: Overall survival for the relapsed patients
B: Event-free survival for the relapsed patients

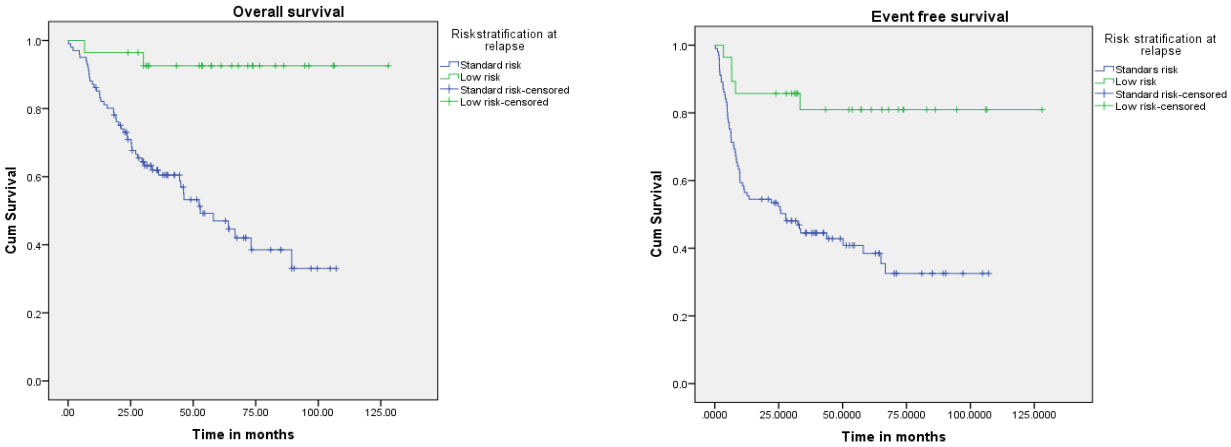

Figure 2

A: Overall survival for the relapsed patients according to risk stratification at relapse (Low risk, Standard risk)
B: Event-free survival for the relapsed patients according to risk stratification at relapse (Low risk, Standard risk)

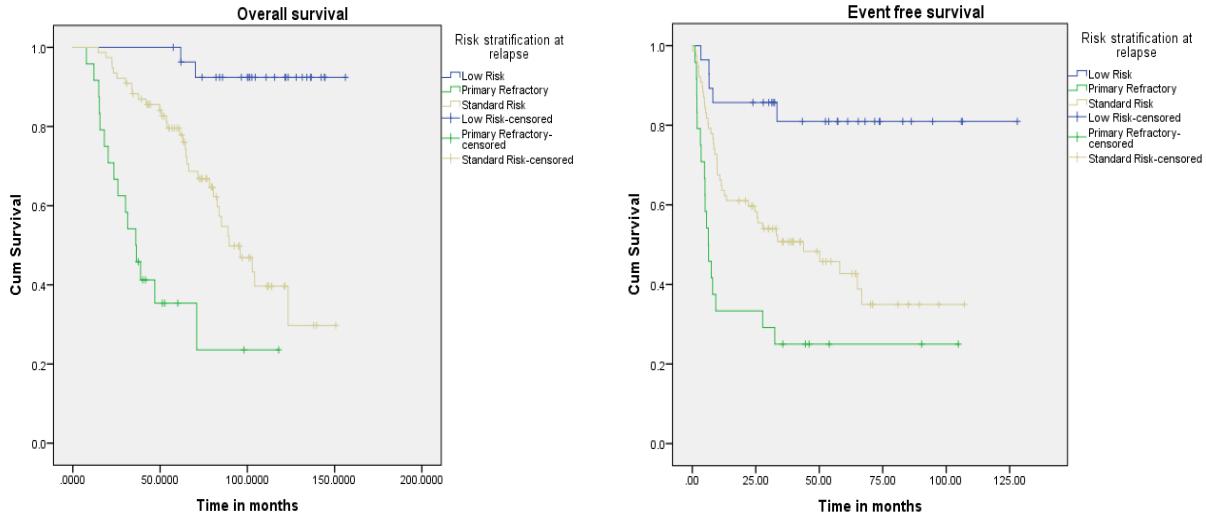

Figure 3

A: Overall survival for the relapsed patients according to risk stratification at relapse (Low risk, Standard risk, Primary refractory)
B: Event-free survival for the relapsed patients according to risk stratification at relapse (Low risk, Standard risk, Primary refractory)

Survival outcomes and prognostic factors at relapse:

The 5-year OS and EFS rates for the whole cohort were 76% and 48.1%, respectively (Figure 1). The survival rates for patients experiencing relapse differed was based on different prognostic factors at the time of relapse. Regarding the stage of the disease at relapse, those with stage I disease had both OS and EFS rates of 100%. However, for individuals with stage II disease, the rates dropped to 80% for OS and 59.3% for EFS. Similarly, for those with stage III disease, the rates were 81.7% for OS and 42.3% for EFS. Finally, for those with stage IV disease, the rates further decreased to 68% for OS and 34.5% for EFS. P values of 0.001 for both OS and EFS indicate that the statistical analysis revealed significant differences. The OS and EFS rates for patients who received 4 cycles of chemotherapy in the first line were found to be 90% and 68.9%, respectively. In comparison, patients who received 6 cycles had rates of 73.5% for OS and 43.8% for EFS, while those who received 8 cycles had rates of 75% for OS and 45.8% for EFS. The p-values associated with these comparisons were 0.04 and 0.18, respectively.

The OS and EFS rates were 79% and 49.6% for those exhibiting negative B symptoms, respectively. In contrast, those with positive B symptoms had OS and EFS rates of 66.1% and 44.7%, respectively. The corresponding p-values for these comparisons were 0.59 and 0.45, respectively. The OS and EFS rates were 77.7% and 49.6% for individuals with non-bulky disease, respectively. In comparison, those with bulky disease had OS and EFS rates of 63.6% and 18.2%, respectively. The corresponding p-values for these comparisons were 0.09 and 0.1, respectively. After completing two cycles of salvage chemotherapy, a PET-CT scan was conducted to evaluate the first response. This step is regarded as the second most crucial after initiating salvage chemotherapy. The PET-CT scan yielded negative results in 60% of cases and positive results in 40%. The OS and EFS rates among patients with a negative PET-CT scan were 91% and 70.1%, respectively. In contrast, patients with positive PET-CT scan had lower OS and EFS rates of 70% and 29.3%, respectively ($p < 0.001$ for both comparisons). Table 4 described the prognostic factors related to OS and EFS for the studied patients. The results of multivariate analysis showed that the duration of remission and response to salvage chemotherapy are significant prognostic markers that might guide treatment strategies during relapse.

We categorized our study patients according to the risk stratification provided by the Euronet pediatric HL group for the purpose of external validation, we observed a 5-year OS rate of 92.6% (CI: 82%–100%) for the LR group, in contrast to 47% (CI: 35.2%–58.76) for the SR group, with a significant p-value of 0.001. Similarly, the 5-year EFS rate for LR patients was 81% (CI: 65.7%–96%), while it was notably lower at 38.4% (CI: 27.6%–49%) for those with SR criteria, also with a p-value of 0. 001.(Figure 2).

After conducting a subsequent analysis and delineating primary refractory cases as a distinct group, the outcomes varied. The OS rates were 92.6% for LR, 54.1% for SR, and notably lower at 35.4% for primary refractory cases, with a statistically significant p-value of 0.001. In terms of EFS, LR patients demonstrated a favorable rate of 81%, while SR patients exhibited a lower rate of 42.7%, and primary refractory cases showed the least favorable outcome at 25%. (Figure 3).

Discussion:

The study reported the outcome of 129 pediatric patients with relapsed and refractory classic HL. In pediatric patients, the standard treatment approach involves the use of conventional chemotherapy, followed by high-dose chemotherapy and ASCT. However, the evidence supporting this approach is primarily based on randomized adult trials, showing that high-dose chemotherapy and ASCT carries better outcomes in relapsed patients. Unfortunately, there is a lack of randomized trials in children to confirm these findings. The use of high-dose chemotherapy followed by ASCT has increased in patients with relapsed or refractory classic HL, where standard chemotherapy offers small chance of cure. [8]

Several pediatric studies have demonstrated that a subset of patients can be effectively treated without requiring high-dose chemotherapy and ASCT. Moreover, various prognostic variables serve as indicators for the prognosis of patients diagnosed with relapsed HL [8, 9]. These prognostic variables encompass specific disease features at diagnosis, including gender, age, pathology, stage, B-symptoms, tumor size, and laboratory test results. During relapse, a number of risk factors may also be evaluated, including the duration of remission, stage of disease, presence of B-symptoms, the occurrence of extra-nodal disease, and recurrence in an area that had been irradiated before [8].

Despite the identification of several prognostic factors, the literature presents inconsistent evidence for some of them. This variability can be attributed to limitations such as small sample sizes and retrospective study designs. It's also hard to compare patient groups from different studies because the diseases and treatment regimens are different. This makes it even harder to figure out what these factors signify. As a result, multivariate analysis often gives different results [14].

Neither pediatric nor adult populations have established prognostic criteria to facilitate personalized salvage therapy plans. The ST-HD-86 study, the largest trial on children with relapsed and refractory classic HL, showed that salvage treatment can be adjusted based on risk. The study found subgroups whose prognoses were much better or worse than those of the average patient [15].

In the current study, the most significant prognostic factors for OS and EFS were time to relapse, stage at relapse, previous chemotherapy burden, and response to salvage treatment. The OS and EFS were 38.8% and 25% for patients with refractory disease, 68.0% and 49.6% for patients with early relapse, and 91.2% and 58.3% for patients with late relapse (P= 0.001 and 0.001, respectively). This was consistent with the

findings of the French SFCE and the UK HD 3 study, which reported a dismal prognosis for refractory patients, with EFS at 35% and OS at 48%. Therefore, patients with HL who relapse after a period of initial remission have an improved prognosis. [16,9]

In this study, the OS rate for patients who received 4 cycles of chemotherapy as initial treatment was 90%, but it was 73.5% for those who received 6 cycles and 75% for those who received 8 cycles. The statistical analysis yielded a p-value of 0.04, indicating a significant difference among the groups. This finding aligns with previous research indicating that a greater initial chemotherapy load is associated with a worse prognostic outcome. Specifically, patients who had more than four cycles of chemotherapy in the first line experienced a lower disease-free survival rate upon recurrence in comparison to those who got less than four cycles of chemotherapy. [15]

We observed on this study that the OS and EFS rates for patients with a negative PET-CT were 91% and 70%, respectively, compared to 70% and 29.3% for those with a positive PET-CT (p = 0.001 and 0.001, respectively). Our findings confirmed the significance of the response to salvage therapy. This was consistent with another study done in St. Jude Children's hospital indicating that initial response to salvage chemotherapy was highly significant, with a 5-year OS of 17% in children with inadequate response compared to 98% in children with excellent response (P value.0001). At the time of relapse, the response to salvage therapy is crucial and should be considered in risk stratification. [10,8] Time to relapse and PET-CT response after two cycles of salvage therapy were identified by multivariate analysis as the two predictors of poor EFS in our patient cohort.

We stratified our study patients into groups based on the Euronet risk stratification upon relapse. We observed within the LR group, an impressive OS rate of 92.6% and an EFS rate of 81%. Our findings corroborate the validity of the risk stratification model, emphasizing that patients with stages I-III, late relapse or early relapse, who received a maximum of four frontline cycles and achieved complete response following two salvage chemotherapy cycles, exhibit reduced likelihood of relapse, as reported by Daw et al. [8]. Such patients may be eligible for less intensive treatment without the need for ASCT. However, it is important to note that the validation of the stratification model remains inconclusive, and further investigation through a prospective cohort study, specifically focusing on patients with LR criteria and their allocation to less intensive treatment without ASCT, is warranted. [8,17]

The group of patients with primary refractory HL had an OS of 38.3 and an EFS of 25%. This was consistent with the UK HD3 Study, which stated that primary refractory HL was the only significant factor correlated with a lower OS. [9] In adults, it was reported that patients with primary refractory disease who received salvage chemotherapy without ASCT had significantly low OS rates. [10.18,19].

The DAL/GPOH-HD Study trial has showed that patients with primary refractory HL who were treated with salvage chemotherapy and radiotherapy had a 41% DFS and a 51% OS after ten years. Therefore, conventional salvage chemotherapy is ineffective in patients with primary refractory classic HL, and there is a limited window of opportunity for intensified therapy to affect the progression of primary refractory disease. Hence, this patient population needs to be treated with intensive chemotherapy and ASCT. [15,9]

Conclusion:

In conclusion, our study's findings indicate the presence of specific favorable prognostic factors at the time of relapse that significantly influence survival outcomes. These factors include time to relapse, stage of relapse, previous burden of chemotherapy, and response to salvage treatment. A subset of patients exhibiting these favorable prognostic factors at the time of relapse demonstrates a notably high survival rate. Therefore, further investigation is warranted, as these patients may benefit from a less intensive treatment approach. The treatment of patients with refractory and relapsed classic HL should incorporate an assessment of pre-salvage prognostic factors in addition to evaluating the response to salvage therapy. This comprehensive approach enables the stratification of patients into different risk groups.

List of abbreviation

ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine.
ASCT: Auto stem cell transplant
CCHE: Children Cancer Hospital of Egypt
CHL: Classis Hodgkin Lymphoma
CR: Complete response
DHAP: Dexamethasone, high dose Ara C, and platinol.
EFS: Event-free survival
HR: High Risk
ICE: Ifosfamide, carboplatin, etoposide
IR: Intermediate Risk
LR: Low Risk
OS: Overall survival
PBSC: peripheral blood stem cell
PD: Progressive disease
PET-CT: Positron emission tomography-computed tomography

Conflict of interest:

The authors confirm that they have no conflicts of interest to waive.

Authors contributions

NA: concept of the study, data analysis, data interpretation, and writing the manuscript. EM, HA, HH, and MH assisted in analyzing the data and drafted the manuscript. MZ participated in the revision of radiotherapy details and interpretation of the data, EK worked in the revision of pathology and data collection, MW and MM contributed to the revision of images and

PET-CT data and data collection, and all authors approved the manuscript.

References:

1. Seyfarth B, Josting A, Dreyling M, et al. Relapse in common lymphoma subtypes: salvage treatment options for follicular lymphoma, diffuse large cell lymphoma and Hodgkin disease. Br J Haematol 2006,133:3-18.
2. Magagnoli M, Castagna L, Balza-rotti M, et al. What is the best option to cure patients with resistant/relapsed Hodgkin's disease? Current stem cell research and therapy. 2006;1(3):419-24
3.Sureda A, Arranz R, Iriondo A, et al. Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea Spanish Co operative Group Autologous stem cell transplantation for Hodgkin's disease: results and prognostic factors in 494 patients from the GrupoEspanol de Linfo mas/Trans de Medula Osea Spanish cooperative group. J Clin Oncol 2001;19:1395-404.
4.Brice P, Divine M, Simon D, et al. Feasibility of tandem autologous stem-cell transplantation in induction failure or very unfavorable relapse from Hodgkin's disease. Ann Oncol 1999;10:1485-8.
5. Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologus stem cell rescue for patients with Hodgkin's disease in first relapse after chemo - therapy: results from the EBMT. Bone Marrow Transplant 1997; 20: 745-52.
6. Lazarus HM, Rowlings PA, Zhang MJ, et al. Autotransplants for Hodgkin's disease in patients never achieving remission: a report from the Autologous Blood and Marrow Transplant Registry. J Clin Oncol 1999;17:534-45.
7. Moskowitz CH, Kewalramani T, Nimer SD, et al. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy proven primary refractory Hodgkin's disease. Br J Haematol 2004;124:645-52.
8. Daw S, Hasenclever D, Mascarin M, et al. Risk and Response Adapted Treatment Guidelines for Managing First Relapsed and Refractory Classical Hodgkin Lymphoma in Children and Young People. Recommendations from the EuroNet Pediatric Hodgkin Lymphoma Group. Hema Sphere, 2020;4:1.
9. Shankar A, Hayward J, Kirkwood A, et al. Treatment outcome in children and adolescents with relapsed Hodgkin lymphoma - results of the UK HD3 relapse treatment strategy. Br J Haematol. 2014;165: 534–544.
10. Metzger ML, Hudson MM, Krasin MJ, et al. Initial response to salvage therapy determines prognosis in relapsed pediatric Hodgkin lymphoma patients. Cancer. 2010;116:4376–4384.
11. Josting A, Rueffer U, Franklin J, et al. Prognostic factors and treatment outcome in primary progressive Hodgkin's lymphoma: a report from the German Hodgkin Lymphoma Study Group. Blood 2000;96:12806.
12. Yuen AR, Rosenberg SA, Hoppe RT, et al. Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent or refractory Hodgkin's disease. Blood 1997;89: 814-22.
13. Rosenberg SA. Report of the committee on the staging of Hodgkin's disease. Cancer Research, (1966) 26, 1310.
14. Lohri A, Connors JM. Identification of risk factors in patients treated for first relapse of Hodgkin's disease. Leuk Lymphoma 1994; 15: 189–200.
15. Schellong G, Dorffel W, Claviez A, et al. Salvage therapy of progressive and recurrent Hodgkin's disease: results from a multicenter study of the Pediatric DAL/GPOH-HD Study Group. J Clin Oncol. 2005; 23:6181–6189.
16. Bonfante V, Santoro A, Viviani S, et al. Outcome of patients with Hodgkin's disease failing after primary MOPP- ABVD. J Clin Oncol. 1997;15:528–534.
17.Longo DL, Duffey PL, Young RC, et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. J Clin Oncol. 1992;10:210–218.
18. Gorde-Grosjean S, Oberlin O, Leblanc T, et al. Outcome of children and adolescents with recurrent/refractory classical Hodgkin lymphoma, a study from the Société Française de Lutte contre le Cancer des Enfants et des Adolescents (SFCE). Br J Haematol. 2012;158:649–656.
19. Daw S, Wynn R, Wallace H. Management of relapsed and refractory classical Hodgkin lymphoma in children and adolescents. Br J Haematol. 2011;152:249–260.
20. Alison M. Friedmann, Julie A. et al. Relapse After Treatment of Pediatric Hodgkin Lymphoma: Outcome and Role of Surveillance After End of Therapy. Pediatr Blood Cancer 2013;60:1458–1463.