


**Addis Ababa University**

**College of Health Sciences**

**School of Medicine**

# Echocardiographic Evaluation of Cardiac Abnormalities in Pediatric Hodgkin Lymphoma Patients and Survivors Following Anthracycline Therapy at Tikur Anbessa Specialized Hospital from 2016-2025 GC:

**A cross-sectional study**

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Investigator- Hiyaw Abebe, MD, Pediatric Hematology Oncology Fellow

Advisors

- Haileyesus Adam, Assistant Professor, Pediatric Hematology-Oncologist
- Helen Mintesinot, Assistant Professor, Pediatric Cardiologist
- Hayat Ahmed, Assistant Professor, Pediatric Cardiologist

**A thesis paper submitted in partial fulfillment of the requirement for the subspeciality in Pediatric Hematology Oncology**

**December, 2025**

## Acknowledgment

First of all, I want to thank God in making this project possible.

I have received an invaluable support, guidance and leadership from my advisors of the Pediatric Hematology-Oncology and Pediatric Cardiology units. The three Assistant professors gave me relentless constructive criticism that helped refine the both the conception and implementation processes.

Financial and Logistic assistance from Tesfa Addis Pediatric Cancer Center Organization (TAPCCO) and the ASLAN Project has been vital to the entire process of the proposal development, patient enrollment, data analysis, thesis defense and final write up preparation. Their sustained support towards pediatric cancer care over the past decade has brought about immense improvement.

A special appreciation goes to the Pediatric Hematology Oncology unit. The under equipped Ethiopian cancer care is a relatively new field of expertise and showed a boundless change in the survival and comfort of patients that used to be labeled incurable only a few years ago. The consistently increasing positive pattern made this research that is mainly done survivors possible. It also encourages future improvements and more sophisticated studies.

I would like to acknowledge all the involved clinical and non-clinical professional that were involved in the process of this study. Their team work, appreciation and positivity made the making a memorable moment.

I am certain that this project could not have been possible without the collective effort of many more participants that I could not possibly fit into my one-page acknowledgment. I would like to say thank you for everyone that had a positive impact into the completion of this study.

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# List of Acronyms

**E/A** — Ratio of Mitral E-wave to A-wave

**E′ (e-prime)** — Mitral Annular Early Diastolic Velocity (TDI)

**E/E′** — Ratio of Mitral E-wave to E′ (estimate of filling pressures)

**EF** — Ejection Fraction

**FS** — Fractional Shortening

**GLS** — Global Longitudinal Strain

**HR** — Heart Rate

**ICU** — Intensive Care Unit

**IVSd** — Interventricular Septal Thickness in Diastole

**LA** — Left Atrium

**LPA** — Left Pulmonary Artery

**LV** — Left Ventricle

**LVIDd** — Left Ventricular Internal Diameter in Diastole

**LVSs** — Left Ventricular Systolic Size

**MPA** — Main Pulmonary Artery

**MV** — Mitral Valve

**MV-A** — Mitral Inflow A-wave Velocity

**MV-E** — Mitral Inflow E-wave Velocity

**PV** — Pulmonary Valve

**PWDd** — Posterior Wall Thickness in Diastole

**PWDs** — Posterior Wall Thickness in Systole

**RPA** — Right Pulmonary Artery

**RV** — Right Ventricle

# Abstract

## Background

The overall survival of Pediatric Hodgkin Lymphoma has increased tremendously in recent years in both low- and higher-income countries. This trend has been possible by the main background therapeutic agents which are anthracyclines. These group of drugs prove to be highly effective at the cost of both short- and long-term treatment side effects. Cardiac dysfunction is one of the main treatment side effects and can happen in acute and late timeframes. Majority of cardiac dysfunction data come from higher income countries with limited evidence from low- and middle-income countries. In Ethiopia, advanced follow-up modalities and structured patient follow-up is constrained. This limitation requires high quality information yet local data is scarce.

## Objectives

The purpose of this study is to assess the cardiac effects of anthracycline-based chemotherapy using echocardiography in pediatric Hodgkin lymphoma patients and survivors treated at Tikur Anbessa Specialized Hospital.

## Methods

We conducted a hospital based cross-sectional study of Pediatric Hodgkin Lymphoma patients and survivors at Tikur Anbessa Specialized Hospital between 2016-2025 GC. The Medical Record Numbers of the patients were retrieved from paper and electronic Health Management Information System. The medical charts were retrieved. Patient phone numbers were then taken from the medical charts and patients were contacted and informed on the intended study and appointed for their respective dates.

Demographic and clinical data including age, sex, weight, height, body surface area, Stage, comorbidities, treatment details and additional therapies such as radiotherapy were recorded from their medical charts. Previous echocardiographic evaluations, including baseline and follow-up data, were reviewed if available, but patients were enrolled regardless of the presence of prior echocardiographic records. Current history and physical examinations were also done once the patients arrived at the evaluation site.

An echocardiographic evaluation was provided for all participants using a standardized protocol. The echocardiograms were conducted by pediatric cardiologists blinded to the patients' characteristics and outcomes to ensure objectivity. Each cardiologist was labeled as Pediatric Cardiologist 1 and 2 to facilitate comparative analysis of resultant cardiac abnormalities. The echocardiographic parameters assessed includes 2D measurements, M-mode measurements and Doppler measurements. Additional indices like the Myocardial Performance Index (Tei Index), isovolumic contraction and relaxation times,

ejection time, and right ventricular function using TAPSE were also recorded. Pulmonary parameters, including the main, left, and right pulmonary artery dimensions were also assessed. Echocardiography interpretations using age and Body Surface Area were done using Z-scores, wherever applicable. Attributes of the documented patient details and imaging results were assessed for the prevalence of cardiac dysfunction and possible associations between the dependent and independent variables using univariate and multivariable logistic regression.

## Results

There were 500 pediatric Hodgkin lymphoma medical record numbers identified in HMIS, 239 charts were available and 228 had phone numbers. Exclusions were made due to non-functional numbers (80), no answer (16), refusal (21), and absence after appointment (16), resulting in 86 participants. They completed a study echocardiogram in 2025. None had a documented baseline echocardiogram, and only 13/86 (15.1%) had at least one previous echocardiogram (and 3/86 [3.4%] had a second prior echo). At diagnosis, 24.4% (21/86) were <5 years, 64.0% (55/86) were 5–11 years, and 11.6% (10/86) were >12 years. Most were male (94.2% [81/86]). Stage distribution showed Stage I- 7.0%, II- 32.6%, III- 34.9%, IV- 19.8%. 55.8% were high risk. All patients received anthracyclines (ABVD 85, OEPA 1), with cumulative dose 100–250 mg/m² in 83.7% and >250 mg/m² in 15.1%; about one quarter received radiotherapy. The primary outcome, LV systolic dysfunction, was detected in 10/86 (11.6%). At least one other echocardiographic abnormality occurred in 78/86 (90.0%). Univariate logistic regression showed no statistically significant determinants and multivariable models were unstable due to few events and sparse categories.

## Conclusion

LV systolic dysfunction was identified in 11.6% of the patients and survivors, while 90% had at least one other echocardiographic abnormality. Baseline and longitudinal echocardiographic surveillance were largely absent, and determinant analysis was underpowered to identify independent predictors. These findings support the need to implement a feasible, standardized, risk-adapted cardiac monitoring pathway for pediatric HL patients receiving anthracyclines in this setting.

# Introduction

## Background

Children and adolescent Hodgkin lymphoma has the highest cure rates with a peak at the age of adolescence and early adulthood years. It is evident that there is a recent increment in the overall incidence and prevalence globally (1) In comparison, the high percentage of patients is coupled with a decreasing magnitude of mortality. This is mostly attributed to the advances made in early diagnosis and treatment. Its younger age predilection coupled with a higher survival rate gives rise to a higher amount of short and long-term complications. (2)

There is a marked difference in the trends of Sub-Saharan African and global childhood cancer prevalence. This study shows that there is a higher prevalence seen in higher income countries, compared to other countries like Uganda. The reasons for this were likely the available of improved diagnostic and treatment tools. In Kenya, greater than 60% children are diagnosed at higher stages showing similar trends and explanations. (3)

It has an age of onset of that is commonly seen in early adulthood. The second rise is seen in late adulthood, these two combined give an average age of around thirty-nine years. The diagnosis is common in teenagers but less common in ages below five years. (4)

American Cancer Society states that based on a 5-year survival rate analysis done for Hodgkin lymphoma shows a percentage of 89% for all combined SEER stages (Surveillance, Epidemiology, and End Results). Localized disease has 93% 5-year Relative Survival Rate followed by 95% and 83% for regional and distant disease respectively. (5)

Chemotherapy and radiation therapy are the main treatment strategies for Hodgkin Lymphoma. Patients at lower stages or diagnoses receive fewer cycles of ABVD to be given monthly. This strategy takes into account the possible outcome of toxicities and tries to lower them by choosing lower number drug cycles. (6)

No matter what the outcome of patients is cardiotoxicity affects quality of lives. Doxorubicin use causes it among its other toxicities. Confirmation is made by depending signs of heart failure subsequently backed by ejection fraction drop. Most recent cut point is a LVEF decrement of greater than 10% or a final number below 53 percent is used. The resultant cardiotoxicity

increases as the dose increases. Increasing doses of anthracycline based on calculation bring about exponentially increasing occurrence of cardiac dysfunction. Drug dosage is one of the associated factors that increase toxicity, examples are very young old very old patients (younger than five and older sixty-five years). Other factors that might worsen or cause toxicity are radiation therapy given especially to the chest, underlying cardiac disease and risk factors. (7)

There seems to be a slow shift of the survivor focus from adult to the currently growing pediatric population. The reason for this is the earlier occurrence of the pediatric Hodgkin lymphoma together with improved patient care giving rise to decades of survivor years and more long-term complications. (8)

In Sub-Saharan Africa, not much is documented about the presence of anthracycline cardiotoxicity and associated risk factors. In addition, most centers lack a structured guideline to follow patients and survivors with. (9)

There is a general lack of usable data on Ethiopia's cancer patients and resultant cardiac dysfunction. Our country's relatively new cancer care is also hampered by the presence of limited resources. The intention of this study is to assess the cardiac effects of anthracycline-based chemotherapy in pediatric HL patients and survivors treated at Tikur Anbessa Specialized Hospital. The observations of this study will in turn contribute vital data to inform local clinical practice and survivor care strategies in the national and international setup.

## Statement of the problem

Recent Hodgkin Lymphoma treatment has improved in achieving survival through the use of risk based multimodal therapy that uses the anthracycline doxorubicin as its main backbone. A downside for this achievement is the emergence of survivors with long term complications (10)

The use of anthracyclines is often restricted due to their well-established toxicity profiles. This fact makes the use of this drug classes much less when compared to their effectiveness.

Significant amount of morbidity and mortality is caused by their resultant cardiotoxicity. A significant risk factor is the drug cumulative dose causing acute, early onset and late onset cardiotoxicities. The spectrum might range from reversible early subclinical toxicity to an irreversible late onset toxicity. (11)

This strategy of early detection and continuous follow-up is not regularly implemented in Ethiopia and no studies have yet been done are mandatory to identify cardiotoxicity, even though it is essential in avoiding further damage and is possibly cardio protective. (12)

The above evidences show that serious threat is posed on the safety of pediatric patients and survivors especially in the presence of toxicities that are not well diagnosed and well-treated. In our country, there are no well-structured and preset patients following tools, worsening an avoidable problem affecting individuals and communities. In setups that are similar to Ethiopia, under detected and under followed subtle cardiac dysfunctions may affect quality of life and life expectancy.

There is shortage of reliable healthcare evidence regarding short and long-term cardiac outcomes, even if these group of drugs are used widely. Deprived of routine cardiac monitoring or established follow-up protocols, many survivors may suffer from undetected and unmanaged cardiac dysfunction. This gap in local evidence hampers timely interventions and poses a substantial hazard to survivor well-being, highlighting the crucial requirement for context-specific research that will help in national strategies.

## Rationale of the study

There is an increasing survival rate of Hodgkin Lymphoma. However, there is a concern for long-term treatment-related complications that can be attributed to recent pediatric oncology improvements in have led to enhanced survival. Anthracyclines are a highly effective group of drugs with a propensity to cause cardiotoxicity that is more pronounced in extremes of age. (13) Subtle cardiac abnormalities may usually worsen through time and progressive treatment causing cancer unrelated deaths, which is why primary diagnosis is a crucial first step. (14)

A few Sub-Saharan Africa studies have started documenting cardiovascular toxicities in childhood cancer survivors, however information from Ethiopia continue to be virtually non-existent. (15)

Our country lacks essential data regarding the prevalence of treatment induced toxicity and there is no structured screening guideline integrated into the patient treatment and survivor follow-up guidelines. Local research is essential in framing a basic understanding of the burden of this

toxicity in order to guide care. The findings from this study will support clinicians and policymakers in formulating follow-up strategies.

This study aims to produce vital local data to inform clinical decision-making and long-term cardiac monitoring in Tikur Anbesa Specialized Hospital and Ethiopian pediatric oncology.

## Review of Related Literature

Anthracycline based chemotherapy use in Pediatric Oncology has brought a revolution in the survival pattern of childhood cancers, including Hodgkin Lymphoma. But the long-term toxicities continue to be a significant concern. This is particularly significant in low-income settings where treatment and follow-up guidelines are often insufficient. The survival profiles are visibly higher in countries when there are better health care setups that guarantee improved patient follow-ups. (16)

The presence of lower quality and access to heath care in lower income countries greatly influences the marked difference as compared to better setups. An extensive difference is evident between mortality rates of these two entities due to disparities including socioeconomic status, access to health care, distance to health care facility, cultural factors and health literacy. (17)

In Sub-Saharan Africa, integrated treatment of patients with chemotherapy and radiotherapy is limited due to inadequate access. In addition, there are additional living conditions affecting this region such as chronic viral infections and protozoal infections that highly prevalent in the population. The presence of these cofounders lowers the quality of health of inhabitants, in turn increasing the gap observed. (18)

Tikur Anbessa Specialized Hospital has the biggest and oldest cancer treatment center in the country and serves a vast number and diversity of patient diagnoses, among which is Hodgkin lymphoma. However, resource constraints have limited the hospital's ability to implement comprehensive survivorship care, leaving many patients at risk for late effects such as cardiotoxicity.

A type of bacteria called Streptomyces peucetius were first used to isolate anthracyclines from and use as chemotherapy drugs. (19) A wide range of other pediatric cancers can be treated with these groups of drugs. Some examples are leukemias, Lymphomas, bone tumors and Wilm’s tumor. The above reason makes this drug group among essential drug list. (20) Anthracyclines have a wide activity against a list of neoplasm in children. (21) A downside for their usage is their high resultant toxicities, cardiac problem being the main one. (22) This untoward effect is worsened by the improved overall survival of cancer patients as reported in the 2023 Cancer Statistics. (23)

It has first been described in 1967 that the pathognomonic indicator of the anthracycline daunomycin toxicity was a hypokinetic cardiomyopathy gradually generating cardiac failure. (24) To this day, the pathways of the cardiotoxicity caused by anthracyclines is not entirely understood. (13) There are a number of proposed mechanisms such as DNA intercalation, Topoisomerase II mediated cytotoxicity, reactive oxygen species and DNA adduct formation. (13) (25) Whatever the mechanism of action of action of these drugs is, they ultimately cause poor cardiac function later causing stiffness, rhythm abnormalities and compromised cardiovascular system.(26)

A practical way of cardiotoxicity classification is based on timing. It can be labeled acute when it happens a week after drug initiation. When it happens up to a year after initiation, we say it is early onset. Late onset is when changes happen after one year (26)(27) In some instances, acute onset cardiotoxicities happen earlier even after just one dose but are reversible. The timing is often flexible and can include those up to two weeks (27)(28) The latter two occur much later and are usually irreversible, having worse prognosis of the three. (28) The principal form of cardiotoxicity which is the most frequent is the early onset subtype. It is the most clinically prevalent usually presenting with dilated and hypokinetic cardiomyopathy culminating in cardiac failure. (27) People often think that cardiotoxicity effects necessarily start with the first dose. Hence, raising the notion that classification of cardiotoxicities is arbitrary and is based on a continuous and not a discrete set of events.

In the realistic approach, most patients taking chemotherapy are not uniformly followed. This can be due to the lack of universally accepted and consistent tools. (26)

A close link exists between risk factors and resultant anthracycline cardiotoxicities with further classifications into treatment related and individual related risk factors. (29) The amount of treatment related risk factors can be affected by different impacts such as drug type, total dose, way of drug administration and presence of additional treatments. Epirubicin is considered to have a roughly comparable cardiotoxicity to doxorubicin (30)(31)

A study done by following pediatric survivors for a long time showed that not all anthracyclines have the same risk of complications. Doxorubicin and epirubicin have comparable risk while daunorubicin has a lower risk. (32)

The total amount of anthracycline given is another significant determinant. Their dose dependent nature is unrelated to the type of anthracycline used. Whichever of the drugs is used, there is always higher risk associated with increasing dose.(29)

A group of researchers evaluated pediatric cancer survivors who are adults now. They found that there was a clear increasing pattern of cardiotoxicity with exposure to anthracyclines. The survivors that took higher doses had much higher chances of ending up with cardiotoxicity, more than twice than those who were not exposed. (33)

The above patients took doses similar to those that are labeled as high risk by an international guideline that classifies pediatric cancer patients in to different risk groups. (34) It is noteworthy that cardiotoxicity also occurs in patients that received lower doses of medications, even below the threshold point (35).

A pediatric survivor study showed the significant impact that combination of treatment has on side effects. The survivors who took additional radiation therapies were assessed and had higher cardiac complications. It was also shown that majority of these effects emerged in young adults. (33)

Some chemotherapy agents that did not cause cardiotoxicity alone but were aggravators of cardiotoxicity when used in combination with anthracyclines. Children might be exposed to cardiotoxic treatments in addition to anthracyclines that may have additive deleterious effects. The combination of the multiple treatments and younger age increase the risk of developing cardiotoxicity in younger survivors. (36) Individual characteristics of patients are determinant factors of the resultant cardiotoxicity. Some of these determining details are age of patients, their sex and the presence of concomitant cardiovascular illnesses that are more common in adults. (36)

Among pediatric patients, age is one of the most studied determinants. These drugs are toxic to all subjects taking them at any time but there is increased risk in those that are young at diagnosis and treatment. A study was done to show the relationship of drug dosage and age. The investigator and his colleagues reported that younger children were more affected as compared to older patients. Their cardiac disease rates increase to two times and four times with increasing doses. (37)

Another group of researchers described how doxorubicin is handled and processed in the body across different pediatric age groups. There was an observed slow drug clearance from the bodies of younger children when compared to the older ones. (38)

A comparable amount of attention has been given toward the effects of sex on resulting cardiotoxicity. These effects were attributable to the presence of sex hormones that cause worse cardiotoxicity in females that is usually readily resolved as compared to the males. (29)(39)

The above study showed a worse effect on females, however, preclinical studies show that females are more protected than their counterparts. (39)

There seems to be discrepancies among the above clinical and preclinical evidences and some reasonings were given. The protective effects of the female hormone estrogen and protective effects of mitochondria are some of the explanations. (39) There seems to be conflicting data regarding gender and predilection of cardiotoxicity, which would necessitate the heterogeneity to be further examined.

In daily clinical practice risk assessment is not done by genetic tests and future predictive tools. But, including these options with in routine practices would markedly improve anticipatory patient management and follow-up. A recent study suggests this practice by incorporating these modalities. (40)

There is a report on children in oncology care displaying the need for genetic evaluation which was proven by the presence of higher cardiac problems in patients that have specific genetic variants. (41)

The above study looked at patients with the intent of finding certain genotypes. And it was revealed that around one third of survivors had cardiac problems while the others did not. There was a clearly visible genetic component to these variations. The genetic effects were more pronounced in lower doses of chemotherapy. On the contrary, the genetic effect decreased with higher drug doses. In patients with no genetic abnormalities, there was the usual dose dependent resultant cardiac dysfunction.

It displayed that a group of patients might be at increased risks cardiomyopathy despite lower drug doses and that combining clinical and. (41)

Most research to date has concentrated on later cardiac effects among childhood cancer survivors who are currently adults. (26) In children and adolescents, the goal is to pick up cardiac injury well before symptoms appear. When subtle damage is identified early there is better chances of early intervention and avoidance of over heart problems. (34)

One of the most crucial early steps is timely diagnosis and documentation. This gives the opportunity to identify and follow patients through out their individual treatment processes. A guidance towards drug adjustments would be a crucial step towards decreasing the resultant complications. It also makes it easier to assess how other cardiotoxic agents contribute to cardiac injury when they are used in combination. However, the substantial inconsistency of monitoring regimens among different centers and literatures has undermined its utility.(42)

Despite all these recommendations, there is a universal wide variation among recommendations with lack of uniformity possibly due to the shortage of evidence from clinical research. Kouwenberg et.al reviewed 3649 unique reports that studied cardiotoxicity among children and adolescents. This team evaluated a number of studies reporting cardiotoxicity by using different means and their combinations. (26)

Before initiation of therapy patients advised to have a mandatory cardiac evaluation. This with in turn help identify ant preexisting problems. It will also help as a benchmark for comparison with evaluation that will be done further into patient treatments.

Echocardiography is among the most widely used modalities owing to its wide availability and the detection rate of LVEF. In addition, it enables the diagnosis of alternate or concurrent cardiac abnormalities (43)

Diverse cancer and cardi-oncology societies have individual recommendations regarding imaging modalities. Owing to the varied evaluation methods that are suggested, institutional guidelines and cut points are typically used to evaluate patients.

As suggested by American and European recommendations, echocardiography is the pillar of cardiac evaluation at baseline, during treatment and during follow-up. The fact that its widely available, easy to reproduce, safe to patients, versatile with no radiation exposure, and concomitant renal disease makes it an optimal choice. (44) Echocardiography can provide a wide

cardiac evaluation by allowing chamber dimensions. It also assesses systolic and diastolic functions along with evaluation of the vessels. (44)

The American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend measuring left ventricular ejection fraction by using the best available method at that moment, this should ideally be done by three-dimensional echo. in the absence of three-dimensional echo, a modified method is suggested. If and when LVEF is done, it should be coupled with wall motion score index. When global longitudinal strain is not available, LV longitudinal function can be evaluated by using M-mode. But this technique can cause subtle missed LV contractility changes. Using another option by measuring the peak systolic mitral annular velocity by doppler imaging can solve this problem. (44)

The British Society of Echocardiography has another set of recommendations to be used for baseline and follow-up of patients. This guideline recommends there needs to be additional research to be used when there is marked decrement in strain patterns especially in cardiotoxic agent use. There is a recommendation for the assessment of two dimensional and three-dimensional echo evaluation of left ventricular ejection fraction and right ventricular function. (45)

In comparison European Society of Medical Oncology (ESMO) suggests that patients should have a baseline cardiac check that includes ejection fraction measurement and an assessment of diastolic function using standard imaging practice. However, routine use of cardiac biomarkers is still not clearly established, and is mainly considered for higher-risk patients such as those with significant pre-existing cardiovascular disease, those receiving higher doses or those with concomitant cardiotoxic agents. (46)
All the above consensus recommendations aim at identifying the burden of pediatric cardiotoxicities following anthracycline therapy. However, there still exists a wide discrepancy regarding guidelines and reporting.

These consensus recommendations are a great tool on identifying current global, continental and country level burden of anthracycline toxicity.

The systematic review mentioned below is unusual because there simply is not much pediatric evidence on cardiotoxicity. And only a few reviews have pulled the existing data together in a

structured way. This review tried to summarize what we know about cardiotoxicity in the first year after childhood cancer therapy. The biggest problem was that the studies did not all measure or define cardiotoxicity the same way. The authors sifted through a huge number of papers and ended up with a smaller set of studies that, altogether, still included many thousands of children. Because some studies relied mainly on echocardiography, others focused on symptoms, and others used biomarkers, the reported rates were all over the place. In some of the cohorts systolic dysfunction was rarely seen, while in others it was fairly common; diastolic abnormalities were often reported with wide variation. When cardiotoxicity was defined using mixed criteria (echo plus clinical findings), symptoms alone, or biomarkers alone, the results were just as inconsistent. Heart failure showed up in only a small proportion of survivors overall, but even that estimate differed from one study group to another. Higher cumulative anthracycline dose was identified as risk factor, along with older age and black race. Contrary to molecular theory beliefs, sex of patients was not shown to have an effect on cardiotoxicity outcome. (26)

Follow-up studies in childhood cancer survivors show that heart related toxicity can appear within a few years of treatment in a meaningful minority of patients. The risk is not evenly distributed and tends to be higher in certain groups, especially those who experience significant infections during treatment, those from particular racial backgrounds, and children treated beyond the infant period. (47)

When evidence from multiple controlled treatment studies is considered together, the overall message is similar. Cardiac toxicity shows up in two ways sometimes as obvious clinical disease, and other times as silent, early changes that are only picked up through monitoring. (30)

Hospital- and country-level reports also point in the same direction. In one large pediatric oncology center review, survivors were routinely screened with echocardiography using predefined cutoffs for ventricular function and structural measurements. A substantial proportion of anthracycline-exposed survivors had abnormal findings on surveillance. The same risk pattern kept appearing: greater total anthracycline exposure, radiotherapy that included the heart region, younger age at treatment, and female sex were repeatedly linked with higher likelihood of cardiotoxicity.

The amount of cardiotoxicity identified during chemotherapy was 23% with reduction to 17 % among survivors after completion of chemotherapy, Male and Female percentage was 13% and 22% respectively. Patients who received radiation had 22% cardiotoxicity as compared to 14% among those that did not take anthracyclines. Patients in the age group of <1year, 1-4 years and >5 years had percentages of 14%, 22% and 15% respectively. Patients who took higher doses of Doxorubicin at >300mg/BSA had a higher cardiotoxicity accounting to 28%. Cardiotoxicity among patients that took lower doses of <200mg/BSA and 200-300mg/BSA was13% and 18% respectively (48)

A study of children treated for AML showed a broadly similar pattern. The cardiac changes were seen early, and some patients improved with time. In that review, early cardiotoxicity could appear within the first few months of starting anthracyclines, but it was also reported much later approaching two years from treatment initiation. Only a small subset developed early dysfunction which was typically reflected by a clear reduction in shortening fraction. A few patients went on to develop cardiomyopathy within the first year after completing therapy, and what stood out was that their baseline echocardiograms were normal. The shortening fraction dropped on follow-up before they developed obvious symptoms of heart failure. Later cardiotoxicity was also reported in a notable minority. The authors, however, acknowledged an important limitation because it was a retrospective chart review a meaningful portion of echocardiograms were not available which could have affected the estimates. (49)

Another study focused on how quickly cardiac changes can appear after anthracycline treatment. The investigators performed echocardiograms shortly before chemotherapy and repeated them about a week after treatment, before any radiotherapy or cardioprotective drugs were introduced. After chemotherapy, the whole group showed changes in left ventricular diastolic function, while a drop in systolic performance was seen mainly in the patients whose post-treatment LVEF fell below the normal range. Overall, the study suggests that diastolic abnormalities can emerge almost immediately after therapeutic anthracycline exposure which is sometimes before more obvious systolic impairment. (50)

The above-mentioned reports were from among high income countries (51) Most of the evidence comes from high-income settings, with fewer reports from upper–middle-income countries. In China, a cohort of children treated for leukemia found that cardiac abnormalities

during therapy were fairly common and tended to occur more often with greater daunorubicin exposure. Overt symptoms were uncommon and usually improved with treatment, while most abnormalities were silent and detected only on ECG or echocardiography. Overall, this supports routine ECG and echo surveillance to pick up early, asymptomatic cardiac changes that might otherwise be missed. (52)

A study from Pakistan followed children receiving anthracyclines and checked heart function with echocardiography at the start of treatment, again soon after, and later during follow-up. With time, more children showed evidence of cardiac dysfunction, suggesting that anthracycline-related toxicity can emerge early and continue to appear over the first year. There was also higher risk with greater cumulative exposure and with regimens involving doxorubicin, whether used alone or together with daunorubicin. Overall, the message is practical: regardless of the dose, children treated with anthracyclines still need long-term follow-up so late cardiotoxicity is not missed. (53)

A study from Sri Lanka followed people who were starting an anthracycline-based chemotherapy regimen. Heart scans were done before treatment, around the start and end of the chemotherapy course, and later a few months later. The researchers noticed that heart performance tended to worsen gradually over time. Big drops were not seen immediately after the last dose, but they became more noticeable at the later follow-up visit. The authors also suggested a simple way, based on the scan results, to help predict who might develop these changes, and they stressed the need for continued follow-up after treatment. (54)

Anthracyclines are widely used because they work but their benefits come with a trade-off. Some patients develop heart problems months or years later. Even as cancer outcomes keep improving, this treatment related risk has not decreased or disappeared. That is why picking up early changes and acting quickly matters because it can reduce the chance of long-term damage.

# Objectives

## General

- To assess the cardiac effects of anthracycline-based chemotherapy using echocardiography in pediatric Hodgkin lymphoma patients and survivors treated at Tikur Anbessa Specialized Hospital.

## Specific

- Estimating the burden of echocardiographic abnormalities across study participants
- Examining determinants that are associated with the development of cardiac abnormalities
- Longitudinally evaluating echocardiographic parameters by comparing baseline and follow-up findings.

# Materials and methods

## Study Area and Setting

The study area is Tikur Anbessa Specialized Hospital, which is located in Addis Ababa city. The patients are in the Pediatrics and Childcare department, Pediatric Hematology oncology unit. The unit contains an emergency, a ward and a follow-up clinic. It is run by Pediatric Hematology Oncology Sub specialists and trainee fellows. Our research focused on pediatric Hodgkin Lymphoma patients at Black Lion Specialized Hospital who underwent anthracycline based lymphoma treatment from 2016-2025.

Patients were identified from HMIS and assessed for their attributes. Participants were later contacted via telephones provided on their charts. They were informed about the echocardiography and appointed for their specific dates. Follow up echocardiography was done for patients and results were interpreted using Z-scores dependent on age, sex and Body Surface Area.

## Study Design

We used a hospital-based cross-sectional study. Patient related data were collected from medical records, while a new, one-time echocardiographic assessment was performed for each participant to evaluate cardiac function. This approach allows for the assessment of current cardiac outcomes in relation to past treatment exposures.

## Source Population

It includes all pediatric patients that were diagnosed with Hodgkin lymphoma and treated at Tikur Anbessa Specialized Hospital (TASH) between 2016 and 2025.

## Study Population

The study population includes all patients from the source population who meet the eligibility criteria, specifically those who received anthracycline-based chemotherapy and are available for a post-treatment echocardiographic evaluation.

## Sample size determination

A census approach was selected for this study to include all eligible pediatric Hodgkin lymphoma. Given the manageable population size and the study's aim capture the burden of cardiotoxicity, including the entire population enhances representativeness and avoids selection bias. As the data collection involves a single echocardiographic evaluation, this approach is both practical and ethically appropriate. Therefore, a formal sampling size determination was not used.

## Sampling Technique

Approximately 500 pediatric Hodgkin lymphoma patients were treated at TASH between 2016 and 2025. All of these patients are expected to have received anthracycline-based chemotherapy. Based on feasibility, data completeness, and patient availability for post-treatment echocardiographic evaluation, it was estimated that approximately 250 to 300 patients were expected to come.

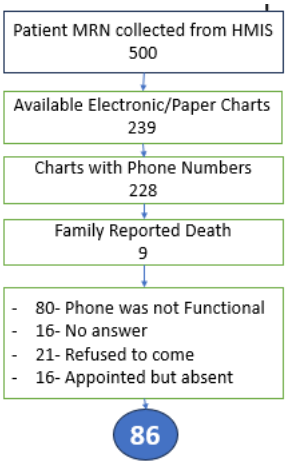



**Figure 1: Patient Flow**

To ensure a high patient presentation rate, a few measures were taken. The transport cost was reimbursed for participants coming from outside Addis Ababa. Each phone number was dialed 4-5 times before labeled ‘not-functional’ or ‘no answer. Accommodation was arranged at TAPCCO for those without a place to stay, with shuttle to and from TASH. Daily refreshments were

provided, including traditional coffee ceremonies and meals in the waiting area while patients wait for echocardiology queue.

## Inclusion Criteria

All pediatric patients diagnosed with HL who received anthracycline-based chemotherapy at Tikur Anbessa Specialized Hospital between 2016 and 2025.

## Exclusion Criteria

1. Patients with pre-existing heart conditions (CHD, cardiomyopathy)
2. Incomplete medical records or lack of follow-up data.
3. Non-consent to participation.

## Study Variables

1. Dependent Variables
    - Primary: LV systolic dysfunction
    - Secondary: Any echocardiographic abnormalities
2. Independent Variables
    - Demographic characteristics
    - Anthropometry
    - Clinical Parameters
    - Treatment related parameters

## Operational Definitions

- *Anthracycline induced cardiotoxicity- includes new CV symptoms, new abnormalities in cardiac function on CV imaging, and/or new increases in cardiac biomarkers. (55)*
- *Acute anthracycline cardiotoxicity- within a week of starting treatment. (26)*
- *Early onset- myocardial damage occurring within a year of starting treatment. (26)*
- *Late-onset- myocardial damage occurring more than a year after start of treatment (26)*
- *LV systolic function (Normal: - EF>55%, FS- between- 26-46%, Mildly reduced: - EF- between 41-55%, Moderately reduced: - EF – between 31-40%, Markedly reduced: EF<30%)*

- *Cardiotoxicity- Echocardiographic LV Systolic function drop >10%, Global Longitudinal Strain >15%, Biomarkers, ECG, Cardiac MRI.*
- *Cumulative anthracycline dose (mg/m²)- Total doxorubicin-equivalent dose from charts, categorized as:<100 mg/m² (low), 100–249 mg/m² (intermediate), ≥250 mg/m² (high-risk)*
- *Baseline echocardiogram- Any documented echo before initiation of chemotherapy.*

## Data Collection

Data was collected using a structured, pretested questionnaire compiled from two components. The first section documented chart review of patient demographics and treatment related factors, while the second captured results from echocardiographic evaluations. Echocardiographic assessments were conducted according to internationally recognized guidelines, adapted to the local clinical context where applicable. Z-Score interpretations were later used for the echocardiography.

Patient medical record numbers were obtained from the hospital's Health Management Information System (HMIS), and corresponding medical charts were retrieved. Patients were contacted using the telephone numbers recorded in their charts and informed about the echocardiographic evaluation. Upon their arrival, informed consent was taken, and the echocardiograms were carried out.

- Echocardiographic evaluations for anthracycline therapy are recommended at the following time points: (44)

- Baseline (within 2 weeks before starting treatment)
- During treatment for high-risk patients (e.g., midpoint or before dose escalation)
- Early post-treatment (within 6 months of completing chemotherapy), and
- Late follow-up at 1-year post-treatment and then every 2 to 5 years based on cumulative dose and risk level.

In resource-limited settings, a single evaluation at ≥6 months post-treatment may serve as a practical alternative.

Although follow-up echocardiography is part of the routine clinical care for these patients, any additional financial burden arising from the study were covered by the primary investigator. In addition, transportation costs were reimbursed for participants traveling outside of Addis Ababa.

### Data Quality Assurance

Data Collection protocol was prepared and all the data was done by the primary investigator. The study echocardiographs were done by the respective pediatric cardiologists. All the echocardiography evaluations were attended by the primary investigator to ensure data quality.

### Data Analysis and Interpretation

Data cleaning was done by checking certificates for completeness. Data entry was done by the primary investigator. Analysis was done using the Statistical Package for Social Sciences (SPSS). Descriptive and analytical statistics were used as applicable. Statistically significant associations were taken for p values of $<0.05$

### Ethical Considerations

Ethical clearance was obtained from the Research and Ethical Committee (REC) of the College of Health Sciences. Participant confidentiality was assured. All participants included in the study were kept anonymous during subsequent analysis and dissemination.

### Dissemination of Results

The outcome of this research was presented on the research defense day and a formal report will be submitted to the institute. The study result will also be published on scientific journals.

## Results

### Study Population and Participant Flow

We had a total of 500 medical record numbers retrieved from the HMIS. 239 of these had available paper or electronic medical charts. Out of these charts, 228 had phone numbers which were used to contact the patients' families. A total of 9 deaths were reported by families that were contacted. The common causes of non-enrolment were non-functional phone numbers (80),

No answer (16), refusal (21) and absence after appointment (16) Each phone numbers were dialed 4-5 times by the primary investigator, giving a final study number of 86 participants.

All of these participants had study echocardiogram evaluations done. Only a small subset of these patients had previous echocardiograms, 13/86. A second previous echocardiogram was only found in 3/86 of the patient charts. None of the participants had baseline echocardiograms before the initiation of chemotherapy.

## Baseline Demographics

There were 86 patients that were evaluated during the study and study echocardiograms were done for all of them. The sex and age distribution of these participants was assessed showing the following results displayed in the figures below.

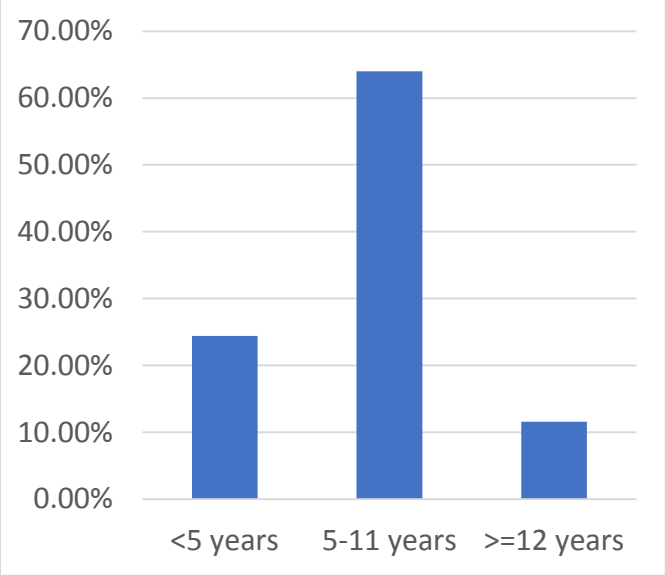



**Figure 2: Age at diagnosis**

The percentage of patients at diagnosis that were younger than 5 years old was 24.4% (21), those between year 5-11 were 64% (55) and those older than 12 were 11.6% (10) of the patients.

Majority of the patients were males at a percentage of 94.2% (81) and 5.8% (5) were females. This sex ratio was at a skewed balance showing a marked male predominance. (M: F ≈ 16:1).

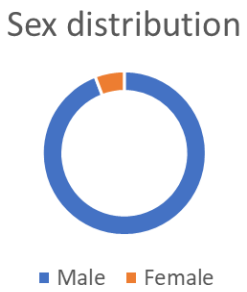



**Figure 3: Sex Distribution**

The other determinant that was assessed is distance from the treatment center, Addis Ababa. A high percentage of the patients traveled from areas that were 200-400km away from the treatment center at a number of 35/86 (40.7%). It was followed by those that traveled from >400km, <100km and 100-200km away from Addis Ababa at percentages of 20.9%, 14% and 10.5% respectively, while 10.5% were from Addis Ababa.

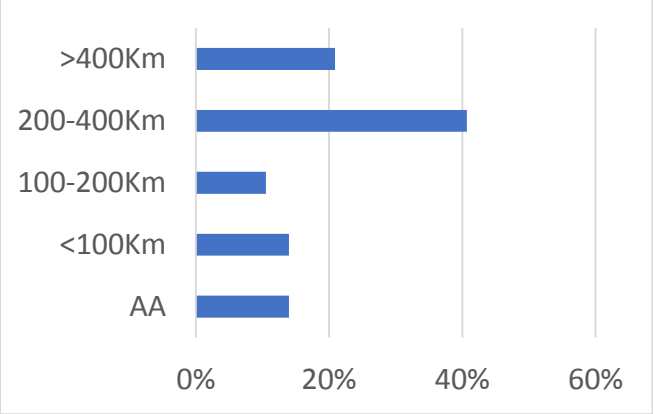



**Figure 4: Distance from the treatment center, Addis Ababa**

Table 1 below shows the percentages and actual numbers of the addresses of the participants. Oromia had the highest percentage of patients at a number of 43/86 (50%) followed by the regions of Amhara, Addis Ababa, Tigray and Other regions at numbers of 15, 12, 1 and 15 respectively.

| Address | Number | Percentage |
|---|---|---|
| Oromia | 43 | 50 |
| Amhara | 15 | 17.4 |
| Addis Ababa | 12 | 14 |
| Tigray | 1 | 1.2 |
| Others | 15 | 17.4 |

**Table 1: Patient Address**

The children were diagnosed between 2016 and 2025 and all study echocardiograms were performed in 2025. Thus, time since diagnosis spans roughly 1–10 years, capturing both recently treated patients and relatively long-term survivors. Most of the patients were diagnosed 1-5 years prior to current presentation at a frequency of 45/86 (52.3%), 23/86 (26.7%) and 18/86 (20.9%) patients were diagnosed below 1 year and above 5 years from current presentation.

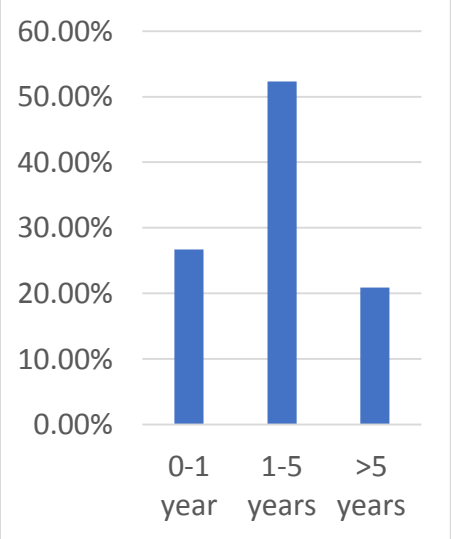



**Figure 5: Time since diagnosis**

## Anthropometry

Comparison of baseline and current nutritional status is shown in figure 6 below.

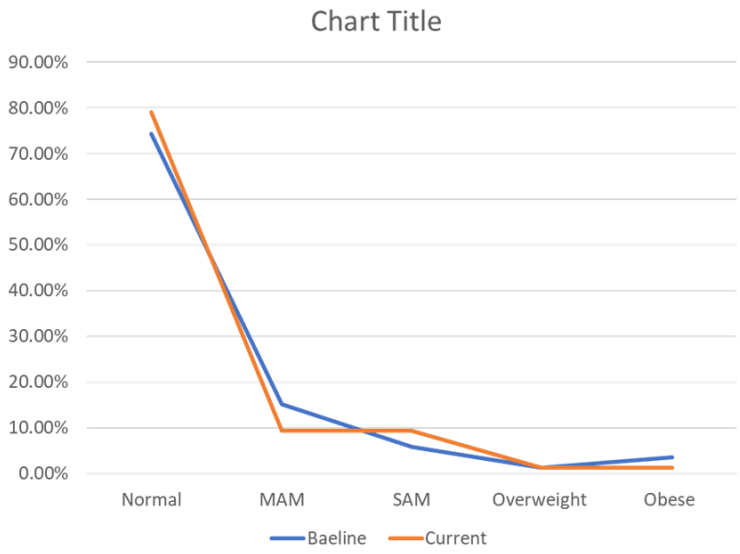



**Figure 6: BMI/ Weight for age Comparison**

At baseline, it is shown that 74.4% of the patients had normal BMI/Weight for age. 15.1% had moderate acute malnutrition and 5.8% had sever acute malnutrition. Being overweight/ Obesity was observed in 4.7% of the patients.

Currently, 79.1% had normal nutritional status, while 9.3% were moderately malnourished, another 9.3% had Severe acute malnutrition and2.3 were either obese or overweight.

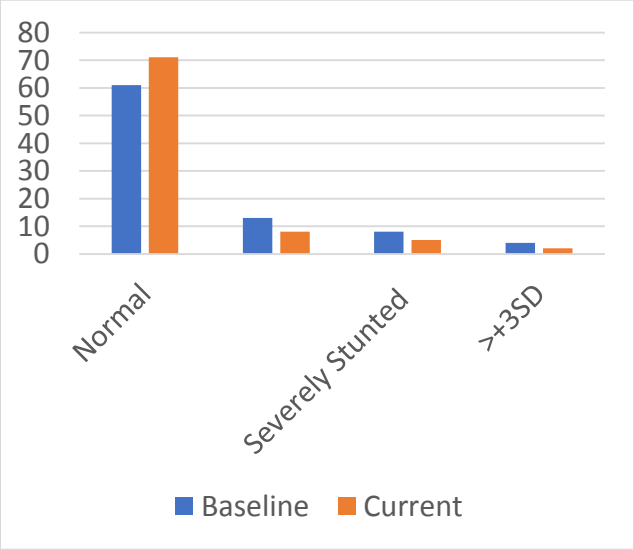



**Figure 7: Height for age comparison**

The figure above, figure 7 compares the baseline and current height for age of the patients. At baseline 70.9% patients (61) were normal, 15.1% (13) were severely stunted and 4.7% (4) were above +3SD. Currently 82.6% (71) had normal height for age, 9.3% (8) were severely stunted and 2 were above +3SD.

## Clinical Parameters

Figure 8 below shows that 6/86 (7.0%) of our children were diagnosed to be Stage I at presentation, 28/86 (32.6%) were Stage II, 30/86 (34.9%) were Stage III, and 17/86 (19.8%) were diagnosed to be Stage IV. Risk stratification showed that most were classified as high risk at a number of 48/86 (55.8%), 22/86 (25.6%) were low risk, and 16/86 (18.6%) were intermediate risk. Most patients were treated for a new Hodgkin Lymphoma diagnosis, while 5/86 (5.8%) were Relapsed Disease.

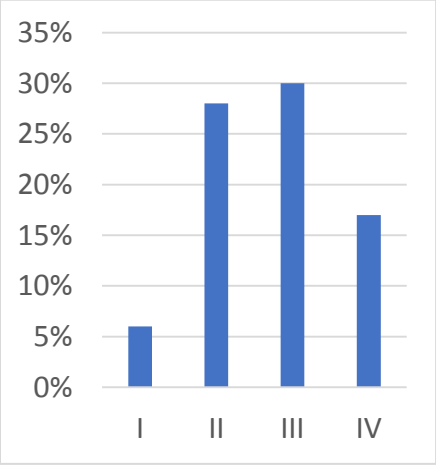



**Figure 8: Disease Staging**

Almost all had no major chronic comorbidities (CVD/HTN/DM) 84/86(97.7%), 1 patient had renal disease and another 1 had thyroid disease. HIV infection was found on 1 patient and 3 patients had TB which were treated.

Vital signs were assessed for all patients, at baseline, 41.9% (36) were tachycardic, currently only 19.8% (17) were tachycardic. Baseline fever was uncommon at 3.5% (3) and there was no fever currently.

Acute infections were documented in the medical charts of 9.3% (8) patients during chemotherapy, with a total of 15 episodes recorded. The commonest diagnosis was GI

infection/Sepsis (4), URTI/ENT infections (3) and CAP (3) followed by Neutropenic fever (2) and Febrile UTI (1)

At baseline, around 30% had anemia and 9.3% were transfused during their chemotherapy phases. There was improvement currently where greater than 90% had no anemia.

Noone had family history, ICU admissions and use of cardioprotective drugs.

2 of the participants reported cardiac symptoms but their complaints were non-specific and could not be reliably classified into the NYHA functional classification.

## Treatment Related characteristics

All of the subjects received anthracycline based chemotherapy (85- ABVD, 1 OEPA). Cumulative anthracycline doses were classified into 100-250mg/m2 having the highest percentage of 83.7% (Table2). A small number of patients received anthracyclines that were higher or lower than this treatment group, 13 patients took doses above 250mg/m2 and only 1 patient received a dose below 100mg/m2.

| Variable | Category | N | % |
|---|---|---|---|
| COPDAC | Yes | 31 | 36 |
| | No | 55 | 64 |
| Cumulative Dose (mg/m2) | <100 | 1 | 1.2 |
| | 100-250 | 72 | 83.7 |
| | >250 | 13 | 15.1 |
| Number of infusions | 1-3 | 1 | 1.2 |
| | 4-5 | 5 | 5.8 |
| | 6-7 | 10 | 11.6 |
| | 8-9 | 57 | 66.3 |
| | >10 | 9 | 10.5 |

**Table 2: Treatment parameters**

Around one quarter of the participants received radiotherapy. Among these patients, doses were evenly divided among two dose groups of 20-30 Gy and >30Gy. Majority of the sites were neck

and only two patients that took mediastinal radiotherapy. Most patients took their treatment for longer than 14 days.

## Echocardiography Parameters: Left Ventricular Dysfunction

Our primary dependent variable, left Ventricular systolic dysfunction was seen in 10 patients of the 86 participants (11.6%).

It was then assessed across all the determinants, Table 3 shows some of the LV dysfunction across determinant representations. Comparison across sex showed that LV dysfunction was slightly more frequent in girls but the actual number is very small. Age at diagnosis did not show any strong age gradient. All LV dysfunction was diagnosed in newly diagnosed patients.

LV dysfunction was checked across all the determinants and it did not show any clear pattern or gradient. There was no cluster in any determinant category.

Most dysfunction was seen in those patients having normal BMI and height-for-age, possibly due to the higher percentages of these groups. Examiner 1 did 60% of the studies while Examiner 2 did 40% of the studies, showing no inter-examiner disproportion.

| Determinant | Category | N | % |
|---|---|---|---|
| Sex | Female | 1/5 | 20 |
| | Male | 9/81 | 11.1 |
| Age | <5 years | 3/21 | 14.3 |
| | 5-11 years | 6/55 | 10.9 |
| | >12 years | 1/10 | 10 |
| Diagnosis type | New | 10/82 | 12.2 |
| | Relapse | 0 | 0 |

**Table 3: LV dysfunction across determinants**

## Echocardiography: Other abnormalities

Other echocardiography abnormalities are secondary dependent variables and at least one abnormality, other than LV dysfunction were seen in 90% (78) of patients. (Figure 9) The common abnormalities seen were chamber abnormalities and great vessel abnormalities.

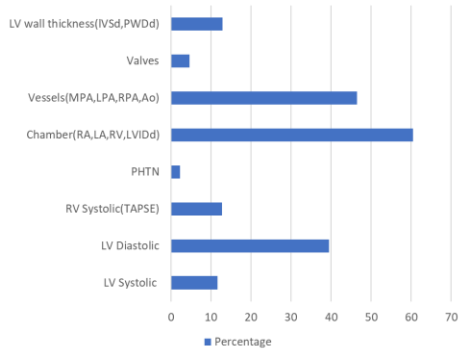



**Figure 9: Echocardiography other abnormalities**

## Previous Echocardiograms

None of the patients had baseline echocardiograms. Only 13/86 patients (15.1%) had at least one previous echocardiogram, 3 had a second one (3.4%). At the first echo, 10/13 (76.9%) were normal, while 3/13 (23.1%) had at least one abnormality. At the second echo, 2/3(66%) were normal. At the study echo, all 13/13(100%) had at least one echo abnormalities.

There appears to be a shift over time from mostly normal to abnormal echocardiograms.

## Logistic Regression

There were constraints in carrying out the logistic regression of this data set. A large multivariate model with all the determinants was not statistically valid and had high standard errors, odds ration and P value of 1, showing signs of failure.

## Logistic Regression: Univariate

A selected set of determinants were chosen to be included in the univariate logistic regression based on their biological credibility and presence of sufficient variations. These determinants were: age at diagnosis, sex, time since diagnosis, COPDAC exposure, Radiotherapy exposure, stage and risk group of disease. Other determinants having zero cells or quasi-complete separation were not included in the logistic regression and were kept descriptive only, these were: Anemia/transfusion, Comorbidities, Cumulative dose, chronic infection, anthropometry, vital signs, Radiotherapy site/dose and number of chemotherapy cycles.

| Determinant | Comparison | OR (95% CI) |
|---|---|---|
| Sex | Male vs female | 0.50 (0.05–4.98) |
| Age | Above 5 vs below 5 | 0.74 (0.17–3.25) |
| | ≥12 vs <5 | 0.67 (0.06–7.35) |
| Time since diagnosis | mid vs short | 1.93 (0.37–10.17) |
| | long vs short | 0.62 (0.05–7.41) |
| COPDAC exposure | COPDAC vs none | 1.36 (0.33–5.69) |
| Radiotherapy | RT yes vs no | 0.27 (0.03–2.28) |

**Table 4: Univariate analysis**

Table 4 shows a summary of the univariate analysis, showing that no determinant reached a statistical significance because all P-values are >0.2. In addition, ORs near 1 with very wide confidence intervals that cross 1. There are some clinically reasonable directions of odds that were evident but with low precision to claim real effects, an example is the slightly higher odds with the COPDAC exposure group.

## Logistic Regression: Multivariable

A multivariable model fitting all the determinants could not be modeled. Thus, determinants were grouped into blocks of their nature such as demographic, disease related, treatment related, vital signs, comorbidity and symptom categories. This did not show any association, there were huge coefficients and confidence intervals. The instability likely came from a mix of issues: the sample was small, there were only a few cases of LV dysfunction, and some subgroups had very few participants. As a result, no single determinant could be identified as an independent predictor of LV dysfunction in the adjusted models. Logistic regression was used, but the study is clearly underpowered for risk-factor modelling. Both univariate and multivariable models show wide CIs and non-significant p-values, reflecting insufficient information, not necessarily absence of a biological effect. None of the determinants stood out as a reliable predictor of LV systolic dysfunction. Although we applied the appropriate statistical methods, the small sample and limited number of LV dysfunction events mean the regression is more reflective of low power and imprecision than true absence of risk factors in this population.

## Discussion

In our study, 86 Pediatric Hodgkin Lymphoma patients and survivors were assessed having 11.6% Left Ventricular Systolic Dysfunction identified at the study echocardiograms. In addition, 90% of the participants had at least one other echocardiographic abnormality. These findings were mainly chamber and great vessel abnormalities. No baseline echocardiograms were documented and only 15.1% had at least one prior echo. The trends that were evident are minor but meaningful LV dysfunction, high 'any abnormality' presence, and lack of implementation of internal recommendations of cardiac follow-up of anthracycline treated patients and survivors. (56)

Participant recruitment was done via telephone tracing and return visits, difficulty was faced due to the high percentage of non-functional numbers, non-response, refusal and missed appointments. This is similar to problems faced by other Pediatric oncology follow-up in Sub-Saharan Countries, along with long traveling distances, financial burden, limited resources and abandoning appointments. (57)

There is potential selection bias as well, families with functional phone numbers and ability to return for echocardiography may differ systematically from those not reached due to socioeconomic status, distance, illness severity. The nine deaths reported by contacted families likely underestimate true mortality among the original HMIS list, since families of deceased patients may be less reachable.

Most patients received their diagnosis between five and eleven years of age., with a smaller percentage diagnosed at the ages of <5 years and >12 years. This trend is comparable to reports from other Sub-Saharan African Studies. These findings reveal a similar late childhood presentation. (58)

There was an extreme sex distribution (M: F 16:1) in our study. There are similar sex distributions but are much less extreme than observed in our study. (58)Possible explanations for this disproportion are the presence of random variation in a small sample size and recruitment artifacts where the males would present more readily.

There was a high presentation of advanced stage at diagnosis at a percentage of 55.8% (Stages III and IV). This is similar to other Sub-Saharan studies where the presentation diagnosis is mainly at worse patient conditions. (58)

Almost all of our patients received ABVD (85) with an intermediate anthracycline cumulative dose. This is comparable to available global data where lower doses are preferred to avoid dose dependent cardiac dysfunction. (59)

About one quarter patients received radiotherapy, but only two patients took mediastinal radiotherapy. This low percentage is important because combined exposure to anthracyclines plus chest/mediastinal radiation is consistently associated with higher long-term risk of clinically significant cardiac events in survivorship studies. (60)Our observation of limited mediastinal exposure may explain the lower prevalence of LV systolic dysfunction despite a higher other abnormality rate.

We observed LV dysfunction prevalence of 11.6% which might be comparable to the presence a wide variety of available literature. This wide variation is caused by the difference in usage of definitions, different modalities, age ranges, time since therapy and differential risk. Other bigger studies exhibit higher rates of cardiac dysfunction. (33)

Our observations is a snapshot at variable times since diagnosis (1–10 years). Some children may develop dysfunction later, while others may recover transient dysfunction related to intercurrent illness, anemia, tachycardia, or loading conditions. Since we used two Pediatric Cardiologists, there might be interobserver variability. There is a need for standardized protocols and consistent readers as suggested by the Pediatric Heart Network “Normal Echocardiogram Database” work.(61)

There is a striking finding of 90% other echocardiographic abnormalities. This finding can be supported by the fact that Left Ventricular dysfunction may be preceded by these subtle changes. (62)

None of our participants had baseline echocardiograms, and only 15.1% had at least one previous echo. This suggests that long-established recommendations for cardiac monitoring during and after anthracycline treatment are still not being consistently followed in practice.. (63)

There was an observed pattern among the 13 patients with prior echo, a shifting from mostly normal earlier studies to universal abnormalities at the study echo. This may represent true progression. However, it may also reflect differences in measurement technique, reader variability, or threshold changes over time.

We used logistic regression to see whether any of the measured variables could help flag children who were more likely to develop LV systolic dysfunction. But data structure poses a higher impact than biologic effect. Our study is an example of few outcome events with multiple candidate predictors. This is worse due to the presence of several predictors that are uncommon or unevenly distributed. This produced unstable estimates (large standard errors, extreme coefficients/odds ratios, and very wide confidence intervals). This is termed as "events per variable" concept, when events are limited, model performance deteriorates rapidly with increasing predictors and sparse cells. (64) This is particularly important in cardio-oncology, where true effects may exist but require adequate sample size, balanced categories, and sufficient follow-up time to be reliably detected.

The modeling difficulties encountered are also consistent with complete or quasi-complete separation. Separation can lead to non-convergence and infinite parameter estimates in ordinary logistic regression. (65)

Future work should aim at determinants from a larger and/or multi-center studies, a pre-specifying a small set of primary predictors, use of collapsing sparse categories where clinically defensible, and using penalized or shrinkage-based regression methods when rare categories cannot be avoided. The key message we obtained is that the regression analysis was methodologically appropriate as an exploratory tool, but the dataset provides limited statistical information for robust risk-factor identification.(64)

## Limitations

Our limitations were the use of a cross-sectional echocardiography, heterogeneous follow-up duration, selection and survivorship bias, phone-based tracing and attendance requirement. Another hinderance was baseline comparison limitations with very limited prior echo data, lack of advanced functional markers, GLS/strain imaging. The fact that our study is done is a single-

center setting may mean that findings may not generalize to other Ethiopian centers or regions with different referral patterns, protocols, supportive care, or follow-up structures.

## Conclusion

Our study evaluated echocardiographic cardiac abnormalities among pediatric Hodgkin lymphoma patients and survivors treated with anthracycline-based chemotherapy at Tikur Anbessa Specialized Hospital from 2016-2025. The study echocardiography performed in 2025. LV systolic dysfunction was identified in some of the participants, while a high proportion of other echocardiographic abnormalities was found. Baseline cardiac assessment prior to chemotherapy was not documented, and only a small subset had prior echocardiograms, indicating limited routine cardiac surveillance in this population.

Determinant analysis using logistic regression did not identify robust predictors of LV systolic dysfunction; however, interpretation was limited by few outcome events and sparse categories, and the absence of statistically significant associations should not be taken as evidence of no biological effect.

In general, the findings support the demand for a feasible, standardized, risk-adapted echocardiographic surveillance approach for anthracycline-treated pediatric HL patients and survivors in the local setting. This should include documentation of cumulative anthracycline exposure and structured follow-up to enable early detection and management of subclinical cardiac abnormalities.

## Recommendation

We recommend the introduction of baseline echocardiography for all pediatric Hodgkin lymphoma patients starting anthracycline-based treatment, and document findings in the chart. Implementing a standardized cardiac surveillance pathway for anthracycline-exposed patients and survivors, with clear follow-up intervals and referral triggers for abnormal findings. Standardize echocardiography formats and reporting using a uniform protocol to reduce measurement variability and improve comparability over time. Strengthen documentation of treatment exposures.

Developing an integrated pediatric cardio-oncology referral pathway is crucial to ensure that children with LV systolic dysfunction or clinically important structural abnormalities are reviewed promptly by pediatric cardiology. Follow-up barriers ought to be addressed by improving survivorship tracking systems, including maintaining reliable phone contacts and considering coordinated echo scheduling with oncology follow-up visits.

In the direction of future studies, we suggest that larger multi-center studies be done to increase sample size and outcome events. Along with use of prospective study designs with repeated echocardiograms to evaluate progression or recovery of abnormalities and to estimate incidence of cardiotoxicity over time.

More sensitive markers of early cardiotoxicity should be used where feasible, such as global longitudinal strain (GLS) and/or cardiac biomarkers, alongside conventional EF/FS. The training of oncology and cardiology teams on survivorship cardiac monitoring would improve outcomes. In addition, institutionalize a survivorship follow-up clinic or registry for childhood cancer survivors to enable systematic long-term monitoring and early intervention for late effects.

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# Annex

## Participants'/ Primary Care Giver's information and consent form

We are carrying out a study at Tikur Anbessa Specialized Hospital to check whether anthracycline chemotherapy can affect the heart in children and adolescents treated for Hodgkin lymphoma.

If you agree to take part, your child will have one heart ultrasound scan (echocardiogram). We will also review your child's medical record and do a brief, simple physical check.

This study is not expected to cause harm. The echocardiogram is painless, does not involve radiation, and is routinely used in children. No medicines or additional treatment will be given as part of this research.

Checking the heart early may help identify changes before they become serious, and it can allow timely follow-up or referral if needed.

Participation is entirely voluntary. You may choose not to take part, or you may withdraw at any time, and this will not affect the care your child receives. All information collected will be kept private and used only for research, and your child's identity will not be included in any report.

I confirm that I have understood the information above. I freely agree for my child to participate in this study, and I allow the study team to use my child's information for research purposes.

**Name of Parent/Guardian:** _____

**Signature:** _____ **Date:** _____

## Contact Information of the Principal Investigator:

**Dr. Hiyaw Abebe**

Pediatric Hematology-Oncology Fellow

Tikur Anbessa Specialized Hospital

Tel: +251-911481660

Email: hiyawabebe@gmail.com የወላጅ/አሳዳጊ የ መረጃ እና የፈቃድ ቅፅ

ይህ ጥናት በጥቁር አንበሳ ሆስፒታል የሆጅኪን ሊምፎማ ሕክምና የተደረገላቸው ህፃናት ላይ የሚካሄድ ሲሆን, አንትራሲክሊን(ዶክሶሩቢሲን) መድሃኒትን መሠረት ያደረገ ሕክምና በልብ ላይ ሊኖረው የሚችለውን ተፅእኦ ለመለየት እና ለመለካት እየተካሄደ ነው። ጥናቱ አንድ ጊዜ የሚደረግ የልብ ምርመራ (ኢኮካርዲዮግራፊ) እና ከካርድ የሚወሰድ የሕፃኑ የህክምና ታሪክ ምልከታን ያካትታል።

በዚህ ጥናት ላይ መሳተፍ ምንም ዓይነት አደጋ አያመጣም ። ኢኮካርዲዮግራፊ ከአደጋ የተጠበቀ የምርመራ መንገድ ነው፣ ህመም አያስከትልም፣ እና ጨረር አይጠቀምም። በዚህ ጥናት ውስጥ ህፃኑ ምንም መድሃኒት ወይም ህክምና አያገኝም።

ልብ ላይ የሚኖሩ ለውጦችን ቀደም ብለን መለየት ተጨማሪ ጉዳትን ለማቆምና በጊዜው አስፈላጊ ህክምናን ለማዋቀር ይረዳል። ውጤቱም ለህፃኑ እና ሌሎች በአካባቢው በተመሳሳይ ሁኔታ ያሉ ህፃናት የወደፊት ህክምናና ክትትል ውስጥ ግብአት ሆኖ ይረዳል።

በዚህ ጥናት ላይ መሳተፍ ፈቃድ ላይ የተመሠረተ ነው። በማንኛውም ጊዜ ውሳኔዎን መቀየር ይችላሉ በጥናቱ ላይ መሳተፍ ወይም ማቋረጥ በህፃኑ የመደበኛ ህክምና ላይ ተፅእኖ አያሳድርም። ስለ ራስዎና ስለ ልጅዎ የምትሰጡት መረጃ በጥልቅ ምስጢርነት ውስጥ ይጠበቃል

ከላይ የተዘረዘረውን መረጃ አንብቤ ተረድቻለሁ። ልጄ በዚህ ጥናት ላይ እንዲሳተፍ ፈቃዴን እሰጣለሁ፣ እና መረጃው ለጥናቱ እንዲገባ እስማማለhu የወላጅ /አሳዳጊ ስም፡ _____ ፊርማ፡ ___ ቀን፡ ___

የጥናቱ መሪ ምርምር አስኪያጅ የመገኛ መረጃ፡ ዶ/ር ህያው አበበ በቀለ የህፃናት የደም እና ካንሰር ሕክምና ሀኪም

0911481660 hiyawabebe@gmail.com

Study Questionnaire **Date…….**

**Echocardiographic Evaluation of Cardiac Abnormalities in Pediatric Hodgkin Lymphoma Patients and Survivors Following Anthracycline Therapy at Tikur Anbessa Specialized Hospital from 2016-2025 GC**

1. Identification,

Patient_ID……. Serial Number……. Medical Record Number (MRN)…….

2. Sociodemographic data

Age at diagnosis (years)……. Current age (years)…… Sex, Male [ ] Female [ ] Address……

3. Current- Pulse rate (PR) Oxygen saturation Temperature (°C) …….

   Baseline (pre-chemotherapy)- Pulse rate Oxygen saturation Temperature (°C)

4. Anthropometry

Current- Height ____ cm, Weight ____ kg, BSA ____ m²

Baseline- Height____ cm, Weight____ kg, BSA____ m²

Height-for-age (current): _____BMI or Wt/Ht (current): _____Interpretation(Current): _____

Height-for-age (baseline): _____ BMI or Wt/Ht (baseline): _____ Interpretation (baseline) _____

5. Disease characteristics

Disease staging- I [ ] II [ ] III [ ] IV [ ], B symptoms- Yes [ ] No [ ]

Risk group- Low [ ] Intermediate [ ] High [ ]

6. Comorbidities and clinical history

| **Condition** | **No** | **Yes / Remark** |
|---|---|---|
| Cardiovascular disease (CVD) | | |
| Hypertension (HTN) | | |
| Diabetes mellitus (DM) | | |
| Renal disease | | |
| Thyroid disorder | | |
| Evidence of current/recent infection | | |

7. Laboratory parameters

Baseline- Hemoglobin (Hb)……. MCV……. RDW…… Interpretation……

Recent- Hemoglobin (Hb)……MCV……. RDW……. Interpretation……..

Transfusion history No [ ] Yes [ ] If yes: _____

8. Infection history during/after therapy

| | |
|---|---|
| Infection confirmation method | |
| Infection type | |
| Antibiotic days | |
| Febrile neutropenia episodes | |
| Infection admissions required | No [ ] Yes [ ] Number: ____ |

9. Treatment characteristics

| **Therapy** | **Yes/No** | **Details** | **Dates** |
|---|---|---|---|
| ABVD | Yes [ ] No [ ] | Number of cycles: _____ | Start: ____ End: ____ |
| COPDAC | Yes [ ] No [ ] | Cycles/notes: _____ | Start: ____ End: ____ |
| Anthracycline exposure summary | Yes [ ] No [ ] | Cumulative dose (mg/m²): _____; No. infusions: _____; Dose/infusion (mg/m²): _____ | |
| Cyclophosphamide | Yes [ ] No [ ] | No. infusions: _____; Total dose: _____ | |

10. Radiotherapy

Radiotherapy received- Yes [ ] No [ ], RT dose and fraction…… Start date…….End date……..

11. Echocardiography history

Previous echocardiogram(s) documented- Yes [ ] No [ ], Number of echocardiograms done……

11.1 Echocardiogram 1

Date……. Phase, Baseline [ ] Mid [ ] End [ ] Follow-up [ ], Time frame (e.g., from last chemo) …….

| **2D(cm)** | | **M-Mode** | | **Doppler** | |
|---|---|---|---|---|---|
| RA | | IVSd | | MV-E | |
| LA | | IVSs | | -A | |
| RV | | LVIDd | | E/A | |
| PVAnn | | PWDd | | TDI –E’ | |
| MVAnn | | PWDs | | E/E’ | |
| TVAnn | | EF | | Peak TR velocity | |
| MPA | | FS | | IVCT | |
| LPA | | TAPSE -Lateral wall | | IVRT | |
| RPA | | | | ET | |
| Ao | | | | Tei index | |

11.2 Echocardiogram 2

Date……. Phase, Baseline [ ] Mid [ ] End [ ] Follow-up [ ], Time frame (e.g., from last chemo) …….

| **2D(cm)** | | **M-Mode** | | **Doppler** | |
|---|---|---|---|---|---|
| RA | | IVSd | | MV-E | |
| LA | | IVSs | | -A | |
| RV | | LVIDd | | E/A | |
| PVAnn | | PWDd | | TDI –E’ | |
| MVAnn | | PWDs | | E/E’ | |
| TVAnn | | EF | | Peak TR velocity | |
| MPA | | FS | | IVCT | |
| LPA | | TAPSE -Lateral wall | | IVRT | |
| RPA | | | | ET | |
| Ao | | | | Tei index | |

12. Study Echo

Done by- Examiner1……. Examiner 2……

| **2D(cm)** | | **M-Mode** | | **Doppler** | |
|---|---|---|---|---|---|
| RA | | IVSd | | MV-E | |
| LA | | IVSs | | -A | |
| RV | | LVIDd | | E/A | |
| PVAnn | | PWDd | | TDI –E’ | |
| MVAnn | | PWDs | | E/E’ | |
| TVAnn | | EF | | Peak TR velocity | |
| MPA | | FS | | IVCT | |
| LPA | | TAPSE -Lateral wall | | IVRT | |
| RPA | | | | ET | |
| Ao | | | | Tei index | |