Addis Ababa University

College of Health Sciences, School of Medicine

Department of Pediatrics and Child Health

Pediatric Hematology and Oncology Unit

IDENTIFY FACTORS RESULTING IN DELAYED DIAGNOSIS AND TREATMENT OF PEDIATRIC RETINOBLASTOMA:MULTICENTER CROSS-SECTIONAL STUDY, ADDIS ABABA, ETHIOPIA

A Research Paper to be submitted to the Pediatric Hematology and Oncology Unit, Department of Pediatrics and Child Health, School of Medicine, College of Health Sciences, Addis Ababa University in Partial Fulfillment of the Requirements for the Sub-Specialty Certificate in Pediatrics Hematology and Oncology

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September 2024 ADDIS ABABA ETHIOPIA

ADDIS ABABA UNIVERSITY, COLLEGE OF MEDICINE AND HEALTH SCIENCES, DEPARTMENT OF PEDIATRICS AND CHILD HEALTH UNIT OF HEMATOLOGY - ONCOLOGY

I, the undersigned Pediatrics and Child Health fellowship declare that I have submitted my original thesis on the title Identifying Factors Resulting in Delayed Diagnosis and Treatment of Pediatrics Retinoblastoma among Selected hospitals in Addis Ababa, Ethiopia 2024 in partial fulfillment of the sub-specialty specialty program.

Submitted by:

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September,2024

Abstract

Background: Retinoblastoma is the most common pediatric intraocular tumor, it is rare compared to other pediatric cancers, accounting for approximately 3 to 4% of all childhood malignancies. More than 60% of cases in low-income countries are advanced retinoblastoma, and mortality is significant due to delayed presentation, diagnosis, and treatment, with more than 50% of patients dying. This study determined the sociodemographic profile, clinical profile, diagnosis and treatment modalities, and factors affecting early diagnosis and treatment of pediatric retinoblastoma who were treated in TASH, St. Paulos, and Menelik specialized hospitals in Ethiopia from April 1, 2023, to June 30, 2024.

Objective: The primary aim of this study was to identify factors resulting in delayed diagnosis and treatment of RB at Tikur Anbessa, St, Paulos, and Menelik specialized hospital, Addis Ababa, Ethiopia

Method: A prospective multicenter study of all pediatric patients diagnosed with retinoblastoma at, Tikur Anibessa, St, Paulos, and Menelik the II specialized hospital, Ethiopia. All 111 newly diagnosed pediatric retinoblastoma cases were included in the analysis to establish the extent of presentation, diagnosis, treatment, delay, and associated reasons. Data was collected prospectively for those who fulfilled the inclusion criteria by using a semi-structured checklist questionnaire prepared from previous literature with amendments. The data was coded, cleaned, and entered into the SPSS version 26 software program, and analysis was done. The data was categorized and summarized with descriptive statistics, and univariate and multivariate binary logistic regression analysis examined the factors associated with the treatment delay of retinoblastoma. Logistic regression results revealed that adjusted odds ratios (OR) with 95% confidence intervals and p-value < 0.05 are statistically significant.

Result: The analysis of 111 newly diagnosed pediatric retinoblastoma cases was conducted. Males accounted for 51.4% of diagnoses. The median age is 40 months for unilateral and 22 months for bilateral retinoblastoma. More than 59.5% of patients have a delayed time to treatment initiation. The median time before starting treatment was 6.2 months. The most prevalent reasons for delayed treatment were the guardian's lack of knowledge of the disease, delayed referral, and being so far from the treatment center.

Moving on to associated factors for delayed presentation, diagnosis, and treatment of retinoblastoma, far residency from treatment (AOR=1.5, p=0.035), lack of caregiver awareness (AOR=3.64, p=0.044), and delayed referral (AOR =2.95, p=0.035) emerged as the most statistically significant variables determining total treatment delay.

Conclusion: Results from our study show that more than half of the pediatric RB patients experienced a total delay of more than 6 months. Lack of RB awareness among guardians, referral delays, and travel challenges, were significant barriers to receiving timely care. As a result, there is an urgent need for high-level actions and an evidence-based approach to addressing determining factors

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Abbreviations Acronyms:

- AAU ----------Addis Ababa University
- CT----------Computed tomography
- CR---------- Complete Remission
- (EBRT)---------- External beam radiotherapy
- HOC---------- Hematology and oncology clinic
- MRI ----------Magnetic resonance imaging
- MDT----------Multidicipline Team
- PLONK----------Post laminar optic nerve invasion
- PR ----------Partial Remission
- PD ----------Progressive Disease
- (PCPs) ----------Primary care physician
- PI----------Principal investigator
- PATE----------Pediatrics and Child Health
- PROF----------Pediatrics hematology and oncology fellow
- RB ----------Retinoblastoma
- R ----------Recurrence
- SAM----------Severe acute malnutrition
- TASH ----------Tikur Anbessa Specialized Hospital.

CHAPTER ONE: INTRODUCTION

1.1. Background:

Retinoblastoma is the most common intraocular cancer and embryonic neural retina malignancy in children(1,2,3, 4). Although it is less common than other childhood cancers, retinoblastoma accounts for 3% to 4% of all pediatric malignancies(5,6,7). Studies show that the majority of retinoblastoma cases occur in Asia (53%), followed by Africa (29%), Latin America (8%), North America (3%), and Europe (6%(2). Retinoblastoma can appear as unilateral, bilateral, and, rare trilateral or quadrilateral. About 10% to 15% of children with unilateral retinoblastoma have a germline mutation({8-11). The disease is unilateral in 60% of cases, with a median diagnosis age of two years, while it is bilateral in 40% of cases, with a median diagnosis age of one year. Clinical signs often include leukocoria (present in approximately 71.8% of cases), strabismus, orbital cellulitis, proptosis, intracranial extension (12.5%), and bone metastases (9.3%). Both leukocoria and strabismus are observed in 60% of cases(12).

Approximately 95% of retinoblastoma cases are identified before the age of 5, with 80% being diagnosed before the age of 3 or 4, and a median diagnosis age of 2 years, though it can occur at any age(13-15). If left untreated, retinoblastoma is life-threatening. In the United States, the 5-year overall survival rate for retinoblastoma improved from 92.3% during 1975–84 to 93.9% from 1985–94, and further to 96.5% from 1995–2004. Conversely, in developing countries, where retinoblastoma is often diagnosed as a more advanced disease, the 5-year survival rate is less than 30 to 50% (14,16). Diagnoses of retinoblastoma are determined through a combination of patient history, physical examination, histological analysis, and radiological imaging. A cranial or orbital computed tomography (CT) scan is useful for detecting intraocular calcifications and assessing the extent of the tumor. Magnetic resonance imaging (MRI) of the brain and orbit is the most sensitive method for evaluating extraocular spread, providing superior detail of the optic nerve and pineal region(17).

The classification of retinoblastoma (RB) depends on the advancement of the disease and the presence of extraocular extension, covering all stages of the disease (16). cases where the disease is intraocular, treatments aimed at preserving the eye include transpupillary thermotherapy, cryotherapy, systemic chemotherapy, and periocular chemotherapy. Globe salvage therapies are employed for eyes classified as group A–C, whether the disease is unilateral or bilateral (15, 17). For unilateral Group D eyes, patients are presented with both enucleation and globe salvage options. In cases of bilateral Group D disease, globe salvage therapy is recommended to preserve at least one eye. If chemotherapy and focal treatment have failed, external beam radiotherapy (EBRT) or enucleation may be suggested. Group E eyes are primarily treated with enucleation. For children with high-risk histopathological features in the enucleated eye, adjuvant chemotherapy consisting of six cycles of intravenous vincristine, etoposide, and carboplatin is administered every 3–4 weeks(16)The standard approach for treating extraocular tumors involves administering 2 to 3 cycles of neoadjuvant chemotherapy, followed by enucleation, external beam radiotherapy (EBRT), and an additional 4 to 6 cycles of adjuvant chemotherapy. For metastatic cases with a very poor survival outcome, palliative care is recommended. Treatment strategies may be influenced by delays in presentation, diagnosis, and the guidelines set by the National Institute for Health and Care Excellence.

There are different lag times identified for diagnosing and treating retinoblastoma. Lag I refers to a lag time greater than two weeks from the initial sign and symptom to the first day of visiting the first health center, with a delay to ophthalmology if not sent in 48 hours. Lag II refers to a delay if the patient does not refer to a retinoblastoma treatment center within two weeks. Lag III refers to a total lag time greater than two months, indicating delayed diagnosis and treatment if the patient is not diagnosed or does not start treatment immediately on the day of diagnosis(18). Delayed diagnosis and treatment varies across institutions, but in most low and lower-middle-income countries delayed diagnosis and treatment are defined if the total lag time is greater than six months. This extended delay in diagnosis is associated with poor EFS and OS (78 vs 91%) (14,15).

1.2. Statement of the problem:

Although survival rates of retinoblastoma are more than 95% in developed nations, only 30 to 50% of patients survive worldwide ((1)). This discrepancy is large as a result of earlier detection in developed nations while in developing countries, most cases of retinoblastoma are detected at advanced stages ((19).

Early diagnosis and treatment of retinoblastoma are crucial to halt its progress. The mortality rate due to retinoblastoma is 3% to 5% in developed countries, 39% in Asia, and 70% in Africa (6,11). In middle-income countries. lag time less than 6 months (91%), in comparison to patients with a longer lag time(delayed time greater than 6 months (78%; $p < 0.001$)(14). Survival from RB in developing countries like Ethiopia is poorer than that of other developing countries ((20, 21),(22)) and it has been suggested that this can be attributed to a more advanced disease stage at presentation related to delayed diagnosis and treatment.

A retrospective analysis conducted at Menelik II Hospital revealed that 68% of cases had been there for more than six months, while 47% of patients had been there for more than a year. According to an unpublished retrospective study conducted at Tikur Anbesa Hospital, the rates of advanced presentation, group D/E, locally advanced, and metastasis are 74 and 24%, respectively, and were linked to delayed diagnosis and treatment. Therefore, the purpose of this study is to evaluate the various risk factors that influence early diagnosis and treatment among a population of pediatric retinoblastoma patients at Tikur Anbesa Specialized Hospital, St. Paulos, and Menelik Hospital in AA, Ethiopia.

1.3. Significance of the study

So knowing the cause of delay and associated risk factors is very important to solve the problem. To date, there are no multicenter prospective studies done in Ethiopia to assess the delayed presentation, diagnosis, and treatment of RB cases. The purpose of this study is to identify the risk factor resulting in delay. Identifying the risk factors will help to decrease advanced disease, preserve vision, and reduce mortality. This study will be used as input for the Federal Ministry of Health to design appropriate strategies to detect patients before reaching an advanced stage of retinoblastoma. In the end, it will help to decrease advanced RB-related mortality and vision loss. Finally, it will be used as a baseline for the next perspective of studying.

CHAPTER TWO: LITERATURE REVIEW

2.1. Globally

The global incidence of retinoblastoma is predicted to be 1 in 16,000-18,000 live births, with an additional 8,000 cases projected each year (6, 20). From 1975 to 2004, research in the United States reported 658 retinoblastoma instances, accounting for 6.1% of all pediatric malignancies in children under the age of five. Of these cases, 26.7% were bilateral and 71.9% were unilateral(13).

A study of 253 patients found that 80.2% had unilateral retinoblastoma, whereas 19.8% had bilateral. The median age of onset was 21 months, and leukocoria was the most prevalent initial symptom (71%). Intraocular tumors were observed in 91.3% of cases, with extraocular tumors reported in 8.7%. Patients with extraocular retinoblastoma had a longer median delay to diagnosis than those with intraocular disease (9 months versus 2 months) ((7)).

A study conducted in England, nearly half of patients were sent to an ophthalmologist within one week of their initial visit, while the other 25% faced delays of more than eight weeks. Diagnostic delays are especially common in younger patients, those who come with squint rather than leukocoria, and those who are first seen by a health visitor rather than a general practitioner. Such delays considerably increase the probability of local tumor invasion ((23)).

An analysis of 327 medical records (171 boys) with an average age of 25 months revealed localized illness in 269 cases. The most frequently reported symptoms were leukocoria (79%), strabismus (10.7%), and tumor mass (3.4%). The typical diagnostic delays were 5.8 months. Patients with strabismus had a significantly longer lag time (8.8 months) than those with tumor mass (2.3 months) or leukocoria (5.6 months; $p = 0.014$). Patients with advanced illness experienced considerably longer lag times (10.6 months; $p < 0.001$)(24).

The study included 572 patients (326 boys), with an average age of 2.6 ± 1.8 years. The average period from symptom discovery to clinical diagnosis and therapy was 4.1 ± 5.9 months, with a range of 3–36 months. A diagnostic delay of more than 6 months was reported in 337 children (59%), while 98 children (17%) experienced such delays(25).

A prospective analysis of 179 patients in Mexico Hospital in Mexico City from 2000 to 2010 found that 60.9% were unilateral. The mean lag time for unilateral disease was 6.73 months (range 0.25 to 66 months), but for bilateral disease, it was 7.54 months (range 0.25 to 24 months; $p = 0.09$). This study found a considerable association between lag time, maternal education, and low socioeconomic status (26).

From 1991 to 2000, in Brazil, a retrospective study was done on 327 patients. This study discovered that 32% of patients had a delayed presentation (>6 months), with an average lag period of 5.8 months. The five-year overall survival rate was 91% for patients with a lag time of less than 6 months, compared to 78% for those with a lag time of more than 6 months ($p = 0.001$). Strabismus had a significantly longer lag time (8.8 months) than mass (2.3 months, $p<0.001$) or leukocoria (5.8 months, $p=0.014$). Metastatic illness was associated with a significantly longer lag time (10.6 months). The mean age of presentation was 25 months, and leukocoria was the most common presentation, occurring in 79% of cases(27).

A tertiary pediatric oncology center conducted a retrospective analysis from 1988 to 2012, which included 140 patients. The study discovered that 65% of the instances were unilateral, 32.9% were bilateral, and 2.1% were trilateral. The average age at which the family first detected symptoms or signs was 18.1 months. The average age at diagnosis was 23.5 months, with a mean lag period of 5.3 months. Leukocoria was the most common sign (73.6%), followed by strabismus (20.7%). 10.7% had metastatic disease. Exenteration had been performed in 11.9% of patients, whereas enucleation was done in 88.1%(28).

A retrospective analysis of 157 cases was undertaken in Tehran from 2007 to 2011, Of the patients, 59 (58%) were male, with a mean age at presentation of one year. The average time between onset of symptoms and diagnosis was 3.4 ± 0.53 months. A total of 55 cases (66.9%) had a diagnostic lag time of less than 5 months, with 9 cases (5.7%) detected after more than 15 months. Among those cases, 93 (59.2%) were unilateral, with 141 (89.9%) being intraocular. Leukocoria was observed in 106 children (67.5%(29)

In Pakistan, a prospective study looked into the factors for the delayed diagnosis of retinoblastoma (RB). It was discovered that parental factors contributed to 52 cases (65%) of delayed presentation, and physician-related problems caused referral delays in 57 cases (71%). Eighty-five cases (81%) of the cases had advanced disease upon presentation. Of the cases, 61 (76.2%) had intraocular,19 (23.7%) had extraocular RB, and 25 (31.25%) had bilateral. Of the cases, 55 (68.75%) had unilateral. For both bilateral and unilateral RB, the average age at presentation was 25 months and 14 months, respectively. There were notable correlations discovered between knowledge of guardian and delayed presentation $p=0.015$ (30).

2.2: Africa

In Egypt, 47 children were involved in a retrospective study between January 2012 and June 2014. For unilateral instances, the median age at presentation was 25 months, but for bilateral cases, it was 11 months (p=0.03). Of the cases, 96% had leukocoria upon presentation, 7% had a familial history, and 52% were unilateral. For unilateral cases, the median time to diagnosis ranged from 1 to 15 weeks, while for those that were bilateral, it was 3 weeks. In comparison to bilateral instances, 62% of unilateral cases experienced diagnosis delays. Referral delays ranged from 0 to 7 weeks for unilateral patients and 0 to 8 weeks for bilateral instances (p=0.07), with 60% of cases experiencing a delay(31).

In a cross-sectional study carried out in Ghana between 2008 and 2011, forty guardians participated in question-based interviews. White spots were recorded as the first presentation symptoms in 87.5% of patients, red eyes in 7.5%, proptosis in 2.5%, and strabismus in 2.5% of cases. Children with more severe diseases were typically brought in by caregivers with lesser educational backgrounds. Thirty-two months later, only fifty percent of the cases had been presented(32).

A retrospective analysis conducted in Kenya between January 2006 and December 2007 found that 206 patients with retinoblastoma had been diagnosed in 51 Kenyan and 2 international medical facilities. The average presentation lag time was 6.8 months (±6.45), while the average referral lag time was 1.7 months (±2.5). The average delay in referrals was found to be 1.7 months (±2.5)(33).

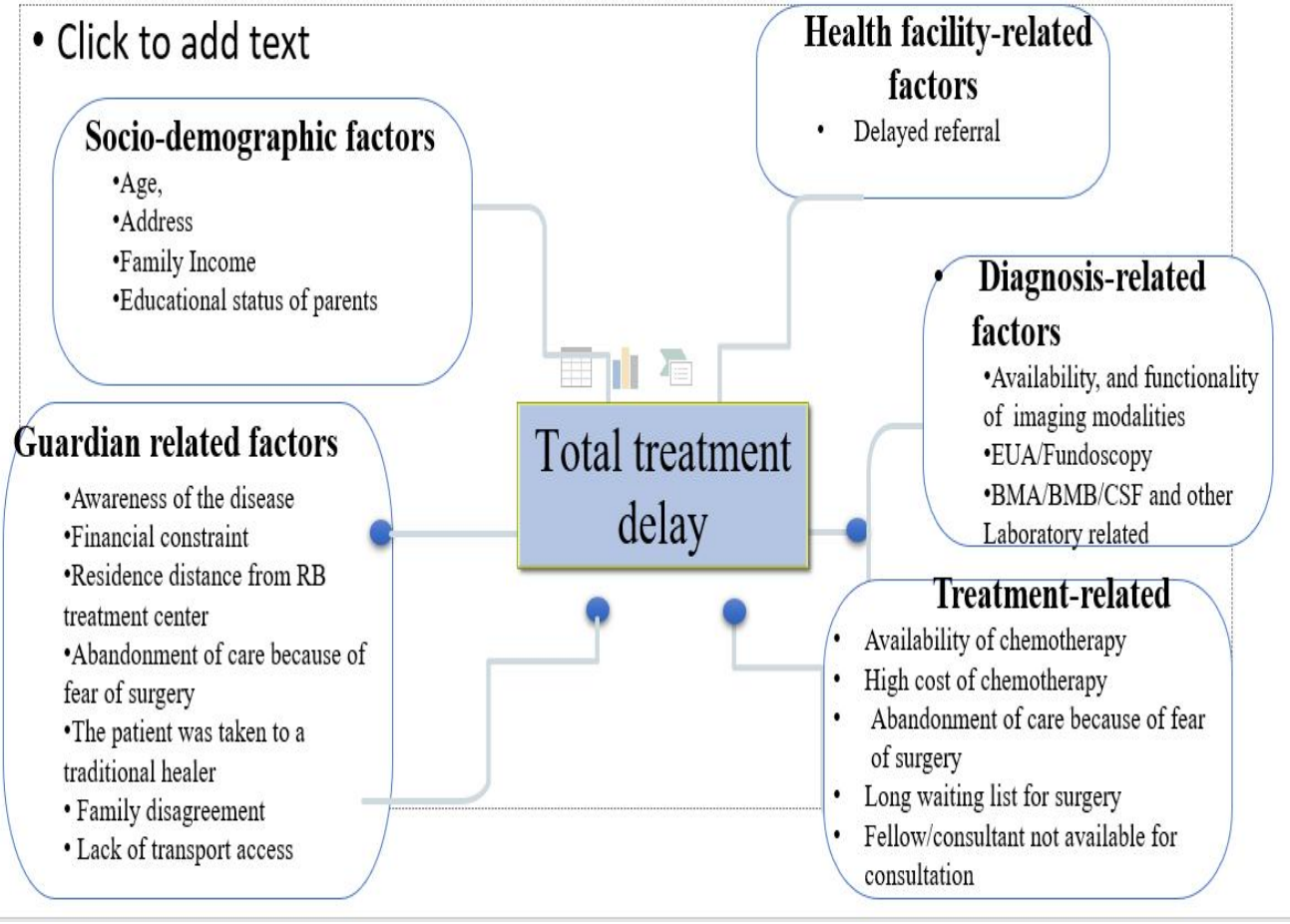
2.3:Ethiopia

Menelik II Hospital analyzed 38 cases as part of a retrospective investigation that took place between 2015 and 2017. Delays of more than three months occurred in 76% of cases, more than six months in 68% of cases, and more than twelve months in 47% of cases. The main reason for these delays was that families were unaware of the disease, with travel expenses accounting for the second most frequent explanation (34).

An additional retrospective study that covered four tertiary hospitals over the period from January 2017 to December 2020 found a total of 221 cases. 52% of these incidents included men, while 48% involved women. In 5% of instances, there was a familial history of retinoblastoma, and 83.7% of cases were unilateral. 38.9% of the patients were from Oromia, 19.9% were from the Amhara area, 16.7% were from Addis Ababa, and 14.4% were from SNNPR (35).

A retrospective analysis of registered instances of retinoblastoma at Jimma between August 2016 and July 2020 showed that 3 cases (9.4%) had bilateral retinoblastoma, whereas 29 cases (90.6%) had unilateral retinoblastoma. For bilateral, the average age of presentation ranged from 3 to 30 months, while for unilateral cases, it ranged from 8 to 84 months. In 21 patients (65.6%), leukocoria was the initial symptom noticed by the family; nevertheless, 24 patients (75%) had advanced stages of the disease, including proptosis and fungating orbital mass. The average time lag between the onset of symptoms and therapy was 1.4 months for bilateral instances and 6 months for unilateral cases, with a range of 2 weeks to 17 months(36).

Conceptual framework



CHAPTER THREE: OBJECTIVE

3.1. General objective.

- To identify determinants of pediatric retinoblastoma treatment delay at Tikur Anbessa specialized hospital, Sent. Paul's Minimum Medical College Hospital, and Menelik referral Hospital in Addis Ababa, Ethiopia from **April 1, 2023, to June 30, 2024**

3.2. Specific objectives

- To identify risk factors contributing to delayed presentation diagnosis and initiation of treatment for retinoblastoma
- To assess the pattern of clinical presentation for retinoblastoma.
- To assess the diagnosis modality of retinoblastoma and the course of treatment.

CHAPTER FOUR: METHODOLOGY

4.1. Study area

This study was carried out in three hospitals in Addis Ababa, Ethiopia: TASH, St. Paulose, and Menelik II referral hospital. TASH was established in 1972 and has been the nation's largest tertiary hospital, with 21 specialty departments, numerous clinical departments, and 200 doctors, 379 nurses, and 115 other health professionals committed to providing health care services(37). Addis Ababa is Ethiopia's capital city and the home of the African Union. Its population, as of the 2007 census, is 2,739,551. Its land size is 527 square kilometers, and it is located 2355 meters above sea level. Its coordinates are 38°44'4"E and 9°1'48"N (38). The first PHO unit in the country was established in April 2013. Monthly assignments include twenty nurses, six fellows, ten residents, and three pediatric hematologist-oncologists. Basic diagnostic procedures are widely accessible, including tests for liver and kidney function as well as complete blood counts. There are currently imaging modalities available, such as computed tomography (CT). Chemotherapy and surgical treatments are available. Radiation therapy for young patients is challenging since the facility's capacity for conscious sedation isn't optimal for treating pediatric patients. TASH has 42 beds available for inpatient care. Every week, the clinic welcomes ten to fifteen new patients on average, and each month, it treats five hundred to eight hundred cases. At TASH, retinoblastoma is treated with radiation, enucleation, and chemotherapy after cases discussed at the multidisciplinary team meeting.

The second area of research was conducted at Menelik II Hospital in Addis Ababa. Menelik II Referral Hospital is situated 10 kilometers northeast of the capital city's core, higher 13 Kebele 06. The hospital was built as a clinic in 1896 E.C. after the Italian military force was defeated in the battle of "Adwa" and Ethiopian patriots settled in Addis Ababa in the area known as Jalmeda. Later, Emperor Menelik II re-established the hospital in 1902 E.C. Now, the hospital is a tertiary eye center that treats patients from all over the nation. Every day, the ophthalmologist and/or residents see all eye patients. Menilik II Comprehensive Hospital is one of the town's historic hospitals and home to the ophthalmology department and medical services. This center has been treating retinoblastoma patients. Patients are referred to the TASH Pediatric Oncology Department after their case has been diagnosed and verified. There, they will receive a multidisciplinary managing team treatment plan. In addition to pediatric ophthalmology, oncology, and wards, Menelik Hospital has 180 beds, 12 community beds, and 5 emergency beds. Eye Care additionally features four surgical rooms, training rooms, and forty-five examination rooms. three to four new pediatric patients on average each week. Four operating theaters, an Average of 3 to 4 new pediatric patients/per week and the clinic gives service to about 15 RB patients per month, a total of 3 to 4 retinoblastoma operations per week which was done by pediatric ophthalmologist (39).

St. Paul's Millennium Medical College was established in 2010 by a decision of the Council of Ministers. Although the medical school started in 2007 and the hospital was founded in 1968 by the late Emperor Haile Selassie, the current name is under the Federal Ministry of Health. The College created Ethiopia's first hybrid, integrated, modular curriculum for undergraduate medical education. It is actively expanding into postgraduate programs and broadening the scope of its undergraduate offerings. In the previous six years, St. Paul's has grown from three to 250 staff members, and the school is currently expanding its teaching facilities to soon reach capacity. The college employs over 2800 clinical, academic, administrative, and support staff to provide medical specialty services to patients referred from across the nation. The college also conducts basic and applied research, teaches medical and nursing students, and sees an average of 1200 emergency and outpatient clients per day (40). The pediatrics hematology-oncology unit at St. Paul was established in 2021 and currently has 18 in-patient beds as well as 2 to 3 new cases per day(40).

4.2. Study design

Hospital-based multicenter prospective cross-sectional study design is conducted.

4.3. Study period.

The study was conducted, at Tikur Anbessa Specialized Hospital, Sent. Paul's Minimum Medical College Hospital, and Menelik referral Hospital in Addis Ababa, Ethiopia from April 1, 2023, to June 30, 2024

4.4. Population

4.4.1. Source population

- All pediatric Cancer patients at TASH, St, Paul, and Menelik II

4.4.2. Study population

- Newly diagnosed RB cases aged <15 years within the study period

4.5 Inclusion and Exclusion Criteria

4.5.1. Inclusion criteria

- All retinoblastoma patients aged less than 15
- Patients who have brain imaging

4.5.2. Exclusion Criteria

- Relapse patient
- A patient who no brain imaging
- Patients referred after starting treatment outside AA
- The patient referred from one treatment center to another center after starting chemotherapy
- Patient referred from one treatment center to another for radiotherapy only

4.5. Sample size determination

Since retinoblastoma is a rare disease the sample size is determined using the adjusted single-population proportion formula. The p-value is taken from a single-center retrospective study done by Menelik II Hospital from 2015 to 2017 in a total of 85 patients. The proportion of patients with lag time≥ 3, ≥6, and ≥ 12 months were 76%, 68%, and 47% respectively.

The total cases of RB in the study period taken from HMIS of the three selected hospitals including TASH, S, Paulose, and Menelik II are 162(76,60 26) respectively. Since the total population is <10,000, I used the reduction formula, and 10% was added.

Sample size: n=Z2P (1-P) =1.962 *0.68*(1-0.6) = 334

d2 (0.05) 2

where: n= desired minimum sample size p= Estimated sample proportion

Adjust the sample size(nf) = $[z^2 * p(1-p)] / e^2 / 1 + [z^2 * p(1-p)] / e^2 * N]$=109.2

P=0.68

N=162

n-334

d-5%

Adding 10% of the calculated value for missing and caregivers refusing the interview or not signing the consent form, the final sample size required was 120.

4.6. Sampling method

- All populations that fulfill inclusion criteria will be included in the study

4.7. Data collection

The questionnaire was modified based on in-depth reviews of the literature. After the patient had given informed consent, data from their caretaker interviews and referral documents were gathered using a semi-structured questionnaire that was given by the interviewer. The survey was created in English and then translated into Amharic. To make sure the questions were pertinent and clear, the questionnaire was pretested with 5% of the sample size before the main data collection. The principal investigator will provide training and supervision to the second or third-year pediatric and child health residents who collected the data. The database compiles To evaluate various degrees of delay, sociodemographic details about the child and the caregiver were first collected.

4.8. Data quality assurance

The principal investigator looked at the suitability of the employed techniques. Weekly checks were made by PI to ensure that the information on completed questionnaires was consistent and comprehensive at the time of data collection. Uncertainties and other issues encountered by data collectors were resolved. The template included checks for internal consistency. The study was carried out following the code of ethics.

4.9. Variables

4.9.1. Independent variables

- Patient factor
    - Age at diagnosis
    - Educational status of parents
    - Cost of travel
    - Residence distance from RB treatment center
    - Abandonment of care because of fear of surgery
    - lack of disease awareness of the family about the illness/not considered a serious problem
    - The patient was taken to a traditional healer
    - family disagreement
    - Lack of transport access

Healthcare provider-related factors

Due to a Lack of awareness about the disease patient was sent back despite presenting early

Treatment center-related factors

- Cost of imaging modality
- The MRI/CT is not functional
- Fellow/consultant not available for consultation
- Related to other laboratories not functional
- BMA, biopsy, CSF,
- For EUA/fundoscopy evaluation
- High cost of medication
- Medication not available
- Long waiting list for surgery
- Fellow/consultant not available for consultation

4.9.2. Dependent variable

Delayed presentation, diagnosis, and treatment

4.10. Operational definitions

- Delayed presentation/parenteral delay when the lag time from family noticed the sign/symptom to the first health care visit ≥2 weeks(18)
- Delayed referral/ health provider referral time is greater than ≥2 weeks(18)
- Total delayed time is the lag time since the family noticed the first symptom and sign to the initiation of treatment is ≥ 6 months
- Delayed treatment when the patient has not started treatment on the day the diagnosis is established
- Total treatment lag time the time interval between the caregiver ***first*** noticed the sign/symptom to the initiation of treatment
- Bilateral when both eyes are involved by retinoblastoma
- Trilateral RB= Retinoblastoma in both eyes and pineoblastoma /pineal involvement
- Quadrilateral suprasellar
- Well-differentiated had rosettes in more than 80% of their area
- Poorly differentiated tumors did not have rosettes,Moderately differentiated < 80%
- Complete Remission; CR- Absence of disease clinically (no signs and symptoms of the disease after clinical and ophthalmologic examination or imaging.
- Partial Remission; PR- Reduction of the tumor (size) and/or signs and symptoms of disease clinically.
- Persistent/Progressive Disease; PD- The signs and symptoms of the disease have either reduced very little, remained constant, or increased clinically over time.
- Pathological high risk: involvement of anterior chamber, sclera, optic, post laminal, diffuse choroidal, surgical margin positive involvement
- Relapse; R- After being in complete remission for some time, signs and symptoms have occurred again clinically
- Lost to follow-up; Those who do not have complete follow-up data due to several reasons at the time of the study.
- Defaulter who initiated treatment but discontinued treatment before completion

4.11. Data analysis

Data extracted from the checklist questionnaire charts were coded and cleaned and the registry was entered into a computer using SPSS version 26 software program for further analysis. Simple descriptive statistics such as frequencies, and percentages, and compared between groups using the chi-square test. The normal distribution of continuous variables was assessed using the Shapiro-Wilk test. The mean and standard deviation were calculated for normality distributed data while the median and interquartile range were calculated for skewed data. Multicollinearity test performed for categorical, continuous, and binary variables. Multicollinearity was measured by variance inflation factor (VIF) and tolerance. When a VIF was below five and tolerance was above 0.1, variables were forwarded to multivariable binary logistic regression analysis. Variables with a VIF score of 5 to 10 and tolerance below 0.1 were excluded from the final model. A univariate and multivariate binary logistic regression analysis was performed to examine the factors associated with retinoblastoma treatment delay. Those variables that will be found to be significant in the bivariate analysis($p < 0.25$) will be retained for further multivariate analysis. A multivariable binary logistic model was employed to adjust cofounder factors. The results of logistic regression reported as adjusted odds ratios (OR) with 95% confidence intervals and p-value < 0.05 were considered statistically significant.

4.12. Ethical considerations

The study was conducted after ethical approval was obtained from AAU, college of health sciences. The study was also approved by the Department of Pediatrics and Child Health Research and Ethical Committee of AAU and the Department of Pediatrics and Child Health of Sent Paulos Hospital. Written consent was taken and signed by the primary caregiver. The objective of the study was briefed to the staff of the documentation department. Documents and Information obtained at each course of study will be kept confidential.

4.13. Dissemination of result

The findings of the study were presented to the Department of PACH /AAU. Depending on the findings from the data, conclusions, and recommendations were made. Then, copies of the research paper were submitted to the AAU College of Health Science and the department of PACH. If possible, it will be published in journals as well.

CHAPTER FIVE:RESULTS

5.1.1.Socio-demographic characteristics

An analysis of 111 newly diagnosed pediatric retinoblastoma cases revealed intriguing insights into the population studied. Among the participants, 51.4 %(n=57), were male, showcasing a male gender predominance within the study, with a male-to-female ratio of 1.1: 1. The study revealed a median age of diagnosis 40 (IQR=30) months with an age range of (4 to 99 months in unilateral and 22 (IQR=10) for those bilateral retinoblastomastoma. Most patients came from the Oromia region (38.7%), and Addis Ababa (15.3%) with 1(0.009%) case from Harar and Diredewa each. None were from Benishangul-Gumuz and Gambela. Parents were the primary caregivers; father (46%), mother (25%), and both parents (34%). non-relatives (6%), From all caregivers 26% had no formal education, (and 46%) had secondary and college-level education. Most caregivers were farmers (40%), followed by Government employees (38%).

We also observed that the overall distance from home to the treatment center has a Median of 280(IQR=405 Km. The average No of healthcare visits before reaching to treatment center was 2.16±0.869. The median family income per month is 15600(IQR16000). Another important finding of this study is that 50.5% of the cases had community-based health insurance reflecting the extent of health coverage. According to these studies around 54% of the family had under-five children.

Table 1: Socio-demographic characteristics of the patient and caregiver among pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

Variable	Response	Frequency	Percentage
Sex	Male	57	51.4
	Female	54	48.6
Family size	1-3	71	64.0
	4-6	32	28.8
	>7	8	7.2
No of under 5 children	0	51	45.9
	1	45	40.5
	2	13	11.7
	3	2	1.8
Distance from home to treatment center	<100 km	25	22.5
	101-300km	38	34.2
	301-500km	15	13.5
	>500km	33	29.7
Primary guardian	Mother	25	22.5
	Father	46	41.4
	Both	34	30.6
	Nonrelatives	6	5.4
Guardian's Level of education	No formal education	26	23.4
	Can read and write	9	8.1
	Grade 1-8	22	19.8
	Grade 9-12	33	29.7
	Collage/University	21	18.9
Guardian's occupation	Government	38	34.2
	Merchant	26	23.4
	Farmer	40	36.0

	Other	7	6.3
Community-based health insurance	Yes	56	50.5
	No	55	49.5
Age at initial symptom in months	Median + IQR	32(IQR=24)	
Age at diagnosis in months	Unilateral Median +IQR	40(IQR=30)	
	Bilateral median	22(IQR=10)	
Family size	Median +IQR	3(IQR=3)	
Distance Km	Median ±IQR	280(IQR=405)	
Distance in Hrs.	Median ± IQR	5(IQR=7)	
Cost of travel	Median ± IQR	500(IQR=600)	
Family income per month	Median ± IQR	15600(IQR=16000)	
No health care visits before reaching to treatment center	Mean ± SD	2.16±0.869	

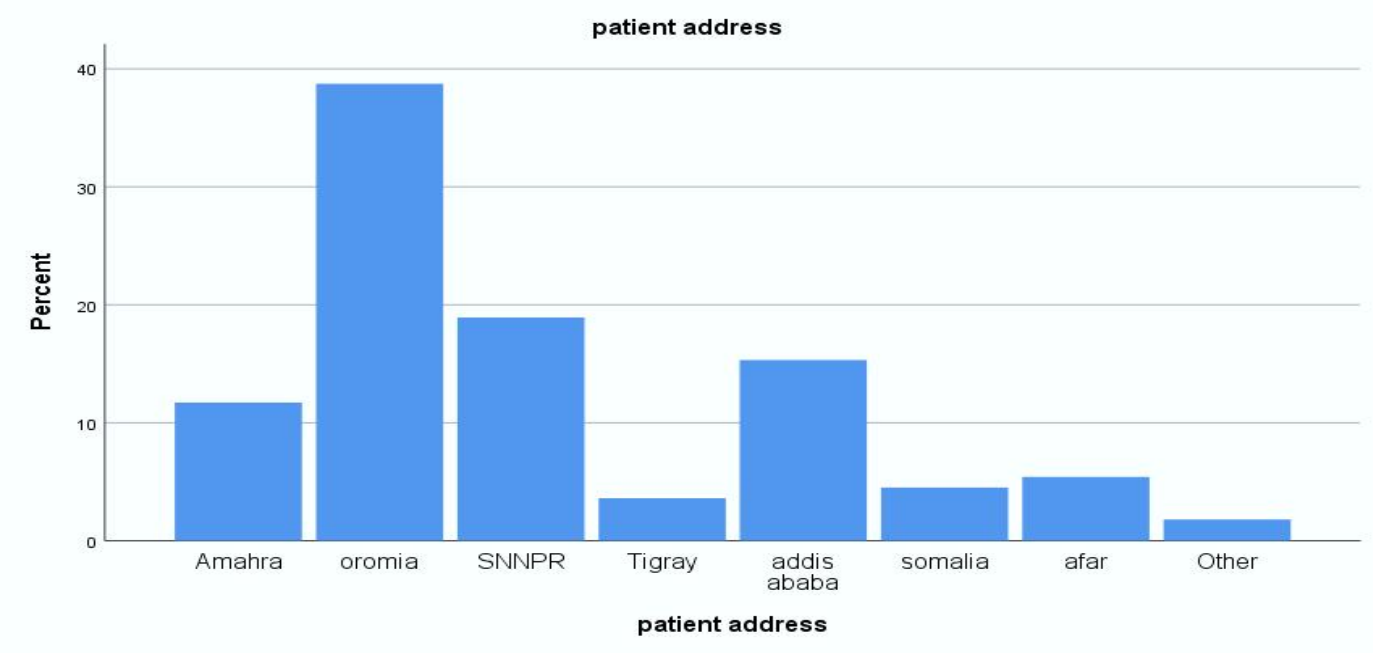


FIGURE: 1 Address of caregivers and patients among pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

Figure Distance from home to RB treatment center in Km among pediatric RB patients AA, Ethiopia, April 1, 2023, to June 30, 2024 (n = 111)

5.1.2.Clinical characteristics and diagnosis:

The most common first symptom of disease, leading parents to seek care at the first care provider level, was leukocoria (78/111, 70.3%), followed by strabismus (13/111, 11.7%). The most common finding on physical examination accounting for more than 2/3 was leukocoria (71.2%), and eye swelling (47.7%) and the uncommon finding was neurological deficit (0.9%). A significant portion, nearly 84.6% of patients had unilateral eye involvement with right side predominance 43.2%, bilateral (11.7%). Trilateral (2.7%) and .9% Quadrilateral.Among the pediatric RB patients, 91.9% had no family history however 4.7 % of fathers had a similar history, followed by 0.9% of brothers but interestingly no family history on the mother's side

Table 2 TO ***show the pattern*** of clinical presentation of RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

Variable	Response	Frequency	Percentage %
The first sign/symptom noticed by a caregiver	Eye discharge	6	5.4
	Strabismus	13	11.7
	Eye swelling	4	3.6
	White eye color change	78	70.3
	Black eye color change	3	2.7
	Decreased vision	3	2.7
	Vision loss	2	1.8
	Other	2	1.8
Leukocoria	Yes	79	71.2
	No	32	28.8
Eye discharge	Yes	33	29.7
	No	78	70.3
Strabismus	Yes	20	18.0
	No	91	82.0
Red eye	Yes	40	36.0

		No	71	64.0
Eye swelling		Yes	53	47.7
		No	58	52.3
Black eye		Yes	3	2.7
		No	108	97.3
Decreased vision		Yes	21	18.9
		No	90	81.1
Vision loss		Yes	13	11.7
		No	98	88.3
P/Epreauricular lymph Node		Yes	4	3.6
		No	107	96.4
Neurologic deficit		Yes	1	0.9
		No	110	99.1%
Laterality		Left	46	41.4
		Right	48	43.2
		Bilateral	13	11.7
		Trilateral	3	2.7
		Quadrilateral	1	.9
Family history of RB	Yes	Father	5	4.5
		Brother	1	.9
		Other Relative	3	2.7
	No		102	91.9
Who noticed first		Family	103	92.8
		Health care provider	8	7.2

At diagnosis, 35.1% of the patients had intraocular, and a significant portion, nearly 64.9% had extraocular RB. Among those with extraocular RB, 43.2% showed locally advanced disease and 21.6% metastatic disease. Furthermore, a notable proportion of those are stage 3 (46.8%) followed by stage 4 (24.3%). Diagnosis was made with clinical evaluation and investigation modalities including ophthalmologic examination with EUA 45%, Fundoscopy 33.3%, and no ophthalmologic examination done for 21.6 % of cases. The majority of patients 97.3% had MRI for diagnosis. Among the total cases, 6(6.8%) had bone marrow aspiration/ biopsy positive. Additionally, 2 out of 111 cases (2.3%) had CSF Positive even though 20.7% of patients have neither BMA/BMB nor CSF Analysis. Coming to family screening 95.5% had no family screening even if most of the Families (54%) had under 5 children in addition to an overall family history of (8.1%) which shows less percentage of screening.

5.1.3.Management and follow-up

In this multicenter study, the intent of treatment is curative in the majority of RB patients around (81.1%) and 18.9 % of patients had palliative intent of treatment. Moreover, the overall treatment for the majority of patients was chemotherapy at 92.7% followed by inoculation at 56.7%, although radiotherapy was planned for 47.41% only 13% of the patients got RT. Cryotherapy was 9%, Even if inoculation was done for 56.7% as a primary and secondary treatment overall only 5.67% of patients with prosthetics. Among surgery done 30.6% of patients had pathologic high risk.

These findings provide crucial insights about the outcome at the end of data collection showing 39.6% are disease-free, followed by RB cases that are alive and on active treatment at 27.9%, disease progression at 12.6 %, and finally death accounts for 7.2 % of RB cases

Table 3: Diagnosis and Treatment of pediatric RB patients in AA RB Treatment Center AA, Ethiopia, 2023 to 2024 (n = 111)

Variables	Response	Frequency	Percentage %
Ophthalmology examination	EUA	50	45.0
	Fundoscopy / US	37	33.3
	Not done	24	21.6
Imaging	MRI	108	97.3

			CT	3	2.7
BMA/BMB (n =88)			Positive	6	6.8
			Negative	82	73.9
			Not done	23	20.7
CSF (n=88)			Positive	2	2.3
			Negative	86	77.5
			None	23	20.7
Diagnosis			Intraocular	39	35.1
	Intraocular	Right eye	Group A	2	5.1
			Group B	2	5.1
			Group c	2	5.1
			Group D	3	7.6
			Group E	8	20.5
		Left	Group A	1	2.6
			Group B	3	7.6
			Group C	3	7.6
			Group D	7	17.9
			Group E	6	15.4
		Bilateral	Group A	0	0
			Group B	1	2.5
			Group C	0	0
			Group E	1	2.5
	Extraocular		Extra ocular	72	64.9
			Locally advanced	48	43.2
			Metastatic	24	21.6
	Stage		0	11	9.9
			1	19	17.1
			2	2	1.8
			3	52	46.8
			4A1	5	4.5
			4B1	9	8.1
			4B2	7	6.3

		4B3	6	5.4
Treatment	Intent of treatment	Curative	90	81.1
		Palliative	21	18.9
	Primary treatment	Cryotherapy	8	7.2
		Inoculation	26	23.4
		Chemotherapy	74	66.7
		None	3	2.7
	Secondary TX	Cryotherapy	2	1.8
		Surgery	37	33.3
		Chemotherapy	29	26.1
		Radio chemotherapy	15	13.5
		cryo-chemotherapy	1	.9
		No	27	24.3

Prosthetic	Yes	8	7.2
	No	103	92.8
Pathologic high risk	Yes	34	30.6
	No	22	19.8
	not specified	55	49.5
Post-chemotherapy ophthalmology response assessment	After 2 cycle	26	23.4
	After 3 cycle	13	11.7
	After 4 cycle	5	4.5
	After 5 cycle	2	1.8
	After 6 cycle	7	6.3
	After 8	8	7.2
	not done	50	45.0
At the end of data collection	Alive and on active treatment	31	27.9
	Disease free	44	39.6
	Progression	14	12.6

	lost to follow-up	9	8.1
	Death	8	7.2
	Unknown	5	4.5

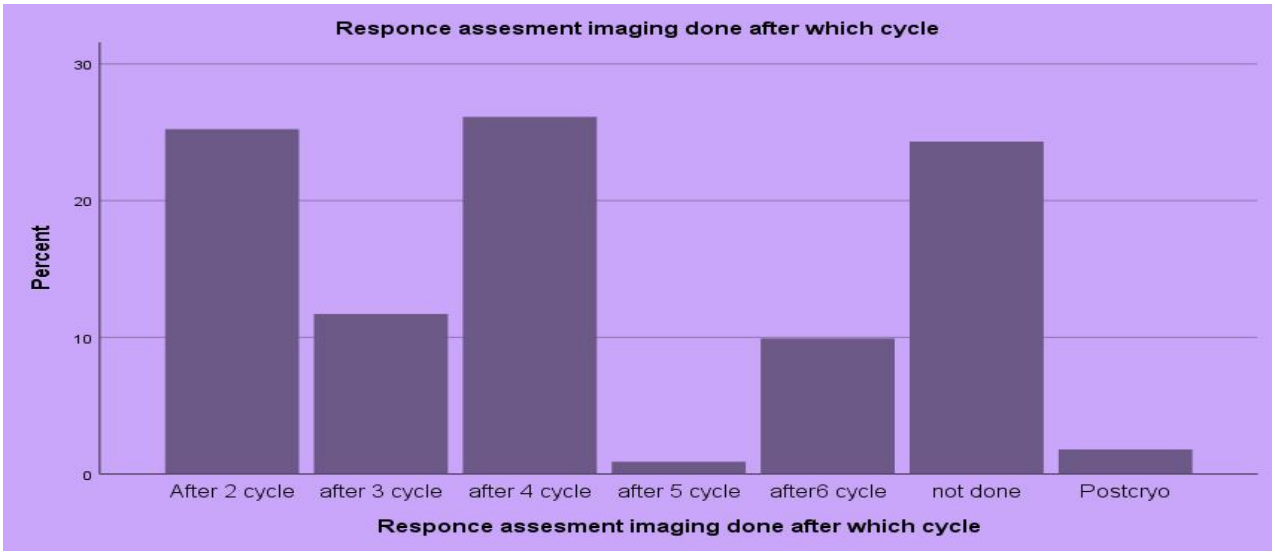


FIGURE 2: Response assessment imaging done after which cycle in pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

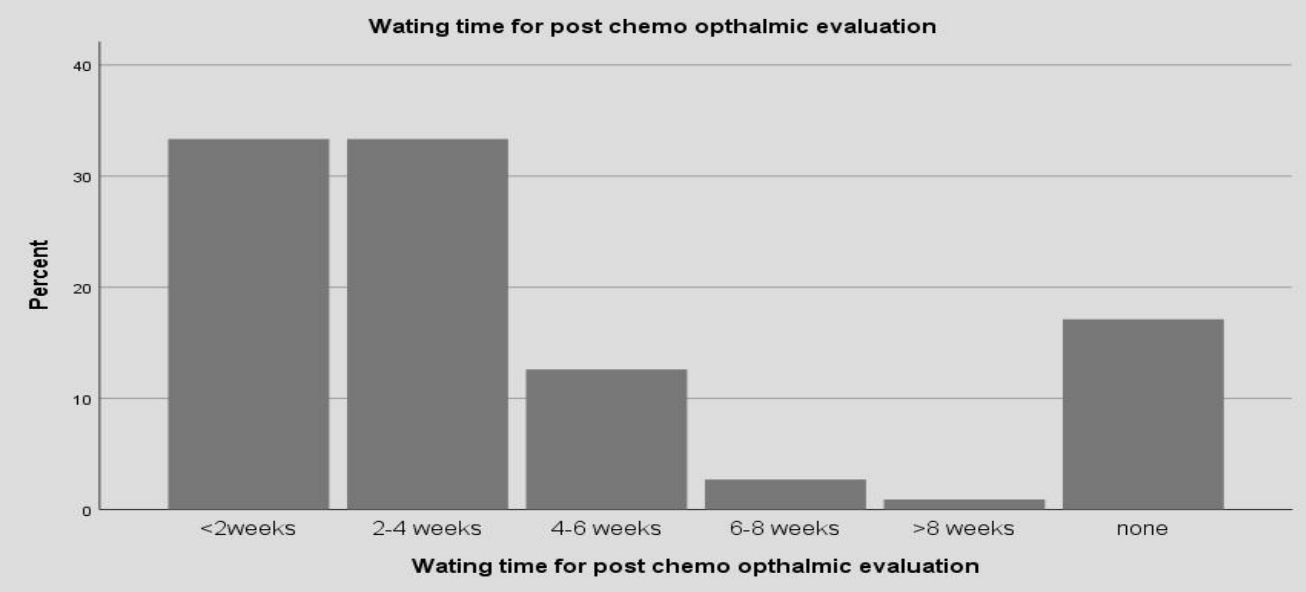


FIGURE 3: Waiting time for post-chemo ophthalmic evaluation pediatric RB patients in AA RB Treatment Center AA, Ethiopia, 2023 to 2024 (n = 111)

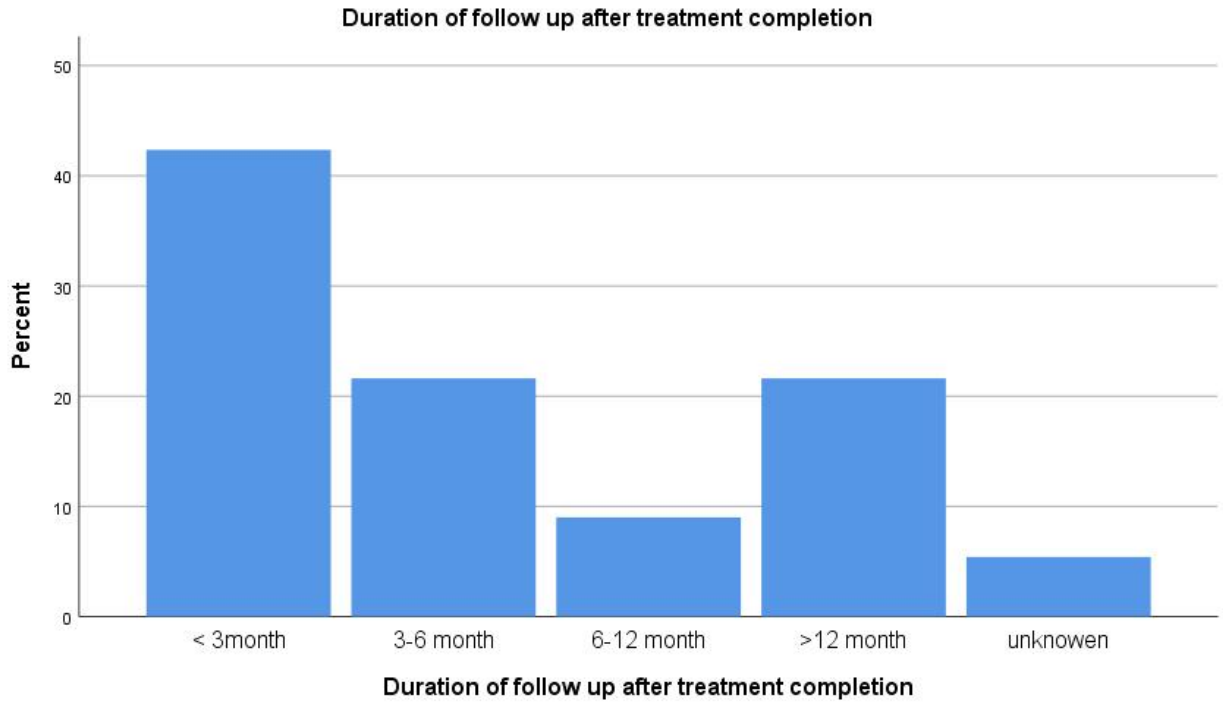


FIGURE 4: follow up after treatment

5.1.4.Referral pathway

Approximately half of the patients 52 (46.8%) visited at least 2 additional healthcare facilities before reaching an RB treatment facility, while 3 (2.7%) came directly to the treatment center on average, RB patients visited 2.16 care providers before arriving at the final RB center. The source of referral was mostly from tertiary hospitals (38.7%), general hospitals (30.6%), and self-referrals (2.7%). Additionally, most cases were referred by an ophthalmologist (47.7%) and pediatrician (34.2%).

Table 4:**referral pathway of caregivers among pediatric RB patients in AA, RB treatment centers AA, Northern Ethiopia, 2023 2024 (n = 111)**

Variable	Response	Frequency	Percentage %
No of them visited the health center before reaching to treatment center	0	3	2.7
	1	19	17.1
	2	52	46.8
	3	31	27.9
	4	6	5.4
Activity done at primary health care center	Reassurance and giving unspecified medication	41	36.9
	Referred to another none treatment center	35	31.5
	Referred to a treatment center	35	31.5

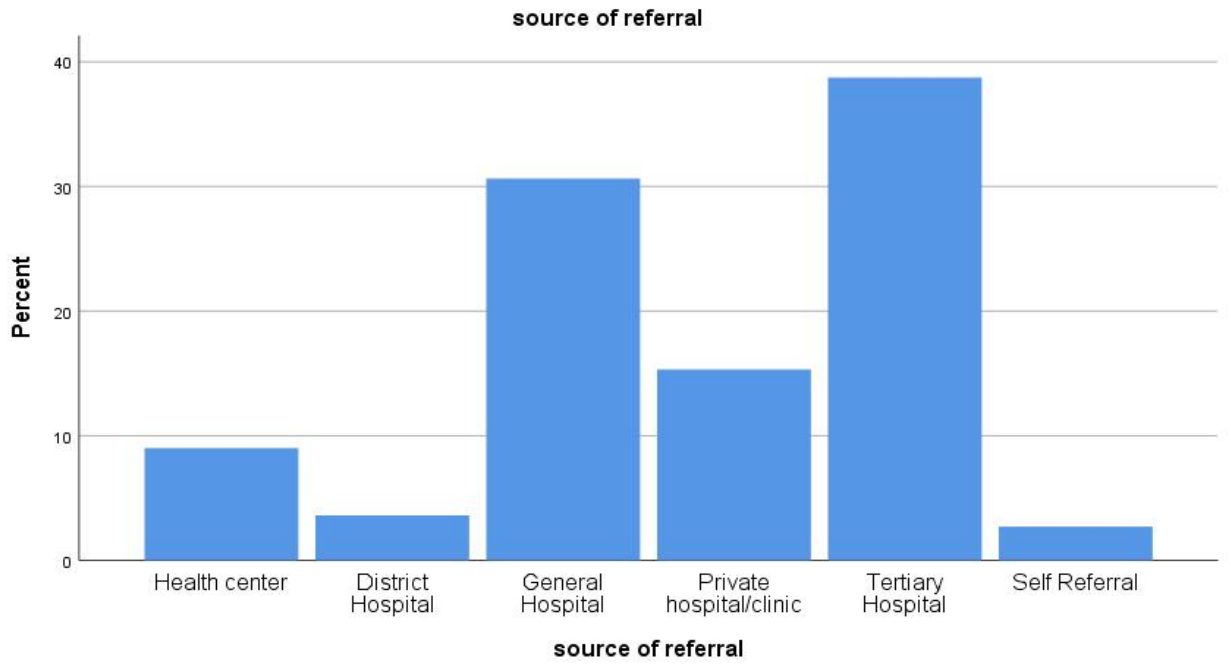


FIGURE 5: Referral hospital for pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

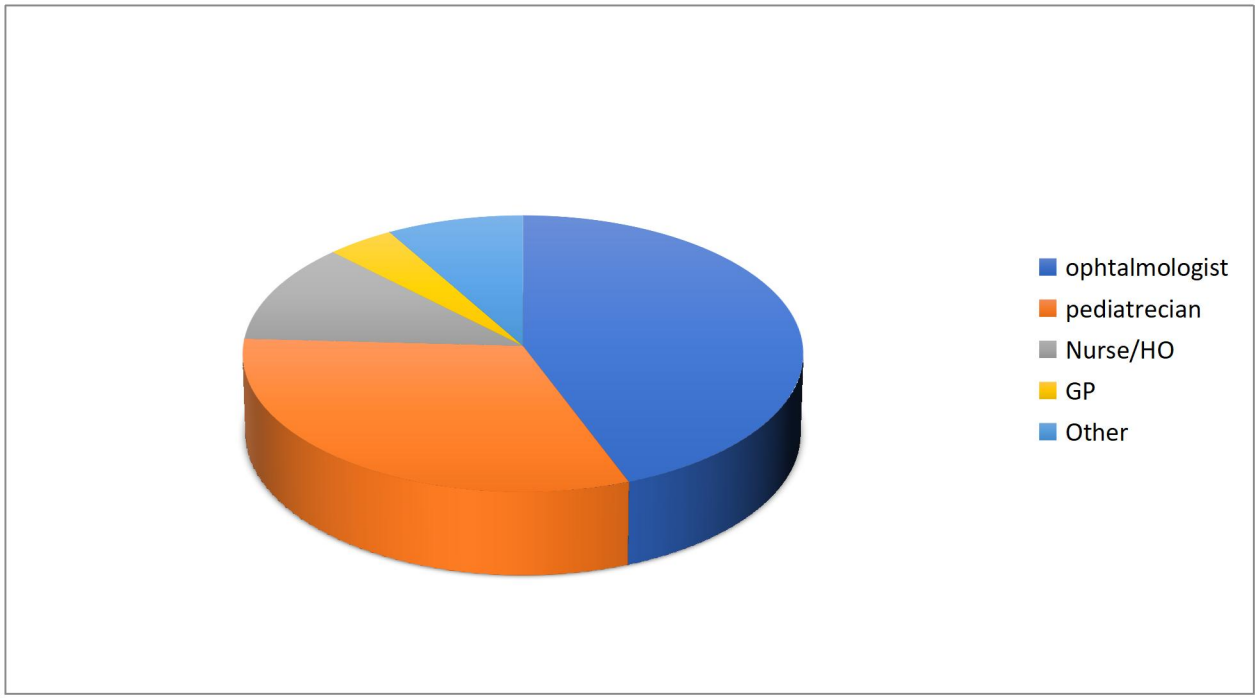


FIGURE 6: clinician referring pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

5.1.5.Levels of delay and reason for a delay

5.1.5.1.Lag time 1 (Delay from Initial presentation to first health care)

This study demonstrated that a delay in seeking care after noticing initial symptoms reaching the first care provider level among pediatric RB patients was common accounting for a total of 111 patients, 90 (81.1%) experienced lag time greater than 2 weeks. The median patient delay was 2 months, the leading cause of delay in seeking care was “Did not think there was a problem”, reported (65.8%) cases, far distance from RB Center (21.6%) Cost of travel 10.8 % of the cases, cost of treatment (9.9%) cases, (8.1%) due to take to a traditional healer.

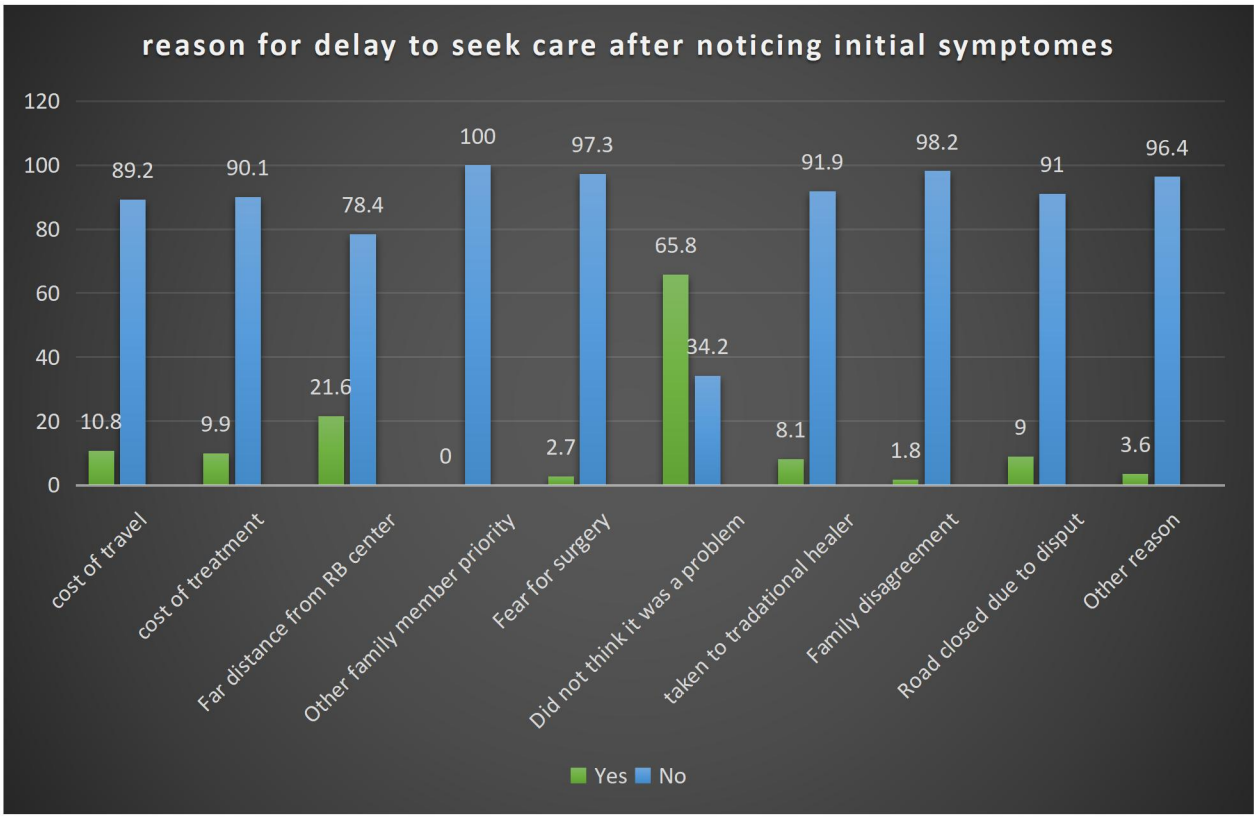


FIGURE 7: Reason for delay in seeking health facility pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

5.1.5.2.Lag time 2 (Delay from first health care visit to RB treatment center)

The study revealed the magnitude of lag time, specifically in the delay from the first health facility to the RB treatment center 91 (82%) out of 111 cases had delay which reveals the highest percentage when compared to other levels of delays. The median ± IQR lag time was 2 (IQR 2), the leading cause of delay to RB treatment center was delayed referral from the first health facility reported in around (57.7%) of cases, didn't think it was a problem (not convinced by advice (15.3%) Cost of travel (15.3 %) of the cases, cost of treatment (14.4%) cases, and strikingly (13.5%) due to road closed due to dispute area, few (6.3%) taken to traditional healer.

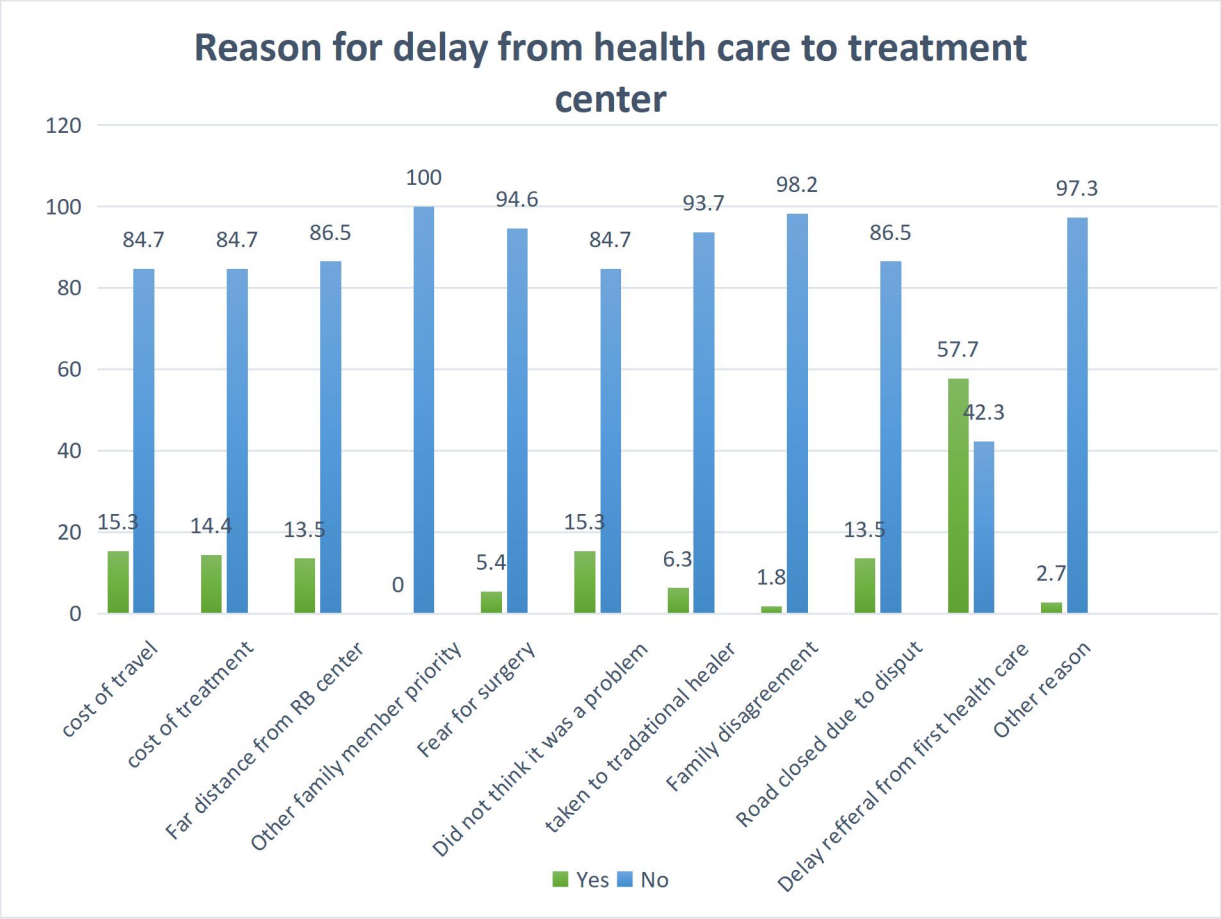


FIGURE 8:Reason for delay from health care to RB treatment center in AA, Ethiopia, 2023 to 2024 (n = 111

5.1.5.3.Lag time 3 (Delay for diagnosis and treatment) at treatment center.

This study demonstrated that a lag time in diagnosis among participants (111 cases) reported was 76.6 %. The median patient delay was 5 weeks much of the reason for the delay was 3 weeks(60%) for ophthalmology evaluation) and 2 weeks (40%), **for** imaging modalities such as MRI/CT are not functional, waiting for BMB/BMA and CSF. The, mean waiting time for Post post-chemotherapy ophthalmology evaluation is 2.68 weeks.

Table 5:Reason for Diagnosis Delay pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

Variable	Response	Frequency	Percentage
Cost of imaging	Yes	27	24.3
	No	84	75.7
MRI/CT not functional	Yes	47	42.3
	No	64	57.7
Fellow/consultant not available for consultation	Yes	1	.9
	NO	110	99.1
laboratory not functional	Yes	3	2.7
	No	108	97.3
For CSF/BMA/BMB	YES	37	33.3
	NO	74	66.7
For ophthalmology evaluation	yes	93	83.8
	ye	18	16.2
Other reason	Yes	1	.9
	No	110	99.1

In this study, 72.1% of cases had treatment delay compared to the other delay's treatment delay had less percentage. The median ± IQR treatment delay was 1.2 weeks. Several factors have been attributed to treatment delay, however, the leading cause of treatment delay at RB treatment center was the High surgical list reported around (13.5%) of cases, strikingly majority of the patients needed chemotherapy (92.7%) as primary and secondary treatment but reason for delay was reported due to cost of medication and medication not availability 12.6 % and 7.2% respectively, few cases because of caregivers fear of surgery (4.5%) and (2.7%) fellow/consultant unavailability.

Table 6:Reason for Treatment delay pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

Variable	Response	Frequency	Percentage
Cost of medication	Yes	14	12.6
	No	97	87.4
Medication not available	Yes	8	7.2
	No	103	92.8
Fear of surgery	Yes	5	4.5
	No	106	95.5
High surgical list	Yes	15	13.5
	No	96	86.5
Fellow/consultant not available	Yes	3	2.7
	No	108	97.3
Other reason	Yes	19	17.1
	No	92	82.9

5.1.5.4.Lag time 4 (overall lag time)

We observed that the overall median lag time from noticing the first symptom to the treatment of RB cases at the RB center was 6.2(IQR=8.2.) More than half of patients (65/111, 59.5 %) delayed > 6 months or more to get treatment once the initial symptom was noticed. Delay from the first symptom to the first day of the first health care center and first health care visit to the treatment center had similar proportions. more than 2/3 of cases (80.1%) had more than 2 visits to a health facility before arrival at the RB treatment center. the second common cause of delay with a high percentage is parental delay accounting for 81.1 % which can be addressed with the majority of caregivers (64.5%) did not think it was a problem at first. Based on this research overall treatment delay (delay >6 months) is 59.5%.

TABLE 7: LEVEL OF DELAY FROM INITIAL PRESENTATION, DIAGNOSIS, AND TREATMENT OF RB AT AA RB TREATMENT CENTER AA, ETHIOPIA, 2023 TO 2024 (N = 111

Lag time	Number of case	%
< one month	3	2.7
1 to 3 month	16	14.4
3 to 6 months	26	23.4
6 to 12 months	37	33.3
12 to 24month	24	21.6
greater 24	5	4.5
≥6 months 66(59.5%)		

Table:8: Level of delay from initial presentation, diagnosis, and treatment of RB at AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = **111)**

Variable	Response	Frequency	Percentage
Parental delay	Yes	90	81.1
	No	21	18.9
Delay from first health care visit to treatment center	Yes	91	82.0
	No	20	18.0
Diagnosis delay	Yes	85	76.6
	No	26	23.4
Treatment delay	Yes	80	72.1
	No	31	27.9

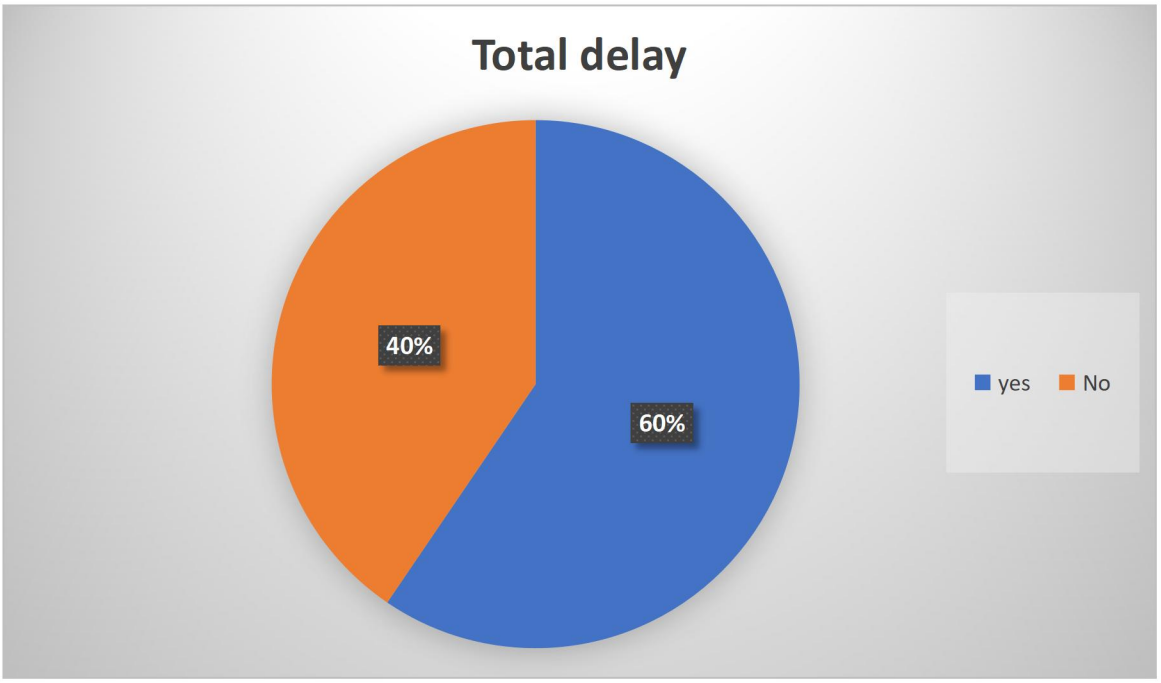


FIGURE 9: overall total delay (Lag 4) of pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111

Table 9: Lag time of pediatric RB patients in AA RB treatment center AA, Ethiopia, 2023 to 2024 (n = 111)

Variable	Response	Frequency
Total Lag time in months	Median ± IQR	6.2(IQR=8.2)
Lag 1 In the month	Median± IQR	2.2(IQR=6)
Lag 2 in a month	Median ± IQR	2.2(1QR=2)
Lag3=Lag for Ophthalmology evaluation in days	Median ± IQR	21 days (IQR) 28 days
Lag for imaging and BMA/BMB, CSF	Median ± IQR	14(IQR=19)
Lag for TX in days	Median ±IQR	10(IQR=14)
Post-chemotherapy ophthalmology evaluation waiting time in weeks	Mean± SD	2.68. ±2.046

The overall delayed time (lag time greater than 6 months) was 59.5%. A comprehensive analysis, comprising both univariate and multivariate approaches, was undertaken to pinpoint the critical determinant factors contributing to delay starting from initial presentation to initiation of treatment In the univariate analysis segment, several key factors stood out significantly to total treatment delay considering p value <0.25 Notably, far distance from home to RB treatment center (COR=1.56, p=0.09), the image that is done at the treatment center (COR=1.67,(0.277, 1.29), p=0.19), Distance from home to the first health center (COR=1.88(0.79, 5), p=0.204), cost of treatment (COR=2.1(0.84, 6.899), p=0.173), caregiver didn't consider it as a problem (COR=3.55, p=0.033), referral delay (COR=3.27, p=0.06), and for Ophthalmologic evaluation in Addis Ababa (COR=1.96 (0.64, 5.9), p=0.22), Vision loss COR=3.79 (0.11, 1.2), p=0.11), were identified as statistically significant factors associated with total treatment delay. Moving on to the multivariate analysis, it was revealed that certain factors emerged as notably influential in predicting delay at a different level of care factors such as the far distance from home to RB treatment center (AOR=1.5, p=0.035), Weren't considered as a problem by caregivers (AOR=3.64,p=0.044), delayed referral (AOR =2.95p=0.035) emerged as the most statistically significant variables determining total treatment delay. These findings provide crucial insights into the factors influencing the delay from initial symptoms to treatment at different levels of care underscoring the importance of early identification and targeted interventions to improve.

TABLE:10: BIVARIANT AND MULTIVARIATE BINARY LOGISTIC REGRESSION ANALYSIS TO IDENTIFY ATTRIBUTABLE RISK FACTORS FOR TOTAL DELAYED TREATMENT AMONG NEWLY DIAGNOSED PEDIATRICS RETINOBLASTOMA AT TIKUR ANBESA SPECIALIZED HOSPITAL, ST. PAULUS MILLENNIUM COLLEGE HOSPITAL) AND MENELIK II REFERRAL HOSPITAL ADDIS ABABA, ETHIOPIA 2024

Variable	Response	Delayed RB treatment		COR 95%CI	P	AOR 95%CI	P
		NO	Yes				
Sex	Male	22	35	1			
	Female	23	31	1.2(0.55,2.5)	0.67		
Family size	1 -3	41	30	1	.653		
	4-6	19	13	1.06(0.4,2.2)	.877		
	>7	6	2	2.2(0.1,2.4)	.356		
Address	*Amhara*	5	8	*1*	0.853		
	Oromia	19	22	0.72(.386-4.944)	0.619		
	SNNPR	6	15	1.56(.148,2.768)	0.550		
	Tigray	2	2	1.600(.168,15.273)	.683		
	Addis Ababa	8	9	0.7(.328,6.174)	.638		
	Somalia	1	4	2.500(.034,4.681)	.465		
	Afar	2	4	1.800(.105,6.104)	.830		
	Other	2		1.600(.168,15.273)	.683		
Distance in km from home to treatment	<100 km		19		.080		

		5					
	101-300km	6	12	1.900(.282,3.021)	.065		
	301-500km	6	9	2.53(.057,1.581)	.202		
	>500km	28	26	4.092(.134,1.704)	.014		
Far distance				1.566	**0.009**	1.506	.035
Religion	Orthodox	17	21		.825		
	Protestant	12	15	.988(0.366.2.6)	.981		
	Catholic	0	1	.000(00,00)	1.000		
	Muslim	16	29	.682(0.3,1.7)	.395		
Caregiver	Mother	12	13		.774		
	Father	17	29	0.635(.237,1.704)	.367		
	Both	13	21	0.671(.236,1.909)	.454		
	Nonrelatives	3	3	1,08(.182,6.439)	.930		
Caregiver's level of education	No formal education	8	18		.737		
	Can read and write	4	5	1.800(.380,8.535)	.459		
	Grade 1-8	7	15	1.286(.386,4.283)	.682		
	Grade 9-12	16	17	1.875(.638,5.513)	.253		
	College/University	10	11	2.045(.619,6.754)	.240		
Continuous	Level of education			1.188(.907,1.556)	0.211	1.16(0.26,5.24)	0.84
Occupation	Government	19	19		.514		

	Merchant	9	17	.529(.189,1.480)	.225		
	Farmer	14	26	.538(.217,1.337)	.182		
	Other	3	4	.750(.147,3.814)	.729		
Continuous	Occupation				0.371		
Community-based health insurance	**Yes**	**20**	**35**	**1**			
	No	**25**	**31**	**1.1(0.33,1.52)**	0.375		
Family income per month	601-1650	1	4		.486		
	1651-3200	5	5	4.000(.323,49.596	.280		
	3201-5250	8	7	4.571(.409,51.138)	.217		
	5251-7800	2	1	8.000(.310,206.371	.21		
	7801-10900	7	7	4.000(.353,45.384)	.263		
	>10900	22	42	2.095(.221,19.903)	.520		
Continuous data	Income per month				0.387		
Symptom/Sign	Eye discharge Yes No	13 32	20 46	1.07(0.466,2.45)	.87		
	Strabismus Yes No	7 38	13 53	1.331(0.45,3.45)	.578		
	Eye swelling yes No	17 28	36 30	1.9(0.92,4.28	0.84		

	Leukocoria yes No	11 34	21 45	1.44(0.695, 3.63)	.0.401		
	Decreased vision yes No	11 34	10 56	1.812(.696,4.715)	.223	1.37(.095,1.477	0.161
	Black eye color change yes No	1 44	2 64	1.375(0.121.15.63)	0.797		
	vision loss yes no	8 37	5 61	13.9(0.115,1.24)	0.11	1.759(.25,2.228	.616
Number of healthcare visits	0	2	1		.198		
	1	12	7	1.16(.200,7.992)	.355		
	2	17	35	4.1(.162,5.839)	.212		
	3	12	19	3.19(.494,23.775)	.975		
	4	2	4	4(.211,75.659)	.804		
Continious				1.689(.438,1.084)	.107		
Laterality	Left	19	27		.673		
	Right	18	30	.853(.372,1.952	.706		
	Bilateral	8	5	2.274(.644,8.033	.0.26		
	Trilateral	0	3	00	.999		
	Quadrilateral	0	1	00	1.000		
	TOTAL				0.64		
Sign/symptom							

first noticed by	*Family*	*3*	*5*				
	Health provider	*42*	*61*	*1.1(0.26,5.06)*	*0.856*		
Sours of referral	Health center	3	7		.935		
	District Hospital	1	3	1.778(0.056,10.8	.852		
	General Hospital	14	20	1.633(0.359.7.4)	.526		
	Private hospital/clinic	8	9	2.074(0.397,10.8	.387		
	Tertiary Hospital	19	24	1.847(0.42,8.1)	.417		
	Self-Referral	0	3	1.02(0.27,3.8)	.999		
Who refer patient	Ophthalmologist	22	31		.673		
	Pediatrician	18	20	1.234(.531,2.868)	.579		
	Nurse/HO	4	10	1.143(.347,3.768)	.381		
	GP	1	4	1.381(.040,3.648)	.365		
	Other	0	1	1.000	1.000		
Image done at	Referral	23	42				
	Treatment center	22	24	1.67 (0.277,1.29	.190	1.392	.499
Pare antral reason for delay		2	10				

	Cost for travel	43	56	3.83(0.799,18.44)	0.09	2.141(.340,13.47)	0.417
		43	57	3.39(0.69,16.5)	0.13	1.730(0.43,2.66)	.646
	Far from home	7	17				
		38	49	1.88(0.79,5.0)	0.204	1.07((.191,2.796	.912
	Other Family Priority	0	66	0.66	0.48		
		0	45				
	Fearing surgery	1	2	1			
		44	64	1.37(0.12,15.6	0.797		
	Not considered as a problem	4	17				
		41	49	3.556	.033	3.644	0.044
	Taken for a traditional healer	3	6				
		42	60	1.400(.33,5.914)	0.65		
	Family disagreement	1	1				
		44	65	.677(.041,11.111)	0.785		
	The road closed due to a dispute	3	7	1			
		42	59	1.67 (.147,2.464)	0.99		
Cause of delay from primary health care center to treatment center delay	Cost of travel	8	9	1.36(.485.3.868)	0.553		
		37	57				
		36	59				
	Other Family	45	66	.682	.48		

	Priority						
	Fearing surgery	2	4				
		43	62	1.387(.243,7.914)	0.713		
	Taken for a traditional healer	3	4	1.107(.236,5.202)	0.89		
		42	62				
	Family disagreement	0	2		0.99		
		45	64				
	The road closed due to a dispute	6	9	.974(.321,2.958)	0,96		
		39	57				
	Referral delay from primary health center to treatment center	25	53				
		20	13	1.923(.892,4.144	0.006	2.952	.035
	Other reason	2	1				
		43	65	3.023(.266,34.381)	0.33		
Diagnosis delay	Cost of imaging	9	18	1.500(.604,3.724)	0.38		
		36	48				
	CT/MRI is not functional	14	33	2.700(1.204,6.055)	0.05	1.627(.6124.325)	0.330
		31	33	2.214(1.000,4.901			
	Fellow/consultant not available	0	1	00(00,00)	1.00		
		45	65				

	Another Lab is not functional	2	1	3.023(.266,34.381	0.37		
		43	65				
	ForBMA/BMB/CSF	13	24				
		32	42	1.407(.622,3.183	0.413		
	For ophthalmology evaluation	5	13				
		40	53	1.962(.647,5.955	0.22	1.6(.345,7.962	.529
	Other reason	0	1				
		45	65	00(00)	1.00		
Treatment center treatment delay	High Cost for treatment Yes	2	9	2.10(.841,6.899)	0.173	1.22(0.05,0.99)	0.049
		2	9				
	Medication not available	4	4		0.57		
		41	61	1.512(.358,6.389			
	Fearing surgery	1	4				
		44	62	2.839(.307,26.271	0.358		
	High surgical list	6	9				
		39	57	1.02(.338,3.115	0.963		
	Fellow /consultant not available	2	1	3.023(.266,34.381	0.37		
		43	65				
	0ther reason	7	12				
		38	54	1.206(.435,3.347	0.719		
Stage of disease	Intraocular				0.049		
	Localy			2.5(0.56,3.6)	0.085		

	advanced						
	Metastatic			3.39(0.230,5.67)	0.015	2.3(0.3,2.9)	0.038

Table 11: bivariant and multivariate binary logistic regression analysis to identify attributable risk factors for parentral ,referral diagnosis and treatment delay at each level of lag time delayed treatment among newly diagnosed pediatrics retinoblastoma at Tikur Anbesa Specialized Hospital, St. Paulus Millennium College Hospital) and Menelik II referral Hospital Addis Ababa, Ethiopia 2024

Lag I				COR	P	COR	P
Variable	Response	No	Yes				
Home to first healh care center							
	Costfor travel	2	10	2.7(.41,8.4)	.998		
		43	56				
	Far from home	43	57	3.9(0.4,05.332			
		7	17				
	Other Family Priority	38	49	1.2(0.6,5.2)	.998		
		0	66				
	Fearing surgery	0	45	2.1(0.47,7.1)6	0.98		
		1	2				
	Not considered as a problem	44	64	18.8(5.27.073	.000	18.8(0.5,27)	P<0.001
		4	17				
	Taken for a traditional healer	41	49	1.6(.563,2.1	0.56		
		3	6				

	Family disagreement	42	60	1.9(0.3,2.762)	.999		
		1	1				
	Theroad closed due to a dispute	3	7	2.62(0.39,4.933	0.999		
		42	59				
Delay from referral to treatment center	Lag 2/referral delay						
	Rsponse	No	Yes	COR	P	ROR	P
	Cost of travel	8	9	1.2(.8, 5.648	.354		
		37	57				
	Other Family Priority				1.000		
		36	59				
	Fearing surgery	45	66	3.3(0.6,9.961	0.01	1.4(.143,14.8)	.749
		2	4				
	Taken for a traditional healer	43	62	1.83(.1 ,2.650	.998		
		3	4				
		42	62	10.2(.255,4.14.	.83		
	Family disagreement	0	2				
		45	64	5.81(.351,96.1)	**.26**		
	The road closed due to a dispute	6	9				
	Referral delay from primary health center to treatment center	39	57	7.05(.234,34.4)	.000	13.3(2.8,61.951	.001
		25	53				

	Other reason	20	13	4.1(0.3,2.4)	0.99		
		2	1				
DX delay	Cost of imaging	43	65.	1.2(.3,4.742	0.782		
		9	18				
	CT/MRI is not functional	36	48	6.7(1.963,22.86)	.002	6.7(2.0,21.90	.002
		14	33				
	Fellow/consultant not available	0 45	1 65	4.30(.26514.674	1		
	Another Lab is not functional	45	65		1.000		
		2	1				
	ForBMA/BMB/CSF	13	24		0.020	4.1(1.2,14.1	.021
		32	42				
	For ophthalmology evaluation	5	13	1.2(0.25,2.45)	.0.033	1.9(.6,6.4.	0.039
		40	53				
	Other reason	0	1				
		45	65				
Treatment dela	Cost of medication	2	9	4.0(.81,19.732.)	0.088	4(0.8,19.7)	0.088
		2	9				
	Medication not available	4	4	2.2(.421,12.3)	0.340		
		41	61				.
	Fearing surgery	1	4	3.2(.319	320		

				33.140)			
		44	62	.			
	High surgical list	6	9	1.2(0.3,2.192	0.503		
		39	57				
	Fellow /consultant not available	2	1	1.807(.4,13.568			
		43	65				

Chapter six Discussion and Recommendation

6.1. Discussion

The most frequent intraocular tumor in children is retinoblastoma, however, in middle-class and lower-class nations, early detection and treatment are still difficult. Many of the patients that come into our setting have advanced diseases. As far as I am aware, this is the first multicenter prospective study conducted in Ethiopia to determine the variables influencing the overall length of treatment delays for retinoblastoma. The complete patient journey—from identifying the initial symptoms of retinoblastoma at home to reaching Ethiopia's three most comprehensive treatment institutions for the disease—was the subject of the study. It evaluated the amount of lag time and the causes of these delays. The results have significant ramifications for creating public awareness campaigns, enhancing healthcare resources, creating health education initiatives, and offering patient caregivers counseling advice.

According to this study, there is a slight male predominance in retinoblastoma cases, with a Male-to-Female ratio of 1.05:1, which aligns with the general trend of the condition being more common in males(1.1:1)(14,15), However, no significant difference in diagnosis delays between genders was found, which is consistent with other studies(14,15). This suggests that health-seeking behavior may be similar regardless of the child's gender.

Our research also identified that the median age at diagnosis is 40 months for unilateral retinoblastoma and 22 months for bilateral cases, which is higher compared to other studies where the median age is around 2 months(14,15,33). This highlights a critical delay in age at diagnosis in our setting. The delay may be attributed to a lack of awareness and delayed referrals, which were significant findings in our study. Most symptoms and signs are first noticed by families, whereas in other settings with retinoblastoma screening programs, early detection is more common. These findings underscore the urgent need for improved screening and early diagnosis of retinoblastoma in our context.

In this prospective study, the most common initial sign and symptom noticed by caregivers was leukocoria, observed in 78 out of 111 cases (70.2%), which is consistent with findings from studies conducted in Ghana and Brazil(32,28). However, some studies in India have reported a higher percentage (96%) of leukocoria as the initial symptom(26). The second most common symptom in our study was strabismus, found in 11.7% of cases, which aligns with studies from Indonesia and Brazil(23,28). Other symptoms included eye discharge in 5.4% of cases and proptosis in 3.6%.

At diagnosis, locally advanced extraocular disease was the most common, accounting for 64.9% of cases, with metastatic disease present in 21.6%. This is higher than figures reported in other studies from Brazil(28) where 7.5% and 12.3% had metastatic disease at diagnosis. The higher prevalence of extraocular and metastatic disease in our study may indicate that parents underestimated the significance of initial symptoms like leukocoria. This underscores the need for improved training for healthcare professionals and public awareness programs to enable earlier identification of retinoblastoma symptoms before the disease progresses.

In our study, more than two-thirds of patients (95%) did not undergo family screening, even though most families (54%) had children under the age of 5. Additionally, while the majority of patients were seen by an ophthalmologist (47.7%) or a pediatrician (34.2%), there were relatively few cases with family screening. This discrepancy highlights a significant gap in the integration of screening programs for retinoblastoma and underscores the urgent need to enhance screening education for healthcare professionals and improve access to health services to raise awareness and suspicion of retinoblastoma early on.

Our findings also reveal that the intent of treatment for many patients was either curative or palliative. Previous research from Kenya(33)and Ghana(32) found that approximately 13% and 19% of patients, respectively, received palliative care. In our study, 18.9% of patients required palliative treatment, which supports the observation that a significant proportion of patients presented with metastatic retinoblastoma, necessitating palliative care.

In our study, 2.7% of cases had a lag time of less than 1 month, while 4.4% of cases had a lag time exceeding 24 months. The median lag time was found to be 10 weeks (38.5%), which aligns with the median lag time of 10 weeks in previous studies. Specifically, the median lag times for different stages were: 3 weeks for ophthalmologic evaluation, 2 weeks for imaging modalities and other investigations, and 1.2 weeks for treatment initiation.

The study identified several significant associations with reasons for treatment delays at different lag times. For lag time 1, the primary reason was not recognizing the issue as a problem (65.8%, $p<0.001$). For lag time 2, delayed referrals were a significant factor (57.7%, $p=0.01$). For lag time 3, issues included non-functional imaging equipment ($p=0.002$), waiting for BMA/BMB and CSF analysis ($p=0.036$), and delays in ophthalmologic evaluation ($p=0.03$). These findings emphasize the need for increased awareness and intervention to address these delays.

Overall, 59.5% of the study population experienced total treatment delays of more than 6 months, which is comparable to studies in Indonesia (58.6%), Ghana (50%)(, and Menelik Hospital, Ethiopia (68%)(. However, this is in contrast to findings from Brazil (38%), Egypt (33%), and the UK (10.7%), highlighting a significant gap in healthcare practices and the urgent need for improvement in our setting(23.32.34,28,31,18).

.In our study, the median total lag time was 6.2 months, which is significantly longer than reported in Brazil (median of 2 months), Tehran (2.6 months), and Egypt (2 months)(28,24,31). This extended lag time could be attributed to factors common in middle-income countries, such as limitations in the healthcare system, including referral processes and advancements in diagnostic and treatment modalities. However, our findings are consistent with those from Kenya where the median lag time was 6.58 months(33).

In contrast, a single-center cross-sectional study conducted at Menelik Hospital in 2018 reported a shorter median lag time compared to our study(34). This difference may be due to improvements in the quality of the healthcare system and interventions over the years, reflecting advancements in the healthcare infrastructure and practices since that earlier research.

Our study identified several key factors influencing delays in retinoblastoma treatment at various levels of care. Notably, distance from home to the RB treatment center (AOR=1.5, p=0.035) and caregivers not recognizing the issue as a problem (AOR=3.64, p=0.044) were significant predictors of delay. These findings underscore the critical need for increased public awareness about the early signs of retinoblastoma. Additionally, delayed referral (AOR=2.95, p=0.035) was found to be the most significant factor contributing to total treatment delay.

In comparison, a cross-sectional study conducted at Menelik Hospital in 2018 highlighted the primary delays as being related to the cost of travel and lack of awareness(34). Similarly, a study from Ghana pointed to lower caregiver education levels as a cause of delay, while research from Pakistan identified lack of awareness, fear of surgery, and lack of transportation as significant factors(32)

Overall, the extended lag time of over 6 months in our study indicates a significant delay compared to other developing countries. To address these delays, it is crucial to implement public education programs, early screening initiatives, and public assistance programs to improve access to care and reduce treatment delays

6.2.Conclusion

Our results indicate that more than half of the pediatric retinoblastoma patients experienced a significant total treatment delay, from the initial observation of symptoms to receiving treatment. This supports our hypothesis that there is a linear relationship between lag time and the advancement of retinoblastoma in this cohort, with the majority of patients presenting after more than 6 months. Key barriers to timely care identified include a lack of awareness about retinoblastoma among caregivers, delays in referral, and travel burdens. These findings highlight the urgent need for targeted, high-level efforts to address these issues. An evidence-based approach is essential to tackle the determinants of delay, including enhancing public awareness, improving referral processes, and reducing the travel burden for patients.

6.3.Recommendation

Drawing on the results of this investigation into the factors that contribute to treatment delays for retinoblastomas, we suggest several measures aimed at helping families seek early medical intervention:

Increase public awareness of the typical symptoms and indicators of childhood retinoblastoma by implementing mass media campaigns and focused health extension training initiatives. This will facilitate early disease recognition and raise social awareness. Enhance Training for Healthcare Providers: Put an emphasis on early detection and improve the referral processes at various healthcare facility levels. This will lessen the effects of delays and guarantee that patients get connected to the right care more quickly.

Enhance Professional Education: Provide education programs for healthcare professionals to increase their index of suspicion for retinoblastoma. This will help in early diagnosis and timely referral. Develop Additional Treatment Centers: Collaborate across sectors to establish multiple retinoblastoma treatment centers. This can help address the issue of long distances and reduce one of the significant barriers to timely care. Implementing these recommendations will contribute to more effective management of retinoblastoma and improve outcomes for affected children. To address the delays in pediatric retinoblastoma treatment, we recommend the following actions:

Invest in Imaging Modalities: Ensure widespread access to essential imaging technologies such as MRI and CT scans. This includes investing in continuous access to diagnostic tools like BMA/BMB and CSF analysis, which are crucial for assessing metastasis. Reducing the waiting time for these diagnostic procedures will enhance timely and accurate diagnosis.

Enhance Ophthalmic Evaluations: Improve access to pre-chemotherapy ophthalmic evaluations, post-chemotherapy assessments, and EUA (examination under anesthesia) coverage. Timely and comprehensive evaluation and follow-up are critical for optimal patient care.

Expand Radiotherapy Resources: Invest in radiotherapy machines to ensure that they are available and widely accessible throughout the country. This will help reduce waiting times for radiotherapy, which is essential for managing retinoblastoma. Additionally, provides training for healthcare providers to optimize the use of radiotherapy and ensure effective treatment. These investments and improvements in diagnostic and treatment infrastructure are crucial for enhancing the management of retinoblastoma and improving patient outcomes. To enhance early detection and management of retinoblastoma, we recommend the following strategies: Integrate Screening Programs: Incorporate retinoblastoma screening into existing pediatric eye disease screening programs at under-five clinics. This integration can improve early detection of retinoblastoma within the healthcare system. Advocate for Health Equity: Neonatal Health Equity Advocates should work to improve access to retinoblastoma treatment for all patients. Emphasis should be placed on reducing diagnostic and treatment delays to lower the frequency of advanced retinoblastoma cases.

Establish a National Task Force: Collaborate across various sectors to establish a national retinoblastoma task force. This task force should focus on implementing action plans to reduce overall treatment delays in this vulnerable population. Promote Standardized Protocols: Advocate for the development and dissemination of standard operating procedures and the publication of existing retinoblastoma guidelines. Ensuring that these resources are widely available and used will help standardize care and improve treatment outcomes. By implementing these recommendations, we can improve early detection, reduce treatment delays, and enhance the overall management of retinoblastoma.

6.4 Strengths and Limitations of The Study

The study design used in this proposal is a new and multicancer, prospective crossectional which is best to study the research question raised. The findings of the study are expected to result in quality improvement in the management of children with RB. Since we include patients with a family history of retinoblastoma, this may positively increase early presentation to the health center and will increase early diagnoses

Anex I:Consent Form

የስምምነት ቅጽ ፡

የጥናቱ የመረጃና ስምምነት ሰነድ:ይህ የመረጃና የስምምነት ሰነድ በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ሕክምናና ትምህርት ክፍል በ Retinoblastoma /የአይን ካንሰር በሽታ ለሚታከሙ ሕጻናትና ልጆች የህክምና ሰነድ፣ ከሚወስዱት መድኃኒት ጋራ ተያይዞ የሚመጡ በሽታ የመቀነስ ፡ ትኩሳት፡ የአፍ መቁሰል ፡ ያለውን ሞት ለማጥናት ለማጥናት የተዘጋጀ ነው።የጥናቱ መነሻ ሐሳብ እና አላማ ይህ ጥናት ጥቁር አንበሳ ሆስፒታል በ Retinoblastoma /የአይን ካንሰር በኬሞቴራፒ የሚታከሙ ህፃናት ከበሽታው ጋር ተያይዞ የሚደርስባቸውን ተያያዥ ጉዳት ያጠናል። የጥናቱ አላማ ታካሚዎች ላይ የሚደርሰውን ጫና በመረዳት አስፈላጊው ድጋፍ እና ትብብር የሚያገኙበትን ሁኔታ መፍጠር ነዉ።ከእርሶ ምን ይጠበቃል? በጥናቱ ለመሳተፍ ከፈቀዱ ስለእርስዎ የማህበራዊ ሁኔታና ስለ ልጅዎ የጤና ሁኔታ መረጃ ይሰጣሉ።በጥናቱ ላይ በመሳተፍ የሚያጋጥሙ ስጋቶች ልጅዎ ወይም እርሶ በዚህ ጥናት በመሳተፋችሁ የሚደርስባችሁ አንዳችም ጉዳት አይኖርም።ምሥጢር ስለመጠበቅ የጥናቱ የተሳታፊዎችን መረጃም ሆነ ማንነት በምሥጢር የሚጠበቅ ይሆናል በመሆኑም የተሳታፊዉ ስም በጥናቱ መጠይቅ ላይ አይካተትም። በጥናቱ ለመሳተፍ ስላለመፈለግ ወይም ተሳትፎን ስለማቋረጥ*በጥናቱ እንዲሳተፉ አይገደዱም። እንዲሁም ተሳትፎዎን በማንኛውም ጊዜ ማቋረጥ ይችላሉ። በመሳተፎ ራስዎን ወይም ልጅዎን በተመለከተ መግለፅ የማይፈልጉት መረጃ ካለ እንዲገልፁ አይገደዱም። በጥናቱ መሳተፍ ባይፈልጉ በልጅዎ የህክምና ክትትል ላይ የሚያሳድረው ምንም ዓይነት ተጽእኖ አይኖርም። የጥናቱ ጥቅም:ከዚህ ጥናት የሚገኘው መረጃ በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ለሚታከሙ የሕጻናት የካንሰር ህመምተኞች የሚደረገውን ህክምና እና ክትትል ለማሻሻል ይጠቅማል። በጥናቱ ወቅት ጥያቄ ቢኖሮትማንኛውም ጥያቄ ካሎት ከዚህ በታች በተገለፀው የዋና ተመራማሪ አድራሻ በመጠቀም መጠየቅ ይችላሉ።የስምምነት ሰነድ ልጁ/ ልጅቱ በዚህ ጥናት እንዲሳተፍ (እንድትሳተፍ) ፈቃደኛ ስለሆኑ ለትብብርዎ በቅድሚያ እያመሰገንን ከበታች በተዘጋጀው ቦታ ላይ እንዲፈርሙ በትህትና እንጠይቃለን።ከዚህ በታች ስምና ፊርማዬ የተገለፀው ግለሰብ ከላይ የተገለፁትን መረጃዎች በማንበብ እና በመረዳት የጥናቱ ተሳታፊ ለመሆን ተስማምቻለሁ።

ስም _____

ፊርማ:_____ ቀን፡_____

ዋና ተመራማሪ፡ ዶ/ር ጌታሰዉ ፍቃድ

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Anex. III:

International Classification of Retinoblastoma-for Intraocular Tumor

Group A:

A small tumor(s) located only in the retina

No tumor is larger than 3 millimeters (mm)

No tumor is closer than 2-disc diameters (DD) from the fovea (the central "pit" of the retina)

No vitreous seeding (tumor floating in the eye) or retinal detachment

Group B:

Tumor(s) located only in the retina

Any location in the retina

No vitreous seeding

No retinal detachment more than 5 mm from tumor base Group A with tumor < 3 mm from the base of the tumor

Group C:

Fine diffuse (spread throughout) or localized (located in 1 spot) vitreous seeding

Retinal detachment: more than Group B and up to total retinal detachment

No vitreous/sub-retinal "snowballs" or masses

Group D:

Massive vitreous/sub-retinal seeds

Vitreous or sub-retinal snowballs/masses

Retinal detachment: more than Group B and up to total retinal detachment

Group E:

No visual potential, or presence of 1 or more, Tumors in the CB/anterior segment

Neovascular glaucoma, Vitreous hemorrhage,Hyphemia, Orbital cellulitis,International Retinoblastoma Staging System

Stage 0: Intraocular retinoblastoma, eye not enucleated

Stage I: Eye enucleated, no residual tumor

Stage II: Eye enucleated, microscopic residual tumor

Stage III: Local/regional disease

a: Overt orbital disease

b: Local/regional lymph node involvement

Stage IV: Metastatic disease

A: multiple organs

B: CNS

1. pre chiasmatic

2. intracranial mass

3. Positive CSF/meningeal enhancement

ANNEX IV: QUESTIONNAIRE

Evaluation of risk factors affecting early diagnosis and treatment of Retinoblastoma, and clinical pattern, in AA Ethiopia, 2023-2024

A. *Instructions – Please take your time to carefully complete the information below.*

Date __/___/_____ IC No. _____

Phone No. _____ Name of hospital _____

I.

No.	**Part I - Socio-demographic Variables of the Patient**	
1.	Age of child at diagnosis	_____years _____ months
2.	Sex of the child	1. Male 2. Female
3.	Birth order of the patient	1. First 2. Second 3. Third 4. Fourth 5. 6. Specific_____
4.	Family size (Total number of children)	_____
5	Number of under 5 children	_____
6.	Specific Address	**I. Region** **1.** Amhara 2. Oromia 3. SNNPR 4. Tigray 5. Addis Ababa 6. Somalia 7. Afar 7. Others (specify) ___ **II. Zone** _____ **II. Woreda**_____
7	Distance from home to AA	In Hours _____ In KM_____
8	Cost of traveling (in birr) From home to AA	Birr_____

9	Religion	1. Orthodox 2. Protestant 3. Catholic 4. Muslim 5. Others_____
No.	**Part II - Family and attendant information.**	
1	Primary Caregiver	1. Mother 2. Father 3. Both parents 4. non-relative caregiver If no parents state why._____
2	level of education of the caregiver	1. father 1.No formal education 2. Can read and write 3. Primary education (1-8 4. Secondary education (9-12)

		5. collage/university 2. Mother 1.No formal education 2. Can read and write 3. Primary education (1-8 4. Secondary education (9-12) 5. collage/university
3	Occupation of the caretakers	1.Father_____ 2. Mother_____ 1. Government 1. Government 2. merchant 2. merchant 3. farmer 3. farmer 4. other _____ 4. Others
4.	Does the family have health Insurance?	1. Yes, 2. No If no reason_____
5.	The family income per year	Birr_____

No.	Part III- Clinical Profile and Related history of the patient	
1	first symptom (Select more than one at a time if there are symptoms that occur simultaneously.	1. eye discharge 2. strabismus 3. eye swelling 4. eye color changes I. white II. Black 5. decreased vision/lost vision 6. other (specify
2	The age of the patient at first symptom/sign noticed	In _____years_____months_____weeks
3	Number of visited health care centers before reaching a treatment center	_____
4	The total duration of the first symptom before reaching the first healthcare center	In weeks_____
5	The total duration of the first symptom before reaching the treatment center	In weeks_____
6	Associated symptoms (You can choose more than one)	1. eye discharge 2. strabismus 3. eye swelling 4. eye color change I. white II. Black 5. decreased vision/lost vision

		6. red eye 7. other (specify
7	Which eye is affected?	1. Left 2. Right 3. Bilateral
8		In month_____
9	Who first noticed it?	1. Family 2. Healthcare provider
10	Family history of retinoblastoma?	1. YES 2.NO
11	If the answer to QN 7 is YES	1. Father 2. mother 3. brother 4. sister 5. other specific relative_____
12	Source of referral to treatment center	1. Health center 2. District hospital 3. General hospital 4. Private clinic/hospital 4. Tertiary referral Hospital 5. Self- referred
13	Who first saw the patient and referred them to the referral hospital?	1. Ophthalmologist 2. Pediatrician 3. nurse/HO
14	Major diagnostic Tests were done at the referring hospital	1. Fundoscopy 2. EUA 3. CT/MRI 4. Bilateral BMA and biopsy 5. Biopsy 6. CSF

15	Diagnoses and staging at referral	_____
16	What was done by the first healthcare provider?	1. Reassured and given unspecified medication 2. Referred to another none treatment center 3. Referred to a treatment center
17	What reason for the delayed presentation to the primary health care center?	1. Cost of travel 2. Cost of treatment 3. Far distance of RB center 4. Other family member priority 5. Fearing surgery 6. lack of awareness of the family about the illness 7.Other(specify)_____
18	Reason for the delayed presentation to the treatment center?	1. Cost of travel 2. Cost of treatment 3. Far distance of RB center 4. Other family member priority 5. Delayed referral from the health care center 6. Fearing surgery 7.Other(specify)_____
18	Date of enrolment to a Treatment center	_____
20	Date of final diagnosis confirmed (imaging	_____

21	Date of treatment started	_____
22	Reason for delayed diagnoses within the treatment center	1. cost of imaging modality 2. the MRI/CT is not functional 3. fellow/consultant not available for consultation 4. related to other laboratories not functional 5. BMA, biopsy, CSF, 6. at the Ophthalmology evaluation center
23	Reason for delayed treatment	1. cost of medication 2. medication not available 3. fear of surgery 4. high surgical list 5. fellow/consultant not available for consultation 6.other reason_____
1.	Initial Physical Examination	1. Vital signs -BP_____ PR _____ RR_____ To_____ 2. Anthropometry WT= L/HT= W/H= MUAC= BMI=
2.	Eye examination	1. Leukocoria 2. strabismus 3. proptosis 4. fungating mass 5. red eye 6. vision I. decreased/ II. lost

		7. other (specify _____
3		1.LAP_____ (Specify location 3. Respiratory Distress __ 4. Pallor, skin lesion or mass ____ 5. Level of consciousness 6. cranial or neurologic deficit
No.	**Part IV: Baseline PRETREATMENT Laboratory and Imaging Profile**	
1.	CBC - WBC count _____ ANC _____ ALC _____Hgb/HCT _____ Plt _____ **ESR ----**	
2.	**Uric acid _____** LDH_____ - RFT (Cr ____ BUN _____ - Serum electrolytes K_____ Na+_____ Cl_____ Ca_____ Mg_____ P_____) - Liver Enzymes (AST _____, ALT _____ ALP _____ - Liver function tests (Albumin_, Bilirubin (T/D _____, PT ____, PTT ____ INR	

	____	
3.	Others - HBsAg - Neg / Pos HCV antibody - Neg / Pos PICT- Neg / Pos	
4.	**RB1 genetic test 1. Yes, 2. No** **If yes result**_____	
5.	**Family screening is done 1. yes 2. No**	
6.	If imaging was done (document the conclusion)	1. Chest X-ray_____ 2. CT scan_____ 3. MRI_____
7.	MRI	1.Calcification A. Yes B.no 2. Choroidal invasion A. Yes, B.no 3. Optic nerve invasion A. Yes B.no 3. if optic nerve involvement A. prelaminar B. laminar C. posts laminar 4. extraocular tissue extension A. YES B. NO 5. intracranial extension A YES B. NO 6. para sellar region involvement A. yes B. No
8.	Ophthalmology examination	1. EUA 2. Fundoscopy
9.	Waiting FOR ophthalmology examination before chemotherapy	In weeks _____

10	Ophthalmic examination result	1. ≤3 mm any dimension 2. >3 mm any dimension 3. Tumor >50% and <2/3 volume of eye 4. Tumor ≥ 2/3 volume eye 5. Diffuse infiltrating
11	IF BMA and BIOPSY	I. Positive II. Negative
12	If CSF done	I. positive II. Negative
11	group according to the ICR	1. Group A 2. Group B 3. Group C 4. Group D 5. Group E
13	stage according to ISSRB	Stage 0 Stage I Stage II Stage III Stage IVA 1 2 stage IV B 1 2 3
14	Lymph node involvement	1. Yes 2. No If yes which lymph nodes
15	Site of RB	1. Left 2. Right 3. Bilateral 4. lateral

16	**Diagnosis with grouping, and staging**	1.intraocular 1.1. group_____ 2.extraocular 2.2. locally advanced 2.3. metastatic If metastatic stage _____
17	**Intent of treatment**	1. Curative 2. Palliative
18	**Treatment**	A. Primary treatment 1. local therapy A. Laser B. Cryotherapy 2. Enucleation 1. R 2. L 3. Both 3. Chemotherapy 4. exenteration 1. R 2. L 3. Both 5. Radiotherapy 6. Palliative B. 2ry treatment 1. Enucleation 1. R 2. L 3. Both 2. Chemotherapy 3. Chemotherapy + radiotherapy
16	**Pathology report /enucleation**	Histologic grading 1.1. poorly differentiated 1.2. Moderate 1.3. well differentiated

		2. Rosettes a. Yes b. No 3 Necrosis a. Yes b. No 4.Calcification a. Yes b. No 5. Hemorrhage a. Yes b. No 6. Scleral invasion a. yes b. no 7. choroidal invasion a. yes b. no 8. Extraocular extension a. yes b. no 9. Optic nerve invasion a. yes b. no 10. If the answer to QN # 9 is yes 1. Prelaminar 2. Laminar 3. post laminar 10. Choroidal invasion a. YES b. NO 11. Optic nerve stump positive a. yes b. 2 no
17	Chemotherapy-related toxicity and delayed chemotherapy	1. chemotherapy toxicity a. YES b.NO If yes delayed in weeks_____ 2. neutropenic fever a. yes b. no 3. PRBC transfusion a. yes b. no 4. platelet transfusion a. yes b. yes 5. nausea & vomiting a. yes b. no 6. Treatment-related mortality a. yes b. no
18	When is a Response assessment ophthalmic examination done**?**	1. After 2 2. After 4 3. after 6 4. after 8 cycles
19	Response to preoperative chemotherapy	1. complete remission 2. partial remission 3. progressive disease 4.no change
20	Post-chemotherapy ophthalmology evaluation (conclusion	1. EUA_____ 2. Fundoscopy _____

	Waiting time post-chemotherapy ophthalmic examination	In weeks_____
21	Is response assessment MRI done after which cycle? And response	1. After 2 2. After 4 1. complete remission 2. partial remission 3. progressive disease 4.no change 3. After 6 4. After 8 5.Other specific_____
22	If radiotherapy is given, a specific indication	-_____
	Dose of radiation	_____GY
23	Duration of follow-up after treatment completion (in month	_____
24	Outcome at last data entry time	1. alive 1.1. disease free 1.2recurrences 1.3. disease progression 2. Lost follow up 3. death 4. unknown

Treatment Profile

Diagnosis: _____ Regimen/protocol: ___ Weight ____Height_____

MUAC__ Cycle of Chemotherapy_____

Daily Assessment tool at each cycle

parameter	0	1	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
WBCs											
ANC											
Hgb											
PLT											
Albumin/protein											
Cr											
LDH											
Uric acid											
Serum electrolytes											
LFTS											
Antibiotics needed (yes/no…. Y/N) **If yes type of antibiotics**											
Missed chemotherapy											
GCSG (Dose)											
TMP-SMX PROPHYLAXIS											
Died/alive (D, A)											
If died, the time of death											