COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE
DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

ASSESMENT OF MAGNITUDE AND OUTCOME OF HEPATOBLASTOMA IN TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

By: Zinet Kedir (MD)

ARESEARCH THESIS SUBMITED TO DEPARTMENT OF PEDIATRICS AND CHILD HEALTH, SCHOOL OF MEDICINE, COLLEGE OF HEALTH SCIENCES, ADDIS ABAB UNIVERSIITY FOR THE PARTIAL FULFILMENT OF THE REQUIREMNTS FOR THE CERTEFICATE IN PEDIATRICS AND CHILD HEALTH

OCTOBER, 2021

ADDIS ABABA, ETHIOPIA

MAGNITUDE AND OUTCOME OF HEPATOBLASTOMA IN PEDIATRICSAGE GROUP IN TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

BY

ZINET KEDIR (MD)

- **ADVISORS:**

ABEBE HABTAMU (MD)
(Consultant pediatrician and gastroenterologist and nutritionist)

DANIEL HAILU (MD)

(Consultant pediatrician and pediatrics hematologist and oncologist)

ARESEARCH THESIS SUBMITED TO DEPARTMENT OF PEDIATRICS AND CHILD HEALTH, SCHOOL OF MEDICINE, COLLEGE OF HEALTH SCIENCES, ADDIS ABAB UNIVERSIITY FOR THE PARTIAL FULFILMENT OF THE REQUIREMNTS FOR THE CERTEFICATE IN PEDIATRICS AND CHILD HEALTH

ADDIS ABABA UNIVERSTY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE

DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

Declaration

I, the undersigned, Pediatrics and Child Health final year resident declare that this thesis done is my original work in partial fulfillment for the certificate of Pediatrics and Child Health.

Title: - Magnitude and outcome of hepatoblastoma in pediatrics age group in Tikur Anbessa hospital, Addis Ababa, Ethiopia.

Submitted by;

Zinet Kedir: ___________________ ___________________

Name of resident Signatures Date

Approved by:

1. **Dr Abebe Habtamu :**___________________ ___________________
   Advisor name 1 Signatures Date

2. **Dr Daniel Hailu:** ___________________ ___________________
   Advisor name 2 Signature Date

ACKNOWLEDGEMENTS

I would like to express my gratitude to TASH department of Pediatrics and Child health for giving me this opportunity to conduct a research on an issue that I am extremely curious about. I would also like to express my heartfelt gratitude to my advisers Dr. Abebe Habtamu and Dr .Daniel Hailu, for their continuous support and constructive advises.

My special appreciation goes to the staff of the Hemato-oncology unit and the patient record office for their facilitation and assistance during data collection.

ACRONYMS

AAU…………….. Addis Ababa Universiy

TASH…………….Tikuranbesa specialized hospital

HP………………. Hepatoblastoma

HCC……………. Hepatocellular carcinoma

HOC……………. Hematooncology center

AFP…………..…. Alpha feto protein

CBC…………..…Complete blood count

BWS……………. BeckwithWiedemann syndrome

FAP…………….. Familial adenomatous polyposis

FAS…………….. Fetal alcohol syndrome

OS……………........ Overall survival

VLBW…………… Very low birth weight

HBsag………….. Hepatitis B surface antigen

HCV……………. Hepatitis C antibody

CHIC………..…. Children's Hepatic Tumor International Collaboration

COG……………. Children's Oncology Group

SIOP…………… The International society of pediatric Oncolog

ABSTRACT

Background: Hepatoblatsoma is the most common primary malignant liver tumor in pediatrics most often occurs within the first 3 years of age. Most common clinical presentation is abdominal distension or abdominal mass. It is more common in south East Asia and Africa. There are multiple associated factors which determine the magnitude and prognosis factor of hepatoblatsoma. Indeed, Knowledge about the magnitude and outcome of hepatoblatsoma will help in designing prevention and early management intervention, thereby reducing the severity of the illness and Death of patients.

Methods: A cross-sectional analytical study was done by collecting retrospective data from patient charts of patient evaluated at pediatrics hemato-oncology unit at TikurAnbesaa Specialized Hospital (TASH) in Addis Ababa, Ethiopia, during the period June 2010 to July 2021GC. All patients whose records meet the inclusion were reviewed. Data cleaning and analysis was conducted by the principal investigator. The data was summarized using frequency distributions and summary tables and figures. The data was further analyzed using descriptive statistics and survival analysis by applying Kaplan Meier statistics. Conclusions of the study were drawn based on the analyses results.

Result: A total of 25 patients fulfill the inclusion criteria were enrolled almost three forth of the study participant were under 2 years, around 52% were females, majority of them were delivered at term (72%) and had normal birth weight (64%).Most of the patient came from rural area (64%).All patients had abdominal ultrasound and abdominal-pelvic CT scan which is suggestive of HB and around 64% of the mass involve both lobe of the liver.

Major clinical manifestations like abdominal mass and abdominal pain were present on all patients followed by weight loss (80%) and anorexia (64%). Most of the patient had elevated AFP >1000ng/ml (80%) and thrombocytosis (56%). 64% of the patients had PRETEXT stage 3 HB.

Magnitude of hepatoblatsoma in the last 10 years in tikuranbesa specialized hospital were (25,2%) when we compared it with total solid tumors seen in the past 10 years .

Most of the patient started chemotherapy (21, 84%) ,Cisplatin based regimen was most commonly used regimen. Surgery was done only for 20% of the patient. Almost all post-surgical patients got improved.

The correlation function of tumor size decrement after treatment with serum AFP after treatment and cycle of chemotherapy had significant correlation with P –value of 0.000 and 0.034 respectively.

Conclusion: hepatoblatsoma is the most common liver tumor in less than 5 year since surgery is the main stay of management most of our patients died within 6month to 1 year after hospital stay even before surgery, almost all of the survived children undergone surgical excision.

Key words: hepatoblatsoma, serum AFP, abdominal mass, lobe involvement, death.

Table of Contents

ACKNOWLEDGEMENTS III

ACRONYMS IV

ABSTRACT V

List of table X

Figures XI

1. INTRODUCTION 1

1.1 Background 1

1.2 Statement of problem 3

1.3 Significance of study 4

2. LITRETURE REVIEW 5

2.1 Prevalence and associated factors of HB 5

2.2 Prognostic factors and comorbid conditions 6

2.3 Management and outcome 7

3. OBJECTIVES 8

3.1 General objective 8

3.2 Specific objectives 8

4. METHODES 9

4.1 Study Area 9

4.2 Study design 9

4.3 Selection of study population 9

4.3.1 Source population 9

4.3.2 Sampling frame 9

4.3.3 Study population 10

4.4 Inclusion and exclusion criteria 10

4.4.1 Inclusion criteria 10

4.4.2 Exclusion criteria 10

4.5 Sample size determination 10

4.6 Data collection procedures 10

4.6.1 Data collection instrument 10

4.6.2 Data collection Method 10

4.7 Study variables 11

4.7.1 Dependent variables 11

4.7.2 Independent variables 11

4.8 Operational definitions 11

4.9 Data quality control 12

4.10 Data analysis techniques 12

4.11 Ethical clearance 12

4.12 Dissemination of results 12

5. Results 13

5.1 Sociodemographic characteristics 13
5.2 Medical characteristics of the patient 15
5.3 Incidence rate of hepatoblastoma 16
5.4 Laboratory and radiologic features of hepatoblastoma 17
5.5 The treatment characteristics of hepatoblastoma patient 21
5.6 The outcome of the hepatoblastoma patient 23
5.7 The cross relation of disease characteristics with patient outcome 24
5.8 The correlation function of tumor size decrement with independent characteristics 25
6. Discussion 26
6.1 Magnitude and clinical presentation of HB 26
6.2 Prognosis and associated factors of HB 26
6.3 Treatment and Outcome of hepatoblstoma 27
7. Conclusion 28
8. Limitation 28
9. Recommendations 29
REFERRENCES 30
ANNEX: 33

List of table

Table 1: The sociodemographic characteristics of study participants having hepatoblastoma in the last ten years, Tikur Anbessa Specialized hospital, Addis Ababa, Ethiopia, 2021 14

Table 2: Medical characteristics of the hepatoblastoma patient 15

Table 3: Laboratory and radiologic features of study participants 20

Table 4: The treatment characteristics of hepatoblastoma patient 21

Table 5: Association between hepatoblastoma metastasis with AFP and Chemotherapy 23

Table 6: The cross relation of disease characteristics with outcome 24

Table 7: The correlation function of tumor size decrement with independent characteristics 25

Figures

Figure 1: Age distribution of hepatoblastoma patients 13

Figure 2: Sex distribution of hepatoblastoma patients... 14

Figure 3: Residence of hepatoblastoma patients.. 15

Figure 4: Most common clinical findings of hepatoblastoma patient... 16

Figure 5: The incidence of hepatoblastoma in the last ten years [2011-2021) 17

Figure 6: Lobe involvement of tumor 18

Figure 7: Age of the patient vs. lobe involvement.. 18

Figure 8: Duration of the mass and lobe involvement 19

Figure 9: Platelet level of the patient 19

Figure 10: Level of serum AFP before and after treatment 21

Figure 11: Tumor size after chemotherapy 22

Figure 12: Tthe outcome of hepatoblastoma patient.. 23

1. INTRODUCTION

1.1 Background

Hepatoblatsoma is rare but the most common primary malignant liver tumor in children especially in infants and under 3 years of age. [1, 3, 4,7]

The histological type is subdividing in to two the epithelial type and mixed type. The epithelial variety is further divided into six patterns: small-cell undifferentiated, embryonal, pleomorphic, cholangioblastic, fetal, and macro trabecular. Over the past 3 decades the management with neoadjuvant chemotherapy and surgery is advanced which has an impact for the survival rate [2].

The overall world standard incidence of liver tumor in children is 2.3 per million people in 2001 to 2010 worldwide of which hepatoblatsoma is the most common malignant liver tumor in children with an increase incidence of 4.3% per year from 1992 to 2014 in children younger than 19 years of age probably due to the survival of extremely LBW infants.[3]

In less than 3 year of age hepatoblatsoma is the 3rd most common abdominal tumor next to neuroblastoma and nephroblastoma. It is 1.5 times higher in males than females.

Epidemiologically hepatoblatsoma is more common in south East Asia and Africa than in Europe and North America. [4]

The most common sign of HB is abdominal distension or abdominal mass. Some children presented with abdominal discomfort, generalized fatigue and loss of appetite probably due to tumor distension or anemia. Serum AFP is the most common clinical marker for HB which is elevated about 80-90% of patients. [6,7]

Factors such as prematurity, low birth weight, maternal smoking, alcohol OCP, methods of assisted reproduction are associated with Hepatoblatsoma .it is also associated with syndromes like BWS, familial adenomatous polyposis, Li-Fraumeni syndrome, Trisomies and other metabolic disorders.[5]

Diagnosing HB is clinical presentation with serum AFP, abdominal Imaging and histopathologic. On abdominal CT usually seen as a well-defined heterogeneous mass, which is usually hypo attenuating compared to surrounding liver. Frequently there are with areas of necrosis and hemorrhage. dense calcifications may be seen in approximately 40% of cases. [1,5,8]

The staging of HB is needed to choose the best treatment and there are two types of staging system the COG staging system and the pre-treatment extent of disease (PRETEXT) staging system. According to COG stage 1 the tumor has completely removed, stage 2 is the tumor is removed surgically but microscopic traces of disease were still present, Stage3 the tumor cannot be removed with surgery at diagnosis because it is too big and there is regional lymph node involvement, Stage 4 distant metastasis of the tumor. According to PRETEXT staging system stage 1 tumor involve one quadrant, stage 2 tumor involve two adjoining quadrants, stage 3 tumor involve 3 adjoining quadrants or 2 non adjoining quadrants, stage 4 tumor involves all quadrants. [8,10]

There are three ways of management of hepatoblastoma Chemotherapy, surgery and liver transplant. With those managements the outcome is greatly improved the long-term survival reaching 75-80 %. [10]

1.2 Statement of problem

Even through; hepatoblastoma is rare disease, it is not uncommon in our hospital. Despite the prognosis is improving for the past 3 decades, in our set up it has still poor out come this can be due to patient presentation in later stages of the diseases, unavailability of neoadjuvant chemotherapy and surgery makes hepatoblastoma in our setup to have lesser outcome.

Since the decision on early diagnosis and management usually delayed the survival rate significantly decreased.

In our setup most of the patients with hepatoblastoma are infants and toddlers whom they need special care on their nutrition, development and vaccination before starting management which has an impact on their survival.

Therefore, this study addressed the aforementioned problem prevalence and outcome of hepatoblastoma.

1.3 Significance of study

This study is primarily to see the prevalence, outcome and associated comorbid conditions affecting the severity of illness and death of patients with hepatoblastoma. It will also help us to understand the burden of liver tumor in pediatrics populations.

Secondly it will forward the information and recommendation to hospital stuffs to have better evaluation and follow up of the patients and also suggest interventions for improving outcome of HB.

Third it will be an input for the scientific community and it will be a source of inquiry for further research based on the gaps they will be identified.

Fourth it will guide policy makers and government bodies on planning and who works on liver tumor in children.

2. LITRETURE REVIEW

2.1 Prevalence and associated factors of HB

Hepatoblastoma is a rare but the most common malignant embryonal liver tumor in infants and young children more often in the right lobe of the liver. [1,4,8,15,18,]

According to CHIC though HB is most common liver tumor in children with increasing annual incidence even major tertiary children's cancer centers may encounter only 1 or 2 newly diagnosed patients per year [18].

The overall prevalence of hepatoblastoma worldwide is 2.3 per million person per year between 2001 to 2010 .it is the most common malignant liver tumor in children with an increase in incidence of 4.3% per year from 1992 to 2004 in children younger than 19 years. [3,17]

In one study done in US on epidemiology of liver tumor among children less than 5 years of age HB was account for 91% of primary hepatic malignancy cases where as among those with 15 to 29 years of age HCC accounted for 87% of the cases. [4,5,17]almost 95% of HB diagnosed before they are 3 years of age [4,9].

In one study done in Chinacollected 11 years data among children 2–4-year-old male patients HB incidence increased significantly from 0.5% to 3.8% ($P<0.05$). The 5- and 10-years overall survival rates were 81.5% and 81.0%. On this study age of 2-4years old, being African-American ethnicity and having no surgery were their independent predictors for short OS.[3].

Most HB occur sporadically however there are some associated factors for the occurrence of HB in young children of which BWS, FAP, FAS, prematurity and low fetal birth weight, Gardner syndrome, glycogen storage disease, biliary atresia, trisomy18, trisomy 21are the common one. [2,4,8,19,20]

In one study done in Japanto see the risk of hepatoblastoma among immature and VLBW infants among 543 HB children and all live births during 26 years from 1969 to 1994 compared with children with birth weight of 2500g or more ,the relative risks of hepatoblastoma among children with birth weights of <1000,1000-1499,1500-1999 and 2000-2499g were 15.64($p<0.001$),2.53,2.71 and 1.21 respectively suggesting the lower the BW the higher the risk of HB this study also showed when the year increased the chance of immature infants survival was also increased.[20].

In multiple studies liver tumors both HCC and HB there is strong association with high platelet count since these tumors produce a thrombopoietin which circulates and stimulates megakaryocytopoisis.Highplatelet level was associated with the chemotherapy sensitivity and good outcome of hepatoblastoma. [4,5,25].

2.2 Prognostic factors and comorbid conditions

Different comorbid factors have to be taken in to account while evaluating pattern and outcome of HB. The factors are often similar in many studies. Histologic type of the tumor, abnormally increased serum AFP, beta catenin expression, multifocality of the tumor, age at diagnosis, ethnicity, stage of the tumor, surgery, tumor rupture during diagnosis, vascular involvement, extra hepatic invasion, are some of the mentioned comorbid factors. [2,3,4,21].

According COG of the histologic type the fetus type, usually diagnosed in stage one as having good prognosis and the main factors of poor prognosis included stage 4 accompanied by distant metastasis and AFP<100 and tumor tissue morphology of 'undifferentiated small round cell' type. [4,22].

In areas where hepatitis B virus is endemic the prevalence of HCC is more common than hepatoblastoma. Generally, hepatoblastomas are chemosensitive while HCC are chemo resistant and has poorer cure rate. [28,29]

2.3 Management and outcome

Survival rate for childhood hepatoblastoma improved for the past 3 decades this may be due to the advances on pathological evaluation, neoadjuvantchemotherapy, imaging, risk stratification and surgery including liver transplantation are some of the mentioned reasons in most studies. [1,3,4,5,7,27].However; successful outcome in developing country like Asians is challenging for the clinicians as well the family. [5,10,11].

Since HB is highly sensitive tumor for chemotherapy combination of chemotherapy with surgery is still the main stay of management. the introduction of strong and effective chemotherapy drugs particularly platinum based chemotherapy improved the outcome with survival rate reaching more than 75%.[4,23,24,26,27].

According to multiple studies including COG and SIOPEL, GPOH,and Japanese liver tumor group recommend Cisplatin and other platinum-based chemotherapy as the core chemotherapy but the mortality rate without surgery more than 90% and 4 cycles of combination chemotherapy is recommended before surgery. [4,7,23,26,27,30].

Surgery plays the critical role in the management of hepatoblastoma and complete resection is the only way to achieve cure. according to recent publications the international childhood Liver Tumors strategy group tends to give neoadjuvant chemotherapy to all hepatoblastoma patients and then performs a delayed surgery this reduce the tumor size and down staging of the tumors achieved in majority of the cases. Advanced stage tumor greatly benefits from the neoadjuvant chemotherapy. While COG recommend upfront surgery for initially resectable tumors. [26,30]

3. OBJECTIVES

3.1 General objective

To see the hospital magnitude and outcome of hepatoblastomain the hematooncology unit at Tikuranbesa specialized hospital.

3.2 Specific objectives

- To determine the magnitude of Hepatoblastoma in TASH.
- To understand risk associated and comorbid conditions of hepatoblastoma.
- To determine the prognostic factors, prognosis and outcome of hepatoblastoma in TASH.

4. METHODES

4.1 Study Area

The study was conducted in Addis Ababa, Ethiopia in the HOC unit in TASH. Addis Ababa is the capital and largest city of Ethiopia. According to the 2007 population census, the city has a total population of 3,384,569. Our study will be conducted in TASH which is located in Addis Ababa and giving considerable hematologic and oncology service. TASH is the teaching hospital of Addis Ababa University. It is also the largest referral hospital in Ethiopia with specialists and sub specialists which offers comprehensive health care service for around half a million patients per year through specialty clinics and inpatient service departments. It has over 700 beds, and about 1,700 professional and support staffs in inpatient, outpatient and emergency units.

Beside this it is the first governmental hospital which both hematologic and oncology service was started. The Pediatrics hemato-oncology unit in particular has 26 beds in TASH oncology ward and 16 beds in the cancer center. The activity is currently run by three pediatric hemato-oncologists, 2 fellow seniors ,12 residents (five first years, five second year, two third year residents) assigned every month. The cancer center has 16 beds and also provides outpatient service every day for more than 600 patients every month, accepting 500-700 new patients every year for both hematology and oncology service.

4.2 Study design

The study was hospital based descriptive retrospective cross-sectional study between June, 2010 to July 2021 GC.

4.3 Selection of study population

4.3.1 Source population

Source population is all pediatrics patients who diagnosed with hepatoblastoma and admitted to TASH hematooncology unit from June 2010 to July 2021GC.

4.3.2 Sampling frame

A list of patients with hepatoblastoma at the pediatric oncology unit.

4.3.3 Study population

The study population was all selected hepatoblastoma patients as registered in the sampling frame.

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria

- ❖ All children under 18 years who fulfill both clinical, radiological and laboratory criteria for the diagnosis of hepatoblastoma

4.4.2 Exclusion criteria

- ➢ Patients who has no imaging
- ➢ Died before settling the diagnoses
- ➢ Above 18 years
- ➢ Have lost chart

4.5 Sample size determination

As mentioned above on the back ground and literature review hepatoblastoma is very rare disease it is difficult to get the P value and calculate the sample size so I took all hepatoblastoma patients for the past 10 years who fulfill the inclusion criteria.

4.6 Data collection procedures

4.6.1 Data collection instrument

Data was collected using a structured questionnaire which was adapted from previously published studies with some modification to ensure applicability, validity, reliability to our current study. The questionnaire consist questions on socio-demographic factors, Major clinical presenting sign and symptoms, associated factories, primary diagnosis, treatment, complications and outcome of hepatoblastoma.

4.6.2 Data collection Method

Data was collected by trained data collectors under the supervision of the Investigator from chart and logbook. Data collectors were selected from among the hospital hematology oncology unit nursing staff. Personnel who assisted in chart retrieval and management were recruited among the staffs of TASH working in the patient records storage and retrieval office. Data collectors

had one-day training on how to extract the required information from patients' charts and complete the structured questionnaire.

4.7 Study variables

4.7.1 Dependent variables

- Presence of hepatoblastoma and its out come

4.7.2 Independent variables

- Socio demographic factors (age, sex, birth weight, Address.)
- Maternal factors (maternal smoking, alcohol, preeclampsia …)
- major presenting signs and symptoms
- Tumor bulk
- Status prior to initiation of the chemotherapy (staging of the tumor…)
- Serum AFP level and Serum platelet level
- viral markers (Hbsag, HCV)
- Imaging findings
- Histopathological finding
- Phase of treatment (phase of chemotherapy, surgery…)
- length of hospital stay
- Death

4.8 Operational definitions

Hepatoblastoma is diagnosed based on imaging findings and/or elevated AFP.

Clinically patients with hepatoblastoma are presented with upper abdominal mass, abdominal distension, anorexia and weight loss. Almost 95% of patients with HB serum AFP is elevated. In most of the patient's serum HBsag, CBC, LFT and abdominal ultra sound done as an initial evaluation then abdominopelvic CT done after the ultra sound result. Some of the patients have histopathological diagnosis.

Elevated AFP is determined based on the pediatrics laboratory reference range.

4.9 Data quality control

The Investigator examined the appropriateness of the methodologies followed. The questionnaire was reviewed for completeness and pre-testing was undertaken. Data collectors were trained and data was collected by the trained nurses and supervised by the Investigator. The Filled questionnaire was checked for completeness and consistency of information by the data collector and the Investigator once weekly during data collection. The template had internal consistency checks and any inconsistency or ambiguity was addressed in time.

4.10 Data analysis techniques

The data was entered onto and analyzed using SPSS version 25. Data cleaning was conducted exclusively by the Investigator. Descriptive summary of the data will be presented in Tables and Figures. Frequency distribution was used to organize the data and present the responses obtained. Measures of central tendency and dispersion were calculated and utilized the study variables as appropriate. The data was categorized and summarized with descriptive statistics, and survival analysis.

4.11 Ethical clearance

Proposal approval was obtained before the beginning of data collection from the Research and Publication Committee (RPC) of the Department of Pediatrics and Child Health (DPCH), College of Health Sciences (CHS), TASH. All information in the charts was kept confidential and the information collected was used solely for the intended purpose. Personal Identifier Information (PII), including names of patients and medical registration number will not be included in the questionnaire. Codes were used instead and completed questionnaire was stored safely by the Investigator.

4.12 Dissemination of results

The study results was disseminated to key stakeholders, including CHS, AAU, TASH, DPCH, Department of Radiology, Department of pathology and other appropriate institutions of higher education. The results were further disseminated to wider scientific community through abstract presentation at a conference and through publication in a peer-reviewed scholarly journal.

5. Results

5.1 Sociodemographic characteristics

Almost three-fourth of the study participants were in the age group between 1 and 2 year old and 52% of the participants were female, 72 % were delivered at term and 64% had normal birth weight and 64% were from rural area and 44% of the patients parent or care givers monthly income were 1700-3000 ETB as shown in the table below.

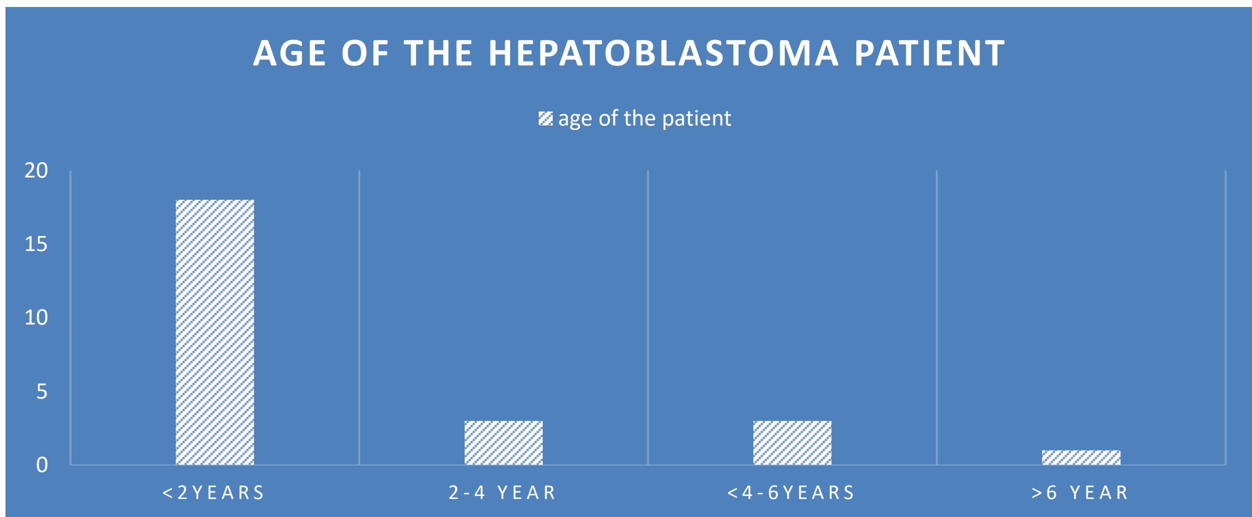

Figure 1: Age distribution of hepatoblastoma patients

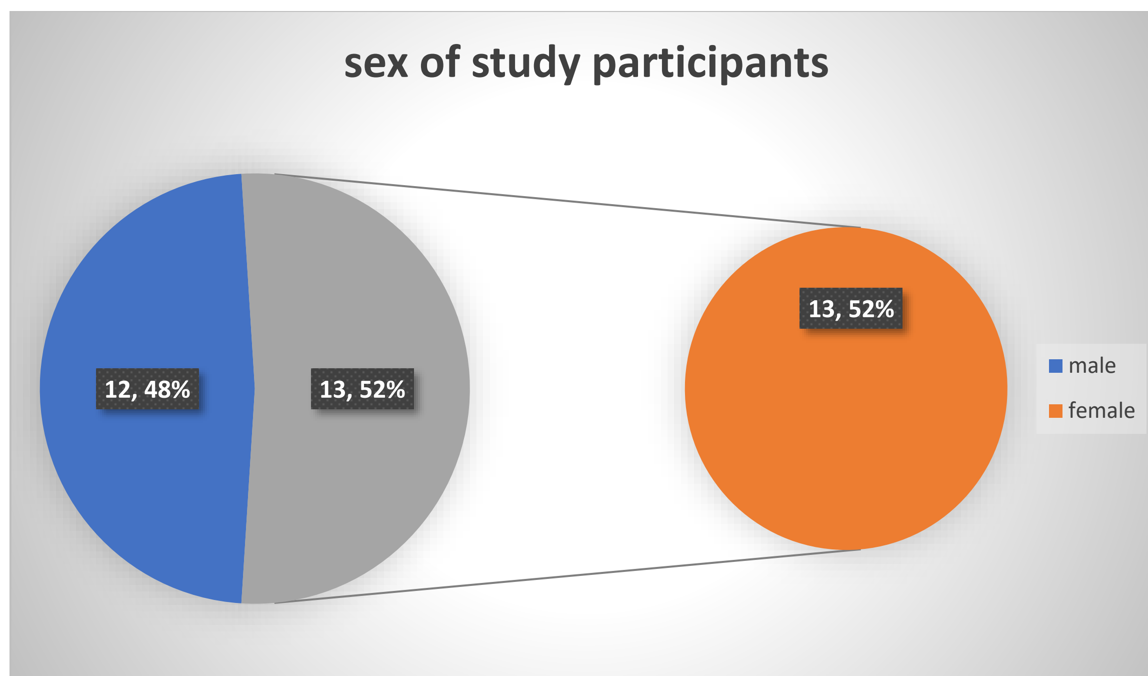

Figure 2: Sex distribution of hepatoblastoma patients

Table 1: The sociodemographic characteristics of study participants having hepatoblastoma in the last ten years, Tikur Anbessa Specialized hospital, Addis Ababa, Ethiopia, 2021

Variable	Frequency	Percent
Gestational age		
term	18	72
preterm	1	4
unknown	6	24
Birth weight		
NBW	16	64
LBW	4	16
Unknown	5	20
Monthly income		
<1700birr	2	8
1700-3000	11	44
3001-10000	7	28
unknown	5	20

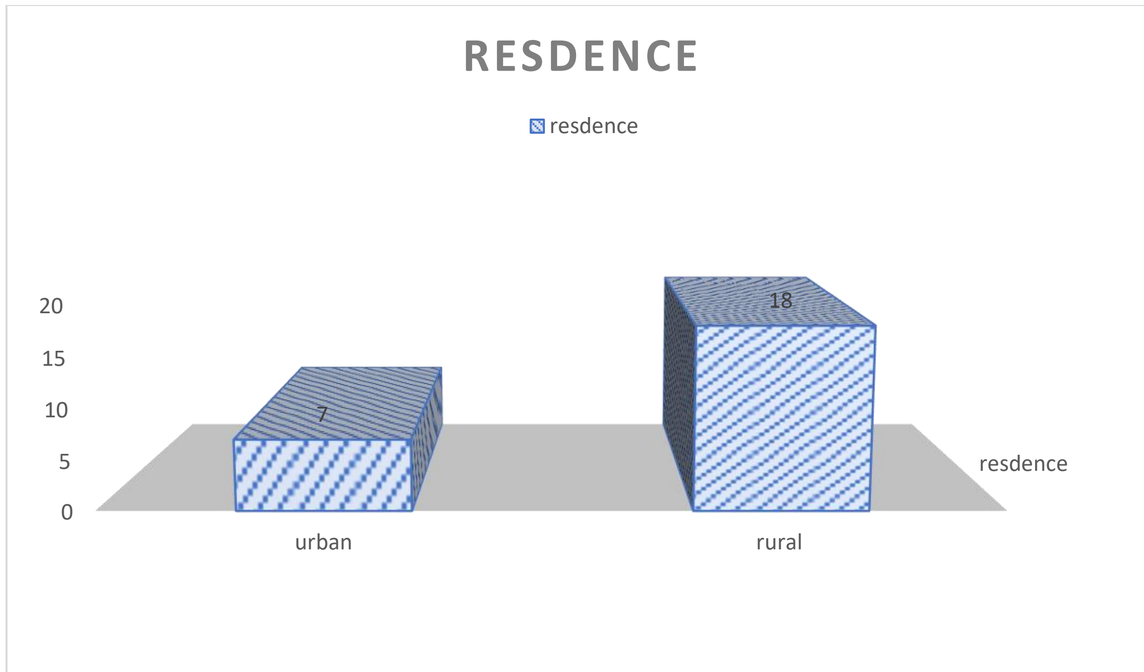

Figure 3: Residence of hepatoblastoma patients

5.2 Medical characteristics of the patient

All (100%) of the study participants initial presentation were progressive abdominal mass , abdominal distension and abdominal pain of this almost for 60% of the patients the duration of the mass lasted for 1-6months. 80% had weight loss and 64% had anorexia and 48% had vomiting as shown the table below.

Table 2: Medical characteristics of the hepatoblastoma patient

Variable	Frequency	Percent
abdominal distention		
Yes	25	100.0
duration of abdominal mass		
<1month	7	28
1-6month	15	60
>6month	3	12
vomiting		
Yes	12	48
No	13	52
pallor		
Yes	14	56
No	11	44

jaundice Yes No	 1 24	 4 96
fever Yes No	 13 12	 52 48
diarrhea Yes No	 2 23	 8 92
constipation Yes No	 1 24	 4 96
Syndromic child Yes No	 2 23	 8 92

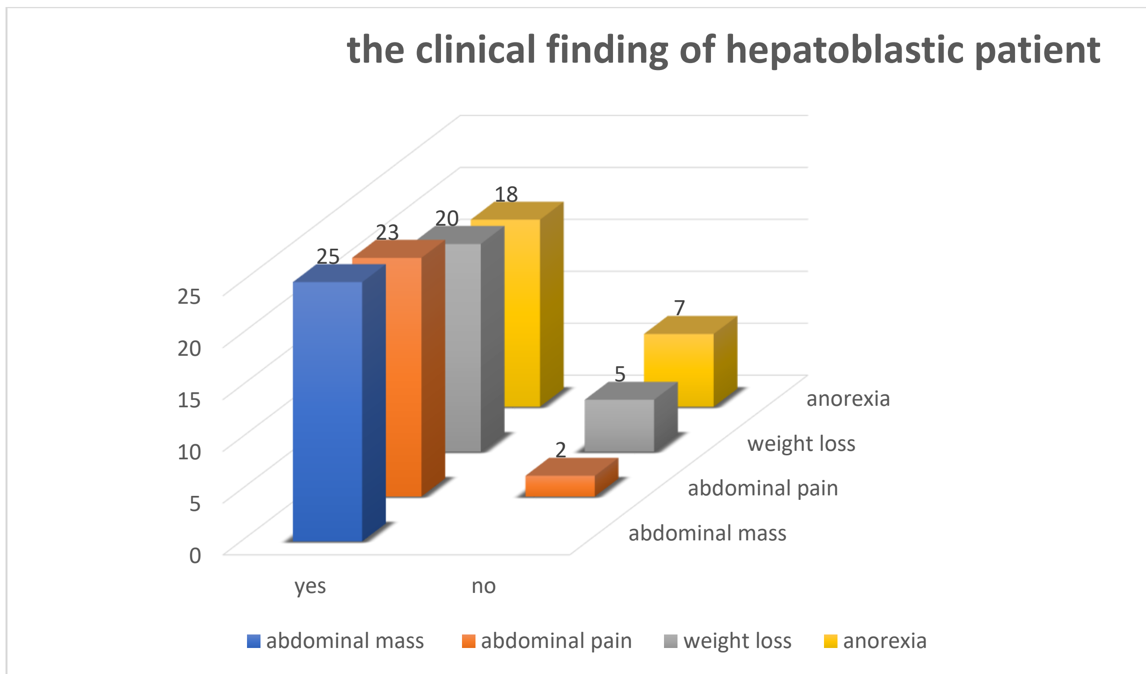

Figure 4: Most common clinical findings of hepatoblastoma patient

5.3 Incidence rate of hepatoblastoma

The study finding showed that from the 10 years retrospectively reviewed patient information chart 1560 solid tumors were reviewed and from these 25 participants were having hepatoblastoma as shown the figure below.

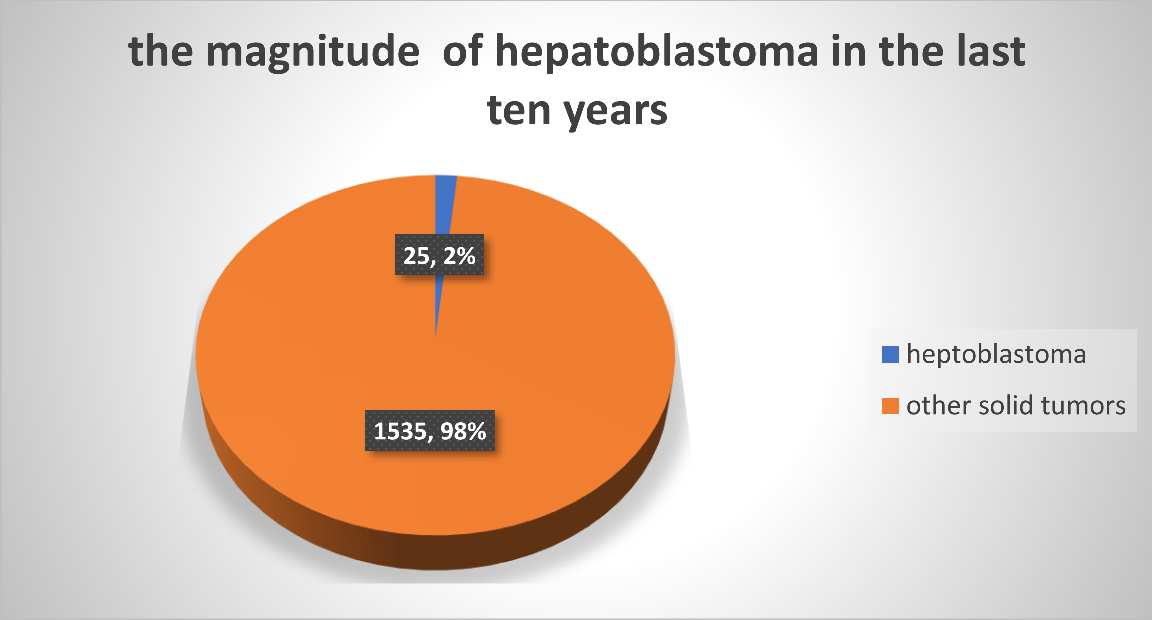

Figure 5: The magnitude of hepatoblastoma in the last ten years [2011-2021)

5.4 Laboratory and radiologic features of hepatoblastoma

All patients had abdominal ultrasound and CT scan which was suggestive for hepatoblastoma.64% of the patient had both lobe involvements, 44% of the patient had metastasis to the lung and 64% of the study groups were PRETEXT stage 4 HB.

Below there are three figures which showed tumor lobe involvement with age the patients and duration of the mass.

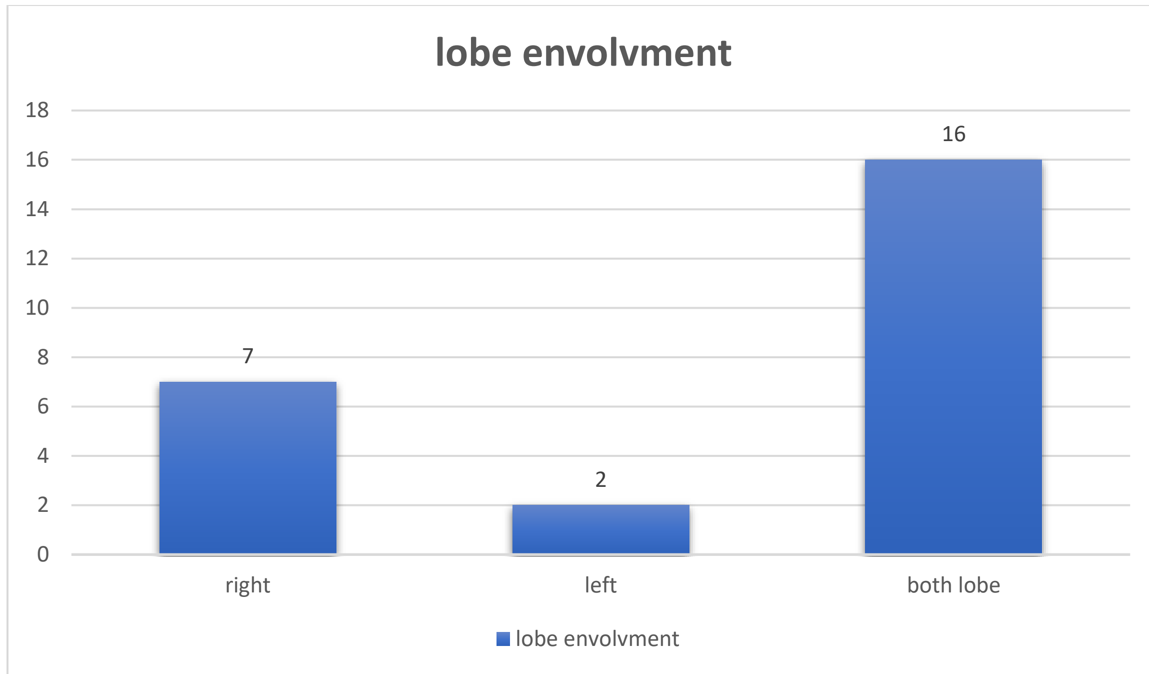

Figure 6: Lobe involvement of tumor

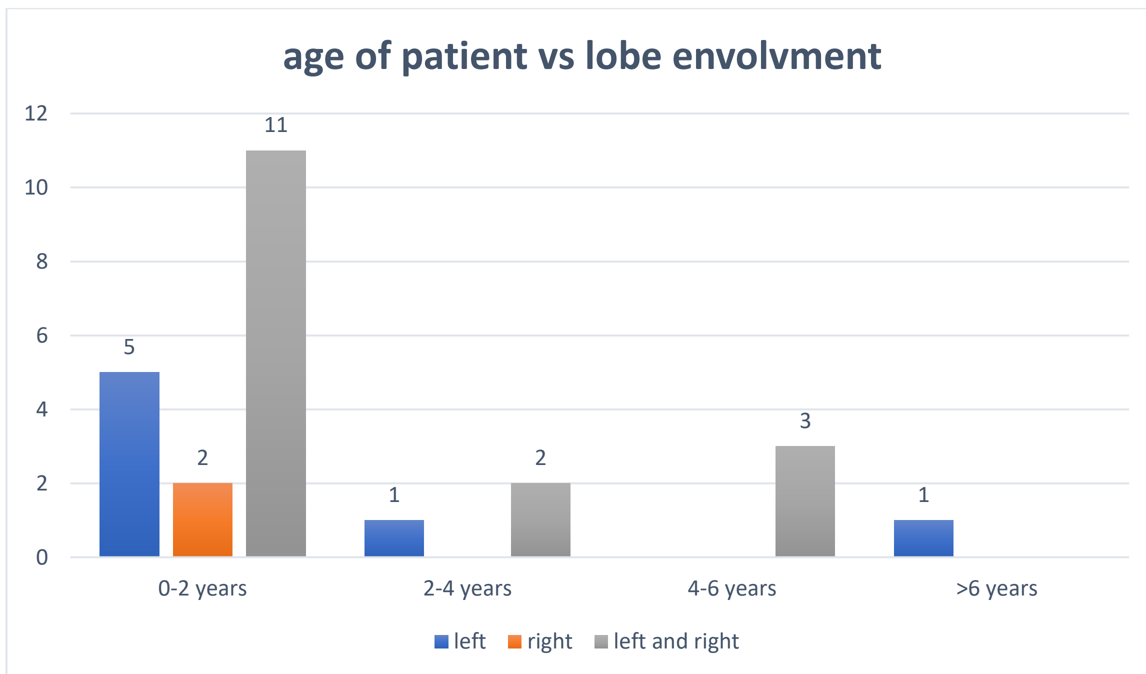

Figure 7: Age of the patient vs. lobe involvement

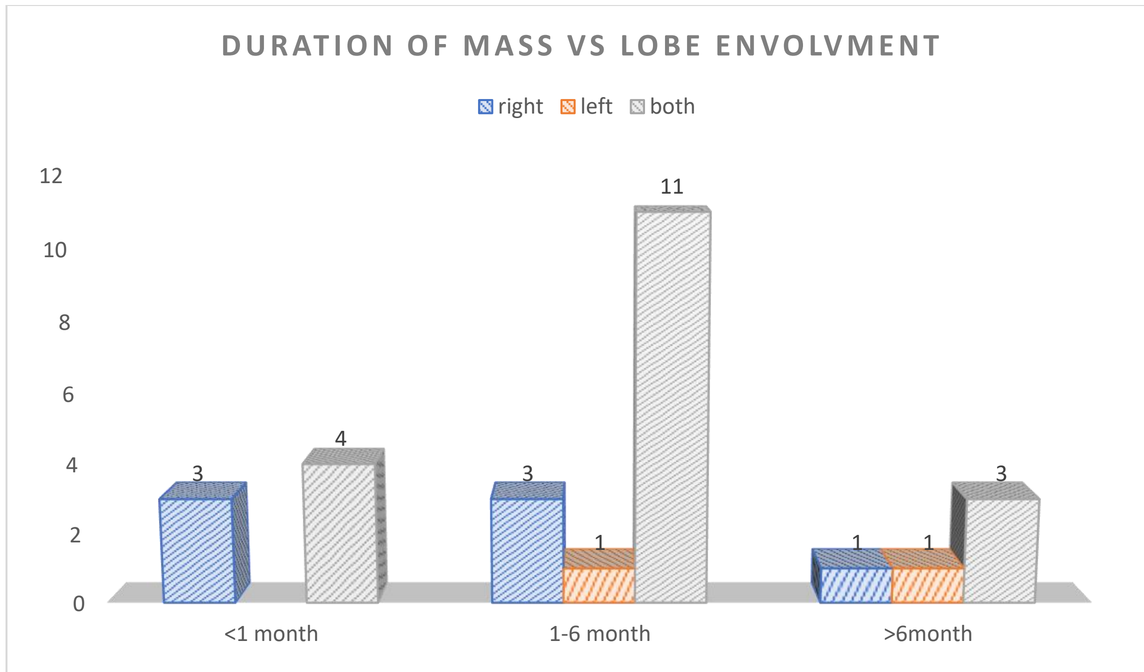

Figure 8: Duration of the mass and lobe involvement

CBC was done for all patients where 92% ofstudy participantshad abnormal CBC profile and from these 56% had thrombocytosis of this 32% had concomitant anemia and 32% had isolated anemia. LFT were affected only in 12% of the study participants the affected variable were ALT,AST and ALP. Only one patient had positive viral marker (HBsAg positive).

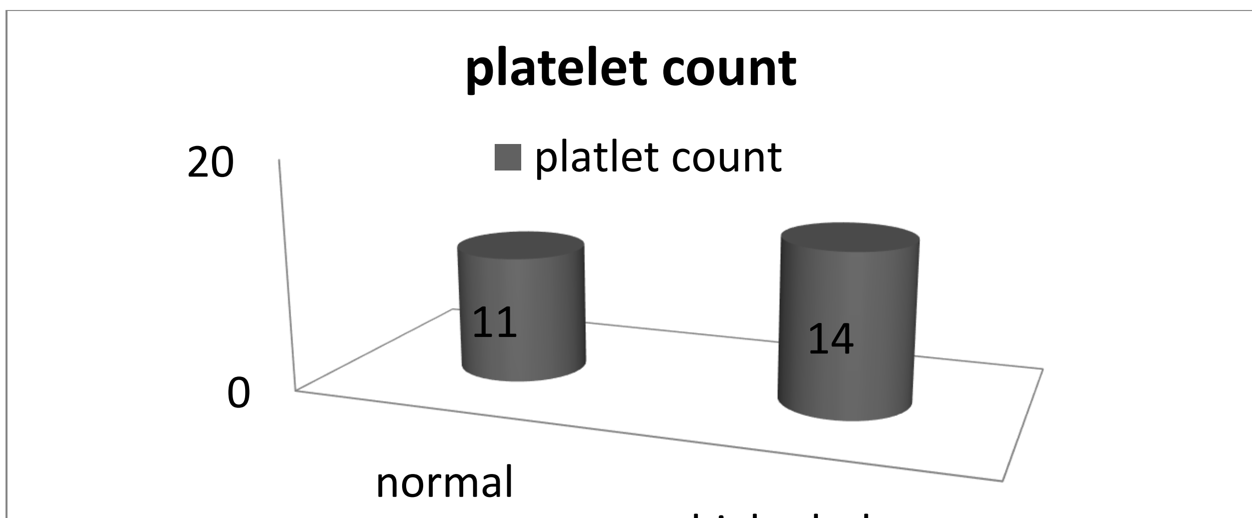

Figure 9: Platelet level of the patient

viral marker of the patient		
positive for HBSAG	1	4
positive for both	1	4
negative for both	23	92
CBC profile with differential		
Normal	2	8
Abnormal	23	92
if abnormal, describe the abnormality		
Anemia	8	36
Thrombocytosis	6	16
Bicytopenia(anemia and leukopenia)	1	8
Thrombocytosis and anemia	8	32
Liver function test result		
Normal	22	88
Abnormal	3	12
Types of abnormal enzyme		
AST	1	33.3
ALP	1	33.3
ALT&AST	1	33.3
Metastasis characteristics		
Yes	11	44
No	14	56
Site of metastasis		
Lung	11	100
clinical and radiographic stage of the tumor		
stage 3	9	36
stage 4	16	64

Table 3: Laboratory and radiologic features of study participants

80% of the study group had significantly elevated AFP (>1000ng/dl) during their initial presentation. Most of the AFP level lie between 50,000 ng/ml to 200,000ng/dl.

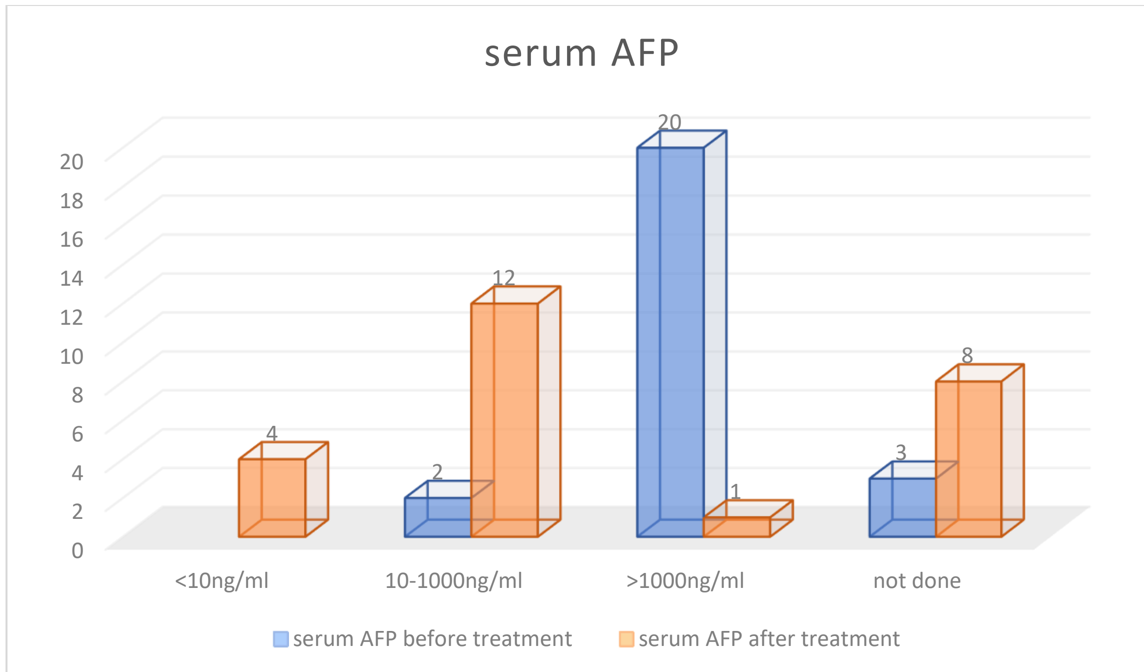

Figure 10: Level of serum AFP before and after treatment

5.5 The treatment characteristics of hepatoblastoma patient

In this study, 84% of the participant were took chemotherapy, and from these 88% took Doxorubicin &Cisplatin regimen and 12% took up to 6 cycle of treatment and all surgery was done after chemotherapy as shown in the table below.

Table 4: The treatment characteristics of hepatoblastoma patient

Treatment characteristics of study participants	frequency	Percent
Patient started chemotherapy		
Yes	21	84
No	4	16
Type of chemotherapy		
Super PLADO	3	12
PLADO	18	88
cycle of chemo started (n=18)		
cycle 1	5	20
cycle 2	2	8
cycle 3	5	20
cycle 4	6	36
cycle 6	3	12

surgery done Yes No	 5 20	 20 80
Time of surgery after chemotherapy	 5	 100
Cycle of chemotherapy before surgery cycle 3 cycle 4 cycle 6	 1 2 2	 25 37.5 37.5
histopathology result suggestive of hepatoblatsoma not done	 5 20	 20 80
duration of hospital stays <1month 1-6month >6month	 4 13 8	 16 52 32

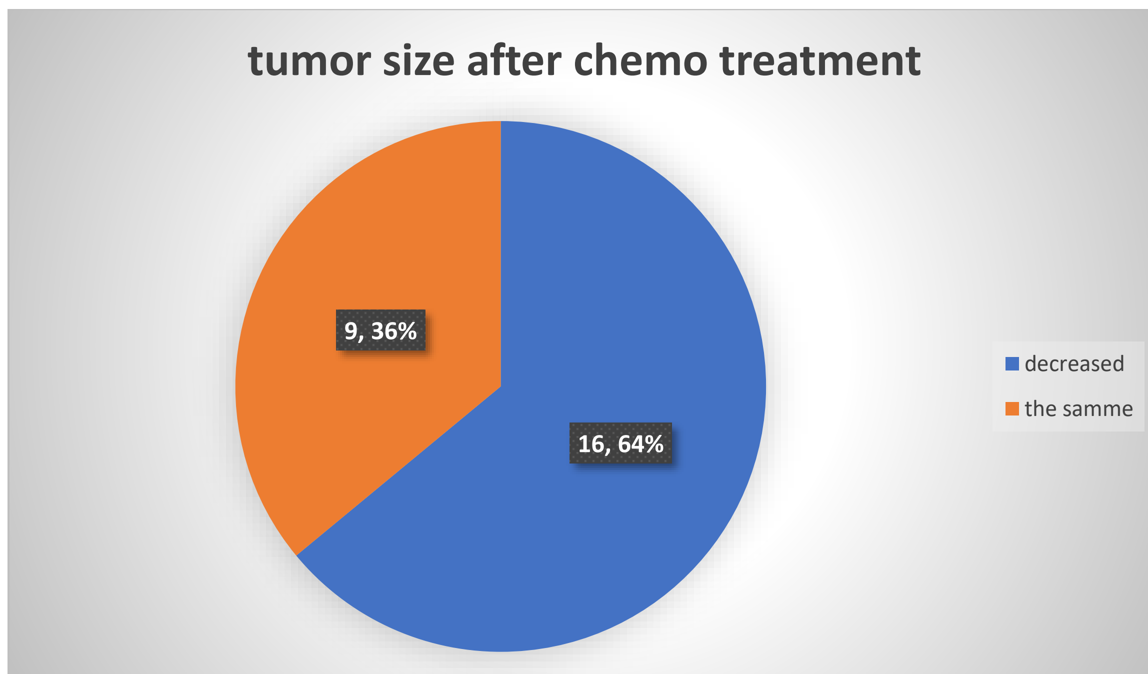

Figure 11: Tumor size after chemotherapy

The X^2 test on different variable with hepatoblastoma cancer metastasis showed that serums AFP before treatment were statistically significant, but serum AFP after treatment and patient with chemotherapy were not significantly associated.

Table 5: Association between hepatoblastoma metastasis with AFP and Chemotherapy

		the patient hepatoblastoma metastasis		p-value
		yes	no	
serum AFP before treatment	10-1000ng/dl	0	2	0.048
	>1000ng/dl	8	12	
	not done	3	0	
serum AFP after treatment	<10ng/ml	2	2	0.389
	10-1000ng/ml	7	5	
	>1000ng/ml	-	1	
	not done	2	6	
the patient started chemo	yes	9	12	0.604
	no	2	2	

5.6 The outcome of the hepatoblastoma patient

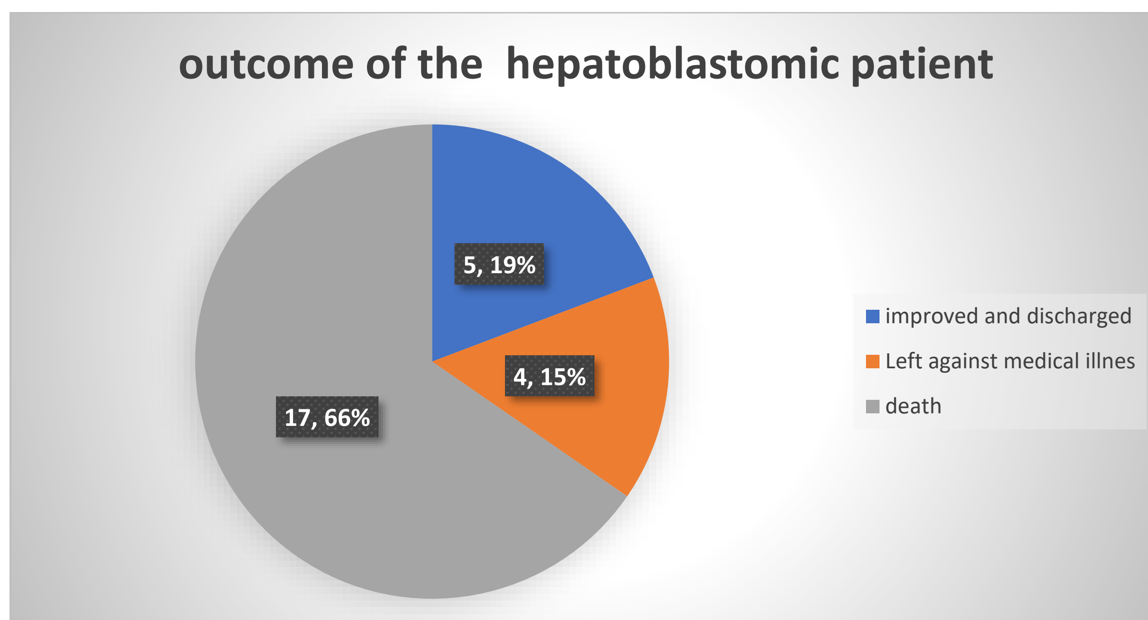

Figure 12: Tthe outcome of hepatoblastoma patient

5.7 The cross relation of disease characteristics with patient outcome

From all hepatoblastoma patients in this study 20% were improved and all of the patients were below 2 year old. Death accounts 64% of the patients among these 48% were from PRETEXT stage 4 tumor 44% of patients from the death category had anorexia as shown the table below.

Variable	Total	Death	Improved and discharged	Left against medical advice
Age of the study participant				
≤2yrs	18	9	5	4
>2-4yr	3	3	1	0
>4-6yr	3	3	0	0
>6yr	1	1	0	0
duration of abdominal mass				
<1month	7	6	1	0
1-6month	15	8	3	4
>6month	3	2	1	0
Anorexia				
Yes	18	11	3	4
No	7	5	2	0
PRETEXT staging of tumor				
stage 3	9	4	3	1
stage 4	16	12	2	3
patient started chemotherapy				
Yes	21	13	5	3
No	4	3	0	1
was surgery done				
Yes	5	0	5	0
No	20	16	0	4
duration of hospital stays				
<1month	5	5	0	0
1-6month	17	9	4	4
>6month	3	2	1	0
disease metastasis				
Yes	11	9	2	0
No	14	7	3	4

Table 6: The cross relation of disease characteristics with outcome

5.8 The correlation function of tumor size decrement with independent variable

The correlation finding showed that, serum AFP after treatment had positive significant relation with Tumor size and cycle of chemotherapy and lobe involvement had also positive significant correlation with size of tumor as shown in the table below.

Table 7: The correlation function of tumor size decrement with independent characteristics

List of dependent variables	Tumor size decrement	
	r (25)	P -value
Age	-0.164	0.434
Lobe involvement	0.915	0.022
serum AFP after treatment	0.741	0.000
cycle of chemo started	0.871	0.034

Characteristics of children who undergo surgery

Number of patient	Age of the patient(in month)	Duration of abdominal mass(in month)	Staging (PRETEXT)	AFP before treatment(ng/dl)	Cycle of Chemotherapy before surgery	AFP post treatment(ng/dl)	Histopathology
1	12	2	4	>1oo	6	Decreased	Mixed epithelial and Mesenchyme type
2	17	4	3	>100	4	deceased	Mixed fetal and embryonal pattern
3	9	1	3	>100	4	decreased	
4	19	4	3	>100	6	decreased	
5	30	5	3	>100	3	decreased	Epithelial type mixed fetal and embryonal pattern
High AFP means >100ng/dl							

6. Discussion

This retrospective cross sectional study conducted to know the magnitude of hepatoblastoma for the past ten years in tikur anbesa specialized hospital, the findings from this result can be used by clinicians for surveillance guidelines and risk stratification study‘s for future prospective or interventional study.

6.1 Magnitude and clinical presentation of HB

Based on the data found for the past 10 years the magnitude of hepatoblastomain this study was found to be 2% compared to other solid tumors. Hepatoblstomais more common in infants and toddlers accounts almost 75% of the study group. the age distribution of this study showed most children with in 3 year old consistent with the literature [1,3,4,7].based on their clinical manifestation the most common presentation was abdominal mass and abdominal distension. In 64% of the weight loss and anorexia are also common manifestations probably due to tumor distension. These clinical presentations are also consistent with the previous studies done by Irene Isabel P. Lim , Alexander J. Bondocet.el[5,6].

Unlike HCC jaundice and constipation is the rare presentation in patients with hepatoblastoma

More than half of newly diagnosed patients had high platelet count (with the maximum platelet count of 1210,10^9 /L these can be attributed by large burden of tumors result increased TPO production in tumors .in one of the literature done inIndia by Yi Zhang, Dongsheng Huang et.el high platelet count is associated with chemotherapy sensitivity and outcome of HB Patients [4]. Similar to our study where most of the patient who took chemotherapy for 4 cycle despite the platelet count they have significant tumor size decrement [16,64%]. 64% of the patient had anemia with the least hgb of 4gm/dl this can have multifactorial causes like tumor burden results in anorexia and vomiting and being in low socioeconomic status can be the reasons like in other literatures done [2,3,4,21].

6.2 Prognosis and associated factors of HB

Though multiple literatures showed multiple associated factors for the occurrence of hepatoblasomalike BWS, FAP, FAS, prematurity and low fetal birth weight, Gardner syndrome, glycogen storage disease, biliary atresia, trisomy 18, trisomy 21 are the common one. [2,4,8,19,20] in our study there was only 4 patients with LBW and 2 of them had microcephaly

otherwise there was no patient who had syndrome this can be due to small sample size we had and poor physicians documentation on patient's physical examinations.

Other factors that affect prognosis, such as age, serum AFP level, tumor stage and distant metastasis, multifocality of the tumors, surgery were also analyzed in this study. High serum AFP (>10000 ng/dl) were seen in 80% of the patients where all the patients were on pretext stage 3 and 4 ,high serum AFP was associated with tumor metastasis which was statistically significant (p =0.048) this can be due to late presentation of the patient as well as the late diagnosis.

But AFP after chemotherapy and chemotherapy treatment has no significant relation with distant metastasis (p value of 0.389 and 0.604).

lobe involvement and age of the patient had also significant prognostic factor in his study more than half had both lobe involvement of this almost 70% of the study group were under 2 year old and most of the deaths were this group of age.

6.3 Treatment and Outcome of hepatoblstoma

HB is highly sensitive tumor for chemotherapy most patients had significant tumor reduction after chemotherapy specially after 3rd cycle of chemotherapy and the introduction of strong and effective chemotherapy drugs particularly platinum based chemotherapy improved the outcome in this study 84%(21) of the patients started chemotherapy of this more than half took 3rd and 4th cycle and there was significant correlation between cycle of chemotherapy and tumor size decrement(r=0.871, p value 0.034) .AFP after treatment had also significant correlation with tumor size decrement after treatment(r=0.741,P-0.000).

Even though; the main stay of management of HP is combination of chemotherapy and surgery which is supported by different literatures done in different countries [4, 23, 24, 26, 27] which is similar to this study survival is significantly compromised in patients who had only chemotherapy with no surgical intervention only 20% of the patient in the study group undergone surgery and only these patients(20% of the study group) had improved outcome.

Death occurred in around 64% of the patients most of the death were from PRETEXT stage 4 diseases and most of them had anorexia.

There are different contributing factors for not having surgical intervention in this group of study some of the reasons are ; lack of skilled surgical professionals and lack of appropriate setup for liver tumor resection, late presentation of the patient after intrahepatic and extra hepatic

metastasis, low socioeconomic condition and poor awareness to detect abdominal tumors by the parents or caregivers because more than 70% of the parents/caregivers were from rural area and some family left against medical advice due to low income or prolonged hospital stay before or during the management.

7. Conclusion

The magnitude of hepatoblastoma in this study was 2% compared to other solid tumors in the past 10 years. Most of the study participants were under 2 year old and most of the patients were PRETEXT stage 3 and stage 4 .The liver is an important organ involved in coagulation the increasing of PLT suggested HB lead to abnormal coagulation and the monitoring of PLT is important in clinics. More than half of the patients died due to absence of surgical intervention and other associated risk factors.

8. Limitation

In our setting, patients' records were generally poorly kept. The overall flow of clinical notes was not streamlined and the bulkiness of the records made it difficult to locate pertinent information. Since I collect ten years patient cards some number of patient cards was missing which were registered in the logbook. This may have potentially biased the measurement of independent factors and the outcome. There was a challenge with the retrieval of patients' records. Some of them were lost, mislabeled or misdiagnosed which might have contributed to underestimation in frequency of observation of some of the study variables.

9. Recommendations

- Early diagnosis and management should be institute.
- As we saw from our study surgical intervention is the corner stone of the management of hepatoblastoma so surgically skilled professionals and setups for surgical intervention should be institute.
- Awareness and health education should be given for both Rural and urban areas about early detection of child hood abdominal mass and early visit to health institutions.
- Patient card keeping methods should be improved like use of electronic recording system so that patient information can be kept for long time.
  Setups for appropriate investigation modalities should be available in the hospital.
- Prospective cohort study with large sample size is recommended.

REFERRENCES

1. Dimple Chaudhary, Latika Gupta, RadhikaAgarwal,VarunaMallya,ReenaTomar, Shramanamandal, et al. Histopathologic patterns of hepatoblastoma in tertiary care hospital, journal of cancer research and therapeutics. October 2021; DOI: 10.4103/jcrt.JCRT_120_19.
2. Sierra Musick,Melinda smith, Audra Rouster ,Hani Babker. Hepatoblastoma. STATPEARLS, January 2021.
3. JinchengFeng, GeorgiosPolychronidis, Ulrike Heger, Giovanni Frongia, ArianebMehrabi and Katrin Hoffmann. Incidence trends and survival prediction of hepatoblastoma in children: a population based study. BMC October 2019; https://doi.org/10.1186/s40880-019-0411-7.
4. Yi Zhang, Dongsheng Huang, Weiling Zhang, Suoqin Tang, Liping Chen, You Yi, et al . Study on the experience on clinical characteristics and outcome of pediatrics hepatoblastoma. Biomedical research January 2017; 28: 7315-7317.
5. B Archana, J Thanka, Latha M Sneha, J Julius Xavier Scott, M Arunan, PrakashAgarwa. Clinicopathological profile of hepatoblastoma :An experience from tertiary care center in India. Indian journal of pathology and microbiology October 2019; 62:557-559.
6. EisoHiyama. Pediatrics hepatoblastoma :diagnosis and treatment. Journal of Translational Pediatrics October 2014; 3:293-295.
7. Irene Isabel P. Lim , Alexander J. Bondoc , James I. Geller and Gregory M. Tiao. Hepatoblastoma: the evolution of biology, surgery and transplantation. PMID December 2018; vol 6 DOI:10.3390/children6010001.
8. Elizabeth McCarville,Wayne L Furman,Bernard D Coombs, john karani, et al. Hepatoblastoma imaging. Medscape June 2016.
9. J D Buckley, H Sather, K Ruccione, P C Rogers, J E Haas, B E Henderson, et al. A case control study of risk factors for hepatoblastoma a report from the children’s cancer study group. ACS September 1989; 64:1169-1174.

10. Giun-YiHung, Li-YihLin, Ting-YenYu,Chih-YingLee ,Hsiu-JuYen, Jiun-LinHorng. Hepatoblastoma incidence in Taiwan: A population-based study. The Chinese medical association June 2018; 81:541-545.
11. Ana Cristina AounTannuri, Lilian Maria Cristofani , Roberto Augusto Plaza Teixeira, Vicente OdoneFilho ,UenisTannuri . New concepts and outcomes for children with hepatoblastoma based on the experience of tertiary center over the last 21 years. PubMed June 2015; 70:387-391.
12. Dra. Alejandra Esperanza GarcíaGuzmán, Dr. Pablo Lezamadel Valle. Hepatoblastoma report of 21 cases in pediatrics tertiary hospital. Mexican journal of pediatrics surgery 2015; 19:101-104.
13. M. Tulla, F. Berthold, N. Graf, S. Rutkowski, D. von Schweinitz, C. Spix, et al. incidence, trends, and survival of children with embryonal tumor. pediatrics September 2015; 136:623-626.
14. Yizhang, Weiling Zhang, Suoqin Tang, Liping Chen, You Yi, Pinwel Zhang, et al. Single center retrospective study of pediatrics hepatoblastoma. Oncology letters August 2016; 12:3919-3922.
15. Zimmerman A, Saxena R. Hepatoblastoma. In: WHO Classification of Tumors of the Digestive System, 4th, Bosman FT, Carneiro F, Hruban RH, Theise ND (Eds). p.229,UpToDate 2010.
16. Colleen C. McLaughlin, Mark S. Baptiste, Maria J. Schymura, Philip C. Nasca, and Michae S. Zdeb. Maternal and Infant Birth Characteristics and Hepatoblastoma. American journal of epidemiology March 2006; 163:818-826.
17. Anil Darbari,Keith M Sabin,Craig N Shapiro,KathleenBschwarz. Epidemiology of primary hepatic malignancies in US children. AASLD 2003; 38:560-564
18. PiotrCzaudernaa,, BeateHaeberleb, EisoHiyamac, ArunRangaswamid,et el.Novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. European journal of cancer January 2016; 52:93-98
19. Hitoshi lkeda,ShiroMatsuyama,MasakoTanimura. Association between hepatoblastoma and VLBW: trend or chance. Pediatrics April 1997; 130:557-560
20. Masako Tanimura,LchiroMatsui,JunAbe,H et al . Increased risk of Hepatoblastoma among immature children with a lower birth weight. PubMed July 1998; 58:3032-3035.

21. Kala GnanasekaranKirythiga, Banumathi Ramakrishna, SoumitraSaha ,Sudipta Sen. Histological and immunohistochemical study of hepatoblastoma :correlation with behavior and survival. journal of gastrointestinal oncology April 2018; 9: 326-332.
22. Logan G.Spector, Jill Birch . Epidemiology of hepatoblastoma. pediatrics blood and cancer June 2012; 59: 776-779
23. JinchengFeng, Ying He, LaiWei, Dong Chen, HuifangYang,et al . Assessment of Survival of Pediatric Patients With Hepatoblastoma Who Received Chemotherapy Following Liver Transplantation Liver Resection. JAMA October 2019; doi :10.1001/jamanetworkopen.2019.12676.
24. E Towu , E Kiely ,A Pierro, L Spitz . Outcome and complications after resection of hepatoblastoma. Journal of pediatric surgery February 2004; 39:199-202
25. E.A shafford,J.pritchard . Extreme thrombocytosis as a diagnostic clue for hepatoblastoma. PubMed July 1993; 69:171.
26. Gregory M.Tiao, Nicola Bobey, Steven Allen, John Bucuvalas, Neris Nieves, Maria Alonso, et al. The current management of hepatoblastoma combination of chemotherapy conventional resection and liver transplantation. Journal of pediatrics February 2005; 146 :204-210.
27. Chengzhan Zhu, Bingzi Dong, Xin Chen, Qian Dong. Diagnosis and treatment of hepatoblastoma an update. MDPI January 2020; doi.org/10.5772/intechopen.90830.
28. Bassan J. Allan, Bo Wang, James S. Davis, Punam P. Parikh,Eduardo A. Perez, Holly L. Neville et al. A review of 218 pediatric cases of hepatocellular carcinoma. Journal of pediatrics surgery 2014; 49:166-170.
29. Christine S. M. Lau, KrishnarajMahendraraj, and Ronald S. Chamberlain. Hepatocellular Carcinoma in the Pediatric Population: A Population Based Clinical Outcomes Study Involving 257 Patients from the Surveillance, Epidemiology, and End Result (SEER) Database (1973–2011). HPB surgery November 2015;p 2-9 doi: 10.1155/2015/670728.
30. Tianyou Yang, Richard S. Whitlock, Sanjeev A.Vasudevan1.Surgical Management of Hepatoblastoma and Recent Advances. MDPI December 2019 doi: 10.3390/cancers11121944

ANNEX:
QUESTIONNAIRE

ASSESMENT OF MAGNITUDE AND OUTCOME OF HEPATOBLASTOMA TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

Part I: Socio-demographic characteristics of the participants		
S.N	**Characteristics**	**Options**
1	Age	❑0-2 yr. ❑ 2-4 yr. ❑ 4-6yr ❑>6 yr.
3	Sex	❑Male ❑ Female
4	Gestational age	❑ Term ❑ Preterm
5	Birth weight	❑NBW ❑ LBW ❑ VLBW ❑ EVLBW
6	Monthly income of the family	❑<1700 birr per month ❑1700-3000 ❑ 3001-10000 ❑>10000
7	Residence	❑ Urban ❑ Rural
8	Region	❑ Addis Ababa ❑Oromia❑Amhara❑ SNNP ❑ Other specify.

Part II: Major clinical presenting symptom and sign				
Signs/symptoms		Response		If yes Duration
		Yes	no	
9	Abdominal mass			
10	Abdominal distension			
11	Abdominal pain			
12	Weight loss			

13	Anorexia		
14	Vomiting		
15	Pallor		
16	Jaundice		
17	Fever		
18	Diarrhea		
19	Constipation		
Part III: Disease related questions			
20	Is the child syndromic?	❑ Yes ❑ No	
21	If yes, which syndrome ?	❑BWS❑Familial adenomatous polyposis❑Li-Fraumeni syndrome ❑ Trisomies ❑other specify	
22	Maternal history	❑ smoking ❑ alcohol ❑ eclampsia ❑ none	
20	Maternal HBSag/HCV status	❑ positive for HBSag❑ positive for HCV ❑ Positive for both ❑negative	
21	Maternal HIV status	❑ positive ❑ negative ❑Uknown	
22	CBC profile of the patient with the differentials	❑ Normal ❑ abnormal	
	If abnormal , describe the abnormality	❑ anemia ❑ polycythemia ❑ thrombocytopenia ❑ thrombocytosis ❑ leukopenia ❑ leukocytosis	
23	Does the patient hashepatoblastoma?	❑ Yes ❑ No	
24	Viral markers HBsag, HCV status of the patient?	❑ positive for HBSag❑ positive for HCV ❑ Positive for both ❑ negative ❑uknown	
25	Serum AFP level before treatment?	❑<10ng/dl ❑10-100ng/dl ❑100-1000ng/dl ❑>1000ng//dl ❑ not done	

26A	Serum AFP after treatment?	❑<10ng/dl ❑10-100ng/dl ❑100-1000ng/dl ❑ >1000ng//dl ❑not done
26B	Serum AFP after treatment	❑the same ❑increased ❑Decreased ❑not done
27	LFT result	❑ normal ❑ abnormal
28	If abnormal ,which enzyme is elevated ?	❑ ALT ❑ AST ❑ALP ❑ALT & AST ❑ ALL
29	Abdominal ultrasound result	❑ Suggestive of hepatoblastoma❑ Not suggestive
30	Abdominal CT result A	❑ Suggestive of hepatoblastoma❑ Not suggestive
	Which lobe of the liver involved B	❑Right lobe ❑Left lobe ❑Both lobe
31	Does the patient have metastasis? ?	❑ Yes ❑ No
32	If yes where is the site?	❑ lung ❑ brain ❑ spine ❑ bone marrow ❑ other specify
33	clinical and radiographic stage of the tumor (PRETEXT staging)	❑ stage 1 ❑ stage 2 ❑ stage 3 ❑ stage 4
34	Does the patient started chemotherapy?	❑ Yes ❑ No
35	If yes for Qs.No 14 which regimen of chemotherapy is he/she on (better to specify the regimen)	

<table>
<tr><td>36</td><td>which cycle of chemotherapy is he /she on?</td><td colspan="5">❑. Cycle 1 ❑Cycle 2 ❑Cycle 3 ❑Cycle 4</td></tr>
<tr><td>37</td><td>Was surgery done?</td><td colspan="5">❑ Yes ❑ No</td></tr>
<tr><td>38</td><td>if yes when was done?</td><td colspan="5">❑ Before surgery ❑ After surgery</td></tr>
<tr><td>40</td><td>if after chemo, in which cycle of chemotherapy was the surgery done?</td><td colspan="5">❑. Cycle 1 ❑Cycle 2 ❑Cycle 3 ❑Cycle 4</td></tr>
<tr><td>41</td><td>Histopathology result?</td><td colspan="5">❑ Suggestive of hepatoblastoma❑ Not suggestive</td></tr>
<tr><td>42</td><td>Duration of stay in the hospital</td><td colspan="5">❑. < 1 month ❑. 1-6 month ❑. > 6 month</td></tr>
<tr><td rowspan="4">43</td><td rowspan="4">Outcome of the patient?</td><td></td><td>Variables</td><td>Yes</td><td>No</td><td>Remark</td></tr>
<tr><td>43.1</td><td>Improved and discharged</td><td></td><td></td><td></td></tr>
<tr><td>43.2</td><td>Deteriorated</td><td></td><td></td><td></td></tr>
<tr><td>43.3</td><td>Abandon</td><td></td><td></td><td></td></tr>
</table>

		43.4	Death			