ADDIS ABABA UNIVERSITY

COLLAGE OF HEALTH SCIENCE AND SCHOOL OF MEDICINE

DEPARTMENT OF PATHOLOGY

HISTOPATHOLOGIC PATTERNS OF LIVER DISEASES: A FIVE YEAR RETROSPECTIVE STUDY IN A TERTIARY LEVEL TEACHING HOSPITAL, TIKUR ANBESSA SPECIALIZED HOSPITAL, ETHIOPIA

A THESIS PROPOSAL SUBMITTED TO THE DEPARTMENT OF PATHOLOGY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE ADDIS ABABA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENT OF POST GRADUATE PROGRAM IN PATHOLOGY.

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This thesis is a presentation of my original research work. Wherever contributions of others are involved, every effort is made to indicate this clearly, with due reference to the literature, and acknowledgment of collaborative research and discussions.

The work was done under the guidance of Dr. Yonas Girma (MD, Associate Professor of Pathology) at Addis Ababa University College of Health Sciences.

Mengistu Shitahun (Pathology resident)

Signature _____ Date _____

In my capacity as supervisor of the candidate's thesis, I certify that the above statements are true to the best of my knowledge.

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Department head	Signature	Date
Dr. Yonas B/Tsion (MD, Associate Professor of Pathology)	_____	_____

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List of Abbreviations and Acronyms

AAU:	Addis Ababa University
CLD:	Chronic Liver Disease
FNH:	Focal Nodular Hyperplasia
HBsAg:	Hepatitis B Surface Antigen
HBV:	Hepatitis B Virus
HCC:	Hepatocellular Carcinoma
HCV:	Hepatitis C Virus
NALD:	Nonalcoholic liver disease
PSC:	Primary sclerosing cholangitis
TB:	Tuberculosis
WHO:	World Health Organization

Abstract

Introduction: Liver diseases account for a significant number of morbidity and mortality worldwide being affected by a wide spectrum of various primary and secondary diseases. The major primary diseases of the liver are viral hepatitis, nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, and hepatocellular carcinoma (HCC).

Distinguishing among them can be challenging, but the distinction is critically important given the differing prognostic and therapeutic implications. These diseases can be diagnosed with the help of clinical, biochemical or radiological examinations. However, liver histopathology remains the mainstay in diagnosis as well as management of various liver diseases.

Objectives: The aim of this study was to assess histopathologic patterns of liver diseases

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Methods and Materials: A retrospective descriptive histopathological analysis of histopathological pattern of liver disease was carried out in the Postgraduate Department of Pathology, college of health sciences, Tikur Anbessa Specialized Referral Hospital (TAH), Addis Ababa, Ethiopia. Patients data was retrieved from the archives of the department of Pathology for a period of 4 years and 8 months from January 2016 to August 2020).

Result

In this study a total of 116 cases were included. Of the total cases 60(51.7%) were females and 56(48.3%) were males with female to male ratio of 1.1:1. Most of the ages ranges from 30 to 79 years, which accounts for 86.2% of cases and with mean, standard deviation, lowest and highest age range of 49, 17.97, 6 months and 79 years respectively. The peak age was the 7^{th} decade. Malignant lesions were the most common diagnoses accounted for 56.9%, HCC being the most frequent malignant lesion 19.8% of all cases followed by secondary carcinoma 17.2%, cholangiocarcinoma 6.9%, neuroendocrine tumor 3.4%, secondary high grade sarcoma 2.6%, adenocarcinoma with neuroendocrine differentiation 1.7%, hepatoblastoma 1.7%, malignant undifferentiated tumor 0.9 %, lymphoma 0.9%, secondary epitheloid GIST 0.9% and suspicious for malignancy 0.9% in decreasing frequency. HCC was more common in males with male to female ratio of 2.8 : 1. Almost all benign liver lesions were found in females with female to male ratio of 12 : 1. Hemangioma was the most common benign neoplastic lesion accounting for 7.8% followed by benign liver cyst 1.7% and FNH 0.95%. TB was most common non neoplastic lesion 3.4%. And the remaining histologic patterns included hydatid cyst 3(2.6%), abscess 2(1.7%), seatosis/fatty change 2(1.7%), cirrhosis 1(0.9%), biliary atresia with cirrhosis 1(0.9 %), chronic active hepatitis 1(0.9%), acute alcoholic hepatitis 1(0.9%), acute complete intrahepatic cholestasis with ascending cholangitis + stage 3 fibrosis 1(0.9%), chronic nonspecific inflammation of the cyst wall 1(0.9%), non diagnostic 1(0.9%) and 3(2.6%) of cases were reported as normal histology. 13.8% of cases were descriptive reports.

Conclusion

HCC is the most common liver lesion and most common malignant histopathologic diagnosis in this study which agrees to some studies in India. In most African studies infectious and inflammatory lesions are the most common. The diagnoses of malignant lesions in this study were at later ages than most of other studies. Hemangioma was significant in amount.

Keywords; HCC, malignant lesions, infectious and inflammatory lesions, hemangioma.

1. Introduction

1.1. Background

The liver is the largest solid organ in the body. In the normal adult it weighs 1400 to 1600 grams. It has a dual blood supply, with the portal vein providing 60% to 70% of hepatic blood flow and the hepatic artery supplying the remaining 30% to 40%. Accordingly, the liver is divided into 1- to 2-mm in diameter lobules that are oriented around the terminal tributaries of the hepatic vein (terminal hepatic veins), with portal tracts at the lobule's periphery. The hepatocytes in the vicinity of the terminal hepatic vein are called centrilobular and those near the portal tract are periportal[1].

With functions ranging from metabolism of fat, synthesis of proteins, storage of glycogen, vitamins and iron to the detoxification of waste products, toxins, drugs and secretion of bile. Thus, the liver is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory, and neoplastic insults. The enormous functional reserve of the liver masks the clinical impact of mild liver damage, but with progression of diffuse disease or disruption of bile flow, the consequences of deranged liver function may become life-threatening[1,2].

Liver diseases account for a significant number of morbidity and mortality worldwide. It is the 8thcommonest cause of death with an annual incidence of 72/100,000 population for newly diagnosed cases and an annual mortality of 27,000 in the United States [1]. It is a major burden in sub-Saharan Africa with high mortality rates. The major primary diseases of the liver in adults are hepatitis from a variety of processes, alcoholic and nonalcoholic liver disease, cirrhosis and hepatocellular carcinoma (HCC). Hepatic damage also occurs secondary to diseases such as cardiac decompensation, extra hepatic infections and disseminated cancer. Other less commonly encountered diseases are autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. While in children, biliary atresia, neonatal hepatitis and liver cirrhosis are commonly seen [2].

Chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) are a global challenge. World Health Organization (WHO, March 2015) estimates that 240 million people live with a chronic infection and 780,000 die each year, 130,000 from acute hepatitis B and 650,000 from complicating cirrhosis and liver cancer. Infection with hepatitis C is generally asymptomatic and a chronic infection occurs in approximately 80% and 130 – 150 million

people live with a chronic infection and 350,000 to 500,000 die from cirrhosis or hepatocellular carcinoma [2,3].

Reports from various studies have shown that infective agents particularly viruses account for the bulk of liver diseases in sub Saharan Africa. The prevalence of CLD in Ethiopia is largely unknown but is assumed to be high [4]. The estimated seroprevalence of hepatitis B surface antigen (HBsAg) in Ethiopia is 6.0% and of HCV-antibody (anti-HCV) 3.1% [5]. Although these data are extracted predominantly from institution-based studies and may not be representative of the situation nationwide, chronic HBV infection is thought to be a major cause of CLD in this region. Chronic liver disease attributes to 2% of the overall deaths in Addis Ababa and a high prevalence of HBsAg and HBV markers have been reported, 6% and 44.8% respectively [6].

Many liver diseases maybe associated with hepatic masses and may come to attention for a variety of reasons. They may generate epigastric fullness and discomfort or be detected by routine physical examination or radiographic studies for other indications. This might be neoplastic or non-neoplastic. Mass-forming non-neoplastic tumour-like lesions in the liver may be solid or cystic, and solitary or multiple. Solid tumour-like lesions include FNH, nodular regenerative hyperplasia, large regenerative nodule, and inflammatory pseudotumour. Cystic neoplasm-like lesions include solitary bile duct cyst, obstructive dilatation of bile duct, ciliated foregut cyst, haemorrhagic cyst, and infective cyst. In addition to various primary benign and malignant liver masses, the liver is a common site for metastatic tumor deposits—most often from carcinomas originating in the abdominal cavity, but also for sarcomas and lymphomas [7,8].

The most frequent and important hepatic neoplasm is the primary hepatocellular carcinoma (HCC). In many parts of the world, in particular Africa and Asia, it poses a significant disease

burden. In these high incidence regions, chronic infection with hepatitis B virus (HBV) is the principal underlying cause, with the exception of Japan which has a high prevalence of hepatitis C infection. HBV vaccination has become a powerful tool in reducing cirrhosis and HCC, but implementation is still suboptimal in several high risk regions. In Western countries, chronic alcohol abuse is a major etiological factor[9].

1.2. Statement of the problem

Since the first documented biopsy by Paul Ehrlich in 1883 by aspiration, subsequently first percutaneous liver biopsy for diagnostic purposes was reported in 1923.The technique has been modified since then and proved to be a revolution in the field of hepatology.

Liver diseases account for a significant number of morbidity and mortality worldwide.And it is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory, and neoplastic insults.Surgical pathologists encounter a wide variety of nodules and tumors of hepatic origin, including both neoplastic and non-neoplastic lesions.

The most frequent and important hepatic neoplasm is the primary hepatocellular carcinoma (HCC). In addition to various primary benign and malignant liver masses, the liver is a common site for metastatic tumor deposits, most often from carcinomas originating in the abdominal cavity, but also for sarcomas and lymphomas.

And thorough knowledge of the clinical setting is necessary for proper interpretation of biopsies and resection specimens. Patient demographics, such as age, can be an important discriminating feature, given that some hepatic tumors (such as mesenchymal hamartoma and hepatoblastoma) are overwhelmingly more common in children than adults, and others (such as cholangiocarcinoma) essentially do not occur in the pediatric population. Pediatricliver diseases also include a broad spectrum of disorders such as developmental abnormalities, metabolic and infectious disorders that finally result in liver cirrhosis and failure. So the spectrum of hepatic lesions varied from males to females as well as from infants to adults.

A clinical history of chronic liver disease, with or without cirrhosis, is also important; for instance, hepatic adenomas are often found in young women without underlying liver disease, whereas a similar-appearing lesion in an elderly man with cirrhosis is more likely to represent well differentiated HCC. Although the majority of malignant liver tumors overall represent metastatic carcinoma, HCC is more common in patients with cirrhosis [10, 8, 11].

Primary liver malignancies , of which HCC accounts for 75-85% of cases (the remainder are mostly intrahepatic cholangiocarcinoma and other rare types), is the six most common cancer and the fourth leading cause of cancer related death worldwide, with an estimated 841.080 new cases 781 631 new deaths in 2018 [3].

According to the Globocan report on the incidence and prevalence of cancer in Ethiopia by 2018, 67,573 new cancer cases were found. Among these 1608 cases were liver cancer ranking 12th as the most common causes of cancer and 9th most common cause of cancer death in Ethiopia [12].

1.3. Significance of the study

Data from the literature shows difference in the relative frequencies of the various neoplastic and non-neoplastic liver lesions. Several reports on this topic from different part of the world showed difference in geographic prevalence among the neoplastic and non-neoplastic lesions. Since there is limited information in the literatures about the prevalence of the neoplastic and non-neoplastic liver lesions in Ethiopia, the objective of the current study was to establish the frequency and type of the various neoplastic and non-neoplastic live lesions diagnosed in core needle biopsy and resected specimens at Tikur Anbessa Hospital from January 2016 – August 2020 and this study may be used as a reference for other studies in the future.

2. Literature review

Histopathological study of liver biopsy is very common and is frequently done for diagnosis of different hepatic lesions, providing information for disease progression and response to therapy.And different studies on histopathological spectrum of hepatic lesions show that there is significant geographic and regional variability in the patterns and prevalence of liver pathologies across the world. One such study done in India at Dr. D.Y.Patil Medical College, Hospital and Research Centre , a prospective study which included 65 liver biopsies found that out of 65 liver biopsies, 4.6% were inadequate for histopathological study. The various histopathological findings included secondary tumour deposits (40.0%), primary hepatic tumours (12.3%), hepatitis (16.9%), cirrhosis (12.3%), extrahepatic biliary atresia (6.15%), secondary biliary cirrhosis (3.0%), glycogen storage disease (1.5%), cystic hydatid disease (1.5%) and fatty liver (1.5%).In this study, age ranged from 3 months to 80 years. Mean age was 42.5 years. Majority of patients belonged to the 5thand 6th decade of life. Out of 65 cases, 43.07% were males and 56.92% were females. Hepatic tumours were the commonest finding 52.30%, of which, 76.47% were secondaries and 23.52% were primary hepatic tumours [13].

Another study from India by Murgod, Doshi and Dombale et al, a retrospective study of 66 liver biopsies on spectrum of hepatic lesions-a histopathological study of liver biopsies (January 2013 to May 2015), consisting of 45 cases of males and 21 cases of females found that 24(36.3%) cases were hepatocellular carcinoma, 13(19.69 %) cases of glycogen storage disorder, 3(4.54%) cases each of fatty liver, hepatitis, cirrhosis & degenerative liver disease. 2(3.03%) cases of liver cell dysplasia and 1(1.51%) case each of biliary atresia , amyloidosis, miliary tuberculosis and liver abscess. Liver biopsy was nonspecific in 4(6.06%) cases & inadequate in 7(10.6%) cases [14].

Study from Brazil by Pereira GH et al. on histopathological hepatic lesions in 52 percutaneous liver biopsies of 50 HIV-infected patients who had at least two of the following conditions: fever of unknown origin, unexplained severe emaciation, hepatomegaly or abnormal liver chemistry. The specimens were cultured for mycobacteria and fungi and stained by standard procedures and found that reactive patterns, granulomatous hepatitis and chronic active hepatitis in 28 (54%), 11 (21%) and 8 (15%) of the patients respectively. Opportunistic infections were diagnosed in 18

(36%) patients: mycobacteria in 12 (24%), Cryptococcus neoformans in 5 (10%) patients and mycobacteria and yeast was isolated from the same liver fragment in one patient [15].

A study from Iran by Dehghani SM et al. onpercutaneous needle biopsy in the diagnosis of Liver diseases in children, a retrospective study conducted on 308 liver biopsy specimens from children suspected to liver diseases who had been referred to Pediatric Gastroenterology Department at Shiraz University of Medical Sciences (March 2003 and March 2008) found that among 308 liver biopsies which included children aged less than 18 years and consisting of 128 girls and 180 boys with mean age of 6.04 ± 5.97 years, the most common pathologic findings diagnoses in children was chronic hepatitis (n =71; 23.1%) followed by metabolic disorders including hereditary tyrosinemia type 1, glycogen and lipid storage diseases (n = 37; 12.1%), cirrhosis (n = 27; 8.8%), secondary hemochromatosis due to major thalassemia (n = 22; 7.1%), neonatal hepatitis (n = 22; 7.1%), hepatic malignancies including hepatoblastoma, hepatocellular carcinoma and lymphoma (n = 21; 6.8%), biliary atresia (n = 14; 4.5%), and familial intrahepatic cholestasis (n = 7; 2.3%) [16].

Study from Dhaka, Bangladesh by Hossain MM et al on clinicopathological correlation of liver biopsy, an observational study which was done on 50 patients at Dhaka Medical College Hospital, Dhaka(May 2008 to June 2009) identified thatcommonest disease was found to be chronic liver disease (48%) of which cirrhosis of liver (30%) was highest followed by severe chronic hepatitis (10%), mild chronic hepatitis (8%). Next common disease was hepatocellular carcinoma (26%). Other diseases found were secondary carcinoma of liver (4%), fatty change (6%), kala-azar (4%), sclerosing cholangitis (2%) and histopothological findings revealed normal hepatic tissue in (10%) cases [17].

A hospital-based clinicopathological study done from Saudi Arabia during the period 1982-1990 on 544 patients with clinical evidence of liver disease at King Fahd University Hospital found that a tissue diagnosis pattern of liver cirrhosis 17.3%, periportal fibrosis 14.3%, metastatic cancer 12.9%, primary hepatoma (hepatocellular carcinoma: HCC) 12.1%, hepatic granuloma 11.2%, chronic active hepatitis 7.7%, chronic persistent hepatitis 2.2%, fatty liver 7.2%, hydatid liver disease 4.6% and others 2.8%. In 7.7% the histology was normal [18].

Another study carried out by Dr.Usman Bello in the Department of Pathology, Ahmadu Bello University Teaching Hospital on histopathological pattern of liver biopsies in Zaria, A Ten Year

Retrospective Analysis [2004-2013] consisting of 197 males and 104 females (M: F; 1.9:1) with the age range of 2months to 80years in which the liver diseases were categorized into congenital (2.3%), infectious conditions (2.9%), hepatitis (56.5%), cirrhosis (15.3%) and neoplastic diseases (18.9%), the study showed that hepatitis was the commonest pathology with 56.5% cases while cirrhosis and hepatocellular carcinoma accounted for 15.3% and 13.6% respectively. Chronic viral hepatitis cases had a male: female ratio of 2.5:1.0 and 42.2% of the cases were mild grade disease while over 70% were stage 0-2 disease using Ishaq histologic activity index. Hepatocellular carcinoma showed a slight male preponderance with peak age distribution in the 4th decade of life and 46.3% of the cases were post-cirrhotic. Hepatotrophic viruses accounted for the bulk of aetiological factorswith hepatitis B virus (HBV) infection recorded in 41.3% of the cases, hepatitis C virus (HCV) in 8.7% and HBV/HCV co-infection in 4.4% cases. Only 6.5% cirrhotic cases were associated with significant alcohol consumption while 32.6% were cryptogenic with no identifiable aetiologic agent clinico-pathologically [2].

A studydone at the University of Benin Teaching Hospital, Benin city, Nigeria by EE Ugiagbe, MO Udoh, a retrospective study of all cases of liver biopsies (January 2005 and December 2011) on the histopathological pattern of liver biopsies on 80 cases of liver biopsies which were reported during the 7‑year period including50 males and 30 females with age range of 4 months to 69 years and a mean age of 38.4 ± 13.3 years, the highest incidence was in the 4th decade. The three common histopathological diagnoses were inflammatory lesions 63.8%, malignant neoplasms 22.5%, and liver cirrhosis in 6.3% of cases. Other less common lesions were alcoholic liver disease and steatosis. The peak age incidence of chronic hepatitis was preceding that of hepatocellular carcinoma by about two decades.Inflammatory lesions of the liver accounted for 63.8% ofcases with a peak age of incidence in the 30‑39 year age group. Of these cases, 55% (28/51) and 43% (22/51) were due to chronic active hepatitis and chronic persistenthepatitis, respectively, of the old classification. Only a single case of neonatal hepatitis was seen and it occurred in a4‑month‑old male patient. HCC was the most common malignant neoplasm seenaccounting for 55.6% (10/18) of cancer cases. Half of thecases occurred between 30 and 59 years with a peak age group of 50‑59 years and a male:female ratio of 4:1. One case each of cholangiocarcinoma and hepatoblastoma were seen. The remaining six cases were metastatic liver malignancies; four of which were adenocarcinoma from the gastrointestinal tract, a case each of renal cell carcinoma and adenoid cystic carcinoma from the breast. Liver cirrhosis was

the third most common lesion accounting for 6.3% of the cases. The male:female ratio was 4:1 with a peak age of incidence in the 30‑39 year age group. Though the primary cause of the disease could not be ascertained on biopsy, a majority of cases showed evidence of on‑going chronic hepatitis [19].

A study from Lagos University Teaching Hospital, Nigeria (1989-2000), a retrospective histopathological study of 345 liver biopsies over a 12-year period consisting of 222 males and 123 females with peak age incidence of 41-50 years identified that three common histopathological diagnoses were hepatocellular carcinoma-33%, chronic hepatitis-17.7%, and liver cirrhosis-17.7%. Thirty percent of hepatocellular carcinoma was post-cirrhotic. The peak age incidence of chronic hepatitis precedes that of liver cirrhosis and hepatocellular carcinoma by one decade [20].

Another study from Nigeria by KA Adeniji and AS Anjorin, aimed at establishing patterns of cirrhosis on 251 liver biopsies. Among 251 specimens 35 were diagnosed with liver cirrhosis-meaning cirrhosis accounted for 13.9 % of liver specimens. It was the second commonest cause of liver disease after hepatocellular carcinoma which constituted 91(36.3%) of cases. Overall 15(42.9%) cases were simply diagnosed as cirrhosis, 14(40%) as macro nodular cirrhosis, 4(11.4%) as micro nodular cirrhosis while 2(5.7%) were diagnosed as biliary cirrhosis. There were 25 males and 10 females giving a male to female ratio of 2.5:1. The age range was 8 months to 78 years. 50 % of cases occurred in age range 30-60 years with highest incidence occurring between 51- 60 years [21].

Another study from Jos University Teaching Hospital (JUTH), Nigeria, a retrospective histopathological study aimed at establishing the pattern of liver disease in the pediatric age group in Jos found that among forty eight needle biopsies of the liver, hepatic Schistosomiasis accounts for (37.5%) and liver cirrhosis (25%) were the most frequently diagnosed lesions. There were only two cases of biliary cirrhosis secondary to biliary atresia. Parasitic infestation of the liver was the most common cause of childhood hepatic dysfunction [22].

Another study done from GaafarIbnoof Specialized Children Hospital, Khartoum, Sudan on

pathologic causes of liver disease in Sudanese childrenpercutaneous 450 liver biopsies, a cohort study consisted of children aged between 1 month and 15 years, of whom 42% were less than 1 year of age and a male to female ratio was 1.4:1 found that the most common histological

diagnosis was liver cirrhosis (26%), where no specific cause could be found, followed by neonatal hepatitis (20%), fatty liver (12%), billary atresia (10%), chronic hepatitis (8%), metabolic liver disease (6%), progressive intrahepatic cholestasis (5.5%), non-specific pathological changes (4.4%) and hepatocellular carcinoma in (4%) [23].

Study done in Ethiopia by D Fekade on histopathological features of liver disease in hospitalized Ethiopian patients,a retrospective analysis of 860 liver biopsy specimens processed by the Department of Pathology of Addis Ababa University was made to determine the frequencies of the various histopathological lesions seen among Ethiopians admitted with liver disease.One hundred fifty six (18.1%) of the specimens were inadequate for precise pathological diagnosis. Liver cirrhosis accounted for 25.4% (179) and primary hepatocellular carcinoma for 19.2% (135) of all diagnoses. Porphyria cutaneatarda was diagnosed in 12.4% (87) of the biopsy specimens. Hepatitis, metastases to the liver, and hepatic granulomata were present in 8.8% (62), 4.5% (32) and 2.8% (20) of the specimens respectively [24].

3. Objective of the study

3.1. General objective

To determine the histopathological patterns of liver diseases diagnosed from liver biopsies submitted to the Department of Pathology at Tikur Anbessa Specialized Hospital from January 2016 to August.

3.2. Specific objective

- To determine the histopathological patterns of liver diseases
- To determine the frequency, age and sex distribution of liver diseases
- To determine the commonest histologic type of liver disease
- To compare the findings with similar studies elsewhere locally and international

4. Method and Materials

4.1. Study Area

Tikur Anbessa Hospital is a university teaching hospital of Addis Ababa University and the largest referral hospital in the country. This study was conducted at pathology department of Tikur Anbessa hospital, which is found in Addis Ababa, Ethiopia. The department provides haematopathology, cytopathology, surgical pathology and neonatal autopsy services.

4.2. Study Design and Period

The study was a cross-sectional retrospective descriptive study where data was retrieved from the archive of the department of pathology that were registered from January 2016 up to August 2020.

4.3. Source Population

All patients whose biopsy specimens were submitted to the department of pathology during the study period.

4.4. Study population

All patients with liver biopsy specimens and whose specimen was submitted to the department of pathology during the study period and meeting the inclusion criteria.

4.4.1. Inclusion criteria

- All resected and core needle liver biopsy specimens having histopathologic reports during the study period.

4.4.2. Exclusion criteria

- Histopathological reports including the primary tumor organ site and additional liver secondary was reported
- Metastases of liver primary reports
- Liver fine needle aspiration specimens
- Postmortem liver samples

4.5. Sample Size

All patients with liver biopsy whose biopsy specimens were submitted to the department of pathology during the study period.

4.6. Data management and Analysis

4.6.1. Data collection procedure

Surgical biopsy request papers were retrieved from the department archives registered from January 2016 – August 2020 and were reviewed for the demographic, clinical, gross, microscopic description and final diagnosis.

4.7. Study variables and Data Analysis

4.7.1. Dependent variables

Histologic diagnosis

4.7.2. Independent variables

Age, Gender

4.7.3. Data Analysis

Descriptive statistical analysis was performed across the different histopathologic patterns after stratifying by sex and age. The data sheets were coded and data entry, cleaning and analysis was done using the Statistical Package for the Social Sciences (SPSS) version 26.

4.8. Ethical considerations

Ethical permission was sought from the Department of Pathology, College of Health Sciences, Addis Ababa University, and ethics committee at Tikur Anbessa Specialized Hospital. Names of patients or their chart numbers were not mentioned in the study to keep the confidentiality of the patients.

5. Result

A total of 116 cases that fulfilled the study criteria were identified. Of the total cases 60(51.7%) were females and 56(48.3%) were males with female to male ratio of 1.1:1. Most of the ages ranges from 30 to 79 years, which accounts for 86.2% of cases and with mean, standard deviation, lowest and highest age range of 49, 17.97, 6 months and 79 years respectively. The mean, std deviation, the lowest and highest age limits for males and females are 51, 17.51, 1,77 and 47, 18.27, 2, 79 respectively. Core biopsy specimens consists of 52(44.8%), resection specimens account of 36 (31%) and 28(24.2%) cases were not specified.

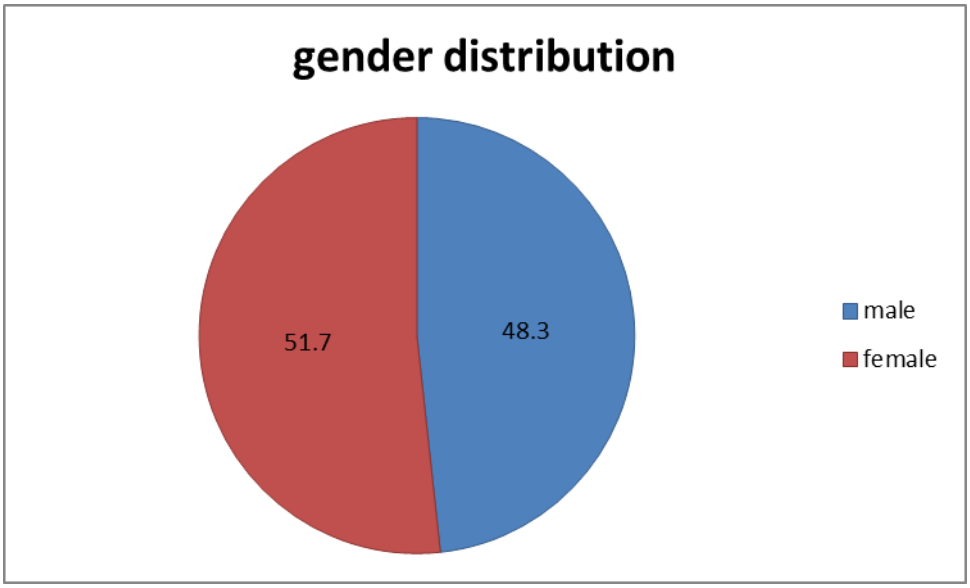

Figure-1. Gender distributions of histopathologic diagnoses.

Age distributions of liver histopathologic diagnoses

The studied cases showed age ranging from 6 months to 79 years old. Most of the cases, accounting for 86 % found between the age range of 30 to 79 years old with highest incidence in the 7th decade. 6 cases were in the paediatric age. Among paediatric age cases 2 were hepatoblastoma and the others were high grade sarcoma, biliary atresia with biliary cirrhosis, chronic nonspecific inflammation and normal histology one case each.

age in years	Frequency	Percent	Valid Percent	Cumulative Percent
<10	5	4.3	4.3	4.3
10-19	2	1.7	1.7	6.0
20-29	9	7.8	7.8	13.8
30-39	14	12.1	12.1	25.9
40-49	23	19.8	19.8	45.7
50-59	19	16.4	16.4	62.1
60-69	29	25.0	25.0	87.1
70-79	15	12.9	12.9	100.0
Total	116	100.0	100.0	

Table 1 . Age distributions of total cases

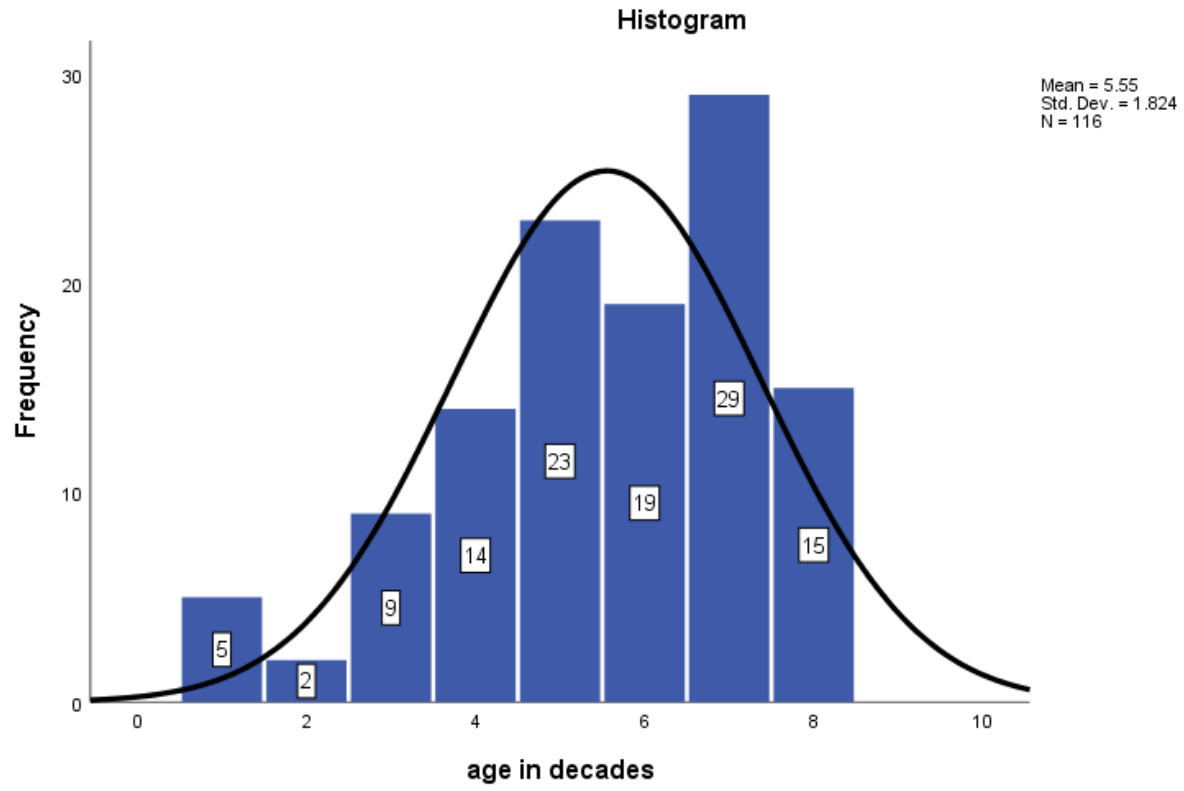

Figure-2. Histogram showing age distributions of liver lesions.

Malignant lesions occurred more in males than females with the pick incidence in ages 60 – 69 years in both genders. In contrary benign neoplastic and tumor like conditions were most commonly occurred in females which included 92.3% of benign neoplastic and tumor like lesions with peak incidence 40 – 49 years of age.

		Sex		**Total**
		Male	**Female**	
age in years	<10	3	2	5
	10-19	0	2	2
	20-29	3	6	9
	30-39	5	9	14
	40-49	9	14	23
	50-59	11	8	19
	60-69	18	11	29
	70-79	7	8	15
Total		**56**	**60**	**116**

Table 2. showing age and sex wise distribution.

Prevalence and types of liver lesions based on histopathologic patterns

From all 116 cases studied, 66(56.9%) cases were malignant, 13(11.2%) were benign neoplastic and tumor like conditions and the rest 37(31.9%) of cases were non neoplastic and non diagnostic/descriptive reports. Among all histopathologic patterns malignant lesions were the predominant one followed by non neoplastic lesions and descriptive/non diagnostic cases which account for nearly one third of liver lesions.

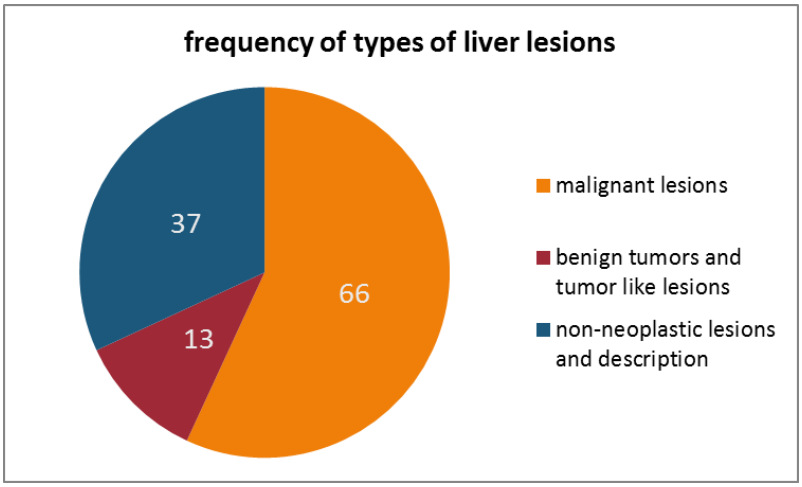

Figure-3. Frequency of neoplastic and non neoplastic liver lesions.

Prevalence and histopathologic patterns of neoplastic and tumor like lesions

Among 79 neoplastic and tumor like lesions 66(83.5%) cases were malignant which accounted for 56.9 % of all liver lesions studied with a relatively male predominance. From 66 malignant cases, 35(53%) cases were males and 31(47%) cases were females with a male to female ratio of 1.13: 1.

Frequency of malignant lesions

		Frequency	Percent	Valid Percent
Valid	hepatocellular carcinoma	23	19.8	34.8
	cholangiocarcinoma	8	6.9	12.1
	secondary carcinoma	20	17.2	30.3
	neuroendocrine tumor	4	3.4	6.1
	hepatoblastoma	2	1.7	3.0
	Lymphoma	1	.9	1.5
	secondary high grade sarcoma	3	2.6	4.5
	adenocarcinoma with neuroendocrine differentiation	2	1.7	3.0
	malignant undifferentiated tumor	1	.9	1.5
	secondary epitheloid GIST	1	.9	1.5
	suspicious for malignancy	1	.9	1.5
	Total	66	56.9	100.0
Missing	System	50	43.1	
Total		116	100.0	

Table 3. Showing frequency of histopathologic patterns malignant lesions.

Hepatocellular carcinoma was the most frequent malignant histopathologic pattern which included 23 cases accounting for 34.8% of all malignant patterns. Secondary carcinoma was the second most common pattern, with hepatocellular carcinoma together consisted nearly two-third of all malignant lesions. Cholangiocarcinoma was the third most common frequent pattern accounting for 12.1% of malignant cases. The remaining malignant histopathologic patterns were neuroendocrine tumor(6.1%) (primary site was not mentioned in all cases), secondary high grade sarcoma(4.5%), hepatoblastoma(3%), adenocarcinoma with neuroendocrine differentiation(3%), lymphoma(1.5%), undifferentiated malignant tumor(1.5%), secondary epitheloid GIST(1.5%) and suspicious for malignancy(1.5%) with decreasing frequency.

In general the majority were between the age of 40 – 79 years old with peak incidence in 60 – 69 years of age in both genders. The peak age for hepatocellular carcinoma was in 60 – 69 years old while secondary carcinoma was peak in 50 – 59 years old. Both cases of hepatoblastoma were under ten years of age (one a 1 year and 3 month child with pure fetal epithelial type hepatoblastoma and the second a 1 year 6 month old child with well differentiated fetal hepatoblastoma).

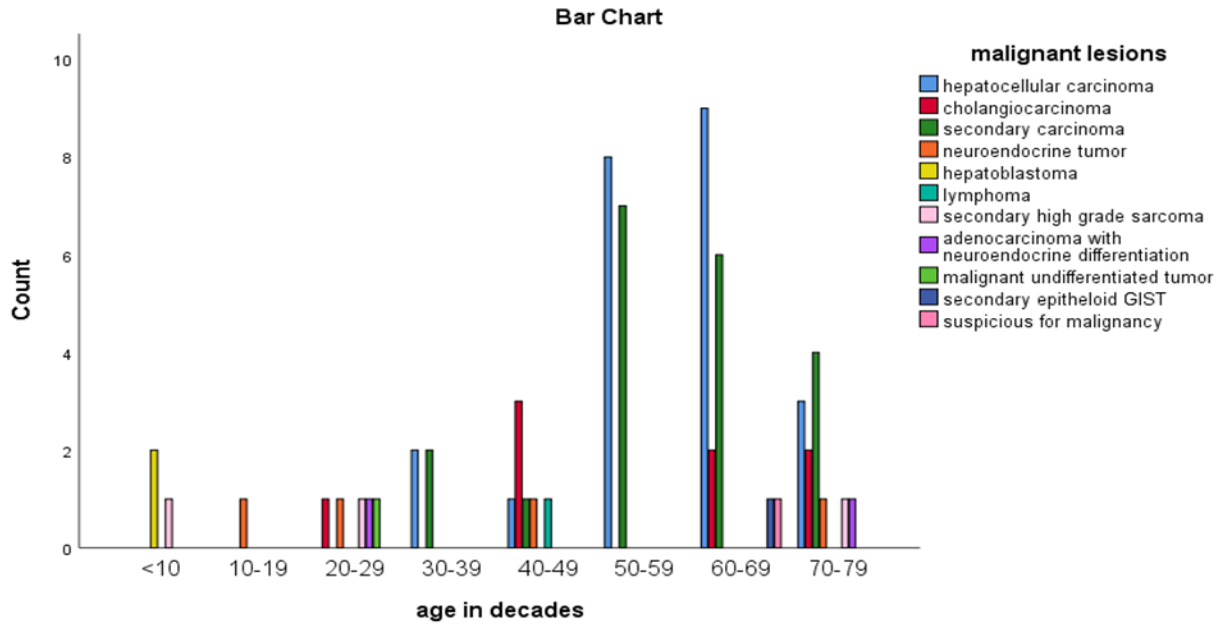

Figure 4. Showing frequency of malignant lesions by age.

Hepatocellular carcinoma was more common in males than females. Among 23 cases of hepatocellular carcinoma 17(73.9%) cases were males with male to female ratio of 2.8: 1. And secondary carcinoma was slightly more common in females (11 cases out of 20 secondary carcinoma cases) than in males with female to male ratio of 1.2 : 1. All 4 cases of neuroendocrine tumors and both 2 cases of adenocarcinoma with neuroendocrine differentiation were found in female patients.

		Sex		Total
		Male	Female	
malignant lesions	hepatocellular carcinoma	17	6	23
	Cholangiocarcinoma	4	4	8
	secondary carcinoma	9	11	20
	neuroendocrine tumor	0	4	4
	Hepatoblastoma	1	1	2
	Lymphoma	0	1	1
	secondary high grade sarcoma	2	1	3
	adenocarcinoma with neuroendocrine differentiation	0	2	2
	malignant undifferentiated tumor	0	1	1
	secondary epitheloid GIST	1	0	1
	suspicious for malignancy	1	0	1
Total		35	31	66

Table 4. Showing gender specific prevalence of malignant lesions.

age in decades * malignant lesions * sex Crosstabulation

Count														
sex														Total
male	age in decades	<10	0	0	0		1		1			0	0	2
		20-29	0	0	0		0		1			0	0	1
		30-39	2	0	0		0		0			0	0	2
		40-49	0	1	1		0		0			0	0	2
		50-59	7	0	3		0		0			0	0	10
		60-69	6	1	3		0		0			1	1	12
		70-79	2	2	2		0		0			0	0	6
	Total		17	4	9		1		2			1	1	35
female	age in decades	<10	0	0	0	0	1	0	0	0	0			1
		10-19	0	0	0	1	0	0	0	0	0			1
		20-29	0	1	0	1	0	0	0	1	1			4
		30-39	0	0	2	0	0	0	0	0	0			2
		40-49	1	2	0	1	0	1	0	0	0			5
		50-59	1	0	4	0	0	0	0	0	0			5
		60-69	3	1	3	0	0	0	0	0	0			7
		70-79	1	0	2	1	0	0	1	1	0			6
	Total		6	4	11	4	1	1	1	2	1			31

Table 5. showing malignant lesions against gender and age distribution.

Histopathologic patterns of benign neoplastic and tumor like lesions

Benign neoplastic and tumor like lesions were least common histopathologic patterns from all studied cases which consisted of 13(11.2%) of the total 116 studied cases. Among these, hemangioma was the most frequent diagnosis accounting for 69.2 %(9 cases) followed by benign liver cyst and focal nodular hyperplasia, accounting for 23 % and 7.8 % respectively.

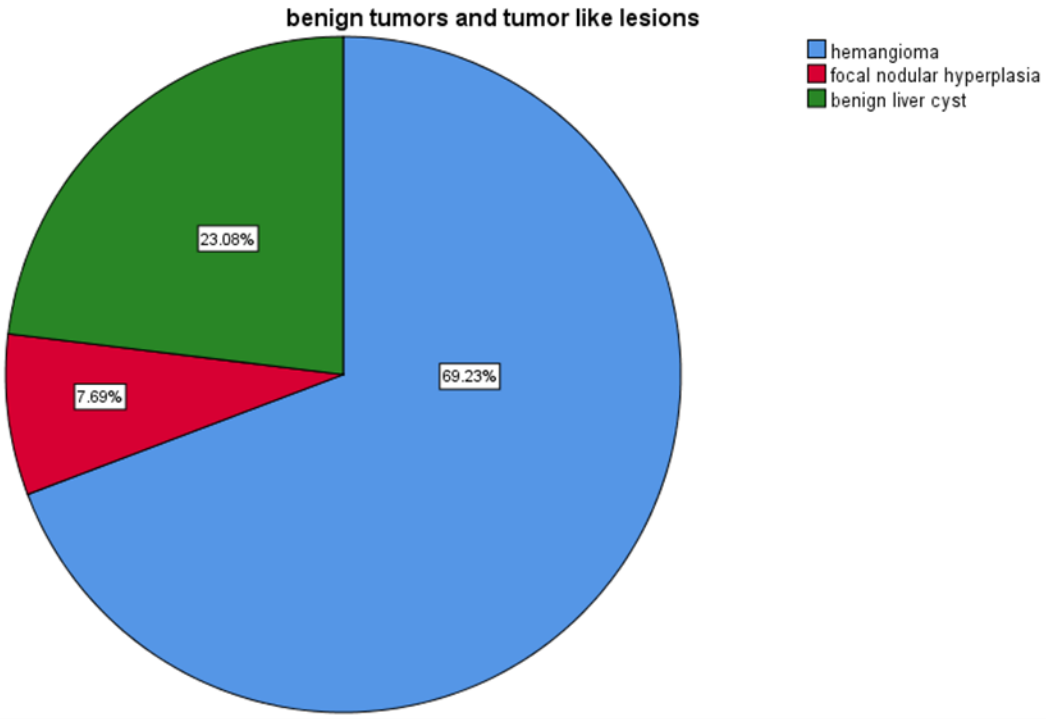

Figure 5. Showing prevalence of benign tumors and tumor like lesions.

Almost all cases of benign neoplastic and tumor like lesions affect females with female to male ratio of 12 : 1. Only one case of hemangioma was found in male.

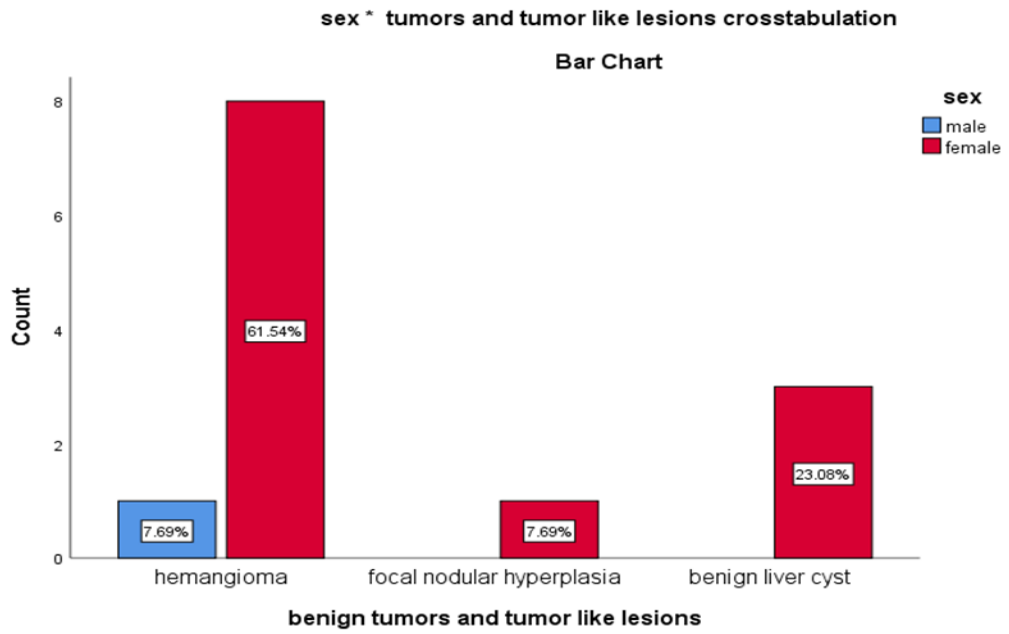

Figure 6. Showing gender distribution of benign tumors and tumor like lesions.

9(70%) of cases found in the age range of 30 – 49 years old with peak incidence in 40 – 49 years old. All case were above 30 years old and below 80 years old.

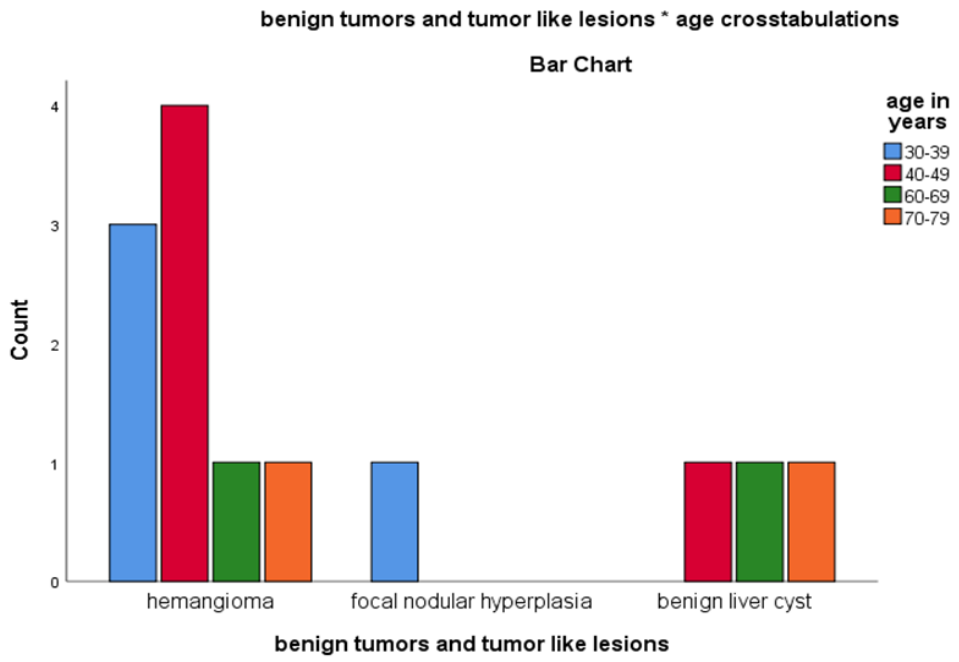

Figure 7. Showing age distributions of benign lesions.

Non neoplastic lesions

Non neoplastic lesions including descriptions consisted 37(31.9%) of total 116 cases. Out of 37 cases 16(43.2%) were descriptions for histopathologic study. Tuberculosis was the commonest cause of non neoplastic liver lesions which account for 10.8%(4/37) of non neoplastic lesions. The other histologic diagnoses included hydatid cyst 3(8.1%), abscess 2(5.4%), seatosis/fatty change 2(5.4%), cirrhosis 1(2.7%), biliary atresia with cirrhosis 1(2.7 %), chronic active hepatitis 1(2.7%), acute alcoholic hepatitis 1(2.7%), acute complete intrahepatic cholestasis with ascending cholangitis + stage 3 fibrosis 1(2.7%), chronic nonspecific inflammation of the cyst wall 1(2.7%), non diagnostic 1(2.7%) and 3(8.1%) of cases were reported as normal histology.

non-neoplastic lesions and description					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	hydatid cyst	3	2.6	8.1	8.1
	tuberculosis	4	3.4	10.8	18.9
	abscess	2	1.7	5.4	24.3
	cirrhosis	1	.9	2.7	27.0
	steatosis/fatty change	2	1.7	5.4	32.4
	biliary atresia with cirrhosis	1	.9	2.7	35.1
	chronic active hepatitis	1	.9	2.7	37.8
	acute alcoholic hepatitis	1	.9	2.7	40.5
	see description	16	13.8	43.2	83.8
	normal histology	3	2.6	8.1	91.9
	non diagnostic	1	.9	2.7	94.6
	acute complete intrahepatic cholestasis with ascending cholangitis + stage 3 fibrosis	1	.9	2.7	97.3
	chronic nonspecific inflammation of the cyst wall	1	.9	2.7	100.0
	Total	37	31.9	100.0	
Missing	System	79	68.1		
Total		116	100.0		

Table 6. distributions of non neoplastic and descriptive/non diagnostic cases.

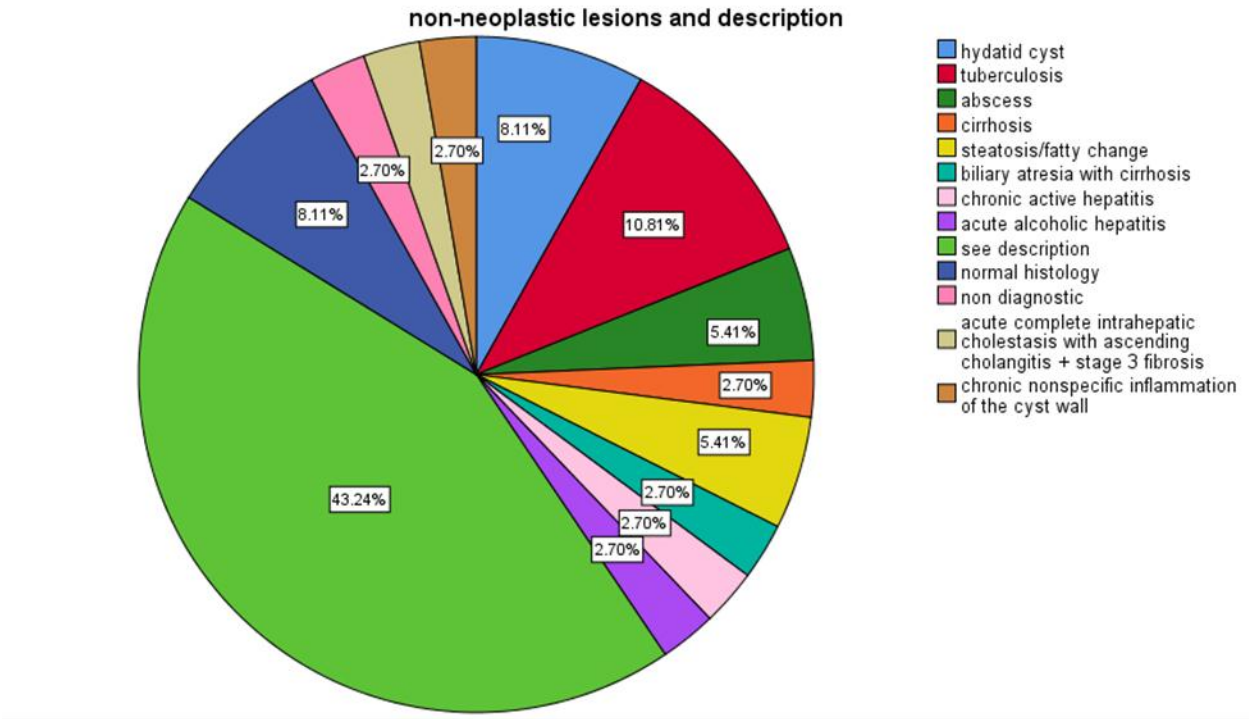

Figure 8. Showing prevalence of histopathologic patterns of non neoplastic/description biopsy results.

Majority of non neoplastic and descriptive results were in 30 – 69 years old patients. And the minimum age was a 6 month old infant with a diagnosis of biliary atresia with biliary cirrhosis. Among these 20(54%) of these cases were descriptive reports, non diagnostic and normal histology, which constituted 43.2%, 2.7% and 8.1% respectively. The remaining 17(46%) of cases are infectious, inflammatory and congenital causes that means 14.7% of all studied cases. Infectious and inflammatory lesions included 11.3% of all lesions. Among these infectious and inflammatory lesions TB accounted for 4 cases (3.4%), hydatid cyst(2.6%), abscess(1.7%), chronic active hepatitis(0.9%), acute alcoholic hepatitis(0.9%), acute complete intrahepatic cholestasis with ascending cholangitis with stage 3 fibrosis(0.9%) and chronic nonspecific inflammation of the cyst wall(0.9%). The remaining 3.4% of cases were 2 fatty change/steatosis, 1 biliary atresia with biliary cirrhosis and 1 case of cirrhosis (1.7%, 0.9% and 0.9%) respectively.

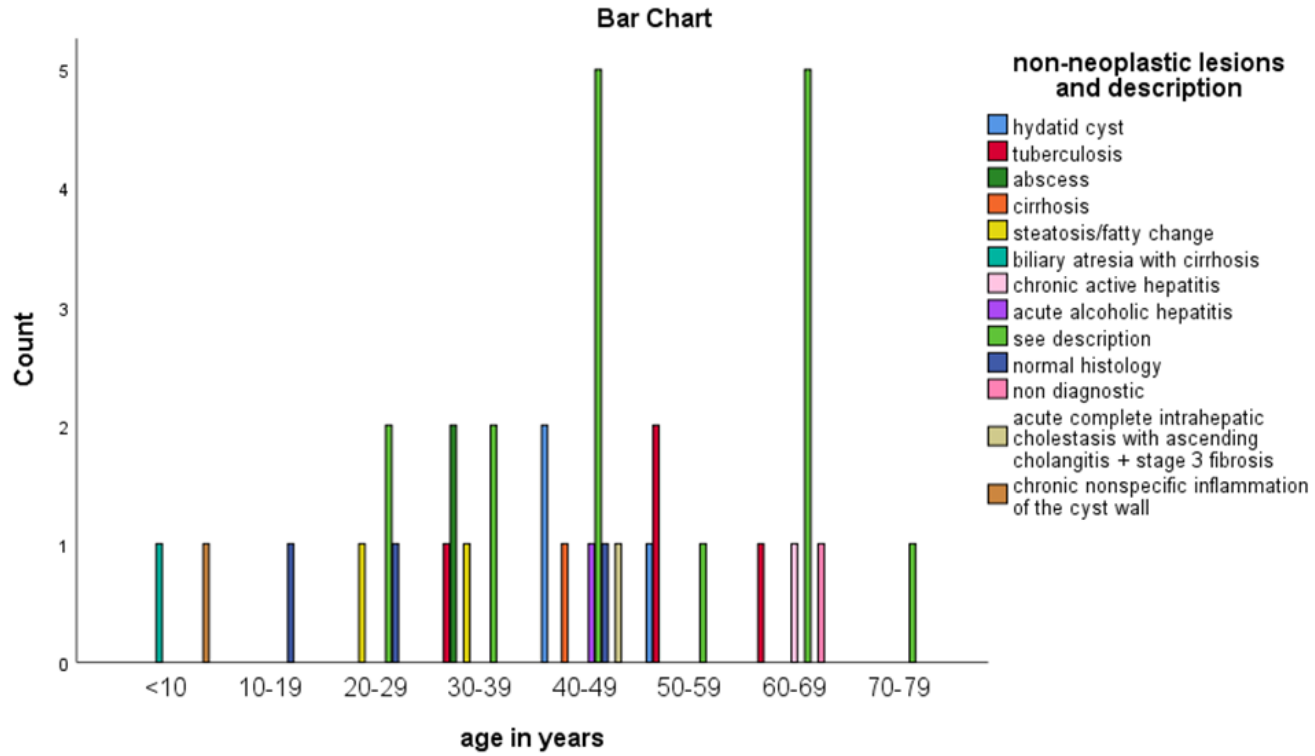

Figure 9. Showing age wise distribution of non neoplastic liver lesions and description reports.

In general hepatocellular carcinoma was the most common etiology of liver lesions in the studied cases accounting for 19.8% of all lesions. Secondary carcinoma was the second commonest etiology covering 17.2% of lesions. Descriptive reports and non diagnostic cases were significant in amount consisting 14.7% of total cases.

Malignant	Percent	Non neoplastic	Percent	Benign neoplastic and tumor like lesions	Percent
hepatocellular carcinoma	19.8	hydatid cyst	2.6	Hemangioma	7.8
cholangiocarcinoma	6.9	Tuberculosis	3.4	focal nodular hyperplasia	0.9
secondary carcinoma	17.2	Abscess	1.7	benign liver cyst	1.7
neuroendocrine tumor	3.4	Cirrhosis	0.9	Total	10.3
Hepatoblastoma	1.7	steatosis/fatty change	1.7		
Lymphoma	0.9	biliary atresia with cirrhosis	0.9		
secondary high grade sarcoma	2.6	chronic active hepatitis	0.9		
adenocarcinoma with neuroendocrine differentiation	1.7	acute alcoholic hepatitis	0.9		
malignant undifferentiated tumor	0.9	see description	13.8		
secondary epitheloid GIST	0.9	normal histology	2.6		
suspicious for malignancy	0.9	non diagnostic	0.9		
Total	56.9	acute complete intrahepatic cholestasis with ascending cholangitis + stage 3 fibrosis	0.9		
		chronic nonspecific inflammation of the cyst wall	0.9		
		Total	31.9		
Total					100

Table 7. Showing summary of prevalence of all histopathologic patterns in all studied cases.

6. Discussion

Histopathological study of liver biopsy is very common and is frequently done for diagnosis of different hepatic lesions, providing information for disease progression and response to therapy. And different studies on histopathological spectrum of hepatic lesions show that there is significant geographic and regional variability in the patterns and prevalence of liver pathologies across the world.

In our study the age range was 6 months to 79 years old with mean age of 49 years majority being in 40 – 79 years of age. And malignant hepatic lesions were the most common finding accounting for 56.9%. This is in agreement with the study by Agrawal et al, India a prospective study which included 65 liver biopsies in which age ranged from 3 months to 80 years. Mean age was 42.5 years. Majority of patients belonged to the 5^{th} and 6^{th} decade of life. Hepatic tumors were the commonest finding 52.30%. Secondary tumour deposits (40.0%), primary hepatic tumours (12.3%), hepatitis (16.9%), cirrhosis (12.3%), extrahepatic biliary atresia (6.15%), secondary biliary cirrhosis (3.0%), glycogen storage disease (1.5%), cystic hydatid disease (1.5%) and fatty liver (1.5%). In our study secondary carcinoma, secondary high grade sarcoma, secondary epitheloid GIST and adenocarcinoma with neuroendocrine differentiation added together made secondary malignancy the most common liver tumor, 39.2% of malignant lesions. Hydatid cyst and fatty liver included 2.6% and 1.7% respectively which is in slight agreement with the above study. But the above study is higher for hepatitis and cirrhosis.

Our study is also comparable with a study by Murgod, Doshi and Dombale et al, India found that age ranged from 6 months to 80 years. 24(36.3%) cases were hepatocellular carcinoma, 3(4.54%) cases each of fatty liver, hepatitis, and cirrhosis. 1(1.51%) case each of biliary atresia, miliary tuberculosis and liver abscess. Liver biopsy was nonspecific in 4(6.06%) cases & inadequate in 7(10.6%) cases. But in contrary to our study there was 19.6% glycogen storage disorders and no cases of secondary tumors and cholangiocarcinoma.

Another study done by D Fekade, Ethiopia on histopathological features of liver disease in hospitalized Ethiopian patients in Tikur Anbessa Hospital found that primary hepatocellular carcinoma accounted for 19.2% and (18.1%) of the specimens were inadequate for precise pathological diagnosis which is comparable to our study but this finding is higher for hepatitis which was present in 8.8% of the specimens and lower for metastases to the liver which was

4.5%. Porphyria cutanea tarda was diagnosed in 12.4% of the biopsy specimens which was not found in the current study. But our current study was discordant with many of the litratures reviewed.

Study from Dhaka, Bangladesh by Hossain MM et al on clinicopathological correlation of liver biopsy, an observational study which was done on 50 patients identified that commonest disease was found to be chronic liver disease (48%) of which cirrhosis of liver (30%) was highest followed by severe chronic hepatitis (10%), mild chronic hepatitis (8%). Next common disease was hepatocellular carcinoma (26%). Other diseases found were secondary carcinoma of liver (4%), fatty change (6%), kala-azar (4%), sclerosing cholangitis (2%) and histopothological findings revealed normal hepatic tissue in (10%) cases.

A study done from Saudi Arabia during the period 1982-1990 on 544 patients with clinical evidence of liver disease at King Fahd University Hospital found that a tissue diagnosis pattern of liver cirrhosis 17.3%, periportal fibrosis 14.3%, metastatic cancer 12.9%, primary hepatoma (hepatocellular carcinoma: HCC) 12.1%, hepatic granuloma 11.2%, chronic active hepatitis 7.7%, chronic persistent hepatitis 2.2%, fatty liver 7.2%, hydatid liver disease 4.6% and others 2.8%. In 7.7% the histology was normal.

A study done by EE Ugiagbe, MO Udoh at the University of Benin Teaching Hospital, Benin city, Nigeria on the histopathological pattern of liver biopsies on 80 cases of liver biopsies which were reported during the 7-year period found that age range of 4 months to 69 years, the highest incidence was in the 4th decade. The three common histopathological diagnoses were inflammatory lesions 63.8% (of these cases, 55% and 43% were due to chronic active hepatitis and chronic persistent hepatitis, respectively), malignant neoplasms 22.5%, and liver cirrhosis in 6.3% of cases. HCC was the most common malignant neoplasm seen accounting for 55.6% of cancer cases, metastatic carcinoma 33.3% and cholangiocarcinoma and hepatoblastoma accounted for 5.56% each.

A study by Abdulkareem et al, Lagos University Teaching Hospital, Nigeria (1989-2000), a retrospective histopathological study of 345 liver biopsies over a 12-year period consisting of 222 males and 123 females with peak age incidence of 41-50 years identified that three common histopathological diagnoses were hepatocellular carcinoma-33%, chronic hepatitis-17.7%, and liver cirrhosis-17.7%.

7. Conclusion

In this study neoplastic lesions were the most common liver lesions. Secondary liver deposits were more common than primary tumors. Among malignant neoplastic tumors HCC was the most common histologic pattern followed by secondary carcinoma. The prevalence of benign neoplastic lesions were higher in this study of which hemangioma was the most common benign lesion. Prevalence of inflammatory, metabolic and infectious lesions were lower in this study. The prevalence of hemangioma was significant in this study.

8. Limitations of the study

- We may not achieve the estimated number of histopathologic reports due to poor data keeping system.
- Knowing the true prevalence of secondary liver deposits was difficult due to lack of specification of some tumors wether the primary organ is liver or distant organ.
- Many of patient history, laboratory data and imaging investigations were lacking so that it would have been challenging for the pathologist to reach a certain diagnosis and correlating histologic diagnosis with clinical compliant and radiologic finding was difficult.

9. **Recommendations**

- It is crucial to improve the data keeping methods
- It is good to stage and grade malignant tumors in resected specimens because prognostically it could be significant.
- Special stains and immunohistochemistry are important and may decrease the number of descriptive reports.
- Complete clinical information and imaging reports are valuable.

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