Original Article

Liver Diseases

The Prevalence of Liver Diseases and Etiological Factors among the Patients of Jinnah Post Graduate Medical Centre (JPMC), Karachi

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ABSTRACT

Objective: To determine the frequency and etiological factors of nonneoplastic and neoplastic liver diseases
Study Design: Observational / analytic study.
Place and Duration of Study: This study was conducted at the Department of Pathology, BMSI, JPMC from 1st January 2012 to 31st September 2014.
Materials and Methods: A total of 288 liver biopsycases of formalin fixed liver tissue biopsies were selected and analyzed for morphological features and grading received from January 2010-December 2012, at the department of Pathology, Basic Medical Sciences Institute, Jinnah Post Graduate Medical Centre.
Most common liver disease was CLD (88.54%). Most common age for CLD was between 3rd-5th decades of life with male predominance. HCV was the most common etiological factor. Out of total cases, 6.59% were hepatocellular and bile duct carcinomas. Most common age for liver cancers was 5th-7th decade of life with male predominance. The data feeding and analysis were on computer package SPSS (Statistical Packages of Social Sciences) version 20.0. In all statistical analysis only p-value <0.05 was considered significant.
Results: The most commonly encountered liver disease CLD was found as a major liver disease (71%) of the samples were suffering from CLD , while 25 % were suffering from HCC, Hepatitis C was the major cause of the liver diseases, (55.56%) of the liver patients were earlier suffering from the Hepatitis C.
Conclusion: In conclusion we observed that the most common liver disease in biopsy cases is chronic liver disease (chronic hepatitis), mostly occur between 21-50 years of age with male predominance and most frequent etiological factor is HCV.
Key Words: Liverdiseases, non-neoplastic liver diseases, neoplastic liver diseases

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INTRODUCTION

JPMC is the biggest and the best equipped public sector hospital in Pakistan. The Section of Histopathology at the JPMC, Karachi is the largest and busiest centre for Histopathology in Pakistan, a country with a population of over 180 million people. Primary liver cancer is the sixth most common cancer in the world, 750000 people worldwide i.e. 6% of the totals were diagnosed with liver cancer[1]. Liver cancer is the fifth most frequently diagnosed cancer in men worldwide and second most common cause of death. While in female it is seventh most common and sixth leading cause of cancer death[2]. In cancer research, UK (2009)[3], around 3960 people were diagnosed with liver cancer.

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In Pakistan the data from Shaukat Khanum Cancer Hospital & Research Centre from Dec 1994 to Dec 2011[4] shows that liver cancer is at number 1 position amongst the top 10 malignancies and accounts 1,926 cases i.e8.8% in males while in females it is 697 i.e. 2.97 %. Incidence in Pakistan for liver cancer is lower than eastern Asia but higher than the sub –continent and west.

The risk is equal in both sexes [5]. Main causes of liver cancer are hepatitis B and C viruses, alcohol, cirrhosis related to B &C viruses and heavy alcohol, smokers, vinyl chloride (occupational exposure) and aflatoxin[3]. HBV and HCV are among the principal causes of severe liver disease, including hepatocellular carcinoma. WHO estimates that there are 350 million people with chronic HBV infection and 170 million people with chronic HCV infection worldwide[6, 7]. Pakistan is among the worst afflicted nations[8]. Chronic inflammation is a known risk factor for carcinogenesis and is thought to play a role in pathogenesis of several types of cancers like cervical, ovarian, oesophageal adenocarcinoma, mesothelioma, colorectal cancer, lung ,initial step in the development of malignancy with genetic changes occurring as a later manifestation of a prolonged inflammatory process.

Hepatitis C virus (HCV) has been identified as one of the leading causes of chronic liver disease with serious sequel as the end stage of cirrhosis and liver cancer [9]. According to recent statistics, the worldwide prevalence of HCV infection is ~3% and affects around more than 170 million people globally[10]. Chronic hepatitis C infection mainly affects liver but can be associated with various extrahepatic manifestations including cryoglobulinemia, sialadenitis, glomerulonephritis, and porphyria cutanea tarda[11]

MATERIALS AND METHODS

This study is based on the analysis of liver diseases biopsies received at department of pathology, BMSI, JPMC from first January 2010 to 31st December 2012.

Inclusion Criteria: All properly fixedliver biopsies received in department of pathology, BMSI, JPMC during the above mentioned time

Exclusion Criteria:

I. Inadequate material
II. Metastatic carcinomas (adenocarcinomas)
III. Cystic lesion (Hydatid cyst)
2) H&E stained slides for all cases.
3) MassonsTrichrome stained slides for all cases.
4) Clinical records
5) Surgical pathological records.

Clinical history and relevant data were recorded on the request form in the Performa.

H&E and mass ontrichromestaining were performed.

All the slides were studied under light microscopy using scanner (4x), low power (10x), and high power (40x) lenses and were revised with supervisor.

4. Various parameters were recorded as mentioned in proforma.
5. Grading and staging was done in all cases.
6. Results were statistically analyzed.

Hematoxylin And Eosin Staining Results:

• Nuclei: stained blue
• Cytoplasm: stained varying shades of pink

Masson Trichrome Staining Results:

Nuclei---------- blue-black
Cytoplasm, muscles and erythrocytes----------red
Collagen----------green.

Interpretation of H&E Staining and Trichrome Staining.

Grading and Staging:

• For the interpretation of grading and staging of all the selected slides we have used the "modified histological activity index" an extension of the original knodell system.

• Modified HAI grading or necroinflammatory scores has maximum possible score is 18(1-4=minimal inflammation, 5-8=mild inflammation,9-12=moderate inflammation and 13-18=marked or severe inflammation).

• Modified HAI staging, is for extent of fibrosis. The maximum score is 6(0=no fibrosis, to gradual increase in fibrosis upto stage 5 which is early cirrhotic change and then definite cirrhosis which is grade 6).

• Severity of steatosis is judged from mild (less than one third), moderate (one third to two thirds) to severe (more than two thirds).but in our study we have only included severe steatosis cases.

• Dysplasia is found in two forms large cell dysplasia and small cell dysplasia. In large cell dysplasia there is cellular enlargement, pleomorphism and multi-nucleation but nucleus cytoplasm ratio will remain same while in small cell there is decreased volume of hepatocytic cytoplasm associated with moderately enlarged nuclear size, resulting in an increased N/C ratio[12]. In our study we had only large cell dysplasia.

RESULTS

Table 1 shows the frequency of various hepatic lesions amongst the liver biopsies received during study period .the most commonly encountered liver disease cases out of the total 288 cases was chronic liver disease (CLD) including 255 cases (88.54%) out of these 12(4.7%) showed full- fledged cirrhotic nodule. liver and bile duct carcinoma were 19 cases (6.59%), metastatic tumors contributes 12 cases (4.1%) and there were two cases of hydatid cyst (0.6%).

Table 2 shows distribution of liver diseases according to age most common age for chronic liver disease is between 3rd ,4th and 5th decade(mean age was 32) , for HCC it is 4th,5th and 6th decades(mean age 48) while for metastatic carcinoma it is 5th,6thand 7th decade of life (mean age 48).

Table No.1: Distribution of various liver diseases amongst liver biopsies received from 2010-2012 (n=288)

Liver Diseases	No. of Cases	%age	95% Confidence Interval
Chronic Liver Diseases (Chronic Hepatitis +Cirrhosis)	255 (243+12)	88.54	81.5 - 89.4
Hepatocellular Carcinoma	18	6.25	3.4 - 8.8
Cholangiocarcinoma Metastatic	01	0.35	0.01-1.6
Adenocarcinoma	12	4.17	2.2-6.7
Hydatid Cyst	02	0.69	0.1-0.2

*C.I =Confidence Interval

Table No.2: Distribution of 288 liver diseases cases according to age (n=288)

Liver Disease	**No. of Cases**	**Age In Years Mean ± S.D**
ChronicLiver Disease (CLD) 255	255	32.9± 14.94
Hepatocellular Carcinoma (HCC) & Cholangiocarcinoma	19	48.5 ± 18.12 *
Metastatic Carcinoma	12	48.9 ± 20.24 *
Hydatid Cyst 02	02	22.9 ± 4.24
P-value		0.001

* Significantly high as compared to CLD and hydatid cyst $p<0.05$

Table No.3: Distribution of 288 liver diseases cases according to gender (n=288). No significant difference was observed p>0.05

Liver Disease	No. of cases	Male	female	M/F ratio
Chronic Liver Disease (CLD)	255	157 (61.5%)	98 (38.4%)	1.6:1
Hepatocellular Carcinoma (HCC) & Cholangiocarcinoma	19	14 (73.7%)	5 (26.3%)	2.8:1
MetastaticCarcinoma	12	4 (33.3%)	8(66.7%)	0.5:1
Hydatid Cyst	02	1 (50%)	1 (50%)	1:1
Total	288	176 (61.1%)	112 (38.9%)	1.5:1

Table 3 shows the gender distribution according to liver diseases in total 288 cases, in CLD cases male were 61.5% and female 38.4%, male female ratio was 1.6:1 while for hepatocellular carcinoma and bile duct carcinoma male were 73.7% and female were 26.3% and M/F ratio was 2.8:1. In total liver diseases male female ratio was 1.5:1.

Table 4 shows the etiological distribution of 255 cases of CLD cases revealing that hepatitis C is the most common cause of chronic hepatitis accounting for 70% of cases followed by equal no. of cases of HBV and HBV&HDV co-infection i.e. 8.6% and 1 case of HBV&HCV co-infection (0.3%) infection .while hepatocellular and bile duct carcinoma shows 31.5% of HCV infection and 15.7% of HBV infection however 52.6% of cases data was not available ,therefore we cannot be sure that what could be the most frequent cause of HCC.

Table No.4: Distribution of chronic liver diseases cases (n=255) and hepatocellular and bile duct carcinoma (n=19) acording to etiology amongst liver biopsies received from 2010-2012

Liver Diseases	HBV	HBV&HDV	HBV&HCV	HCV	drug	unknown	Total
CLD	22(8.6%)	22(8.6%)	3(1.17%)	180(70%)	1(0.3%)	27(10.58%)	255
HCC & cholangiocarcinoma	3 (15.7%)	-	-	6(31.5%)	-	10(52.6%)	19

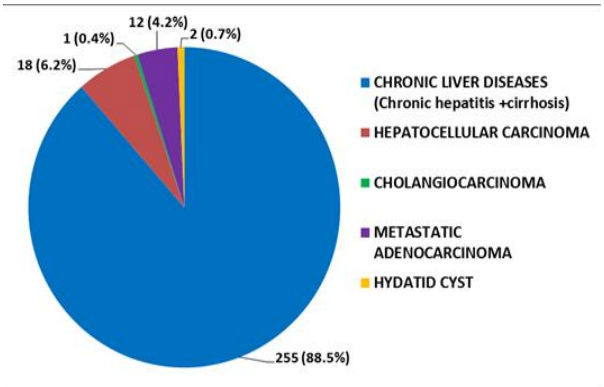

Figure No.1; Various Liver Disease Amongst Liver Biopsies In The Year 2010-2012 (N=288)

DISCUSSION

In this study we attempted to determine the frequency of various types of liver diseases including neoplastic lesions amongst the cases received in pathology department of JPMC from January 2010 to December 2012.

In our study out of total 288 cases of liver biopsies 88.54% had chronic liver disease showing various grades of chronic hepatitis, including 4.1% cases with cirrhosis. Our study is in accordance with the Khokar study[13] reporting 77.8% of chronic liver disease including chronic hepatitis (68.3%), chronic hepatitis with early cirrhotic changes (4.8%), and cirrhosis (3.1%).A PMRC study from 1987 to 2007[14], findings differ with our study and reports chronic hepatitis as 44.2%, cirrhosis 27.5% while 20.8% were carriers and 6.7% had acute hepatitis. This discrepancy may be due to a longer duration i.e. 21 years of their study. Moreover, this study includes additional cases of acute hepatitis and carriers also.

The minimum age of CLD cases in our series is 2 years and maximum 80 years while mean age is 36.2.Most common ages is 4th, 5th decade followed by 3rd decade. Ullahet al.[15] also reports commonest affected age group as 4th and 5th decade. In the NHANES study**,** the chronicity rate was estimated at 30% in subjects below the age of 20 years, and 76% for those older than 20 years[16].

Our study shows male predominance with 61.5% males and female were 38.4%. Male to female ratio was1.5: 1. Our finding are supported by the study of Ahmed[14], in which total 62.5% were males and 37.5% were females which giving a male / female ratio of 1.7:1. Devrajani et al. (2010)[17] also report similar results that 60% were males and 40% were females, M/F ratio was 1.4:1.While Ullah et al. (2012)[15] reports 51.6% males and 48.4% female.

According to etiological factors our series shows 70% cases of hepatitis C and 8.6% of hepatitis B. Our study is in close proximity with Ahmed [14], showing that hepatitis C was the most common infection (58.8%), followed by hepatitis B cases (32.6%). Khokhar[13] also reported HCV 86% followed by HBV 10%, comparable findings are shown by Ullah[15] and Almani[18]HCV 61.66% and HBV 18.94 % and HCV 52 % & HBV 16% respectively. In a USA based study[19]has given lower frequency compare, but also shows Hepatitis C is the most common cause i.e. 42% alone and 22% with alcohol combination. According to Beynon&

Hungerford[20], Alcohol-related liver disease accounted for the greatest proportion of liver disease deaths in the North West during 2010.

Approximately 1.7% of our cases showed HBV & HCV co-infections .Our findings are comparable with Khokar[13] reporting 3.1% and Ullah et al.[15]5.3% . Almani[18] however giving a higher figures of HBV &HCV co –infections as 16%. Our findings are similar with a study of India by Kumar[21] which reports HBV &HCV co-infections is 1.7%. Different studies have shown variable percentages as in China by Chen[22], it is 14.47%, in a Japanese study bySato[23] it is 23% and in Taiwan by Liaw[24] , it is 12%.

HBV &HDV co-infection was found in our cases is 8.6% while Ullah[15] has reported lower figures of 4.2%. while Kumar[21] reports 2.2% of HBV&HDV co-infection .Another study by Zaidi[25] shows high positivity rate of anti HDV i.e. 88.8% in HBV positive patients. Khan[26]study reports prevalence of HDV in Sindh 67%, Khyber Pakhtoonkhaw (KPK) 6% and Punjab 4%.Both these studies, Zaidi[25]&Khan[26]shows higher percentage because the study focuses on HDV detection in an extensive groups of patients showing HBsAg positivity only.

In the present study period we had total 6.59% liver and bile duct carcinomas and 4.1% metastatic adenocarcinoma in received liver biopsy cases. Our findings are comparable with the other study reports with slight variations from higher to lower figures as Khokar[13]finds 7.9% of hepatocellular carcinoma and 4.6% of adenocarcinoma (metastatic). However, Ahmed[14] from PMRC gives 0.8% of HCC, lower percentage may be due to a longer study period (21 years) including all cases of CLD with carriers as well as acute inflammation .In Shaukat Khanum annual collective cancer registry report (1994-2011) liver and bile duct malignancies were 5.22% and by Bhurgri[27] ,it is 5.7% in male and 3.7% in female. According to Parkin[28], in USA SEER white population shows 3.0% in male and 1.2% in females. As indicated by cancer research UK (2010)[29] rate of liver cancer in England 4.6%, Wales 4.9%, Scotland 5.1%, northern Ireland 3.7% and in UK 4.6%.

In our study HCC and bile duct carcinoma were found b/w age groups of 27-80 years. Mean age was 54.2. Most common age was 5th to 7th decade. According to SKMCH cancer registry report (2011)[4] most common age for liver and bile duct cancer is also between 5th, 6th and 7th decade of life. In cancer research UK (2010)[29], an average of 70% of cases was diagnosed in men and women aged 65 years and over.

In our study gender frequency of liver cancer in male 68.4% and female 31.5% .M/F ratio was 2.1:1. SKMCH &RC (2011)[4] reports male 71.84% and female 28.1%. M/F ratio was 2.5:1. WhileBosch et al. (2004)[30]pointed out that worldwide rate of liver cancer in men are typically 2 to 4 times higher than in women.

Out of 19 cases of liver and bile duct cancer 6(31.5%) had HCV and 3(15.7%) HBV positive, for remaining 10 (52.6%) cases data was not available. Ahmed et al. (2010)[14] report 40 HCC cases in which 40% had HBV, 47.5% HCV, 2.5% had HCV&HBV co-infection and 21% had others. While Khokar (2002)[13], had 41 cases in which 29.3% had HCV and 14% HBV, remaining 53% cases had no data provided. Patients with cirrhosis have the highest risk of developing HCC[31]. Hepatitis C is the most common cause of HCC in Europe. According to GLOBOCAN data 2000, the percentage of worldwide HCC associated with HBV is 53%, HCV 25% and others 22 % [32].

CONCLUSION

Hepatocellular carcinoma (HCC) is a neoplasm the incidence of which is increasing worldwide, but striking geographical differences are observed for both risk factors and occurrence. The incidence in developing countries is two to three times higher than in developed countries. Male sex is associated with a higher incidence. The incidence also increases with age. The most powerful risk factor is the existence of liver cirrhosis regardless of its etiology. In Pakistan, liver cirrhosis is mostly associated with viral infection i.e. HBV &HCV.Most common liver disease was CLD (88.54%). Most common age for CLD was between 3rd-5th decades of life with male predominance. HCV was the most common etiological factor. Out of total cases, 6.59% were hepatocellular and bile duct carcinomas. Most common age for liver cancers was 5th-7th decade of life with male predominance.

In conclusion we observed that the most common liver disease in biopsy cases is chronic liver disease (chronic hepatitis), mostly occur between 21-50 years of age with male predominance and most frequent etiological factor is HCV.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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