Histological and laboratory features of patients undergoing liver biopsy at a university hospital in Central Saudi Arabia

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ABSTRACT

Objectives: To identify the most common liver pathologies seen in our center, to find the prevalence of advanced fibrosis and cirrhosis in patients with chronic hepatitis B and C, and to correlate the histological and laboratory features of the most common diseases and compare between them.

Methods: Liver biopsy procedures performed in our Gastroenterology Unit at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia were traced from records between the years 1997-2003. Clinical, histopathological, and laboratory features were recorded.

Results: We identified 574 liver biopsies during the study period. Of the 502 included patients, males were 58.6%. The mean age of the patients was 43.5 years. Approximately half of the biopsies (49%) were performed for patients with hepatitis C, followed by hepatitis B, for which 17% of the biopsies were performed. Patients with hepatitis B were approximately 10 years younger than patients with hepatitis C (p=0.01). They were 10% more likely to be males. In terms of fibrosis, only approximately 17% of patients with hepatitis B and 27% of patients with hepatitis C had advanced fibrosis.

Conclusion: Most liver biopsies performed in our center are performed for patients with hepatitis C. Rates of advanced fibrosis in our series are significantly lower than what was previously reported in other studies.

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Despite recent advances in the ability to diagnose liver diseases by laboratory and radiological tests, liver biopsy continues to be an integral part in the diagnosis of the majority of liver diseases.[1] It helps to confirm the diagnosis, grade and stage of the liver disease, predict outcome, direct management, and follow progression of many liver diseases.

In this study, we reviewed all liver biopsies performed in the last 5 years in our gastroenterology and hepatology unit. Our aims are to: 1. identify the most common liver pathologies seen in our center, 2. find the prevalence of advanced fibrosis and cirrhosis in out chronic hepatitis B and C patients, and 3. correlate the histological and laboratory features of the most common diseases and compare them.

Methods. Liver biopsy procedures performed in our Gastroenterology Unit at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia were traced from records between the years

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Table 1- Mean values of laboratory parameters in all patients (n=502).

Parameter	Mean	Range (Minimum - Maximum)
WBC (X10^9/L)	7.47	(2.2 - 79)
Hg (g/L)	13.2	(74 - 175)
MCV	85	(57 - 103)
Platelet (X10^9/L)	222	(48 - 671)
T. Bili (umol/L)	24	(2 - 529)
Albumin (g/L)	35	(14 - 52)
ALP (U/L)	184	(39 - 2432)
ALT (U/L)	120	(7 - 1203)
AST (U/L)	91	(7 - 1506)
GGT (U/L)	164	(7 - 2311)

WBC - white blood cell, Hg - hemoglobin, MCV - mean corpuscular volume, T. Bili -total bilirubin, ALP - alkaline phosphate, ALT - alanine aminotransferase, AST - aspartate aminotransferase, GGT - gamma-glutamyl transpeptidase

Table 2 - Presence of selected histological features in all patients (n=502).

Parameter	%
Architecture distorted	15.9
Portal tract inflamed	86.0
Interface hepatitis present	57.0
Cholestasis	6.6
Bile duct damage	6.8
Liver cell abnormal	7.2
Steatosis present	35.0
Grade (0 or 1) inflammation	29.7
Grade (2) inflammation	39.6
Grade (3) inflammation	21.9
Grade (4) inflammation	8.0
Stage (0 or 1) fibrosis	33.3
Stage (2) fibrosis	31.1
Stage (3) fibrosis	16.1
Stage (4) fibrosis	9.5

1998-2003. Patients were excluded from the study if the histopathology report did not specify any of the collected histological features or if the clinical or laboratory data were missing.

The following histological parameters were collected: overall liver architecture, portal tract inflammation, interface hepatitis, cholestasis, bile duct injury, liver cell abnormalities, presence of steatosis, grade of inflammation, and stage of fibrosis according to the METAVIR liver histology classification system.[2] Advanced fibrosis was defined as a fibrosis score of 3 or 4.

The hospital computer database was then accessed and the following laboratory data were collected on each patient: WBC count, hemoglobin, mean corpuscular volume (MCV), platelet count, total bilirubin, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), and viral hepatitis serology.

Table 3 - Final diagnosis of all patients (n=502).

Final diagnosis	Frequency n (%)
Hepatitis C	246 (49.0)
Hepatitis B	82 (16.3)
Autoimmune hepatitis	40 (8.0)
Steatohepatitis	35 (7.0)
Non- specific hepatitis	35 (7.0)
Drug induced hepatitis	14 (2.8)
Normal biopsy	11 (2.2)
Hepatitis C and B	8 (1.6)
Granulomatous hepatitis	7 (1.4)
Primary biliary cirrhosis	5 (1.0)
Extrahepatic tissue	5 (1.0)
Tuberculosis	5 (1.0)
Hemochromatosis	3 (0.6)
Wilson disease	2 (0.4)
Congestive hepatopathy	2 (0.4)
Herpes hepatitis	1 (0.2)
Primary sclerosing cholangitis	1 (0.2)

Statistical analyses. The data was entered in MS Excel software. The Statistical Package for Social Sciences for personal computer was used for the statistical analyses. Categorical variables were compared by X^2 or Fisher exact test, while continuance variables were compared with the student's t test, for 2 independent groups.

Results. We identified 574 liver biopsies during the study period. Data were missing on 28 patients and so they were excluded from the study. In addition, 44 other patients were excluded from the analyses as they did not represent the primary goal of this analysis, which is primary liver disease. Of these 44 excluded patients, 4 had insufficient sample for histological analyses, 5 had extra-hepatic tissue, 15 had hepatocellular carcinoma, 10 had liver metastases, 1 had a hepatoblastoma, one had a cholangiocarcinoma, 1 had a neuroendocrine tumor, 1 had a carcinoid tumor, and 6 had lymphoma. All the following data is on the remaining 502 patients.

Of the 502 included patients, males were 58.6%. The mean age of the patients was 43.5 with the youngest patient being 13 years old and the oldest patient being 95 years old. The main histological and laboratory findings of the entire cohort of patients are shown in **Tables 1 & 2**.

The final diagnosis of the patients based on the liver biopsy and the clinical and laboratory parameters is shown in **Table 3**. Approximately half of the biopsies were performed for patients with hepatitis C,

Table 4 - Comparison between hepatitis C, hepatitis B, viral hepatitis, AIH, and non-specific hepatitis patients in laboratory features.

Features	Hep C	Hep B	*P* value	Non-specific	AIH	*P* value	AIH	Viral Hep	*P* value
Males (%)	59	75	0.004	45	37	0.47	37	63	0.001
Age	45	35	0.016	45	41	0.29	41	43	0.42
WBC (X10^9/L)	6.6	6.2	0.45	11.9	8.4	0.26	8.4	6.5	0.02
Hg (g/L)	136.7	142.4	0.013	117	120	0.45	120	138	0
Plt (X10^9/L)	200	212	0.197	265	240	0.26	240	203	0.002
T.Bili (umol/L)	13.94	11.77	0.42	44	81	0.15	81	13	0
Albumin (g/L)	36.59	38.86	0.004	31	30	0.33	30	37	0
ALP (U/L)	131	110	0.20	302	265	0.62	265	126	0
ALT (U/L)	112	99	0.14	91	252	0.002	252	109	0
AST (U/L)	74	56	0.008	71	273	0.001	273	69	0
GGT (U/L)	141	71	0.009	206	204	0.97	204	123	0

WBC - white blood cell, Hg - hemoglobin, MCV - mean corpuscular volume, T. Bili -total bilirubin, ALP - alkaline phosphate, ALT - alanine aminotransferase, AST - aspartate aminotransferase, GGT - gamma-glutamyl transpeptidase, Hep - hepatitis, Non-spec - non-specific, AIH - autoimmune hepatitis,

Table 5 - Comparison between hepatitis C, hepatitis B, viral hepatitis, AIH, and non-specific hepatitis patients in histological features.*

Features	Hep C	Hep B	*P* value	Non-specific	AIH	*P* value	AIH	Viral Hep	*P* value
Architecture distortion	20.3	11	0.03	14	22	0.35	22	18	0.56
Interface hepatitis	74	61	0.02	14	62	0	62	71	0.26
Cholestasis	0.8	2.4	0.37	20	12	0.38	12	1	0.03
Bile duct destruction	7.3	2.4	0.03	5	12	0.30	12	6	0.22
Steatosis	38	35	0.60	17	22	0.55	22	37	0.03
Inflammation Grade 1	19	42	0.0001	51	20	0.004	20	25	0.45
Inflammation Grade 2	49	31	0.004	40	35	0.65	35	44	0.23
Inflammation Grade 3	28	23	0.38	0	16	0	40	26	0.10
Inflammation Grade 4	3.7	2.4	0.531	8	5	0.54	5	3	0.69
Fibrosis Stage 0 or 1	33	59.7	0.001	36	30	0.69	30	34	0.72
Fibrosis Stage 2	40.7	23.2	0.002	25	35	0.38	35	36	0.87
Fibrosis Stage 3	21.5	15.9	0.24	5	25	0.01	25	19	0.47
Fibrosis Stage 4	4.8	1.2	0.39	34	10	0.01	10	11	0.84

*All numbers are percentages, Hep - hepatitis, Non-spec - non-specific, AIH -autoimmune hepatitis

followed by hepatitis B. Eight percent of the patients had autoimmune hepatitis (AIH), and 7% had non-alcoholic state hepatitis (NASH). Other less frequent diagnoses were also seen.

The main demographic, laboratory, and histological features of patients with hepatitis C, hepatitis B, AIH, and non-specific hepatitis are shown in **Tables 4 & 5.** We found that patients with hepatitis C had a mean age of 45 years and approximately 60% were males. The mean ALT was 112. On histology, typical histological features of hepatitis C were found in the majority of patients with no peculiar histological features. Most patients had either grade 2 or 3 inflammation (77%), while only a minority had grades 1 or 4. On the other hand, the majority of patients had stage 0 or 1 (33%) and stage 2 (40%) fibrosis while only approximately 27% had advanced fibrosis.

In patients with hepatitis B, the mean age was 35 years, significantly younger than patients with hepatitis C. Seventy-five percent of hepatitis B patients were males. The mean ALT was 99. Most patients had grade 1 (42%) and grade 2 (31%) inflammation. Most patients had stage 0 or 1 (59.7%) and stage 2 (23.2%) fibrosis with only approximately 17% having advanced fibrosis. We had 35 patients with NASH. These patients had normal CBC, normal

mean bilirubin, normal mean albumin, and normal mean ALP. They had an elevated mean ALT=124, AST=94, and GGT=203. On histology, more than 80% had infiltrated portal tracts, only 8% had interface hepatitis, 14% had cholestasis, while less than 5% had bile duct injury. The majority of the patients had only grade 1 inflammation. Interestingly, approximately half of these patients had more than stage 2 fibrosis with approximately 30% having cirrhosis exceeding patients with viral hepatitis. Patients with drug induced hepatitis were more likely to be males (64%), had a mean age of 47 years, a normal mean CBC, a mean bilirubin of 62, a mean ALP of 364, a mean ALT of 163, a mean AST of 94, and a mean GGT of 432. On histology, approximately 80% had portal tract inflammation, 28% had interface hepatitis, 14% had cholestasis, approximately 15% had bile duct injury, and approximately 35% had steatosis. Interestingly, approximately 50% of these patients had advanced fibrosis with 35% showing cirrhosis.

When patients with hepatitis B were compared to patients with hepatitis C, we found that patients with hepatitis B were approximately 10 years younger than patients with hepatitis C (p=0.01). They were 10% more likely to be males. There were no statistically significant differences between the 2 groups in terms of ALT, but patients with hepatitis B had significantly lower AST and GGT levels. Patients with hepatitis B were more likely to have grade 1 inflammatory changes while patients with hepatitis C were more likely to have grade 2. In terms of fibrosis, approximately 33% of patients with hepatitis B had stage 0 or 1 disease compared to 60% in hepatitis C (p=0.01), but overall, although patients with hepatitis C had more advanced fibrosis compared to patients with hepatitis B, this difference did not reach statistical significance. Results of comparisons between other groups of patient are found in **Tables 4 & 5**.

Discussion. Despite major advances in our understanding of many liver diseases and the development of new laboratory and radiological diagnostic techniques, assessing the liver tissue itself after obtaining a liver biopsy continues to be an integral part in the diagnosis of the majority of liver diseases. In patients with viral hepatitis, liver biopsy helps to exclude other forms of liver diseases, provide baseline histology for further reference, and predict responsiveness to antiviral therapy. More importantly, liver biopsy helps prognosticate the patient and hence reach more reasonable decisions regarding their need for antiviral therapy.[3] Liver biopsy in patients with AIH and cholestatic liver diseases is essential in confirming the positive serological markers and assessing severity of the liver disease. More and more experts are now also encouraging a liver biopsy in selected patients with NASH in which predictors of advanced fibrosis is present.

In this study, we have reviewed all the liver biopsies performed in our unit in the last 5 years. This revealed that the majority of our liver biopsies are performed on patients with viral hepatitis mainly hepatitis C. This is consistent with the majority of centers all over the world in which viral hepatitis has become the major liver pathology seen in daily practice.[4]

In an effort to find useful clinical predictive differences between viral hepatitis and other forms of hepatitis, we compared between viral hepatitis and AIH, viral hepatitis and non-specific hepatitis, AIH and non specific hepatitis in all laboratory and histological parameters. Other than specific disease diagnostic tests like viral serology and autoimmune markers we found no clinically meaningful differences between these groups although there were some statistically significant differences that we do not feel are particularly clinically useful **(Tables 4 & 5).**

We found no peculiar laboratory or histological features in our patients with hepatitis C compared to other published data except in the rate of fibrosis. In patients with hepatitis C, approximately 27% of patients had advanced fibrosis while only 5% had cirrhosis. This prevalence of cirrhosis in our series of hepatitis C patients is significantly lower than similar retrospective biopsy studies performed in Western countries reporting 17-55% rate of cirrhosis in chronic hepatitis C patients.[5] The difference between the 2 reported fibrosis scores may be secondary to the younger age of infection in our population compared to Western populations, a factor that has been shown to be associated with lower rates of progression to cirrhosis.[6,7] The low alcohol consumption rate in our community is also probably contributing to this low rate to cirrhosis. It is unlikely that this observation is secondary to differences in HCV genotypes given the well established observation of the absence of a significant effect of HCV genotype on the overall progression of liver disease and prognosis of patients with chronic hepatitis C.[5]

Our hepatitis B patients, as well, showed surprisingly low prevalence of advanced fibrosis (17%) with only one patient having cirrhosis. In addition, despite the fact that all of these patients had elevated liver enzymes at the time of biopsy, approximately 70% of them had only grade 1 or 2 inflammation. These findings are different from the published literature on HBeAg negative patients in which many studies have suggested that HBeAg negative patients (such as the majority of our patients) have a

more progressive course than patients with positive HbeAg.[8] For example, in a large series from the Mediterranean area, 29-38% of patients had cirrhosis at the time of their first presentation, at least double the rate of cirrhosis we have observed in our series.[9,10] Two possible explanations come to mind. First, the relatively younger age of our patients compared with the published literature. In most series, the median age of HBeAg negative patients was significantly older at presentation compared to HBeAg positive patients with typical age of 35-45 years,[8] while the median age in our series was 34 years. Second, recently much emphases has been focused on the effect of HBV genotype on the progression of liver disease and so, differences in HBV genotypes between our patients and the published literature could account for some differences in advanced fibrosis rates. Clearly, this data should not be generalized to assess the natural history of chronic hepatitis B and C in our general patient population due to the obvious referral bias and because a liver biopsy is typically performed in patients with signs of active liver disease (such as elevated ALT), who are expected to be more likely to progress to advanced liver disease compared to patients with normal ALT. Nevertheless, this data suggests that the rate of progression to advanced fibrosis is possibly lower in Saudi Arabia compared to what is reported in the international literature. A large prospective database is required to confirm this interesting and important observation. Meanwhile, our data supports the importance of a liver biopsy in patients with chronic viral hepatitis patients and calls for a more selective approach to the management of these patients especially in patients with hepatitis B where an effective treatment is still lacking.

Similarly, the high rate of advanced fibrosis in the NASH and drug induced hepatitis patients most likely reflects a referral bias rather than actual risk of cirrhosis as typically only patient who show evidence of active or advanced liver disease are biopsied.

Our study suffers from most traditional limitations of a retrospective analysis. In addition, error in interpreting the fibrosis score on liver biopsy is always a possibility. This could result from sampling error, from small biopsy size (not recorded in our study), and from inter- and intra-observer discrepancies which have been reported in approximately 10-20% of cases.[11] All these factors may overestimate, but usually underestimate the stage of fibrosis.

In conclusion, after reviewing all our liver biopsies over the last 5 years, we found that approximately half of our biopsies were performed for hepatitis C, followed by hepatitis B and AIH patients. Comparing hepatitis C and hepatitis B patients, hepatitis B patients were found to be younger but the rates of advanced fibrosis were comparable. The rate of cirrhosis and advanced fibrosis in both hepatitis C and hepatitis B patients was significantly lower than described in similar international studies.

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