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Clinical, Biochemical, Virological and Histopathological Profile of Incidentally Detected Hepatitis C

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Abstract:

Background and Aim*: Hepatitis C virus (HCV) is a major global health problem involving an estimated 185 million people.*

Hepatitis C follows a variable course with some patients developing fibrosis, cirrhosis and hepatocellular carcinoma while others have minimal or no significant liver disease. Clinical spectrum of these patients ranges from asymptomatic to full-fledged chronic liver failure and its complications. However a big group of patients which comes to hepatologist include incidentally detected HCV patients. These patients have normal/ deranged LFT, low to high viral load and other related parameters without any significant relation to liver histopathology. These patients form a big chunk of the group among HCV positive patients and these patients pose special problem both at health care facility and community level. Incidentally detected patients who otherwise are asymptomatic may have varied status of liver disease. The authors studied the clinical, biochemical, virological and histopathological profile of incidentally detected HCV positive patients.

***Methods**: From July 2011 to July 2013, thirty incidentally detected HCV positive patients were enrolled in the study in Division of Gastroenterology department of Medicine, Government Medical College Srinagar after getting an Ethical clearance from departmental Ethical committee. Their clinical, Biochemical, Virological and Histological parameters were noted.*

***Results**: 28 (93.33%) patients were asymptomatic and clinical examination was unremarkable in 26 (86.67%). Varices were present in 12 (40%) of patients. Genotype 3 was the most common genotype involving 25(83.33%) patients followed by genotype 4 (13.33%).*

Neither AST, ALT, AST/ALT ratio nor HCV RNA viremia reflects the histological liver changes accurately. APRI <0.5 rules out significant fibrosis while as APRI > or equal to1.5 predicts fibrosis.
Advanced stage of fibrosis was seen among genotype 1 patients. Predominant histological finding was steatosis, seen in 19 (63.33%) patients.

***Conclusion**: Most of the incidentally detected HCV positive patients are asymptomatic and have unremarkable clinical examination, however a significant number of them have asymptomatic portal hypertension. No clinical, biochemical, or virological indicator except for APRI is reliable in demonstrating the stage of liver fibrosis in patients with incidentally detected Hepatitis C. Liver biopsy remains the gold standard for evaluating the severity of fibrosis in incidentally detected Hepatitis C.*

Key words: incidentally detected Hepatitis C, Viral load, Genotype, Histopathology, APRI

Introduction:

Hepatitis C is pandemic with over 185 million patients all over the world infected with this virus[1]. It is the most common chronic blood borne infectious disease in United States[2]. The prevalence ranges from as low as 0.4% in Western Europe to as high as 22% in Egypt and Other parts of Afarica[3-5].

Infection with HCV has no boundaries and affects individuals from all walks of life ranging from children to elderly, with highest incidence from 20-49yrs, males out numbering females. The prevalence in children ranges from 0.05% to 0.4%. HCV infection was predominantly transmitted through parenteral (i.e. blood transfusion and I.V drug use before 1992) exposure. Sexual transmission is relatively uncommon route of transmission[6]. Defining natural history of hepatitis C is challenging because it is difficult to precisely define the onset of infection, the disease course is slow and may stretch over several decades and progression of disease is variable. It is further limited by the fact that the course of disease progression can be affected by age at the onset of infection, duration of infection, gender[7-9], race[10-11] and coexistence of other hepatic injuries (alcohol, NASH etc)[8]. Two to 24% patients develop cirrhosis after 20 years of infection[12]. Insights into natural history are provided by studies like Irish and German women infected with contaminated anti-D immunoglobulin[13,14].

Established or possible factors associated with progression of hepatic fibrosis include Age more than 40 years, Alcohal consumption, hepatitis B or HIV co infection, immunocompromised state, insulin resistance, obesity, severe hepatic necroinflammation, smoking , white race, increased

hepatic iron load, male gender, high ALT levels, and viral load and genotype [15-19]. Up to one half of anti-HCV-positive persons have a normal serum ALT levels at any given time, and ALT levels will remain normal for at least six months in 8% to 20% of them. HCV RNA levels, inflammation and fibrosis are lower in this class of patients[20]. Patients with humoral or cellular immune impairement have significantly higher rates of progression to cirrhosis[19,21,22]. Recurrence of HCV is almost universal in patients who undergo transplantation and who are positive for HCV RNA. Progression of hepatic fibroses is accelerated in HIV/HCV coinfected patients when compared with HCV mono infected patients [23,24]. 10.6% of co infected patients and 1.6% of monoinfected hemophiliac develop fibrosis. Viremia increases at least one log following transplantation. Majority of Fibrosing Cholestatic hepatitis patients progress to fibrosis**.** Assessment of liver disease severity is required prior to therapy. Identifying patients with cirrhosis is of particular importance as their likelihood of responding to therapy and post treatment prognosis depends on stage of fibrosis[25]. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT pattern. Though liver biopsy remains the reference method, it is an invasive choice carrying the risk of morbidity and mortality. To avoid biopsy alternative means of establishing information on the extent of fibrosis by focusing on noninvasive blood marker pannel are under investigation. These markers are useful for establishing two ends of fibrosis spectrum but less helpful in assessing the mid-ranges of fibrosis or for tracking of fibrosis progression[26]. Transient elastography that uses ultrasound and low frequency elastic waves to measure liver elasticity has improved the ability to define the extent of fibrosis without a liver biopsy, particularly if combined with other non invasive markers[27].

Methods:

Between July 2011 and July 2013 thirty consecutive patients of incidentally detected hepatitis C patients were investigated in Division of Gastroenterology, Department of medicine, Government Medical College Srinagar as per a set protocol after obtaining the Ethical committee clearance. Both inpatients and outpatients were included in the study. Only patients native to Kashmir valley were studied. Patients detected incidentally and recently, either as a part of routine investigations, evaluation of abnormal LFT, or pre-operative screening were enrolled in the study. Patients excluded from the study were those having diagnosed hepatitis C, patients with co-infection or super infection, organ transplantation, those with renal failure on dialysis, immunocompromised patients, those in whom liver biopsy could not be done or inadequate liver tissue was obtained. After proper patient selection a detailed history and clinical examination was done. All baseline investigations included haemogram, KFT, LFT, coagulation profile, complete hepatitis serology, AST/ALT ratio (AAR) and AST/Platelet ratio (APRI) noted. Detailed abdominal ultrasound and upper GI endoscopy done. Hepatitis C viral RNA (quantitative) and genotype was done by Real Time PCR using Cobas Ampliprep and Taqman. Liver biopsy was done using 18 Guage Baxter liver biopsy gun aiming at a tissue length of approximately 1.5 cms. Histopathological evaluation was performed by a single expert pathologist who knew the clinical and laboratory details of the patients. Necroinflammatory score (using Ishaq's modification of Knodel scoring) and Staging was done according to modified Ishak scoring. The total necro-inflammatory score (18) was divided into minimal (score 1-3), mild (4-8), moderate (9-12) and severe hepatitis (>13) score. Stages of fibrosis classified from stage 0- 6 with stage 0 having no fibrosis, stage 1 having only fibrous expansion of some portal areas with or without short fibrous

septa, stage 2 having fibrous expansion of most portal areas with or without short fibrous septa, stage 3 having fibrous expansion of most portal areas with occasional portal-portal(p-p) bridging, stage 4 in addition to stage 3 have portal-central (p-c) bridging, stage 5 having marked bridging (p-p and/or p-c) with occasional nodules and in stage 6 having cirrhosis.

Results

Mean age of presentation was 46.17 years with the range of 15-76 years. Mean age for males was 44.33yrs (range 15-70yrs) and for females the same was 48.92yrs (range 25-76yrs)

Eleven patients (36.67%) were detected on pre-operative screening, 10 patients (33.33%) were detected during evaluation of abnormal LFT, two patients were IV drug users, one each as blood donor and employment recruitment, one having abnormal liver appearance during surgery and three patients during were detected during family [Table 1]

All patients were asymptomatic. 86.67% patients had unremarkable clinical examination at presentation. One patient each had ascites and Prurigo nodularis. Almost 1/3rd of patients had normal AST/ALT.

More than two fold elevation of ALT/AST was found in 11 (36.67%) and 12 (40%) respectvely. 83.3% of patients had CTP class A , rest had CTP class B. No one was in class C. 2/3rd of patients (66.67%) had no features of portal hypertension on USG with normal echotexture of liver and normal portal vein size. 60% (n=18) had no varices, 23.33% (n=7) had grade I and 16.67% (n=05) had grade II varices. None of the patients had large varices[Table 2]

53.33% of CTP class A and 80% of class B patients had HCV RNA < 600,000IU/ml.

Mean HCV level in class A was 1648660 IU/ml (range 950-19800000IU/ml). Mean HCV RNA for child B was 347536IU (range 55-7901431 IU/ml).

Majority of studied patients had genotype 3; only 13.33 had genotype 1.

Biopsy: Child class A patients had mean necro-inflammation score of 5.32 with the range of 1-13, while as child class B had necro inflammation size of 5.50 with range of 3-9. Child class A patients had histological score of 5.32 with the range of 1-13, while as child class B had necro inflammation score of 5.50 with range of 3-9. Child class A patients had histological score of 2.24 (0-6) and child B had score of 5.60 (range 5-6).

Histopathological profile [Table 3]:

Liver architecture was maintained in 46.67% of cases and altered in 53.33%. Maximum number of patients with altered echotexture were in age group of 46-60yrs (26.67%).

Hepatocyte changes: 30% of studied population had unremarkable changes (20% males, 10% females). In both genders predominant changes were steatosis (10% males, 3.33% females). Ballooning was seen only in patients in the age group of 46-60yrs. Ballooning and steatosis were seen in patients in the age group of>46yrs. More severe changes were seen in patients with increasing age. Statistically significant correlation existed between hepatocyte changes and age group (p value 0.0)

Lobular inflammation :

Lobular inflammation was absent in 80% of cases especially in younger and older age group though it was not statistically significant.

Portal Tract Fibrosis:

It was absent in 33.33% of patients (16.67% males and 16.67% females). In the age group of $\leq$ 15 and $\geq$ 76, all the patients had periportal fibrosis. Most of the patients among lower age

group had absent portal tract fibrosis. Predominant age group involved was 46-60yrs (26.67%)

Bridging fibrosis :
It was absent in 46.67% of cases among which 30% were males and 16.67% were females.

Occasional portal to central fibrosis was seen in 6.67% and occasional portal to portal fibrosis was seen in 13.33% of cases while as the marked portal to portal fibrosis was seen in 33.33% cases. Less than 15yrs age group had absent bridging fibrosis. In the age group of 16-30yrs, 31-45yrs, 46-60yrs and 61-75yrs, bridging fibrosis was absent in 83.33%, 22.22%, 6.67% and 6.66% respectively. None of the patients above the age of 75yrs had ascitis or fibrosis.

Interphase hepatitis: it was absent in 23.35% of cases . mild, moderate and severe interphase hepatitis was seen in 36.67%, 36.67% and 3.33% of patients respectively.

All patients with age of $\leq$15yrs had mild interphase hepatitis whereas patients above 75yrs of age had moderate interphase hepatitis.

Necrosis:
Necrosis was absent in 36.67% of cases, spotty confluent in 60% and 3.33% respectively.

Cholestasis:
Cholestasis was absent in 26.67% of cases. Intrahepatic cholestasis was present in 13.33% of patients. Majority of patients had absent cholestasis irrespective age.

Ductular proliferation:
It was absent in 56.67% of cases and rest of the patients mild to moderate ductular proliferation. Moderate ductular proliferation was seen in patients of above 45yrs of age.

Lymphoid Follicle Formation:
It was present in 30% of patients and absent in 70% of cases. Iron staining of liver tissue was absent in all cases.

Cirrhosis:
No cirrhosis was found in 56.7%. occasional nodules were seen in 20% of patients, definite cirrhosis was seen in 10% of cases (13.33% males , 10% females)

Necroinflammatory score:
It ranged from 1-9 in males, 1-13 in females. Minimal score was seen in age group of 16-30yrs and maximum was seen in age group of 46-60yrs.

Staging:
Stage 0 was seen in 36.67% of cases, stage 1 in 20%, stage 2 and 3 in 3.33% each, stage 4 in 6.67%, stage 5 in 13.33% and stage 6 in 26.6% of cases.

There was no statistically significant correlation between HCV RNA and cirrhosis, necroinflammatory score and staging. (p value 0.772, 0.807 and 0.764)

36% of Genotype 3 had cirrhosis with occasional nodules in 20% and definite cirrhosis in 16%. Seventy five of genotype 4 had definitecirrhosis.

The results were analyzed using SPSS version 20 (USA), Student 't' test and Chi Square Test were used.

Discussion

The present study was a prospective Hospital based study conducted in post graduate Department of Medicine, Division of Gastroenterology, Government Medical College Srinagar and Associated hospitals. In this study, a total of thirty patients diagnosed incidentally for the first time as having Hepatitis C infection were included. Among them, 18 (60%) patients were

males and 12(40%) patients were females. 28 (93.33%) patients were asymptomatic without any liver disease or extra-hepatic disease, whereas 1 (3.33%) patient was admitted with symptoms suggestive of chronic liver disease (ascites) and 1 (3.33%) patient had prurigo nodularis. Graf J et al in 1996[28] studied 163 HCV positive patients and found that 85% of the patients were clinically asymptomatic. Wong et.al [29] also in their study of 140 HCV positive patients found that 69% had no clinical sign of chronic liver disease. Upper Gastrointestinal (UGI) endoscopy evaluation revealed that 12 (40%) patients had esophageal varices, whereas 18 (60%) of our patients had no varices. Out of 12 (40%) patients with oesophageal varices, 7 (58.33%) had grade I and 5 (41.66%) patients had grade II esophageal varices (using PAQUET classification for variceal grading). The review of literature reveals that 40% of the patients with compensated cirrhosis have esophageal varices on UGI endoscopy and 60% of the decompensated patients have varices on UGI endoscopy[30]. However the study quoted here has included all the patients of Chronic Liver Diseases(CLD) without any special stress on etiology.

The study of the patients with respect to *Child-Turcotte-Pugh Score* (CTP) class revealed that 25 (83.33%) patients were in CTP class A ,5 (16.67%) were in CTP class B, while none of the patients were in class C. However it deserves to be mentioned here that the 2(6.67%) patients who had ascites in our study belonged to CTP class B.

While studying the genotype in the patients population, we found that the genotype 3 was the most common present in 25 (83.33%) patients followed by genotype one, in four (13.33%). In one (3.33%) patient genotype couldn't be detected because of low viral load. We didn't study the patients for subtypes with regard to genotypes, the result of our study is in accordance to study conducted by Eric Chak et al[31]. They studied the diversity of HCV genotype in Northern India and found genotype 3 to be the most common followed by genotype 1. While studying the

genotype of our patients in relation to CTP class, we found that among genotype 3 patients, 22 (73.33%) patients had CTP class A and 3 (10%) patients had class B. Among the patients with genotype 1, 3 (10%) had CTP class A and 1 (3.33%) patient had CTP class B. An extensive search of the literature didn't revealed a single study wherein the genotype had been studied with respect to CTP class.

20 (66.67%) patients had HCV RNA < 600000 I.U/mL (0.6×10^6 I.U/mL), 8 (26.56%) patients had HCV RNA levels between 600000 I.U/mL and 3,000000 I.U/mL (0.6×10^6 to 3×10^6 I.U/mL) and 2 (6.67%) patients had HCV RNA >3000000 I.U/mL(>3×106 I.U/mL). While studying HCV RNA in relation to Genotype, we observed that among genotype 1 patients, two (6.67%)patients had HCV RNA < 600000 I.U./mL, 1(3.33%) patient had HCV RNA >3000000 I.U./mL and 1(3.33%) patient had HCV RNA in between 2400001 I.U./mL and 3000000 I.U./mL. Among genotype 3 patients, 17(53.67%) patients had HCV RNA < 600000 I.U./mL, 1 (3.33%)patient had HCV RNA > 3000000 I.U./mL and 7(23.33%) patients had HCV RNA in between 600000 I.U./mL to 3000000 I.U./mL. Minimum and maximum HCV RNA among genotype 1 patients (total 4 patients) were 93695 I.U./mL and 19800000 I.U./mL respectively whereas minimum and maximum HCV RNA among genotype 3 patients (total number 25) were 950 I.U./mL and 5953470 I.U./mL respectively. Mean HCV RNA viral load in genotype 1 was 5721753.00 I.U./mL and in genotype 3 was 802684.48 I.U./mL. Overall minimum HCV RNA load was 55I.U/ ml(genotype could not be detected in one patient because of low viral load).

In our study mean HCV RNA levels among patients with genotype 1 were higher than genotype 3. The correlation is significant at the 0.05 level (2-tailed). Anita Chakravarti et al in 2011[32] studied the distribution pattern of HCV genotype and its association with viral load in their study and they found that average viral load of the patients infected with genotype

1 was significantly higher than average viral load of the patients infected with genotype 3 and 2. The result of our study are in accordance to the above mentioned study.

The parameters that were studied on liver biopsy tissue were (i) Liver architecture (ii) Hepatocyte changes (iii) Portal tract inflammation (iv) Lobular inflammation (v) Portal tract fibrosis (vi) Bridging fibrosis (vii) Interface hepatitis, (viii) Necrosis, (ix) Cholestasis (x) Ductular proliferation (xi) Lymphoid follicle formation (xii) Cirrhosis (xiii) Necroinflammatory score and (xiv) Staging (using modified Ishak classification for liver fibrosis).

We observed that liver architecture was maintained in 14 (46.67%) patients and it was altered in 16 (53.33%) patients. Hepatocytes were unremarkable in 9 (30%) patients, ballooning in 2 (6.67%) patients, steatosis in 12 (40%) patients and ballooning with steatosis in 7 (23.33%) patients. Portal tract showed mild chronic inflammation in 5 (16.67%) patients, moderate chronic inflammation in 16 (53.33%) patients and severe / dense chronic inflammation was seen in 9 (30%) patients. Lobular inflammation was absent in 24 (80%) patients and present in 6 (20%) patients. Portal tract fibrosis was absent in 10 (33.33%) patients and was present in 5 (16.67%) patients with periportal fibrosis in 15 (50%) patients. Bridging fibrosis was absent in 14 (46.67%) patients, occasional portal to central fibrosis in 2 (6.67%) patients, occasional portal to portal fibrosis in 4 (13.33%) patients whereas marked portal to portal fibrosis was seen in 10 (33.33%) patients. Interphase hepatitis was absent in 7 (23.33%) patients with mild, moderate and severe interface hepatitis was seen in 11 (36.67%), 11 (36.67%) and 1 (3.33%) patients respectively. Necrosis was absent in 11 (36.67%) patients with spotty necrosis in 18 (60%) patients and confluent necrosis in 1 (3.33%) patient. Cholestasis was absent in 26 (86.67%) patients and intrahepatic cholestasis was present in 4 (13.33%) patients. Ductular proliferation was absent in 17 (56.67%) patients, mild in 10 (33.33%) patients,

and moderate in 3 (10%) patients. Lymphoid follicle formation was absent in 21 (70%) and present in 9 (30%) patients. Iron stain for liver tissue was negative in all the cases. Cirrhosis was absent in 17 (56.67%) of the cases, occasional nodule were seen in 6(20%) and definite cirrhosis was seen in 7 (23.33%) cases. Necroinflammatory score of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 13 were seen in 2 (6.67%), 5 (16.67%), 4 (13.3%), 3 (10%), 1 (3.33%), 4 (13.33%), 4 (13.33%), 3 (10%), 4 (13.33%) and 1 (3.33%) cases respectively. Necroinflammatory score of 1 was seen in one case (3.33%) who was 28 years old and was intravenous drug abuser and had HCV genotype 3. In patients with necroinflammatory score of 2, the patient's ages were 15, 30, 32, 35 and 70 years. Maximum necroinflammatory score of 13 was seen in 47 years old female who had prurigo nodularis as an extrahepatic manifestation of chronic hepatitis C. The youngest patient in our study was 15 years old and had necroinflammatory score of 2. He was a diagnosed case of leukemia and had received multiple blood transfusions since the age of 5. In our study, among the patients with age less than 45 years, 10(76.92%) patients had necroinflammatory score ≤5 and only 3(23.08%) patients had necroinflammatory score of more ≥6. Among patients with age ≥46 years, 13(76.47%) patients had necroinflammatory score of ≥6 and only 4(23.52%) patients among this group had necroinflammatory score ≤5. In our study there was statistically significant correlation exist between necroinflammatory score and age of the patients (p value 0.01). An extensive search of literature did not show any study in which necroinflammatory score has been studied in relation to the age.

Staging (modified Ishak) of 0, 1, 2, 3, 4, 5 and 6 were seen in 11 (36.67%), 3 (10%), 1 (3.33%), 1 (3.33%), 2 (6.67%), 4 (13.33%) and 8 (26.67%) cases respectively. All the patients with fibrosis score of 6 were of age >31 years. Among patients with age ≤45 years, 11(84.61%) patients had Ishak staging <2. Among patients with age of ≥ 46 years, 13 patients (76.47%)

had Ishak staging ≥ 3. Statistically significant correlation existed between Ishak staging and age (p value <0.05). The result of our study are in accordance to the study conducted by Wong et al[29] in 1997 in which they concluded that increasing age was associated with liver fibrosis. Moreover in our study a significant correlation was seen between necroinflammatory score and Ishak staging (p <0.01). However, review of literature revealed that Activity grade, which represents the necrosis feature, is not a good predictor of fibrosis progression and fibrosis alone is the best marker of ongoing fibrogenesis. Fibrosis stage and inflammatory grade are correlated but for approximately one-third of patients, there is discordance[33].

In our study steatosis was seen in 19(63.33%) patients (steatosis 40% and ballooning with steatosis in 23.33%). The results of our study are in accordance with the study conducted by N. Khokhar et al in 2004 in which they studied a total of 109 liver biopsy samples and found that nearly 62% of their liver biopsy samples had some degree of steatosis[30].

Out of 20 (66.67%) patients with HCV RNA <600000 I.U/mL, 8 (26.67%) cases had Ishak stage 0 and 6 (20 %) cases had Ishak stage 6 whereas 1 (3.33%) each had Ishak staging of 1, 3, 4 and 3 (10%) had score of 5 respectively. Out of 2(6.67%) patients who had HCV RNA >3000000 I.U./mL, 1 (3.33%) patients had stage 0 and 1(3.33%) patients had stage 6. Statistically no significant correlation existed between HCV RNA (quantitative) and staging. The results of our study are in accordance with the study conducted by Saleem et. al in 2002[34] in which they evaluated fifty five patients of chronic hepatitis C and liver biopsies were performed and staged according to Knodell's histological activity index system. In their study, 5 patients had mild, 43 had moderate and 7 had severe viremia. Seven patients had minimal disease, 9 had mild, 22 had moderate and 17 had severe chronic hepatitis. Eight patients had no fibrosis, 20 had fibrous portal expansion, 19 had bridging fibrosis, and 8 patients had cirrhosis. No significant

correlation was found between serum HCV RNA levels and histopathological grade or stage of the disease, with correlation coefficients of rs = -.054 and .034 respectively. Moreover, no individual component of the HAI correlated with serum HCV RNA levels. Further in their study they concluded that serum HCV RNA level does not determine the degree of hepatic injury precisely and liver biopsy is necessary to accurately evaluate the extent of liver damage. In the study performed by Fanning L et al[35] in 1999 no significant correlation was observed between serum viral load and degree of fibrosis.

Out of 20(66.67%) of the patients with HCV RNA <600000 I.U/ml, 1(3.33%) had necroinflammatory score of 1 and 1(3.33%) had necroinflammatory score of 13. 4(13.33%), 3(10%), 2(6.67%), 3(10%), 1(3.33%), 1(3.33%) and 4(13.33%) patients had necroinflammatory score of 2, 3, 4, 6, 7, 8, and 9 respectively. The patients who had HCV RNA >3000000 IU/ml, had necroinflammatory score of 3 and 1(3.33%) had score of 6. Statistically no significant correlation exist between HCV RNA (quantitative) and necroinflammatory score. The result of our study is consistent with study performed by Reddy DW et al[36] (1998) in which they studied 73 chronic hepatitis C patients and found no correlation between necroinflammatory score and serum HCV RNA levels. Study done by Y.S. Lee[37] in 2001 found no statistical relationship between HCV RNA titer and HAI score. Saleem et al (2002)[34] also found no correlation between serum HCV RNA and histopathology grades. However in the study performed by Fanning L et al[35] found a weak but statistically significant correlation (rs=.26;P <0.05) between serum viral load and degree of inflammation.

In our study among 7(23.33%) patients with definite cirrhosis, 5(16.67%) had HCV RNA <600000 I.U/ml where as only one (3.33%) had HCV RNA >3000000 IU/ml and 3.33% had HCV RNA in between 2400000 and 300000 IU/ml. So according to our study, majority of the patients with definite cirrhosis had viral load less than 600000 I.U/ml. This

observation of our study is in accordance to the study conducted by Adinolfi LE in 2001[38] in which they studied 298 patients of different genotypes and evaluated the role of HCV RNA levels and host factors in the severity of liver injury. They observed that cirrhotic patients had significantly lower levels of viremia than those with chronic hepatitis with a similar *Histological Activity Index* (HAI) .

Among 4(13.33%) patients with genotype 1 ,one (3.33%)patient had Ishak stage 1, and three (10%) patients had stage 6 i.e. 3 (75%) of the patients among genotype 1 had Ishak stage 6 whereas only 1(25%) cases among genotype 1 had Ishak stage 1 whereas among genotype 3 , ten (33.33%) patients (i.e.40% among genotype3) had Ishak stage 1 and six (20%) had Ishak stage 6 (i.e.24% among genotype3). For comparision purpose, staging was divided into two parts[39], (I) none to mild fibrosis (score 0-3) and (II) extensive fibrosis to cirrhosis (score 4-6) and the total necroinflammatory score was divided into following groups[40]: (I) minimal hepatitis (score1-3), (II) mild hepatitis (score 4-8), (III) moderate hepatitis(score 9-12) and (IV) severe hepatitis(score 13-18). As per this division, all the cases with genotype 1 in our study were in minimal to mild hepatitis group (score 0-8) whereas among patients infected with genotype 3, 24 (80%) were in minimal to mild hepatitis group (score 1-8) and 6(20%) were in moderate to severe hepatitis group (score of 9-18). Maximum necroinflammatory score in cases with genotype 1 and genotype 3, were 7 and 13 respectively. Among genotype 1, three patients (10%) i.e. 75% among genotype 1, had extensive fibrosis to cirrhosis (score 4-6) and among genotype 3, 18(60%) had none to mild fibrosis (score 0-3). The result of our study for Ishak staging (fibrosis) for genotype 3 are in accordance with the study done by Sompal Singh et al in 2010[40] in which they found that out of the 19 patients infected with genotype 3, 10(52.6%) were in none to mild fibrosis (score1-3), whereas 9(47.4%) were in extensive fibrosis to cirrhosis group (Ishak stage 4-6). Among patients

infected with genotype 3, 13(68.4%) were in minimal to mild hepatitis group (score 1-8), whereas 6(31.6%) were in moderate to severe hepatitis group (9-18). All cases (100%) with genotype 1 infection were in moderate to severe hepatitis group (score 9-18) in contrast to our study. All cases (100%) with genotype 1 infection in their study showed extensive fibrosis to cirrhosis (score 4-6). In contrast to above mentioned study (Sompal Singh et al)[40] the study conducted by Y.S.Lee et al in 2001[37] in which they studied 34 patients with genotype 1 and genotype 2 and found that HCV genotype had no significant correlation with RNA titers, HAI score or with serum ALT levels. None of the patient in this study was of genotype 3.

Among 9 (30%) patients with normal Alanine Amino Transferase (ALT), 5 (16.67%) patients had no fibrosis (Ishak stage 0), whereas 3 (10%) patients had incomplete to definite cirrhosis (Ishak staging score of 5 & 6) and 1 (3.33%) patient in this group had Ishak score of 3 while in patients with ALT >160 U/L , one patient (3.33% patients) had no fibrosis (Ishak score 0) . Thus we observed that a person with even normal ALT can have definite cirrhosis where as a person with ALT >4UNL can have no fibrosis/cirrhosis. Among patients with ALT < 40 U/L, Necroinflammatory score of 1, 2, 3, 4, 6 and 9 was seen in 1 (3.33%), 1 (3.33%), 2 (6.67%), 2 (6.67%), 2 (6.67%) and 1 (3.33%) cases respectively. Among patients with ALT > 161, necroinflammatory score of 6 was seen in 1(3.33%) patient.

In our study among 11 (36.67%) patients with normal aspartate aminotransferase (AST) , 6 (20%) patients had no fibrosis (Ishak stage 0), whereas 3 (10%) patients had definite cirrhosis (Ishak staging score of 6), 1 (3.33%) patient in this group had Ishak score of 3. Among patients with AST >161 U/L one (3.33%) patients had definite cirrhosis (Ishak staging score of 6). It is observed that all the patients with AST >100U/L had Ishak staging score ≥4. It is thus concluded that a person with normal AST as well as AST >100 U/L can have definite cirrhosis. Necroinflammatory score of 1, 2, 3, 4, 6 and 9

was seen in 1(3.33%), 1 (3.33%), 4 (13.33%), 8 (26.67%), 2 (6.67%) and 1 (3.33%) cases respectively. Among patients with AST > 161 necroinflammatory score of 9 was seen in one patient.

It is thus concluded from our study that neither serum Aspartate Amino Transferase (AST) nor serum Alanine Amino Transferase **(**ALT) ALT can predict or exclude liver fibrosis.

Review of literature regarding the correlation of serum transaminase levels with histopathology of liver revealed conflicting results and are summariesd as under:

Zechini B et al (2004)[41] performed a retrospective study on 112 patients with chronic hepatitis C. They found a statistically significant correlation between histological activity index (HAI) and both baseline AST and ALT levels i.e. higher the transaminase levels higher the histological activity index (HAI). Further they also concluded that the fibrosis score was significantly and independently associated with baseline AST and ALT values i.e. higher the transaminase levels higher the fibrosis score.

Bartos V et al (2007)[42] retrospectively studied 58 chronically HCV-infected adult patients who had undergone core needle liver biopsy to determine the predictive value of ALT, AST levels and AST/ALT ratio compared to histological grading and staging in patients with chronic hepatitis C. They found that most patients with chronic hepatitis C manifested only mild histological findings. In their study they concluded that although liver enzymes levels in general, corresponded with the activity of the disease, even a normal level did not exclude a serious histological liver damage. It was because of this finding that they recommended to perform a liver biopsy prior to therapy. The results of our study are similar to this study.

Gebo et al (2002)[43] carried a systematic review in which they studied the results of Studies on Serum Aminotransferases (performed between January 1985 to March

2002).They found that serum ALT was associated with fibrosis stage in 11 of 15 studies, with sensitivity ranging from 61% to 71%and specificity ranging from 66% to 94%. Serum ALT as a single marker of fibrosis showed areas under the curve of 0.75 or less by receiver operating characteristic (ROC) analysis. They concluded that the studies were relatively consistent in showing that serum aminotransferases have only modest value in predicting fibrosis on liver biopsy (Evidence Grade B).

Reham Al Swaff et al in 2012[44] studied the correlation between alanine aminotransferases level, HCV-RNA titer and fibrosis stage in chronic HCV genotype 4 infections. They studied 138 patients and it was concluded that neither ALT level nor HCV viremia can reflect the histological liver change accurately. Moreover they recommended that liver biopsy or other noninvasive procedures that measure liver stiffness (i.e. Fibroscan) remain essential for accurate staging of liver fibrosis in patients with genotype 4 chronic HCV infection (this study may not apply to our population as none of the patients in our study was of genotype 4). The result of this study were similar to our study however in this study they studied only genotype 4 while as in our study patients have infected with genotype 1 and genotype 3.

Conclusion

Majority of chronic hepatitis C patients are asymptomatic at presentation.

No clinical, biochemical, viorological or radiological data studied in our study except for Asparatate Amiotransferase to Platelet Ratio Index (APRI) is reliable in discriminating stage of liver fibrosis in patients with chronic hepatitis C.

APRI (Asparatate Amiotransferase to Platelet Ratio Index) <0.5 rules out significant fibrosis whereas APRI ≥1.5 suggests significant fibrosis.

Advanced stage of fibrosis is seen in patients of genotype 1.

Age and duration of infection are major variable to be considered.

Liver biopsy remains gold standard for evaluating the severity of chronic hepatitis C precisely.

The final message of the study is that even if patients are diagnosed incidentally for hepatitis C they always have some type of biochemical, virological and histological abnormality, some even have an advanced liver disease. No patient of incidentally detected hepatitis C is having normal melio. Hence we recommend that all of them should be thoroughly evaluated for status of liver disease and treated with appropriate regimens.

REFRENCES:

1. Khayriyyah Mohd Hanafiya, Justina Groeger, Abraham D, Flaxman and Steven T Wiersma. Hepatology 2013; 57:1333-1342.
2. Alter MJ. The epidemiology of acute and chronic hepatitis C. Clin. Liver Dis 1997;1:559.
3. Bialek SR, Terrault NA. The changing epidemiology and natural history of Hepatitis C virus infection. Clin Liver Dis 2006; 10: 679.
4. Tauzet s, kraemer L, Collin C, et. al. Epidemiology of hepatitis C virus in seven Europian Union countries: a critical analysis of literature. HENCORE Group. Hepatitis Europian Network for cooperative research. Eur J Gastroenterol Hepatol 2000;12:667.
5. Grebely J, Conway B, Raffa JD, et t. Hepatitis C virus infection in injection drug users. Hepatology 2006; 44: 1139.
6. Alter MJ, Hadler SC, Judson CN et al. Risk factors for acute non-A, non-B hepatitis in United State and

association with chronic hepatitis C infection. JAMA 1990;264 (17):2231-5.

7. Poynard T, bedossa P, Opolan P; For the OBSVERC, METAVIR, CLINIVIR and DOSVIRC Groups. Natural history of liver fibrosis progression in chronic hepatitis C. Lincet 1997;349:825-32.
8. Wright M, Goldin R, Fabre A et al. Measurement and determinants of the natural history of liver fibrosis in hepatitis C virus infection; a cross sectional and a longitudinal study. Gut 2003; 52: 574-9.
9. Ratziu V, Munteanu M, Charlotte F et al. LIDO Study Group. Fibrogenic impact of high serum glucose in chronic hepatitis C. J Hepatol 2003; 39:1049-55.
10. Wiley TE, Brown J, Chan J. hepatitis c virus infection in African Americans: its natural history and histological progression. Am J Gastroenterol 2002;97:700-6.
11. Sterling RK, Stravitz RT, Luketic VA et al. a comparison of the spectrum of chronic hepatitis C virus between Caucasians and African Americans. Clin Gastroenterol Hepatol 2004;2:469-73.
12. Freeman AJ, Dore GJ, Law MG, et al: Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001; 34:809-16.
13. Kenny-Walsh E: Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. *N Engl J Med* 1999; 340:1228-33.
14. Wiese M, Berr F, Lafrenz M, et al: Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: A 20-year multicenter study. *Hepatology* 2000; 32:91-6.
15. Poynard T, Ratziu V, Charlotte F, et al: Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. *J Hepatol* 2001; 34:730-9.

16. Wiley TE, Brown J, Chan J: Hepatitis C infection in African Americans: Its natural history and histological progression. *Am J Gastroenterol* 2002; 97:700-6.
17. Missiha SB, Ostrowski M, Heathcote EJ: Disease progression in chronic hepatitis C: Modifiable and nonmodifiable factors. *Gastroenterology* 2008; 134:1699-714.
18. Chang MH, Chen CJ, Lai MS, et al: Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997; 336:1855-9.
19. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008; 57(RR-08):1-20.
20. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep* 1991; 40(RR-13):1-25.
21. Hoofnagle JH, Schafer DF: Serologic markers of hepatitis B virus infection. *Semin Liver Dis* 1986; 6:1-10.
22. Lopez P, Rubiano L, del Pilar Rubio M, et al: Immunogenicity and reactogenicity of DTPw-HB/Hib vaccine administered to Colombian infants after a birth dose of hepatitis B vaccine. *Expert Rev Vaccines* 2002; 1:277-83.
23. Chao M, Hsieh SY, Taylor J: Role of two forms of hepatitis delta virus antigen: Evidence for a mechanism of self-limiting genome replication. *J Virol* 1990; 64:5066-9.
24. EASL Clinical Practice Guidelines. Management of hepatitis C virus infection. Journal of Hepatology 2011;55:245-264.
25. Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology 2002; 36(Suppl): S152-S160.*

26. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. *Hepatology 2006; 43 (Suppl): S113-S120.*
27. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M, Palau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol 2003; 29: 1705-1713.*
28. Graf J, Toriyama K, Itakura H. A clinico-pathological study of 163 untreated cases of chronic hepatitis C. *Rev Soc Bras Med Trop. 1996 Jan-Feb; 29(1):21-5.*
29. Wong V et al. Importance of age in chronic hepatitis C virus infection. *J Viral Hepat. 1997 Jul;4(4):255-64.*
30. N. Khokhar, M. Mushtaq, A. S. Mukhtar, F. Ilahi. Steatosis and Chronic Hepatitis C Virus Infection. *JPMA 2004; 54: 110.*
31. Eric Chak, Andrew H. Talal, Kenneth E. Sherman. Diversity of genotype in Northern India. *Saudi Journal of Gastroenterology 2011; Volume 17, Issue 4: Page 241-244.*
32. Anita Chakravarti, Gaurav Dogra, Vikas Verma, and Amit Parkash Srivastava. Distribution pattern of HCV genotypes & its association with viral load. *Indian J Med Res. 2011 March; 133(3): 326–331.*
33. Rubbia-Brandt L, Leandro G, Spahr L, Giostra E, Quadri R, Malé PJ, Negro F. Liver steatosis in chronic hepatitis C: a morphological sign suggesting infection with HCV genotype 3.*Histopathology 2001; 39:119-124.*
34. Saleem N, Mubarik A, Qureshi AH, Siddiq M, Ahmad M, Afzal S, Hussain AB, Hashmi SN. Is there a correlation between degree of viremia and liver histology in chronic hepatitis C. *J Pak Med Assoc. 2004 Sep; 54(9): 476-9.*
35. Fanning L, Kenny E, Sheehan M, Cannon B, Whelton M, O'Connell J, Collins JK, Shanahan F. Viral load and clinicopathological features of chronic hepatitis C (1b) in

a homogeneous patient population. Hepatology. 1999 Mar; 29(3):904-7

36. Reddy, K. Rajender, Teresa L. Wright, Paul J. Pockros, Mitchell Shiffman, Gregory Everson, Robert Reindollar, Michael W. Fried et al. "Efficacy and safety of pegylated (40-kd) interferon α-2a compared with interferon α-2a in noncirrhotic patients with chronic hepatitis C." *Hepatology* 33, no. 2 (2001): 433-438.
37. Y. S. Lee, S. K. Yoon, E. S. Chung, S. H. Bae, J. Y. Choi, J. Y. Han, K. W. Chung, H. S. Sun, B. S. Kim, and B. K. Kim. The relationship of histologic activity to serum ALT, HCV genotype and HCV RNA titers in chronic hepatitis C. *J Korean Med Sci. 2001 October; 16(5): 585–591.*
38. Adinolfi LE, Utili R, Andreana A, Tripodi MF, Marracino M, Gambardella M, Giordano M, Ruggiero G. Serum HCV RNA levels correlate with histological liver damage and concur with steatosis in progression of chronic hepatitis C. *Dig Dis Sci. 2001 Aug; 46(8):1677-83*
39. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, et al. Histological grading and staging of chronic hepatitis. *J Hepatol 1995; 22: 696-699.*
40. Sompal Singh, Ruchika Gupta, Veena Malhotra, Shiv K Sarin. Predictors of histological activity and fibrosis in chronic Hepatitis C infection: A study from North India. *Indian Journal of Pathology and Microbiology 2010; 53(2): 238-243.*
41. Zechini B et al. Correlation of serum aminotransferases with HCV RNA levels and histological findings in patients with chronic hepatitis C: the role of serum aspartate transaminase in the evaluation of disease progression. *Eur J Gastroenterol Hepatol. 2004 Sep; 16(9): 891-6.*
42. Bartos V, Krkoska D, Slavik P, Lauko L, Adamkov M. Histological status of the liver in relation to serum

aminotransferase levels in patients with chronic hepatitis C. *Bratisl Lek Listy. 2007; 108(12):522-5*

43. Kelly A. Gebo, H. Franklin Herlong, Michael S. Torbenson, Mollie W. Jenckes, Geetanjali Chander, Khalil G. Ghanem, Samer S. El-Kamary, Mark Sulkowski, and Eric B. Bass. Role of Liver Biopsy in Management of Chronic Hepatitis C: A Systematic Review. *Hepatology, November 2002*
44. Bartos V, Krkoska D, Slavik P, Lauko L, Adamkov M. Histological status of the liver in relation to serum aminotransferase levels in patients with chronic hepatitis C. *Bratisl Lek Listy. 2007; 108(12):522-5*

ABREVATIONS:

1. AAR- AST/ALT Ratio
2. AASLD- American Association For Study Of Liver Diseases
3. ALT- Alanine Aminotransferase
4. ALP-Alkaline Phosphatase
5. APRI- Aminotransferase/Platelet Ratio Index
6. AST- Aspartate Aminotransferase
7. CBC-Complete Blood Counts
8. CHC- Chronic Hepatitis C
9. CTP -Child Turcotte Pugh score
10. HAI- Histology activity index
11. HBV- Hepatitis B virus
12. HCC- Hepatocellular Carcinoma
13. HCV –Hepatitis C Virus
14. HIV- Human Immunodeficiency Virus
15. LFT-Liver Function Test
16. NASH- Non alcoholic steatohepatitis
17. PCR- Polymerase chain reaction
18. RNA- Ribonucleic acid
19. SVR-Sustained virological response

Table – 1: Factors which lead to detection of HCV (n=30)

Factors which lead to detection of HCV	Gender		Total
	Male	Female	
Routine screening during blood transfusion	01 (3.33%)	00 0.00%	01 (3.3%)
Rountine screening at employment recruitment	01 (3.33%)	00 0.00%	01 (3.3%)
Family screening	02 (6.67%)	01 (3.33%)	03 (10%)
Screening of i/v drug abuser	02 (6.67%)	00 0.00%	02 (6.67%)
Screening prior to surgery/other surgical procedures	06 (20%)	05 (16.67%)	11 (36.67%)
First time presented as CLD	01 (3.33%)	00 0.00%	01 (3.3%)
Abnormal LFT during base line investigation for some other surgical reasons	05 (16.67%)	05 (16.67%)	10 (33.33%)
Intraoperative observation of Abnormal appearance of liver	00 (0.00%)	01 (3.33%)	01 (3.33%)
Total	**18 (60%)**	**12 (40%)**	**30 (100%)**

Table – 2: Esophageal varices (n=30)

Gender	Esophageal varices			Total
	Absent	Grade 1	Grade 2	
Male (no/%)	10 (33.33%)	04 (13.33%)	04 (13.33%)	18 (60%)
Female (no/%)	08 (26.67%)	03 (10%)	01 (3.33%)	12 (40%)
Total	18 (60%)	07 (23.33%)	05 (16.67%)	30 (100%)

Table – 3: Histopathological Profile of the Studie Population (n=30)

Histolopathology parameters		Gender			Age Group (Years)					
		Male	Female	Total	= 15	16-30	31-45	46-60	61-75	=>76
liver architecture	maintained	09 (30%)	05 (16.67%)	14 (46.67%)	00 0.00%	05 (16.67%)	04 (13.33%)	03 (10%)	02 (6.67%)	00 0.00%
	altered	09 (30%))	07 (23.33%)	16 (53.33%)	01 (3.33%)	01 (3.33%)	02 (6.67%)	08 (26.67%)	03 (10%)	01 (3.33%)
hepatocytes change	Un-remarkable	06 (20%)	03 (10%)	09 (30%)	01 (3.33%)	04 (13.33%)	02 (6.67%)	01 (3.33%)	01 (3.33%)	00(0.00%)
	Ballooning	02 (6.67%)	00 0.00%	02 (6.67%)	00 0.00%	00 0.00%	00 0.00%	02 (6.67%)	00 0.00%	00 0.00%
	Steatosis	07 (23.33%)	05 (16.67%)	12 (40%)	00 0.00%	02 (6.67%)	04 (13.33%)	04 (13.33%)	02 (6.67%)	00 0.00%
	Ballooning with steatosis	03 (10%)	04 (13.33%)	07 (23.33%)	00 0.00%	00 0.00%	00 0.00%	04 (13.33%)	02 (6.67%)	01 (3.33%)

Lobular inflamation	Absent	15 (50%)	09 (30%)	24 (80%)	01 (3.33%)	05 (16.67%)	05 (16.67%)	08 (26.67%)	04 (13.33%)	01 (3.33%)
	Present	03 (10%)	03 (10%)	06 (20%)	00 0.00%	01 (3.33%)	01 (3.33%)	03 (10%)	01 (3.33%)	00 0.00%
Portal Tract Fibrosis	Absent	05 (16.67%)	05 (16.67%)	10 (33.33%)	00 0.00%	04 (13.33%)	03 (10%)	01 (3.33%)	02 (6.67%)	00 0.00%
	Portal tract fibrosis	05 (16.67%)	00 0.00%	05 (16.67%)	00 0.00%	02 (6.67%)	01 (3.33%)	02 (6.67%)	00 0.00%	00 0.00%
	Periportal fibrosis	08 (26.67%)	07 (23.33%)	15 (50%)	01 (3.33%)	00 0.00%	02 (6.67%)	08 (26.67%)	03 (10%)	01 (3.33%)
bridging fibrosis	Absent	09 (30%)	05 (16.67%)	14 (46.67%)	01 (3.33%)	05 (16.67%)	04 (13.33%)	02 (6.67%)	02 (6.67%)	00 0.00%
	Occasional portal to central	01 (3.33%)	01 (3.33%)	02 (6.67%)	00 0.00%	00 0.00%	00 0.00%	02 (6.67%)	00 0.00%	00 0.00%
	Occasional portal to portal	02 (6.67%)	02 (6.67%)	04 (13.33%)	00 0.00%	01 (3.33%)	01 (3.33%)	02 (6.67%)	00 0.00%	00 0.00%
	Marked portal to portal	06 (20%)	04 (13.33%)	10 (33.33%)	00 0.00%	00 0.00%	01 (3.33%)	05 (16.67%)	03 (10%)	01 (3.33%)
Interphase Hepatitis	Absent	04 (13.33%)	03 (10%)	07 (23.33%)	00 0.00%	03 (10%)	02 (6.67%)	01 (3.33%)	01 (3.33%)	00 0.00%
	Mild	07 (23.33%)	04 (13.33%)	11 (36.67%)	01 (3.33%)	02 (6.67%)	03 (10%)	04 (13.33%)	01 (3.33%)	00 0.00%
	Moderate	06 (20%)	05 (16.67%)	11 (36.67%)	00 0.00%	00 0.00%	01 (3.33%)	06 (20%)	03 (10%)	01 (3.33%)
	Severe	01 (3.33%)	00 0.00%	01 (3.33%)	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	00 0.00%	00 0.00%
Necrosis	Absent	07 (23.33%)	04 (13,33%)	11 (36.67%)	01 (3.33%)	04 (13.33%)	02 (6.67%)	02 (6.67%)	02 (6.67%)	00 0.00%
	Spotty	10 (33.33%)	08 (26.67%)	18 (60%)	00 0.00%	02 (6.67%)	04 (13.33%)	08 (26.67%)	03 (10%)	01 (3.33%)
	Confluent	01 (3.33%)	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%
Cholestasis	Absent	15 (50%)	11 (36.67%)	26 (86.67%)	01 (3.33%)	05 (16.67%)	05 (16.67%)	09 (30%)	05 (16.67%)	01 (3.33%)
	Intrahepatic Cholestasis	03 (10%)	01 (3.33%)	04 (13.33%)	00 0.00%	01 (3.33%)	01 (3.33%)	02 (6.67%)	00 0.00%	00 0.00%
Ductular Proliferation	absent	10 (33.33%)	07 (23.33%)	17 (56.67%)	00 0.00%	06 (20%)	05 (16.67%)	05 (16.67%)	01 (3.33%)	00 0.00%
	mild	06 (20%)	04 (13.33%)	10 (33.33%)	01 (3.33%)	00 0.00%	01 (3.33%)	05 (16.67%)	03 (10%)	00 0.00%
	Moderate	02 (6.67%)	01 (3.33%)	03 (10%)	00 0.00%	00 0.00%	00 0.00%	01 (3.33%)	01 (3.33%)	01 (3.33%)
Lymphoid Follicle Formation	Absent	11 (36.67%)	10 (33.33%)	21 (70%)	01 (3.33%)	05 (16.67%)	05 (16.67%)	05 (16.67%)	05 (16.67%)	00 0.00%
	present	07 (23.33%)	02 (6.67%)	09 (30%)	00 0.00%	01 (3.33%)	01 (3.33%)	06 (20%)	00 0.00%	01 (3.33%)
iron stain of liver tissue	Negative	18 (60%)	12 (40%)	30 (100%)	01 (3.33%)	06 (20%)	06 (20%)	11 (36.67%)	05 (16.67%)	01 (3.33%)
Cirrhosis	absent	10 (33.33%)	07 (23.33%)	17 (56.67%)	00 0.00%	05 (16.67%)	05 (16.67%)	05 (16.67%)	02 (6.67%)	00 0.00%

	occasional nodule	04 (13.33%)	02 (6.67%)	06 (20%)	01 (3.33%)	01 (3.33%)	00 0.00%	03 (10%)	01 (3.33%)	00 0.00%
	definite cirrhosis	04 (13.33%)	03 (10%)	07 (23.33%)	00 0.00%	00 0.00%	01 (3.33%)	03 (10%)	02 (6.67%)	01 (3.33%)
necro inflammatory score	1	01 (3.33%)	01 (3.33%)	02 (6.67%)	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	00 0.00%	00 0.00%
	2	04 (13.33%)	01 (3.33%)	05 (16.67%)	01 (3.33%)	01 (3.33%)	02 (6.67%)	00 0.00%	01 (3.33%)	00 0.00%
	3	03 (10%)	01 (3.33%)	04 (13.33%)	00 0.00%	02 (6.67%)	00 0.00%	01 (3.33%)	01 (3.33%)	00 0.00%
	4	01 (3.33%)	02 (6.67%)	03 (10%)	00 0.00%	01 (3.33%)	01 (3.33%)	01 (3.33%)	00 0.00%	00 0.00%
	5	01 (3.33%)	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	00 0.00%
	6	02 (6.67%)	02 (6.67%)	04 (13.33%)	00 0.00%	01 (3.33%)	00 0.00%	03 (10%)	00 0.00%	00 0.00%
	7	01 (3.33%)	03 (10%)	04 (13.33%)	00 0.00%	00 0.00%	01 (3.33%)	02 (6.67%)	01 (3.33%)	00 0.00%
	8	02 (6.67%)	01 (3.33%)	03 (10%)	00 0.00%	00 0.00%	00 0.00%	01 (3.33%)	02 (6.67%)	00 0.00%
	9	03 (10%)	01 (3.33%)	04 (13.33%)	00 0.00%	00 0.00%	01 (3.33%)	02 (6.67%)	00 0.00%	01 (3.33%)
	13	00 0.00%	01 (3.33%)	01 (3.33%)	00 0.00%	00 0.00%	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%
Staging (modified ishak)	0	06 (20%)	05 (16.67%)	11 (36.67%)	00 0.00%	05 (16.67%)	03 (10%)	01 (3.33%)	02 (6.67%)	00 0.00%
	1	02 (6.67%)	01 (3.33%)	03 (10%)	00 0.00%	01 (3.33%)	01 (3.33%)	01 (3.33%)	00 0.00%	00 0.00%
	2	01 (3.33%)	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	00 0.00%
	3	01 (3.33%)	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%	00 0.00%	01 (3.33%)	00 0.00%	00 0.00%
	4	01 (3.33%)	01 (3.33%)	02 (6.67%)	00 0.00%	00 0.00%	00 0.00%	02 (6.67%)	00 0.00%	00 0.00%
	5	03 (10%)	01 (3.33%)	04 (13.33%)	01 (3.33%)	00 0.00%	00 0.00%	02 (6.67%)	01 (3.33%)	00 0.00%
	6	04 (13.33%)	04 (13.33%)	08 (26.67%)	00 0.00%	00 0.00%	01 (3.33%)	04 (13.33%)	02 (6.67%)	01 (3.33%)