A Histo-Pathological Study of Liver in 118 Cases of Cirrhosis

Nikhil K Majethia*, Milind V Patil and AD Kalgutkar

Department of Pathology, Lokmanya Tilak Municipal General Hospital and Medical College, Sion, Mumbai, India

Abstract

The day has not arrived when predictive value of liver disease can be given like many laboratory tests. Autopsy studies provide us with useful baseline data to start a step towards achieving good morphological accuracy. The present study comprised of 118 cases of cirrhosis detected from the period January 2008 to December 2013. 3960 autopsies done during this period were scrutinized and 824 cases had liver pathology. Out of the 824 cases 118 had cirrhosis as the liver pathology, which makes incidence of cirrhosis at autopsy as 14.3% of all liver pathology, which shows a decreasing incidence of cirrhosis which may be due decrease in autopsy rate over the years, the reasons for the continuing decline are complex and include attitudes toward autopsies of hospital administrative staff, medical staff, and family members and also because of increase in diagnosis by liver biopsy and introduction of antifibrotic therapy.

Keywords: Cirrhosis; Liver; Wilson’s disease

Introduction

Liver diseases and cirrhosis contribute to 23.59% of mortality in world and ranks 27th as major cause of death in world and it is 2.74% of all the causes of death in India [1] but still the exact prevalence of cirrhosis is not known because the disease is often silent so 30% to 40% of cases are discovered at autopsy, indicating that in substantial proportion of people, the disease goes undetected during life. There are various etiologies if cirrhosis and all these causes leave specific imprints upon the liver so as to be identified histologically.

Due to varied etiologies like alcohol which being the commonest, obesity diabetes, hepatitis B, C, all these don’t offer any frontline diagnostic tool nor any treatment modalities to cirrhosis. Histology only remains a full proof diagnostic tool by which one can hope to identify various causes so quite right fully liver is called as “the custodian of milieu interior”, therefore autopsy study is a need of an hour. I our study we found 118 cases of cirrhosis out of 3960 autopsies which contributes to 14.3% as annual incidence most commonly affecting between 30-50 years of male population. Various gross and microscopic findings were also studied. Such study would be helpful to identify the cause and decide the line of treatment.

Aims and Objectives

1. To classify liver cirrhosis on morphological basis. 2. To establish etiology of cirrhosis if possible. 3. To study the gross and microscopic changes in cirrhosis. 4. To study histopathology of liver in cirrhosis.

Materials and Method

This was a descriptive cross sectional retrospective (2008-2011) and prospective (2012-2013) study carried out at Lokmanya Tilak Memorial Municipal General Hospital which is a tertiary care hospital in the Department of Pathology which is having Post mortem Histopathology Subunit where daily autopsies are done and prompt histopathology reporting is done. All Cases diagnosed as cirrhosis by gross and microscopic examination duly recorded in autopsy records, included in this study. Out of the total 824 Liver Pathology Cases the 118 number of cases with diagnosis of cirrhosis were selected for the study. All data were obtained from the autopsy history sheet and autopsy records.

Data entry and statistical analysis

Data entry and analysis was done in Microsoft Office Excel 2007. Master Chart was prepared in Excel.

Observation and Result

A total of 118 patients of cirrhosis were studied. The results obtained are analyzed as follows:

- Total number of autopsies done during Jan 2008 till December 2013 - 3960
- Total number of autopsies with liver pathology - 824
- Total number of autopsies with cirrhosis as liver pathology - 118

The year wise and sex distribution of cases of cirrhosis is shown in the (Tables 1 and 2) above which shows a decreasing number of autopsy and decreasing trend of incidence of cirrhosis on autopsy from 2008 to 2013 in men and a slight increase in incidence of cirrhosis in women. Maximum number of cases was in the age group of 31–40 years (25.4%). The youngest case of cirrhosis was of 1 year of age and oldest case was of 90 years of age. 84 patients (71%) were males and 34 patients (29%) were females, when expressed in the ratio the male to female ratio is 2:1. 97 patients (82%) were having positive history of alcoholism; remaining 21 patients (18%) were nonalcoholic. The youngest case with history of alcoholism was 18 years and eldest was 90 years (Table 3). The weight of liver between 1200-1300 grams was taken as normal, which seen in 65 cases (55.1%). According to above criteria weight <1200 grams was considered as shrunken in 20 cases (16.9%) and weight >1300 grams was considered enlarged in 33 cases (28%). In the present study mean weight of liver was 1360grams. Other gross finding like color was studied. Yellow was most common...
color (57.6%). 97 patients (83.2%) had alcohol associated cirrhosis, 2 patients (1.6%) had viral associated cirrhosis like Hepatitis B, Hepatitis C each. Three patients (2.4%) had Wilson’s disease, one patient each of hemochromatosis secondary to thalassemia sickle cell anemia, post necrotic cirrhosis, cirrhosis secondary to storage disorder and NASH. 10 patients (8%) had cryptogenic cirrhosis (Table 4). Majority of the patients (50.5%) consumed 100-200 ml/day, 20.6% consumed between 200-400 ml/day (Graphs 1 and 2). 36% of the alcoholics were consuming alcohol for duration 10-20 years. 24% alcoholics were consuming for a period more than 20 years. Mean duration of alcohol consumption was 11 years in females and 18.4 years in males. Nodularity (Table 5) was the other gross finding seen. Out of which micro nodularity was seen in 48 cases and macro nodularity was seen in 39 cases and remaining 31 cases showed mixed features. Out of 118 cases of cirrhosis the most common microscopic finding (Table 6) was loss of lobular architecture of liver (Figure 1) in 114 (96.6%) cases. 93% (110) of cases showed fibrosis of which portal to portal, portal to central and both were 8%, 38% and 50% respectively. 43 cases (36%) showed inflammatory infiltrate. Bile duct proliferation was seen in 51.6% cases. Hepatocytes changes like ballooning (Figure 2), steatosis, necrosis and cholestasis in 0.8%, 67% and 9.3% respectively. Of the 80 cases of steatosis most common type of steatosis was macro vesicular type in 83% cases. 2 cases (1.6%) showed hemosiderin deposition. 2 cases showed features of malignancy. 12 cases (10%) of cirrhosis showed associated TB granuloma. Out of 97 patients of alcohol induced cirrhosis, 48.4% showed micronodular cirrhosis, 29.8% showed mixed cirrhosis (Figure 3), 19.5% showed macro nodular cirrhosis, of these 43 cases (44.3%) of micronodular cirrhosis 4 cases had features of alcohol induced hepatitis , and early cirrhosis. Three cases showed fatty change and necrosis. Two cases of alcohol induced cirrhosis had associated findings of hepatocellular carcinoma.

| Year | Total no. of autopsy | Autopsies with liver pathology | Autopsy with cirrhosis | Percentage of cirrhosis(%) |
|------|----------------------|-------------------------------|------------------------|---------------------------|
| 2008 | 1248                 | 309                           | 28                     | 11.8                      |
| 2009 | 1025                 | 178                           | 21                     | 12.7                      |
| 2010 | 456                  | 79                            | 10                     | 21.1                      |
| 2011 | 390                  | 90                            | 19                     | 23.6                      |
| 2012 | 414                  | 89                            | 21                     | 23.6                      |
| 2013 | 427                  | 79                            | 19                     | 24.0                      |
| Total| 3960                 | 824                           | 118                    | 14.3                      |

Table 1: Year wise presentation of cirrhosis at autopsy.

| Study                           | Number of Cases | Alcohol Induced | Viral | Biliary/ Autoimmune | Wilson's | Hemochromatosis | Nash | Post Necrotic | Cryptogenic | Others |
|---------------------------------|-----------------|-----------------|-------|---------------------|----------|-----------------|------|--------------|-------------|--------|
| Manjunath et al. KIMS Hospital [3]| 50              | 80%             | 16%   |                     |          |                 |      |              | 4%          |        |
| Goncalves PL et al. [20]        | 262             | 40.50%          | 26.70%|                     |          |                 |      |              | 10.60%      | 3.80%  |
| Medha Y Racone et al., MS Ramaiah Medical College, Bangalore [21] | 43              | 58.10%          | 16.60%|                     |          |                 |      |              | 4.60%       | 18.60%  |
| Nandakumar et al. [4]           | 46              | 65%             | 25%   |                     |          |                 |      |              | 5%          | 5%     |
| Terada et al. [22]              | 209             | 12.40%          | 80.30%| 5.10%               | 0.40%    | 1.40%           |      |              | 0.40%       |        |
| Present study                   | 118             | 83.20%          | 1.60% | 0.80%               | 2.40%    | 1.60%           |      |              | 0.80%       | 8%     |

Table 2: Etiological comparison of cirrhosis with other studies.

| Parameter                              | Findings |
|----------------------------------------|----------|
| Age (30-50 years)                      | 49.1%    |
| Sex (Male: Female)                     | 84:34    |
| History of alcoholism (Male: Female)   | 93:4     |
| Mean gross weight of liver             | 1200-1300 grams |
| Colour of liver (yellow)               | 57.6%    |

Table 3: Parameters and findings.

| Causes                        | No. of Cases | Percentage |
|-------------------------------|--------------|------------|
| Alcoholic Cirrhosis           | 97           | 83.2%      |
| Viral- HBV                    | 1            | 0.8%       |
| HCV                           | 1            | 0.8%       |
| Biliary Cirrhosis             | 1            | 0.8%       |
| Wilson’s Disease              | 3            | 2.4%       |
| Hemochromatosis Secondary To  | 1            | 0.8%       |
| Thalessemia                   | 1            | 0.8%       |
| Sickle anemia                 | 1            | 0.8%       |
| NASH                          | 1            | 0.8%       |
| Post Necrotic                 | 1            | 0.8%       |
| Cryptogenic                   | 10           | 8%         |
| Storage Disorder              | 1            | 0.8%       |
| Total                         | 118          | 100%       |

Table 4: Causes in different cases.
Discussion

The day has not arrived when predictive value of liver disease can be given like many laboratory tests. Autopsy studies provide us with useful baseline data to start a step towards achieving good morphological accuracy. The present study compromised of 118 cases of cirrhosis detected from the period January 2008 to December 2013. 3960 autopsies done during this period were scrutinized and 824 cases had liver pathology. Out of the 824 cases 118 had cirrhosis as the liver pathology. Out of the 824 cases 118 had cirrhosis as the liver pathology, which makes incidence of cirrhosis at autopsy as 14.3% of all liver pathology, which shows a decreasing incidence of cirrhosis which may be due decrease in autopsy rate over the years, the reasons for the continuing decline are complex and include attitudes toward autopsies of hospital administrative staff, medical staff, and family members and also because of increase in diagnosis by liver biopsy and introduction of antifibrotic therapy. The result shows a decreasing trend as evident by the Table 1 showing year and sex distribution of cirrhosis on autopsy. The findings are comparable to study conducted by Bal et al. [2] in which the incidence of cirrhosis was 14%.

Age and sex distribution of cirrhosis

Out 118 cases 48.1% cases were in the age group 31-50 years, and mean age of cirrhosis was 43.67 years. It is occurred a decade earlier than the study by Bal et al. [2] in which 42.8% cases of cirrhosis were in age group 41-50 years. It is also similar to study conducted by Manjunath et al. [3] were mean age was 48.6 years and most common age group affected was 40-70 years. Many other studies by Nandkumar et al. [4] and Chakrabati et al. [5] also the most common age group affected were 41-60 years. There was male preponderance seen in our study. The male to female ratio was 2:1. In study conducted by Bal et al. [2] there was only single female case of cirrhosis. Male predominance was also seen in study by Manjunath et al. [3] were only 16% of cases were females. In other studies like also males were more affected.

Distribution of cases according to etiology of cirrhosis

Though identification of cirrhosis at autopsy is easy on gross as defined by a working party for the World Health Organization (WHO) in 1978 as "a diffuse process characterized by fibrosis and
the conversion of normal liver architecture into structurally abnormal nodules, but etiologic characterisation may be difficult. The results of various causes illustrated earlier results identified alcoholic as the most common cause.

In a study conducted in Delhi it was found that that there is decline in prevalence of HBV infection as a cause of chronic liver disease in the past five years. In the present study decreased incidence of HBV associated chronic liver disease can be attributed to this. So according to the above mentioned result there is a need to create more awareness among general population regarding adverse effect of alcohol consumption [3].

A single case of biliary cirrhosis (0.8%), in which we came across a case of biliary cirrhosis secondary to extra hepatic biliary atresia in a 12 month old male, which was a operated case of extra hepatic biliary atresia. The histopathology of the liver showed cholestasis, portal fibrosis, and ductular proliferation, expansion of the portal areas due to fibrosis nodular transformation is evident as a prelude to the development of secondary biliary cirrhosis.

3 cases (2.4%) of cirrhosis were secondary to Wilson’s disease. The average age of onset of Wilson’s disease is 11.5 years and die before age of 30 years as quoted by Ronald F. Pfeiffer [6] in his article on Wilson’s disease, there is progressive copper accumulation ultimately compromising hepatic function, the hepatic storage capacity is also eventually exceeded and unbound copper spills out of the liver and is deposited in other organs and tissues like heart, kidney, pancreas, brain etc. where it also provokes damage and dysfunction. In our study the average age were 15 years which is earlier than the average age for cirrhosis in rest of cases, the liver sections from cases of Wilson’s showed ballooning and feathery degeneration of hepatocytes, cholestasis, fibrous band showed lympho-plasmacytic infiltrate and bile duct proliferation. Special stain for copper like Orcein showed reddish brown cytoplasmic granules.

There were two cases (1.6%) of hemochromatosis secondary to thalassemia and sickle cell anemia, on autopsy liver was shrunked in size and it showed bridging fibrosis vague nodules and pigment in hepatocytes more in periportal areas. The special stain for hemosiderin, Prussian blue reaction was positive showed iron deposition in periportal hepatocytes and bile duct epithelium, kupffer cells absence of iron in septate which are seen in cases of secondary hemochromatosis. In both the conditions cirrhosis was secondary to hemochromatosis because of iron overload due to repeated blood transfusions for haemolytic anaemia.

Other causes included a case of NASH, post necrotic cirrhosis, and fatty acid oxidation.

Obesity, diabetes, hyperlipidemia and female sex are important factors in the progression of liver disease.
risk factors for NASH as mentioned by K Das, in our study it was in a 65 years old female known diabetic and hypertensive, admitted for acute coronary insufficiency. No liver function tests were done in this case. The liver showed extensive fatty change and fibrotic band extending between the portal tracts giving rise to ill formed nodules which are common in almost all cases of cirrhosis but due to presence of above history diagnosis of NASH was reached Nadkumar et al. [4].

Reported 5% of cirrhosis secondary to NASH. While the post necrotic cirrhosis was seen in 0.8% patient in present study, reported 4.6% of postnecrotic cirrhosis. The case storage disorder induced cirrhosis was of defect in fatty acid oxidation in a 3 year old male with complaints of developmental delay, the MRI of this case showed fatty change in neck muscles, ante-mortem liver biopsy showed diffuse macro vescicular steatosis with mixed inflammatory infiltrates and portal to portal bridging fibrosis, post mortem section from liver showed altered liver architecture with thin fibrous septa forming nodules infiltrated by mononuclear infiltrate and bile duct proliferation and macro vescicular steatosis. Enzyme levels of carnitine and other biochemical tests were not done. Special stain of Glycogen like PAS and PAS with diastase is negative.

Cryptogenic cirrhosis contributed only 8% of total cases as series of discoveries in the laboratory and a few clinical observations have helped to established the aetiology of cirrhosis in the vast majority of patients, and the diagnosis of cryptogenic cirrhosis is infrequent now a days as shown, while it contributed 61.9% of cirrhosis in study by MacSween [7]. Histologically these cases showed thick fibrous bands incircled hepatocytes nodules with pseudocarcin transformation. These hepatocytes showed not much fatty change and few showed cholestasis. This could be the end stage of many disorders like metabolic defects or infective etiology, thus was labelled as cryptogenic as no other history and investigations were available to classify these cases.

Alcoholism and sex predilection in cases of alcoholic cirrhosis

As present study comprised of large number of cases of alcoholic cirrhosis the alcoholism history was obtained from autopsy records. Studies show that the amount of alcohol consumed and the duration of that consumption are closely associated with cirrhosis. 97 cases were having history of alcoholism. Of those, 95% were male. Similar results were seen in study where 92% alcoholics were male and 8% were female. In study by Gronbaek et al. [8] the alcoholic male contributed to cirrhosis was 72%. Women are less likely to be suspected of alcohol abuse, even if they develop withdrawal symptoms in hospital. There are several reasons like social stigma a woman is less likely to admit to alcohol abuse but at any given level of alcohol consumption, women have a higher likelihood of developing cirrhosis than men. This phenomenon is poorly understood, but several possible explanations exits like levels of alcohol dehydrogenase may be lower in the stomachs of females than in males, which would result in a higher blood alcohol content for females than for males who consume equivalent amounts of alcohol according to Frezza et al. [9]. Because damage to the liver is a function of blood alcohol levels and exposure time, factors that lead to higher blood alcohol concentrations could at least partially explain females’ higher risk for alcohol related cirrhosis. Another possible explanation is that estrogen may increase the susceptibility of the liver to alcohol related damage Ikejima et al. [10] and Colantoni et al. [11].

Behavioural factors, including drinking patterns and diet, also may contribute to females’ higher risk of cirrhosis.

Quantity of alcohol consumed (1ml=0.789g)

Majority of the patients 50.5% were consuming 100-200 ml/day, Van Waes and Leiber [12] in their study of alcoholic patients the average intake was 90-180g/day. The prospective study on 258 alcohol abusing men showed that 22% of the patients consumed 100-125g per day. 21% consumed more than 250 grams per day and only 5% consumed 50-75g/day. Morgan and Sherlock [13] in their study evaluated 100 alcohols the amount was greater than 100g/day.

Duration of alcohol consumption

36% of the alcoholics were consuming alcohol for duration 10-20 years. Our study correlates with that mean duration of alcohol consumption was 10-13 years. Morgan and Sherlock [13] in their study revealed that mean duration of alcohol intake was 20.4 years in men and 16.8 years in women.

Morphological findings

In an autopsy study gross examination is most important in diagnosis and classifying of cirrhosis according to Gall [14]. In the present study mean weight of liver was 1360 grams suggesting that there was hepatomegaly, it was shrunken (<1200 grams) in 20 cases (16.9%), enlarged in 33 cases (28%) and normal in 65 cases (55.1%). In study conducted by Agrawal et al. [15] from PGIMER, 2014 the liver was studied on similar criteria and was found that in majority of cases the liver (288 cases 74%) was also enlarged and 90 cases (23%) were shrunken while only in 12 cases it was normal in weight.

Nodularity: Among the systems of morphological categories currently in use, the division of cirrhosis into micronodular, macronodular (Figure 4) and mixed forms is preferred. It can be applied macroscopically and microscopically 79. In present study liver on gross examination showed micronodularity (<0.3cm) in 48 cases (40.6%) and micronodularity (>0.3cm) in 39 cases (33.0%). Mixed nodularity was seen in remaining 31cases (26.2%). Among the alcoholics, 48.4% showed micro nodular cirrhosis , 29.8% showed mixed cirrhosis, 19.5% showed macro nodular cirrhosis, similar results were observed in study done by Agrawal et al. [15] were micronodularity was in 49% and macro nodularity was in 26% cases. Other etiological causes of cirrhosis contributed quite less in number, type of cirrhosis is like biliary cirrhosis showed micronodularity (Figure 5), similar to study by Aishima et al. [16] in 2006, in which out of 26 cases of biliary cirrhosis 12 had micro nodular cirrhosis. Macro nodular cirrhosis was seen in varied aetiology like secondary to virus (2 cases), hemochromatosis (2 cases), Wilson’s disease (3 cases), post necrotic (1 case), storage disorder like defect in fatty acid oxidation (1 case) and cryptogenic cirrhosis (8 cases). All these cases macro nodularity was secondary to hepatic necrosis caused by either virus, iron over load, copper deposition, enzyme deficiency leading to fatty acid accumulation. Other gross finding like color of liver was observed. It serves as an indication of underlying pathology, like yellow discoloration indicates fatty liver, greenish discolouration indicates bile stasis. In cases of hemochromatosis liver is brown in color. In present study yellow was most common color (57.6%), Green colouration (bile stasis) was seen in 55 of cases. In study conducted by most common color observed was yellow in 31% cases and consistency was soft and on cut surface was greasy [2].

Microscopic findings in cirrhosis

Similar to gross examination microscopic examination is an integral part of autopsy. The microscopic evaluation of cirrhosis is essential to identify the underlying aetiology and mechanism of fibrosis leading to cirrhosis, as it is the end result of variety of liver pathology, criteria indicating cirrhosis in decreasing order are nodules surrounded by septate with or without portal and central canal, hepatic vein tributaries in contact with fibrous septa (Figure 6), connective tissue...
septa linking central with portal canals, irregularity of architecture. In present study microscopy of all cases revealed loss of architecture in 96% cases prominently in cases of alcoholic cirrhosis, equivalent results were seen in Spahr et al. [17] (n=163).

Portal triaditis i.e. inflammatory infiltrate which is an indicator of underlying activity of regeneration and repair was seen in 37% cases; similarly 46% cases in study by Agrawal et al. [15] showed this feature. Depending on which type of fibrosis is prominent in initial stages it is possible to know the underlying cause of cirrhosis. In post necrotic central vein to portal areas is seen with displaced, disarranged central vein and portal tracts. Creeping fibrosis/bridging or fibrillar tongues central vein to portal areas is seen with displaced, disarranged central vein and portal tracts. Creeping fibrosis and portal septa linking central with portal canals, irregularity of architecture. In present study microscopy of all cases revealed loss of architecture suggests nutritional cause (alcohol) in pathogenesis of cirrhosis as it is a centrolobular process of collagen deposition. While in Agrawal et al. [15] study portal portal was seen in 58% and portocentral in 47% cases. Large steatosis droplet is one of criteria in diagnosis of alcoholic cirrhosis with Mallory Denk bodies, pericellular fibrosis, hypo cellular central or portal bridges. In present study steatosis was seen in 68% cases, equivalent results (63.8%) were seen in Spahr et al. [17]. Bile duct reaction/proliferations the marker of regeneration in liver, more prominent in case of biliary cirrhosis secondary to EHBA. It is seen in 61% cases in present study. The results varied in other studied were in Spahr et al. [17] it was 37% and in Agrawal et al. [15] it was only 12%.

Necrosis was present in 9% of cases and Cholestasis which is also a feature of biliary cirrhosis, occurs because of bile duct destruction or obstruction. In present study it was seen in 2.5% cases, in Agrawal et al. [15] study these parameters were also observed less namely 16% and 10% respectively.

Hemosiderin deposition in hepatocytes which simulates fibrogenesis, most iron overload cirrhosis show little inflammation, diagnosis is possible ante-mortem when iron deposition precedes fibrosis, post-mortem hemosiderin deposition is also seen in alcoholic cases. In present study hemosiderin deposition was seen in two cases of hemochromatosis secondary to thalassemia and sickle cell anaemia. Likewise it was seen in 15% cases of Agrawal et al. study [15].

The frequent association of hepatocellular carcinoma with cirrhosis. In present study HCC was seen in 2 cases, both were of alcoholic cirrhosis with macro nodularity. The study by Kew [18], demonstrated HCC to be more in macro nodular cirrhosis and was secondary to alcohol, Hepatitis B virus.

There has been a massive increase in alcoholism in India contributing to an increase in chronic liver disease including cirrhosis. This leads to an immunodeficient state and along with malnutrition which is commonly present in such patients, may increase the risk of tuberculosis. 12 cases (10%) were associated with tuberculosis granuloma, while no such findings were seen in Agrawal et al. [15] study. While it has been emphasized by Lin et al. [19] that cirrhotic patients have a greater risk of TB than non-cirrhotic patients, particularly those with alcoholism and hepatitis C infection, while in their study of 2.32% have a greater risk of TB than non-cirrhotic patients, particularly those with alcoholism and hepatitis C infection.

Conclusion

Cirrhosis is still a common liver pathology and alcohol was found to be a common etiology. The amount and quantity of alcohol are directly related to cirrhosis. The classical microscopic feature was loss of architecture, fibrosis and portal triaditis. So a public awareness of an hour to avoid such dreadful disease which is completely preventable by simple absentee from alcohol unlike other etiologies which may require vaccination antiviral therapy, frequent iron levels, enzyme levels and liver biopsy to monitor ongoing disease process.

References

1. India: Liver Disease. [Internet] WHO data published in 2011 April.
2. Bal MS, Singh SP, Bodal VK, Oberoi SS, Surinder K (2004) Pathological Findings In Liver Autopsy. JIAFM 26: 0971-0973.
3. Manjunath R, Nagesh HN, Bharadwaj V (2014) Clinical Co Relation between Arterial versus Venous Ammonia Levels in Hepatic Encephalopathy in Cirrhosis of Liver. JEMDS 3: 5322-5333.
4. Nandakumar R, Naik AS, Pandit B, Kamat R, Bhatia SJ (2003) Effect of Helicobacter pylori eradication on serum ammonia levels in patients with chronic liver disease. Indian J Gastroenterol 22: 221-223.
5. Chakrabarti P, Zullo A, Hassan C, Pandit A, Chowdhury A, et al. (2002) Helicobacter pylori, gastric juice, and arterial ammonia levels in patients with cirrhosis. J Clin Gastroenterol 34: 578-581.

6. Pfeiffer RF (2007) Wilson’s Disease. Semin Neurol 27: 123-132.

7. MacSween RN, Scott AR (1973) Hepatic cirrhosis: a clinicopathological review of 520 cases. J Clin Pathol 26: 936-942.

8. Granbaek M, Jensen MK, Johansen D, Sørensen TI, Becker U (2004) Intake of beer, wine and spirits and risk of heavy drinking and alcoholic cirrhosis. Biol Res 37: 195-200.

9. Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, et al. (1990) High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med 322: 95-99.

10. Ikejima K, Enomoto N, Iimuro Y, Ikejima A, Fang D, et al. (1998) Estrogen increases sensitivity of hepatic Kupffer cells to endotoxin. Am J Physiol 274: G669-676.

11. Colantoni A, Idilman R, De Maria N, La Paglia N, Belmonte J, et al. (2003) Hepatic apoptosis and proliferation in male and female rats fed alcohol: role of cytokines. Alcohol Clin Exp Res 27: 1184-1189.

12. Van Waes L, Lieber CS (1977) Glutamate dehydrogenase: a reliable marker of liver cell necrosis in the alcoholic. Br Med J 2: 1508-1510.

13. Morgan MY, Sherlock S (1977) Sex-related differences among 100 patients with alcoholic liver disease. Br Med J 1: 939-941.

14. Gall EA (1960) Posthepatitic, postnecrotic, and nutritional cirrhosis: a pathologic analysis. Am J Pathol 36: 241-271.

15. Agrawal P, Vaiphei K (2014) Histomorphological features of pancreas and liver in chronic alcoholics—an analytical study in 390 autopsy cases. Indian J Pathol Microbiol 57: 2-8.

16. Aishima S, Kuroda Y, Nishiara Y, Taguchi K, Yoshizumi T, et al. (2006) Characteristic differences according to the cirrhotic pattern of advanced primary biliary cirrhosis: Macronodular cirrhosis indicates slow progression. Hepatol Res 36: 188-194.

17. Spahr L, Rubbia-Brandt L, Genevay M, Hadengue A, Giostra E (2011) Early liver biopsy, intraparenchymal cholestasis, and prognosis in patients with alcoholic steatohepatitis. BMC Gastroenterol 11: 115.

18. Kew MC (2014) The role of cirrhosis in the etiology of hepatocellular carcinoma. J Gastrointest Cancer 45: 12-21.

19. Lin YT, Wu PH, Lin CY, Lin MY, Chuang HY, et al. (2014) Cirrhosis as a risk factor for tuberculosis infection—a nationwide longitudinal study in Taiwan. Am J Epidemiol 180: 103-110.

20. Gonçalves PL, Gonçalves CS, Pereira FE (2014) Mortality from liver cirrhosis in Espírito Santo State, Brazil. Cad Saude Publica 30: 1335-1340.

21. Rao MY, Raghu J, Deshmukh S, Amaravathi KS, Sudhir U (2008) Arterial hypoxemia in patients with cirrhosis of liver. J Assoc Physicians India 56: 681-684.

22. Terada T, Terasaki S, Nakamura Y (1993) A clinicopathologic study of adenomatous hyperplasia of the liver in 209 consecutive cirrhotic livers examined by autopsy. Cancer 72: 1551-1556