The Histological Assessment of Hepatitis B Viral Activity in Patients with Heavy Alcohol Consumption

Chih-Wen Lin¹,2,3*, Chia-Chang Hsu¹,2, Daw-Shyong Perng¹, Matthew M Yeh⁴ and Sien-Sing Yang⁵,6*

¹Division of Gastroenterology and Hepatology, Department of Medicine, E-Da Dachang Hospital, I-Shou University, Kaohsiung, Taiwan
²Health Examination Center, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan
³School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan
⁴Department of Pathology, University of Washington School of Medicine, Seattle, Washington, USA
⁵Liver Unit, Cathay General Hospital, Taipei, Taiwan
⁶School of Medicine, Fu-Jen Catholic University, New Taipei, Taiwan

Abstract

Objectives: Taiwan has a high prevalence of hepatitis B viral (HBV) infection with rising alcoholic liver disease. We investigated the histological assessment of viral hepatitis B activity in patients with concomitant HBV infection and alcoholism.

Methods: 229 patients (33 with concomitant heavy alcoholism and HBV infection, 114 with HBV infection alone, and 82 with heavy alcoholism alone) were enrolled between 2009 and 2012 at Cathy General hospital and E-Da hospital.

Results: Patients with concomitant alcoholism and HBV infection are male predominant and younger. 97.4% and 91.4% patients have detectable HBV DNA in patients with HBV infection without or with alcoholism, respectively. Patients with concomitant HBV infection and alcoholism have much piecemeal necrosis, confluent necrosis, focal necrosis, portal inflammation, necroinflammatory grading, and cirrhosis with Ishak stage 5-6 fibrosis. Moreover, patients with concomitant HBV infection and alcoholism also have much pericellular fibrosis, sclerosing hyaline necrosis, non-alcoholic fatty liver disease (NAFLD) ballooning, NAFLD activity score (NAS) and NAFLD Stage 4 fibrosis (P<0.001). However, patients with alcoholism alone have much more steatosis than those with HBV infection with and without alcoholism.

Conclusions: Patients having concomitant alcoholism and HBV infection develop the histological features of both alcoholic liver disease and viral hepatitis B. The assessment of hepatitis B viral activity in alcoholic liver disease depends on detectable viral load and histological features of viral hepatitis B in patients with concomitant HBV infection and alcoholism.

Keywords: Hepatitis B virus infection; Alcoholism; Histology; Viral activity; Steatosis

Abbreviations: HBV: Hepatitis B Virus; CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; NAFLD: Non-alcoholic Fatty Liver Disease

Introduction

Asia-Pacific region is a region with a high prevalence of hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC) [1,2]. Alcoholic liver disease is a major cause of chronic liver disease worldwide and can lead to fibrosis, cirrhosis, HCC, and mortality [3,4]. Economic progress in this region has led to an increase of alcohol consumption and changes in drinking behavior, which have resulted in an increased number of cases of alcoholic liver disease in Taiwan [5-8].

Alcohol abuse is not uncommon among those patients with HBV infection. The synergism and interaction between HBV infection and alcohol consumption have been reported [9-12]. Alcoholic consumption may increase viral replication and exacerbate liver injury, which results in the much more rapid progression of chronic hepatitis to cirrhosis and HCC [9-13]. Our recent study confirmed that the heavy alcohol consumption significantly increased the risk of HCC in HBV-related cirrhotic patients [13]. The clinical diagnosis for the role of concomitant HBV infection in alcoholic patients is difficult and remains uncertain. Furthermore, the histological assessment between chronic hepatitis B (CHB) and alcoholic liver disease has never been discussed in the literature. Thus, we investigated the impact of heavy alcohol consumption and HBV infection on histological findings and clinical diagnosis.

Patients and Methods

Patients

We prospectively collected 229 patients (33 with concomitant heavy alcoholism and HBV infection, 114 with HBV infection alone, and 82 with heavy alcoholism alone) at the Cathay General Hospital/ Fu-Jen Catholic University, Taipei, Northern Taiwan, and E-DA Hospital/I-SHOU University, Kaohsiung, Southern Taiwan, between 2009 and 2012. The evaluations commenced after approval of the
study protocols by the Institutional Review Board of Cathay General hospital and E-DA hospital. The behavior of alcohol consumption was routinely evaluated by interviewing patients and family members for the duration, types, and amount of alcohol consumed per day. Heavy alcoholism was defined as consuming more than 80 g of ethanol each day for at least 5 years.

**Hepatitis B marker**

All patients had blood chemistry and were tested for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and anti-HBe antibody (Abbott Laboratories, Chicago, IL, USA), α-fetoprotein (AFP), and serum HBV DNA (Cobas Amplicor, Hepatitis B Virus Test; Roche Diagnostics, Branchburg, NJ, USA) with a minimum detection limit of 300 copies/ml. CHB was defined as the positivity for serum HBsAg for more than 6 months as well as chronic liver disease based on the clinical findings of laboratory tests, sonography, and upper gastrointestinal endoscopy. All patients had blood sampling and liver biopsy collected on the same day. All patients without liver histology due to decompensated liver function, international normalized ratio>1.5 and the occurrence of ascites were excluded. All patients with other hepatitis or liver malignancies were excluded.

**Scoring system of alcoholic liver disease according to histology**

The clinical classification of alcoholic liver disease was based on the histological changes as steatosis, alcoholic hepatitis, alcoholic fibrosis, alcoholic cirrhosis, and alcoholic hepatitis on cirrhosis [14]. The scoring system for alcoholic liver disease was based on the Kleiner non-alcoholic steatohepatitis scoring system [15,16]; briefly defined as steatosis (0: <5%, 1: 5%-33%, 2: >33%-66%, 3: >66%), lobular inflammation (0: no foci, 1: <2 foci, 2: 2-4 foci, 3: >4 foci per 200X field), hepatocellular ballooning (0: none, 1: few, 2: many/prominent balloon cells), and fibrosis (0: none; 1A: mild, zone 3, perisinusoidal; 1B: moderate, zone 3, perisinusoidal, 1C: portal/perisinusoidal; 2: zone 3/perisinusoidal and portal/perportal; 3: bridging fibrosis; 4: cirrhosis). Two key histological features of alcoholic liver disease were also defined [17]; briefly defined as Mallory’s hyaline (0: absent, 1: occasional, 2: several) and perisinusoidal fibrosis in zone 3 (0: none, 1: <33%, 2: 33%-66%, 3: >66%) [18].

**Histology of chronic hepatitis**

The histological features of chronic hepatitis were based on Ishak Hepatic Activity Index (HAI) for necroinflammatory grading (periportal or perisepal piecemeal necrosis: 0-4; confluent necrosis: 0-6; focal lytic necrosis: 0-4; and portal inflammation: 0-4) and fibrosis staging (0-6) [19,20].

**Statistical analysis**

Data were expressed either as median (range) or percentage (%). Continuous variables were analyzed using Student’s t-test. Categorical variables were analyzed using Pearson’s Chi-square test or Fisher’s exact test, as appropriate. All analyses were performed using the Statistical Package for Social Sciences (SPSS, version 15.0; Chicago, IL, USA).

**Results**

**Baseline demographic data**

The clinical and biochemical features of all patients were shown in Table 1. Patients with concomitant alcoholism and HBV infection were younger, less platelet, and less platelet to spleen ratio than patients with alcoholism alone or HBV infection alone. Compared with patients with HBV infection with and without alcoholism, patients with alcoholism alone had significantly lower body mass index, hemoglobin, leukocyte, and albumin but higher mean corpuscular volume, serum bilirubin, alkaline-phosphate, gamma-glutamyl transpeptidase, and AST/ALT ratio (p<0.001). For the patients with HBV infection alone, 111 of 114 (97.4%) patients with HBV infection had detectable HBV DNA. For the patients with concomitant HBV infection and alcoholism, 29 of the 32 (90.6%) patients with HBV infection had detectable HBV DNA. None of the patients with alcoholism alone had detectable viral load (p<0.001).

**Histological features of viral hepatitis B**

The histological features of viral hepatitis B were shown in Table 2. Compared with those patients with alcoholism alone, patients with HBV infection with and without alcoholism had much more piecemeal necrosis, confluent necrosis, focal necrosis, portal inflammation and necroinflammatory grading (p<0.001) regardless of HBV infection. However, patients with concomitant HBV infection and alcoholism or alcoholism alone had much more cases having cirrhosis with Ishak stage 5-6 fibrosis than those with HBV infection alone (p<0.001).

**Histological features of alcoholic liver disease**

The histological features of alcoholic liver disease are shown in Table 3. Compared with those with HBV infection alone, patients

| Characteristics | HBV+Alcoholism (n=33) | HBV (n=114) | Alcoholism (n=82) |
|-----------------|-----------------------|-------------|------------------|
| Age (year)      | 41.29 ± 9.98**        | 47.63 ± 9.32 | 45.78 ± 8.42     |
| Sex (male)      | 31 (93.2)             | 66 (58.3)   | 74 (90.2)        |
| Body mass index (kg/m²) | 25.3 ± 3.7*     | 25.0 ± 3.7   | 23.6 ± 3.8       |
| Alcohol intake amount (g/day) | 179 ± 47*       | 0*          | 165 ± 41         |
| Alcohol intake duration (year) | 16.8 ± 4.3*    | 0*          | 18.8 ± 6.7       |
| Presence of Diabetes | 5 (15.2)       | 12 (10.5)   | 13 (15.9)        |
| Presence of Hyperlipidemia | 3 (9.1)      | 13 (11.4)   | 15 (18.3)        |
| Hemoglobin (g/dL) | 13.5 ± 2.1*        | 14.2 ± 1.7   | 12.9 ± 2.6       |
| Mean corpuscular volume (fl) | 89.7 ± 6.3*   | 89.6 ± 4.9   | 97.0 ± 11.0      |
| White blood cell (10³/μL) | 5890 ± 1926*    | 5779 ± 1634  | 2877 ± 1040      |
| Platelet count (x10³/μL) | 152 ± 61*        | 172 ± 53*   | 193 ± 87         |
| Platelet/spleen | 1599 ± 779*         | 1857 ± 749*  | 2125 ± 1116      |
| INR             | 1.18 ± 0.27          | 1.10 ± 0.14  | 1.12 ± 0.24      |
| Total bilirubin (mg/dl) | 1.36 ± 1.89*    | 0.85 ± 0.51* | 2.02 ± 2.46     |
| Albumin (g/dL)  | 3.65 ± 0.36*         | 4.11 ± 0.42* | 3.55 ± 0.67      |
| Globulin (g/dL) | 3.10 ± 0.56          | 2.86 ± 0.46  | 2.94 ± 0.70      |
| AST (IU/L)      | 130.5 ± 169.9*       | 79.1 ± 94.7  | 87.7 ± 72.0      |
| ALT (IU/L)      | 193.5 ± 265.3*       | 137.6 ± 197.0 | 68.7 ± 68.6    |
| AST/ALT         | 0.89 ± 0.60*         | 0.69 ± 0.26* | 1.62 ± 0.63      |
| Alkaline phosphatase (IU/L) | 105.2 ± 54.5*  | 75.6 ± 46.5  | 150.1 ± 109.0   |
| γ-glutamyltransferase (IU/L) | 162.8 ± 210.1* | 72.1 ± 78.5 | 484.5 ± 506.7  |
| Ferritin        | 579 ± 631*          | n.a.         | 953 ± 1431       |
| α-fetoprotein (ng/ml) | 16.4 ± 20.8b     | 27.8 ± 193.0 | 10.3 ± 38.1     |
| HBV DNA: positive | 29 (90.6)        | 111 (97.4)   | 0 (0)            |

Data shown as mean ± standard deviation (SD) or number (%). AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; INR: International Normalized Ratio; HBV: Hepatitis B virus; N.A: Data not Available.

Table 1: Demographic data of all patients.
and alcoholism. Moreover, some studies show that chronic ethanol 
alcoholic liver disease depends on detectable viral load and histological 
HBV infection and alcoholism. The assessment of viral activity B in 
histological changes of viral hepatitis B in patients with concomitant 
their underlying hepatitis activities in patients with concomitant 
progression [21,24].

HBV infection and heavy alcohol consumption has been recognized as 
major risk factors for fibrosis, cirrhosis, and HCC [10,24]. Our recent 
study presented that heavy alcohol consumption significantly increases 
the risk of HCC in HBV-related cirrhotic patients and elevated baseline 
serum HBV DNA is a strong risk predictor of HCC [11]. In this study, 
patients with concomitant HBV infection and alcoholism had much more 
cirrhosis with Ishak stage 5-6 fibrosis and NAFLD activity score 
with stage 4 fibrosis than those with HBV infection alone in histological 
findings. Our study demonstrates that patient with concomitant HBV 
infection and alcoholism have more advanced fibrosis and cirrhosis.

Alcohol intake increases the prevalence of fatty liver and hepatic 
steatosis is positively associated with moderate alcohol consumption 
[25]. Our study presented that patients with alcoholism alone had much more 
stearosis than those with HBV infection with and without 
Table 2: Histological features of viral hepatitis B in all patients.

| Viral hepatitis histology features | HBV+Alcoholism (n=33) | HBV (n=114) | Alcoholism (n=82) |
|-----------------------------------|-----------------------|-------------|-------------------|
| Piecemeal necrosis                |                       |             |                   |
| 0                                | 1 (3.0)               | 8 (7.0)     | 41 (50.0)         |
| 1                                | 13 (39.4)             | 47 (41.2)   | 33 (40.2)         |
| 2-4                              | 19 (57.6)             | 59 (51.8)   | 8 (9.8)           |
| Confluent necrosis               |                       |             |                   |
| 0                                | 18 (54.5)             | 66 (57.9)   | 76 (92.7)         |
| 1                                | 5 (15.2)              | 26 (22.8)   | 5 (6.1)           |
| 2-6                              | 10 (30.3)             | 22 (19.3)   | 1 (1.2)           |
| Focal necrosis                   |                       |             |                   |
| 0                                | 1 (3.0)               | 1 (0.9)     | 6 (7.3)           |
| 1                                | 11 (33.3)             | 40 (35.1)   | 42 (51.2)         |
| 2-4                              | 21 (63.7)             | 73 (64.0)   | 34 (41.5)         |
| Portal inflammation              |                       |             |                   |
| 0                                | 1 (3.0)               | 4 (3.5)     | 52 (63.4)         |
| 1                                | 11 (33.3)             | 43 (37.7)   | 24 (29.3)         |
| 2-4                              | 21 (63.7)             | 67 (58.8)   | 6 (7.3)           |
| Necroinflammatory Score: Grading |                       |             |                   |
| Mean ± SD                        | 6.39 ± 2.89           | 5.56 ± 2.55 | 3.13 ± 2.27       |
| Ishak Fibrosis: Staging          |                       |             |                   |
| F1-4                             | 17 (51.5)             | 89 (78.1)   | 45 (54.9)         |
| F5-6                             | 16 (48.5)             | 25 (21.9)   | 37 (45.1)         |
| Mean ± SD                        | 3.76 ± 1.98           | 3.08 ± 1.72 | 3.39 ± 2.18       |

Data shown as mean ± standard deviation (SD) or number (%).

Table 3: Histological features of alcoholic liver disease in all patients.

| Alcoholic liver disease histology features | HBV+Alcoholism (n=33) | HBV (n=114) | Alcoholism (n=82) |
|------------------------------------------|-----------------------|-------------|-------------------|
| Pericellular fibrosis                    |                       |             |                   |
| 0                                        | 9 (27.3)              | 112 (98.2)  | 3 (3.7)           |
| 1                                        | 13 (39.4)             | 2 (1.8)     | 31 (37.8)         |
| 2-3                                      | 11 (33.3)             | 0 (0.0)     | 48 (58.5)         |
| Sclerosing hyaline necrosis              |                       |             |                   |
| 0                                        | 18 (54.5)             | 113 (98.1)  | 5 (6.1)           |
| 1                                        | 11 (33.3)             | 1 (0.9)     | 47 (57.3)         |
| 2-3                                      | 4 (12.1)              | 0 (0.0)     | 30 (36.6)         |
| Kleiner NAFLD score                     |                       |             |                   |
| NAFLD steatosis                         |                       |             |                   |
| 0                                        | 19 (57.6)             | 67 (58.8)   | 28 (34.1)         |
| 1                                        | 8 (24.2)              | 29 (25.4)   | 23 (28.0)         |
| 2-3                                      | 6 (18.2)              | 18 (15.8)   | 31 (37.9)         |
| NAFLD inflammation                      |                       |             |                   |
| 0                                        | 0 (0.0)               | 1 (0.9)     | 5 (6.1)           |
| 1                                        | 13 (39.4)             | 38 (33.3)   | 44 (53.7)         |
| 2-3                                      | 20 (60.6)             | 75 (65.8)   | 33 (40.2)         |
| NAFLD ballooning                         |                       |             |                   |
| 0                                        | 8 (24.2)              | 34 (30.1)   | 6 (7.3)           |
| 1                                        | 10 (30.3)             | 56 (49.1)   | 39 (47.6)         |
| 2-3                                      | 15 (45.5)             | 24 (20.8)   | 37 (45.1)         |
| NAFLD activity score: Grading            |                       |             |                   |
| Mean ± SD                               | 3.79 ± 2.01           | 3.34 ± 1.63 | 4.27 ± 1.98       |
| NASH fibrosis: Staging                  |                       |             |                   |
| 0-3                                      | 18 (53.8)             | 88 (77.0)   | 46 (55.6)         |
| 4                                        | 15 (46.2)             | 26 (23.0)   | 36 (44.4)         |
| Mean ± SD                               | 2.91 ± 1.16           | 2.12 ± 1.38 | 2.82 ± 1.21       |

Data shown as mean ± standard deviation (SD) or number (%). NAFLD: Non- 
alcoholic fatty liver disease. 

Discussion

Liver biopsy has been the most sensitive and specific method for 
evaluating the degree of hepatic injury and fibrosis to help the clinical 
diagnosis and therapeutic decision [20,21]. In the present results, the 
patients having concomitant alcoholism and HBV infection developed 
the histological features of both alcoholic liver disease (steatosis, 
hepatocyte ballooning, focal necrosis and fibrosis) [17] and viral 
hepatitis B (piecemeal necrosis, confluent necrosis, focal necrosis, 
portal inflammation and fibrosis) [19]. Typical histological changes 
of viral hepatitis B are important in the clinical differentiation from 
alcoholic liver disease. Furthermore, typical histological changes of 
alcoholic liver disease were also important in the clinical differentiation 
from viral hepatitis B in high HBV endemic area, such as Taiwan and 
Asian Pacific region. To the best of our knowledge, this result has not 
previously been reported in the literature.

All but three patients had detectable hepatitis B viral load showing 
their underlying hepatitis activities in patients with concomitant 
HBV infection and alcoholism. The histology also showed that typical 
histological changes of viral hepatitis B in patients with concomitant 
HBV infection and alcoholism. The assessment of viral activity B in 
alcoholic liver disease depends on detectable viral load and histological 
features of viral hepatitis B in patients with concomitant HBV infection and alcoholism. Moreover, some studies show that chronic ethanol 
consumption stimulates hepatitis B virus replication in animal [22,23]. 
In clinics, our study presents that patients with concomitant HBV 
infection and alcoholism have high percentages of hepatitis B viral load 
and high levels of HBV DNA. This could be possibly due to patients 
with alcoholic liver disease having poor nutrition status and relatively 
weaker immune status. HBV replication is mediated by immune 
system and is the key role of immune-mediated liver injury and disease 
progression [21,24].

HBV infection and heavy alcohol consumption has been recognized as 
major risk factors for fibrosis, cirrhosis, and HCC [10,24]. Our recent 
study presented that heavy alcohol consumption significantly increases 
the risk of HCC in HBV-related cirrhotic patients and elevated baseline 
serum HBV DNA is a strong risk predictor of HCC [11]. In this study, 
patients with concomitant HBV infection and alcoholism had much more 
cirrhosis with Ishak stage 5-6 fibrosis and NAFLD activity score 
with stage 4 fibrosis than those with HBV infection alone in histological 
findings. Our study demonstrates that patient with concomitant HBV 
infection and alcoholism have more advanced fibrosis and cirrhosis.

Alcohol intake increases the prevalence of fatty liver and hepatic 
steatosis is positively associated with moderate alcohol consumption 
[25]. Our study presented that patients with alcoholism alone had much more 
stearosis than those with HBV infection with and without 

Citation: Lin CW, Hsu CC, Perng DS, Yeh MM, Yang SS (2016) The Histological Assessment of Hepatitis B Viral Activity in Patients with Heavy 
Alcohol Consumption. J Liver 5: 204. doi: 10.4172/2167-0889.1000204
alcoholism. However, patients with concomitant HBV infection and alcoholism had much less steatosis than those with alcoholism alone. In some studies, HBV infection is associated with a lower prevalence of fatty liver, hypertriglyceridemia and metabolic syndrome [26]. Moreover, hepatitis B viral replication may affect lipid metabolism and the secretion of various adipokines [25–27]. Indeed, hepatitis B viral load is negatively associated with hepatic steatosis and may suggest a protective effect on hepatic steatosis in alcohol and non-alcohol induced hepatic steatosis and liver disease.

The current study excludes patients with decompensated liver function, who were unsuitable for liver biopsy. Most alcoholic patients with decompensated liver function developed severe degree of alcoholic hepatitis or cirrhosis clinically. The percentage of patients having alcoholic hepatitis and alcoholic cirrhosis in this study was less than our previous studies and was underestimated.

Conclusion

The patients having concomitant alcoholism and HBV infection had developed the histological features of both alcoholic liver disease and viral hepatitis B. In high HBV endemic area, the histology presents the features of alcoholic liver disease (steatosis, hepatocyte ballooning, and focal necrosis) in patients with HBV infection. These patients should provide full details of their alcohol consumption history and the disease prognosis should be handled with extra care. Furthermore, the assessment of hepatitis B viral activity in alcoholic liver disease depends on detectable viral load and histological features of viral hepatitis B in patients with concomitant HBV infection and alcoholism.

Acknowledgments

We thank Tsung-Ching Chou, Chih-Yuau Lee, Yu-Chan Lee, and Shuting Lin for their help in collecting and analyzing the data. This study was supported by grants from Ministry of Science and Technology (MOST 105-2314-B-650-004-MY3), E-Da Hospital-National Taiwan University Hospital Joint Research Program (105-EDN13), and E-Da Hospital (EDAHP104016, EDAHP104047, and EDAHP104055).

References

1. Sung JL, Chen DS, Lai MY, Yu JY, Wang TH, et al. (1984) Epidemiological study on hepatitis B virus infection in Taiwan. Gastroenterol J Taiwan 1: 1-9.
2. Chen DS, Kuo GC, Sung JL, Lai MY, Sheu JC, et al. (1990) Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. J Infect Dis 162: 817-822.
3. Gao B, Batailler R (2011) Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 141: 1572-1585.
4. O'Shea RS, Dasarathy S, McCullough AJ; Practice Guideline Committee of the American Association for the Study of Liver Diseases, Practice Parameters Committee of the American College of Gastroenterology (2010) Alcoholic liver disease. Hepatology 51: 307-328.
5. Lin CW, Chen YS, Lai CH, Peng DS, Weng HC, et al. (2010) Esophagogastroduodenoscopy predicts mortality in hospitalized patients with alcoholic liver disease in Taiwan. Hepatogastroenterology 57: 305-308.
6. Hu JT, Huang SF, Lin CL, Lin PH, Tseng TL, Yang SS (2011) Current status of alcoholic liver disease in Taiwan. Gastroenterol J Taiwan 28: 234-241.
7. Yang SS (2008) Alcoholic liver disease: clinical and Sonographic features. Journal of Medical Ultrasound 16:140-149.
8. Huang YW, Chen PJ (2010) Overview of alcoholic liver disease in Taiwan. J Clin Hepatol 26:247-248.
9. Gao B (2002) Interaction of alcohol and hepatitis viral proteins: implication in synergistic effect of alcohol drinking and viral hepatitis on liver injury. Alcohol 27:69-72.
10. Balasubramanian S, Kowdley KV (2005) Effect of alcohol on viral hepatitis and other forms of liver dysfunction. Clin Liver Dis 9: 83-101.
11. Morgan TR, Mandayam S, Jamal MM (2004) Alcohol and hepatocellular carcinoma. Gastroenterology 127: 837-859.
12. Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, et al. (2002) Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 36: 1206-1213.
13. Lin CW, Lin CC, Mo LR, Chang CY, Peng DS, et al. (2013) Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 58: 730-735.
14. Alcohol liver disease: Morphological manifestations (1981) Review by an international group. Lancet 1: 707-711.
15. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, et al. (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 41: 1313-1321.
16. Yeh MM, Brunt EM (2014) Pathological features of fatty liver disease. Gastroenterology 147: 754-764.
17. Crawford JM (2012) Histologic findings in alcoholic liver disease. Clin Liver Dis 16: 659-716.
18. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR (1999) Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 94: 2467-2474.
19. Ishak K, Bapista A, Bianchi L, Cella F, De Groote J, et al. (1995) Histological grading and staging of chronic hepatitis. J Hepatol 22: 696-699.
20. Bedossa P, Yovandt T (1996) An algorithm for the grading of activity in chronic hepatitis C. The METAIVIR Cooperative Study Group. Hepatology 24: 289-293.
21. Talley NJ, Roth A, Woods J, Hench V (1988) Diagnostic value of liver biopsy in alcoholic liver disease. J Clin Gastroenterol 10: 647-650.
22. Larkin J, Clayton MM, Liu J, Feitelson MA (2001) Chronic ethanol consumption stimulates hepatitis B virus gene expression and replication in transgenic mice. Hepatology 34: 792-797.
23. Min BY, Kim NY, Jang ES, Shin CM, Lee SH, et al. (2013) Ethanol potentiates hepatitis B virus replication through oxidative stress-dependent and -independent transcriptional activation. Biochem Biophys Res Commun 431:92-97.
24. Lieu YF, Chu CM (2009) Hepatitis B virus infection. Lancet 373: 582-592.
25. Machado MV, Oliveira AG, Cortez-Pinto H (2011) Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol 26: 1361-1367.
26. Wong VW, Wong GL, Chu WC, Chim AM, Ong A, et al. (2012) Hepatitis B virus infection and fatty liver in the general population. J Hepatol 56: 533-540.
27. Wong VW, Wong GL, Yu J, Choi PC, Chan AW, et al. (2010) Interaction of adipokines and hepatitis B virus on histological liver injury in the Chinese. Am J Gastroenterol 105: 132-138.

OMICS International: Open Access Publication Benefits & Features

Unique features:
- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

Special features:
- 700+ Open Access Journals
- 50,000+ Editorial team
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at major indexing services
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: http://www.omicsonline.org/submission