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Spectrum of hepatic disorders encountered in the Hepatology Clinics of RIPAS Hospital

Jalihal ANAND, Vui Heng CHONG,
Division of Gastroenterology and Hepatology, Department of Medicine,
RIPAS Hospital, Bandar Seri Begawan, Brunei Darussalam

ABSTRACT

Introduction: In the Southeast Asian region where chronic hepatitis B virus (HBV) infection remains prevalent, HBV related disorders comprise a significant proportion of cases managed by the Hepatology clinics. Additionally, non-alcoholic fatty liver disease (NAFLD) is becoming an increasingly common condition referred to Hepatology clinics for management. We prospectively assessed the spectrum of hepatic disorders managed by the Hepatology clinics in RIPAS hospital, the only tertiary referral centre in Brunei Darussalam. **Materials and Methods**: All patients seen for hepatic disorders (new referral or follow-up) during a 32 working days period were included in this study. Patients attending for non-hepatic disorders were excluded. **Results**: During this period, hepatic disorders accounted for 32.2% of the cases managed. The mean age of patients with hepatic disorders was 43.3 ± 12.2 years old with more male patients (65.7%). New referrals accounted for 10%. Overall, 49.6% were positive for HBV, 12% for chronic hepatitis C virus (HCV) infection and 42.1% had evidence of NAFLD. There were overlap of disorders in 15.5% (12.5% HBV/NAFLD, 2.1% HCV/NAFLD and 1.2% HBV/HCV). Nineteen cases (5.75) had cirrhosis, most commonly associated with HBV and HCV. A quarter were cryptogenic. Patients with NAFLD were significantly heavier than those with HBV, HCV/HBV and the 'Others' group. There was also a significant trend for elevated serum alanine aminotransferase among those with NAFLD. **Conclusion**: Chronic HBV infection is still the most common hepatic disorder encountered in our Hepatology clinics. However, NAFLD is becoming an increasingly more common condition.

Keywords: Chronic liver disease, chronic hepatitis, fatty liver disease, viral hepatitis

INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains endemic in the Asia Pacific region with almost three quarters of the world's affected population residing in this region. [1] In South–east Asia most countries continue to be categorised as highly endemic (>8% infection rate). [2] HBV is the leading cause of acute and chronic hepatic failures in regions with high infection rates and is the leading cause of liver cirrhosis and hepatocellular carcinoma. [1, 3] However, the infections rates are declining with the introduction of effective vaccination programmes, blood screening and better

Correspondence author: Anand JALIHAL
Division of Gastroenterology and Hepatology,
Department of Medicine, RIPAS Hospital,
Bandar Seri Begawan, Brunei Darussalam.
Tel: +673 2242424 Ext 5233 Fax: +673 2242690
E mail: manikjali@hotmail.com

understanding of the infection. Despite this, chronic HBV infections continues to the most common hepatic disorder managed in the Hepatology clinics.

As the standards of living improve with major changes in lifestyle, the incidence of weight disorders along with the associated metabolic disorder also increases. Non-alcoholic fatty liver disease (NAFLD) is part of the metabolic syndrome and can progress to end stage liver disease with its associated complications. [4] The prevalence of NAFLD is increasing. This situation is also true in Brunei Darussalam, a developing nation where previously such problems had been considered as uncommon. To date, there is no published data available on the spectrum of hepatic disorders in our local setting. This study assessed the spectrum of hepatic disorders managed in the Hepatology clinics of RIPAS hospital, a tertiary referral centre for the whole of Brunei Darussalam. We also assessed the differences between these hepatic disorders.

MATERIALS AND METHODS

This study was conducted in a 550 bed tertiary referral centre (RIPAS Hospital), which has all major speciality services providing care for a population catchment of approximately 320,000 (three of the four districts). The Hepatology clinics are managed by three specialists. Three clinics per week are specifically dedicated to hepatic disorders with occasional extra clinic on other days.

All patients being managed for hepatic disorders (new referral or follow-up) during a designated 32 working days period were studied. Where patients had defaulted their clinic appointments, the case notes were reviewed. Patients who had attended for non-hepatic disorders such as gastrointestinal disorders or for endoscopy were excluded from the study. Data on demographics (age, gender, ethnicity and weight), co morbid conditions and types of hepatic disorders (HBV, HCV, NAFLD, 'Others' such as primary biliary cirrhosis, primary sclerosing cholangitis and non-specific hepatitis of unknown aetiologies)

Table I: Demographic and previous medical history of subjects

Demographic data	**n (%)**
Gender	
Male	220 (65.7)
Female	115 (34.3)
Race	
Malays	255 (76.1)
Chinese	60 (17.9)
Indigenous	9 (2.7)
Others	11 (3.3)
Co morbid conditions	159 (47.5)
Hypertension	52 (15.5)
Diabetes mellitus	54 (16.1)
Hyperlipidemia	83 (24.8)
New patients	33 (9.9)
Follow up patients	302 (90.1)

were collected. Diagnoses of hepatic disorders were confirmed on retrospective review of all blood investigations (viral serologies, autoimmune markers, metabolic markers such as copper and iron studies) as well as following ultrasound examination. NAFLD was diagnosed where there was either presence of abnormal liver profiles in the absence of other aetiologies with typical phenotypes, or ultrasound detection of fatty liver. Overlap was defined where there was combination of the various aetiologies. The study was conducted in accordance to the standard set out in the Declaration of the Helsinki.

The data were coded and entered into the Statistical Program for the Social Studies (SPSS, Version 10.0, Chicago IL, USA) for analysis. *Chi square* and ANOVA tests were used where appropriate with the level of significance taken at $p < 0.05$.

RESULTS

Over the study period, there were a total of 1,041 patients, of which hepatic disorders accounted for 32.2%. The mean age of patients with hepatic disorders was 43.3 ± 12.2 years old with more male patients (65.7%) being represented. New referrals accounted for 10%. The demography of patients is shown in Table 1.

The spectrum of hepatic disorders is shown in figure 2. Overall, 49.6% were positive for HBV, 12% for chronic hepatitis C virus (HCV) infection and 42.1% had evidence of NAFLD. There were overlap of disorders in 15.5% (12.5% HBV/NAFLD, 2.1% HCV/NAFLD and 1.2% HBV/HCV). Only one patient (0.3%) had overlap of the three major disorders. The other hepatic disorders consisted of autoimmune hepatitis [AIH]/cholangitis (n=5), primary biliary cirrhosis (n=3), toxic hepatitis (n=3), hepatitis of unknown aetiology (n=3), hepatic cysts (n=3), Gilbert's syndrome (n=3), alcoholic hepatitis (n=1), hepatic tuberculosis (n=1) and miscellaneous (n=4).

Among the chronic HBV patients, 22.3% were positive for 'e' antigen and 8.8% were under treatment, mainly with anti-viral

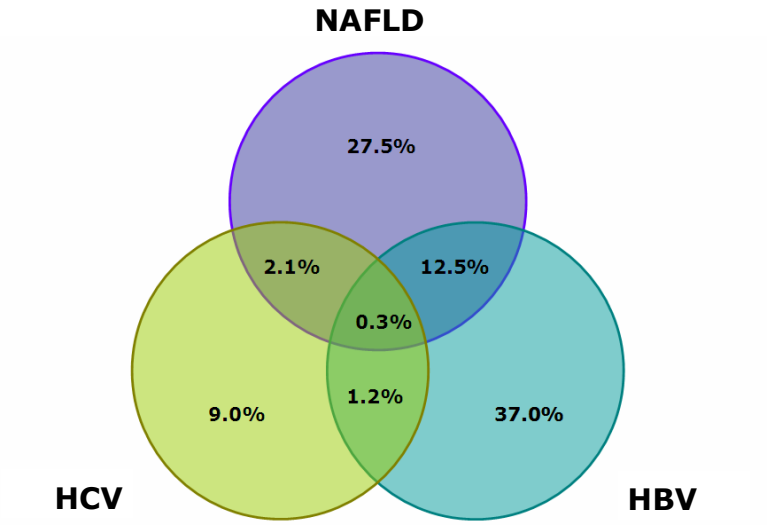

Fig. 1: Distributions of the three common hepatic disorders.

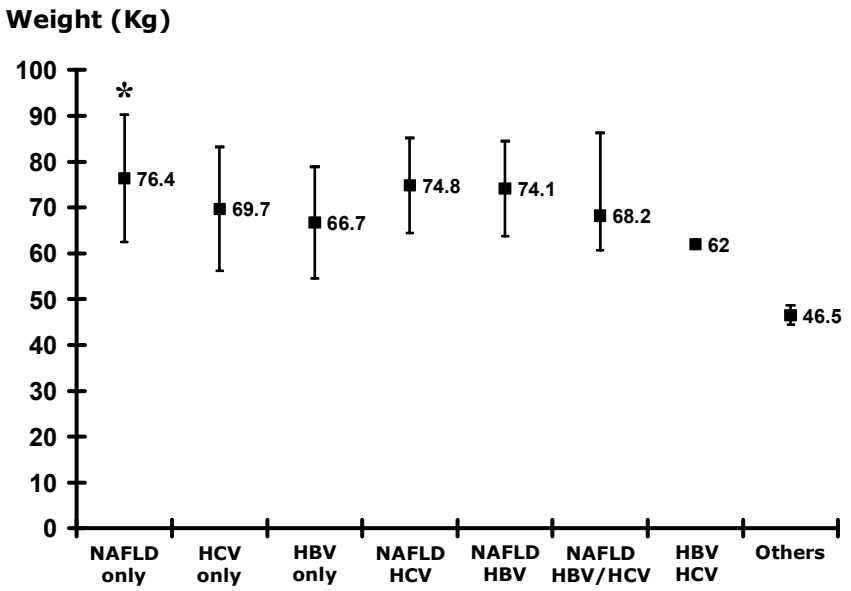

Fig. 2: Weight distributions of the various hepatic disorders. * $p<0.05$ between NAFLD only and HBV only and 'Others'

nucleotide analogue. Among the patients with chronic HCV infection, 52.5% were positive for HCV RNA. Nineteen patients (5.7%) were found to have liver cirrhosis secondary to chronic HBV (n=6), HCV (n=3), HBV/HCV (n=1), cryptogenic (n=5), AIH (n=1), alcoholic liver disease (n=1), biliary atresia (n=1) and association with hepatic cyst (n=1). Three of the patients with cryptogenic cirrhosis had NAFLD documented.

There were five cases with hepatocellular carcinoma (HCC) where all had chronic HBV infection. One case had overlap with chronic HCV infection and two cases had liver cirrhosis.

Results of serum alanine aminotransferase (ALT) levels were available for 333 patients. This was elevated in 151 (51%) patients, indicating disease activity. There was also a significant trend for elevated serum ALT among those with NAFLD.

In generally, patients with NAFLD were heavier. Patients with only NAFLD were significantly heavier than those with only HBV or the 'Others' catergory (Figure 2). Patients with NAFLD had significantly ($p<0.001$) more metabolic disorders (diabetes, hypertension and hyperlipidemia) compared to the 'Others (HBV, HCV or other hepatic disorders) (Figure 3).

DISCUSSION

Our study showed that patients with hepatic disorders accounted for almost a third of those attending at the Division of Gastroenterology and Hepatology. When the cases were divided into the three major categories; for endoscopy, evaluations or follow up of gastrointestinal complaints, or hepatic abnormalities, it would appear that the case mix were equally distributed.

Among the group of patients with hepatic disorders, chronic HBV infection accounted for the majority of cases followed by NAFLD and chronic HCV infection. This is not unexpected as Brunei Darussalam is located within the endemic zone for HBV infection where infections rate is still reported as being

over 8%. Two previous studies conducted on blood donors had shown lower rates at 4.7% (1989) for Suri Seri Begawan Hospital and 6.0% (1990) for RIPAS Hospital. [5, 6] However, a recent study (2008) had reported a rate of less than one percent amongst blood donors. [7] The exact overall infection rates for the whole population is likely to be higher as blood donors are generally healthy. Another reason for the large proportion of HBV infection seen in the clinic is that RIPAS is a tertiary referral centre which follows up most, if not all of the patients who are detected to have chronic HBV infection. At the present time, peripheral clinics do not regularly follow up chronic HBV patients. Furthermore, it is likely that a proportion of patients with asymptomatic disease remain undetected.

Among our patients with chronic HBV infection, only 22.8% were positive for 'e' antigen and this was designated as a replicative stage of the infection that could either be in the immune-tolerant or immune-clearance. Among our chronic HBV patients, only 8.8% were under treatment. This consisted mainly of treatment with lamivudine with only a small proportion on pegylated interferon. The few patients being treated indicated that the majority of our patients were in the non active or immune-tolerant phase based on serum transaminase results. The use of lamivudine or other nucleoside or nucleotide analogues for treating chronic HBV is a reflection of the preference of the treating physicians. However, more patients are now being treated with pegylated interferon. It is important to note that the findings may not accurately reflect our patients with chronic HBV due to being based on a single centre and the limited sampling period.

NAFLD was first described in the late seventies and early eighties but did not gain prominence or attention until the last decade. [8] There is now much interest in this entity due to increasing prevalence secondary to the rise in prevalence of the overweight and obese. This situation is also true in our local setting. A recent study of patients from various clinics in the government hospitals showed 63.3% were overweight. Of these, 28.3% were obese. Of those with overweight, with obesity in two third of the patients. [9] Of major con-

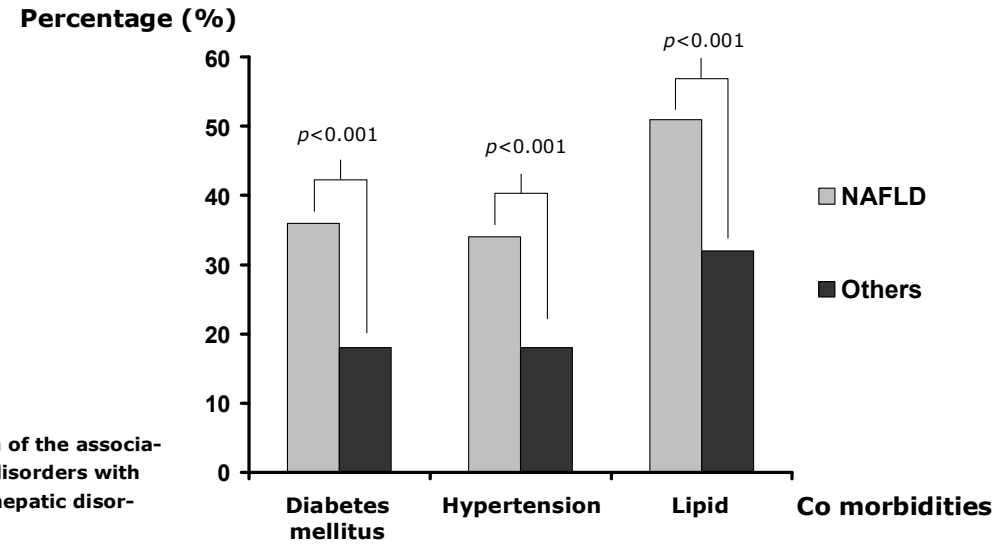

Fig. 3: Comparison of the association of metabolic disorders with NAFLD and other hepatic disorders.

cern was the result of the recent integrated health screening of government servants which indicated that 60% are either obese or overweight. [10] Another study carried out in the primary health setting showed metabolic disorder to be common. [11] It is also not surprising that, compared to other hepatic disorders, a larger proportion of our NAFLD patients had chronic disorders associated with metabolic syndrome such as diabetes mellitus, hypertension and hyperlipidemia. Our previous study had also shown similar findings. [9] It is very likely that in the future, the proportion of patients with these conditions will increase corresponding to the increase in the incidence of weight disorder or obesity.

Chronic HCV infection was the third most common disorder and in our setting, the most common aetiology is intravenous drug use followed by haemodialysis. [12, 13] The number of patients infected with HCV through dialysis is fortunately decreasing with the introduction of infection control measures especially with the segregation of dialysis point for patients infected with HCV. [13] As the infection rate through blood products transfusion and haemodialysis is decreasing, intravenous drug use is becoming the main cause of HCV infection in our local setting. Among our patients with chronic HCV infection, 52.5% were positive for serum HCV RNA. This is lower than expected where approximately three quarters of patients are expected to have active infection. Our findings can be explained by the fact that we routinely follow up our treated patients to monitor for relapse or for other conditions. Fortunately, in our setting, the predominant genotypes consist mainly of genotypes 2 and 3, which have more favourable responses to current standard therapy. [14]

Among the 'Other' group, AIH and primary biliary cirrhosis accounted for a small proportion. [15, 16] There was only one case of alcoholic liver disease and this patient was already cirrhotic. The low prevalence of alcoholic liver disease in our setting is attributed to the strict restrictions and control on alcohol consumption.

Where overlap of the various disorders occurred, the most common was NAFLD with HBV and NAFLD with HCV. Overlap of NAFLD/HBV is not unexpected due to the increasing prevalence of weight disorder. This is similarly true for HCV patients. However, it is also known that patient with genotype 3 are associated with increase steatosis and it has been shown to be due to the viral effect.

Among our patients with hepatic disorders, there were 19 cases (5.7%) with liver cirrhosis where the majority were associated with HBV and HCV infections. Interestingly, cryptogenic cirrhosis accounted for a quarter of the causes. Of the five cases of cryptogenic cirrhosis, three patients had NAFLD documented. It is possible that some of these cryptogenic cirrhosis patients may actually have seroconverted from their chronic HBV infection as some may not have had the complete evaluation, including testing for 'e' and core antibodies. For these cases, in the absence of HBsAg, the patient is usually labeled as cryptogenic. To date, we have not encountered any case of chronic liver disease secondary to Wilson's disease or haemachromatosis, which are conditions considered as extremely rare in our region.

Our study also showed that patients with components of NAFLD are generally

heavier than the other group. This is also reflected by the finding that larger proportions of patients with NAFLD have co-morbidities (diabetes mellitus, hypertension and hyperlipidemia) categorised as part of the metabolic syndrome. We also showed that transaminitis was commonly seen in patients with NAFLD when compared to the other disorders. However, this is likely a reflection of current practice rather than NAFLD patients having more disease activities. In the current setting, diagnosis of NAFLD can only be made after an ultrasound scan which, in most cases are requested for the evaluation of abnormal liver profiles. Those found to have abnormal liver profiles and NAFLD are more likely to have been referred from the peripheral clinics. It is likely that there are more patients with NAFLD who remain undetected as the majority will have minimal or normal liver profiles. Although chronic HBV infection represents a large proportion of our patients, only a small proportion had abnormal liver profiles. Even among our patients with 'e' antigen, the majority were in the immuno-tolerant phase and thus did not have any disease activity.

There are several limitations with our study. First, the study period of 32 days may be considered short and thus may not provide a true representative sample of the Hepatology work load. Second, we had reviewed all patients including the new referrals and those already on follow up. This can explain some our findings such as the lower rates of 'e' antigen positive for chronic hepatitis B or RNA positive for chronic hepatitis C patients. Despite the limitations, our results will form the foundation for further studies on the spectrum of hepatic disorders. It will also provide a platform for future comparisons as the demography and disease spectrums change with time.

In conclusion, we showed that hepatic disorders accounted for almost a third of the total cases managed in our clinics. The majority of these patients had chronic HBV infection followed by NAFLD and chronic HCV infection.

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WORLD HEPATITIS DAY

28 July 2011

~500 million (1 in 12 person) have either hepatitis B or hepatitis C infection

1.5 million die from either hepatitis B or hepatitis C infection each year