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## PUBLIC HEALTH RESEARCH

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### **Aetiologies of Liver Cirrhosis among Adult Patients Attending A Hepatology Clinic at Selangor, Malaysia**

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#### **ABSTRACT**

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<b>Introduction</b>	Liver cirrhosis is an important cause of morbidity and mortality.
<b>Methods</b>	Our study aimed to describe the aetiologies of liver cirrhosis and its associated risk factors among adult patients attending the Hepatology Clinic, Serdang Hospital, Malaysia from 1st January 2010 to 30th June 2017. Aetiology was determined by patients' medical history as well as biochemical and/or histological findings. The severity of the liver cirrhosis, together with the presence of complications and incidence of hepatocellular carcinoma were documented.
<b>Results</b>	A total of 357 adult patients were diagnosed with liver cirrhosis including 199 male patients (55.7%) and 158 female patients (44.3%), with a mean age of 54-year-old (range: 28–84 –year-old). The determined most likely causes of liver cirrhosis were chronic hepatitis B (N=145, 40.6%), chronic hepatitis C (N= 67, 18.8%), cryptogenic liver disorder (N= 63, 17.6%), alcohol (N=42, 11.8%), non-alcoholic fatty liver disease (N=25, 7.0%), and others (N=15, 4.2%). Chronic hepatitis B was predominant among Chinese whereas alcohol consumption was mainly found among Indians, and Hepatitis C-linked liver cirrhosis was highest among Malays. Majority of the patients had compensated cirrhosis with Child-Pugh A (N=221, 61.9%) at the time of diagnosis. 80.4% (N=287) of the cirrhotic patients had performed at least one endoscopy surveillance, with 28.6% (82/287) of them had endoscopic evidence of portal hypertension. 32.2% of patients had at least one hospitalization due to complication of cirrhosis. 41 patients (11.5%) had concurrent hepatocellular carcinoma during the follow up.
<b>Conclusions</b>	Hepatitis B viral infection remains the most common cause of cirrhosis among patients attending Hepatology Clinic, Serdang Hospital.
<b>Keywords</b>	Aetiology - liver cirrhosis - Malaysia.

Article history

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### INTRODUCTION

Liver cirrhosis is a progression of hepatic fibrosis and replacement of the healthy liver tissues by scarring, that takes few months to years. Cirrhosis is one of common causes of mortality and morbidity worldwide and remains a burden to public health.<sup>1</sup>

The aetiology of cirrhosis differs geographically and socioeconomically, with alcoholism, chronic hepatitis C (CHC), and non-alcoholic fatty liver disease (NAFLD) being more common reported in western countries,<sup>2-4</sup> while chronic hepatitis B (CHB) as the most common cause of liver cirrhosis in Asia (Hong Kong,<sup>5</sup> South Korea,<sup>6</sup> India,<sup>7</sup> Iran,<sup>8</sup> Singapore).<sup>9</sup> However, this was different in Japan<sup>10</sup>, in which CHC was the major aetiology leading to the cirrhosis. In recent years, the increasing incidence of overweight or obesity, diabetes mellitus and metabolic syndrome among the younger population in Malaysia, which could be due to sedentary lifestyle, may have an incremental impact on the risk of developing NAFLD among Malaysians.<sup>11</sup>

The indication for hospitalization among cirrhotic patients is frequently due to consequences of portal hypertension, decompensation or complication, especially ascites, variceal bleeding, jaundice, hepatic encephalopathy, and hepatocellular carcinoma (HCC).<sup>12</sup> Approximately half of the cirrhotic patients have endoscopic evidence of varices, and one-third of them developed variceal bleeding.<sup>13, 14</sup> Therefore, esophagogastroduodenoscopy (OGDS) was advised to be performed early to evaluate the risk of variceal bleeding, followed by appropriate prophylactic management either by pharmacologic or endoscopic variceal band ligation (EVL).

Cirrhosis itself is well known as a factor leading to development of HCC.<sup>15</sup> Based on GLOBOCAN 2020,<sup>16</sup> HCC contributed to 4.4% of new cases of malignancies and 6.9% of cancer mortalities in Malaysia. The risk of developing HCC depends on the underlying aetiology of the cirrhosis. Kato Y et al. had noticed the rate of developing HCC was significantly higher in the CHB or CHC group than in the non-B non-C groups.<sup>17</sup> This was further reported in the REVEAL-HBV study that involved 3160 participants: CHB with a higher viral load had been reported as a strong factor leading to HCC.<sup>18</sup>

Malaysia is a country with national population of approximately 32 million, with three major ethnic groups, Malays (61.7%), Chinese (20.8%) and Indian (6.2%) who have different beliefs and cultural practices. This unique multi-ethnic makeup of population is quintessential in studying the impact of ethnicity on the characteristics of a variety liver diseases. Viral hepatitis was known as the major aetiology of cirrhosis among Malaysians.<sup>19, 20</sup> It was transmitted by vertical transmission during birth or shortly after birth, and horizontal transmission via exposure to

infected blood or body fluids. However, according to the scarce data describing the patterns of liver cirrhosis in Malaysia, the epidemiology of liver cirrhosis is different between ethnic groups, gender, and geographic regions.<sup>19</sup> This could be explained by the epidemiology of CHB and CHC and also the alcohol drinking pattern in the population.

The study aimed to determine the association between the demographic factors and the aetiologies of liver cirrhosis among the patients at Serdang Hospital. Besides, the prevalence of complications of liver cirrhosis together with incidence of HCC were further analysed as well.

### MATERIALS AND METHODS

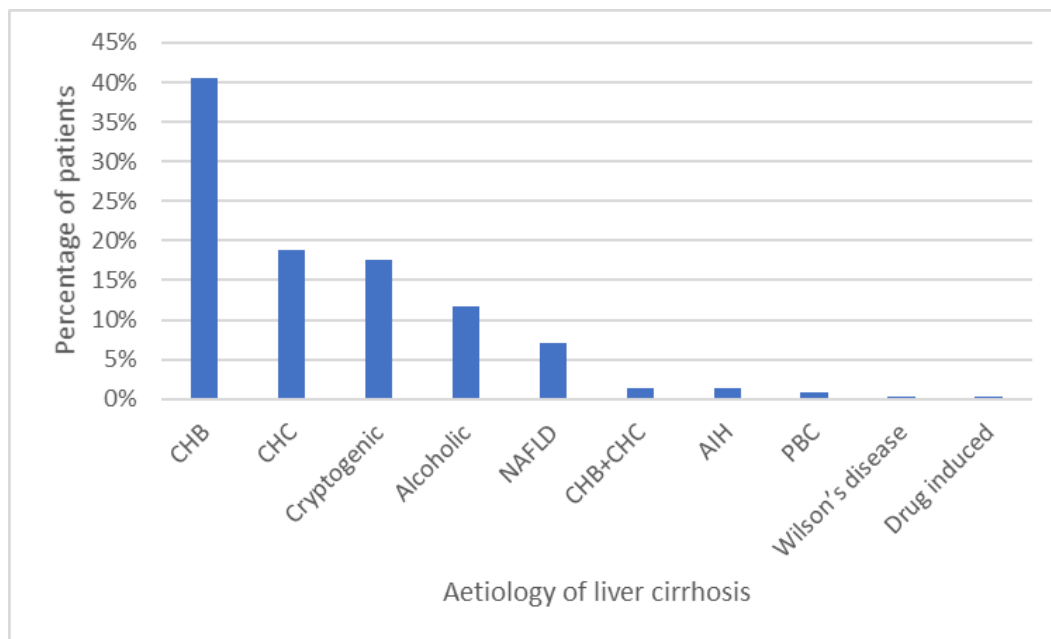
Retrospectively, the data among cirrhotic patients attending the Hepatology Clinic at Serdang Hospital from the period of 1<sup>st</sup> January 2010 to 30<sup>th</sup> June 2017 were collected via hospital Electronic Health Information System (EHIS). Serdang Hospital is a government-funded multi-specialty hospital with 620 beds, which is located in Sepang district, Selangor. All cirrhotic patients aged at least 18-year-old, with complete records and follow-up were included. The diagnosis of liver cirrhosis was made based on patient's clinical data with either a positive radiologic or pathologic result (i.e., ultrasonography, computerized tomography (CT) scan or liver biopsy). Patient's demographic characteristics (gender, age, ethnicity), aetiology of liver cirrhosis (based on patient's history and clinical presentation, biochemical, serological and histological tests), OGDS findings, Child-Pugh scoring at the time of diagnosis, together with complication, and incidence of HCC during the time of clinic follow up were extracted and further analysed. Paired t test and one-way ANOVA were performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, [www.graphpad.com](http://www.graphpad.com). This research was registered in accordance with the National Medical Research Register Malaysia and ethics approval was granted before the commencement of the data collection.

### RESULTS

Demographics characteristics and aetiology distribution analysis

A total of 357 patients were recruited in this study. Fig. 1 provided the overall aetiological profile of liver cirrhosis among the collected data. CHB (40.6%) was the most common aetiology of cirrhosis among the patients. This was followed by CHC (18.8%), cryptogenic (17.6%), alcoholic (11.8%), and NAFLD (7.0%), AIH (1.4%), co-infection of hepatitis B and C (1.4%), PBC (0.8%), Wilson's disease (0.3%) and drug induced (0.3%). Among these patients, 55.5% of the patient belonged to the age group of 40-59 years, and the mean age

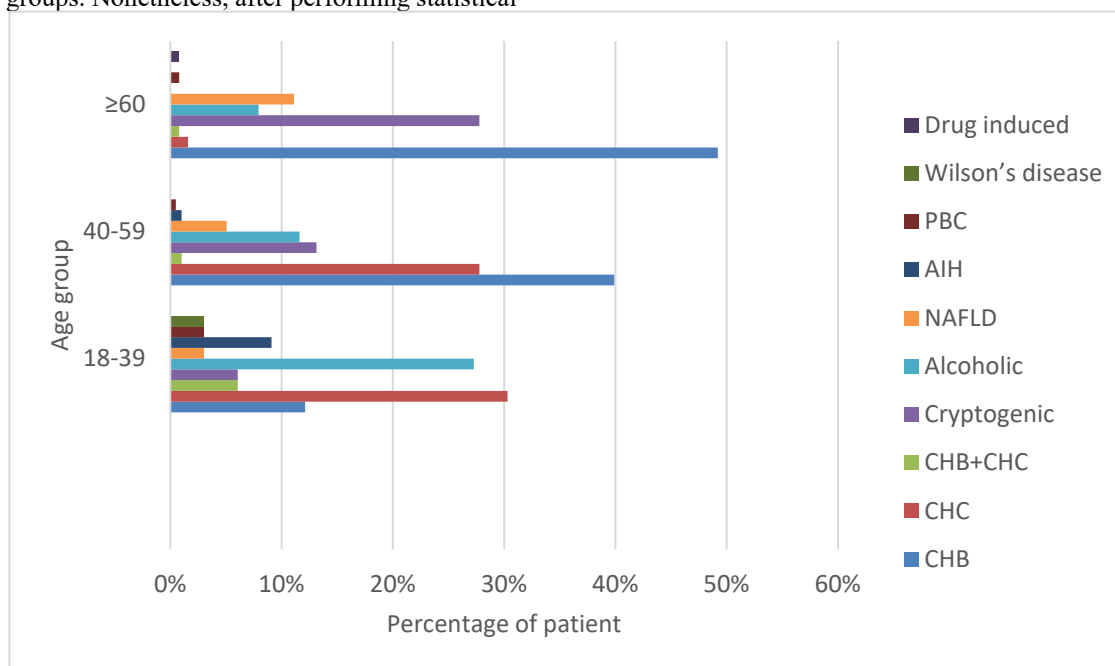
was 54 years. The youngest patient was 28 years old and oldest 84 years.



**Figure 1** Overall aetiology distribution of liver cirrhosis. CHB=chronic hepatitis B; CHC=chronic hepatic C; NAFLD=non-alcoholic fatty liver disease; AIH=autoimmune AIH=autoimmune hepatitis; PBC=primary biliary cirrhosis

Figure 2 demonstrated variations in terms of causes leading to liver cirrhosis among different age groups. Nonetheless, after performing statistical

analysis (one-way ANOVA), no statistical significance ( $p=0.0878$ ) was observed.



**Figure 2** Distribution of aetiology among different age groups. CHB= CHB=chronic hepatitis B; CHC=chronic hepatic C; NAFLD=non-alcoholic fatty liver disease; AIH=autoimmune AIH=autoimmune hepatitis; PBC=primary biliary cirrhosis

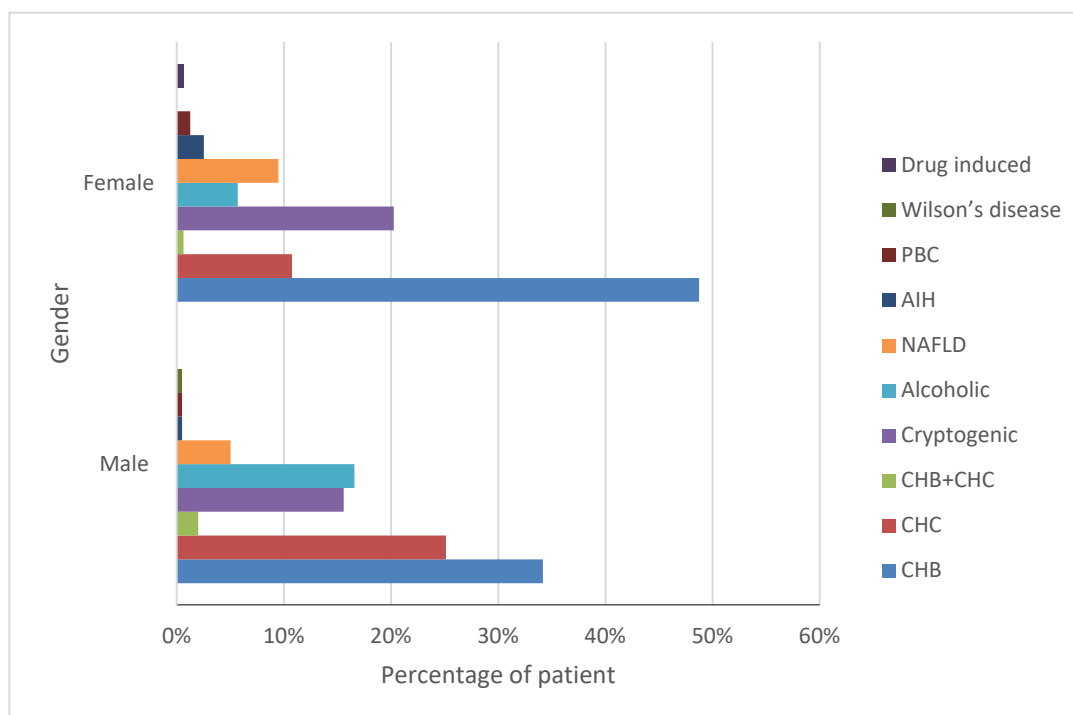
Among these 357 patients with liver cirrhosis, 55.7% of patients were male, with the male to female ratio of 1.26:1. The distribution of

aetiology of for male and female was illustrated in Fig. 3, and further statistical analysis (paired t test) did not show statistically significant difference

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between these two genders ( $p=0.3598$ ). For both genders, CHB (34.1% in male and 48.7% in female)

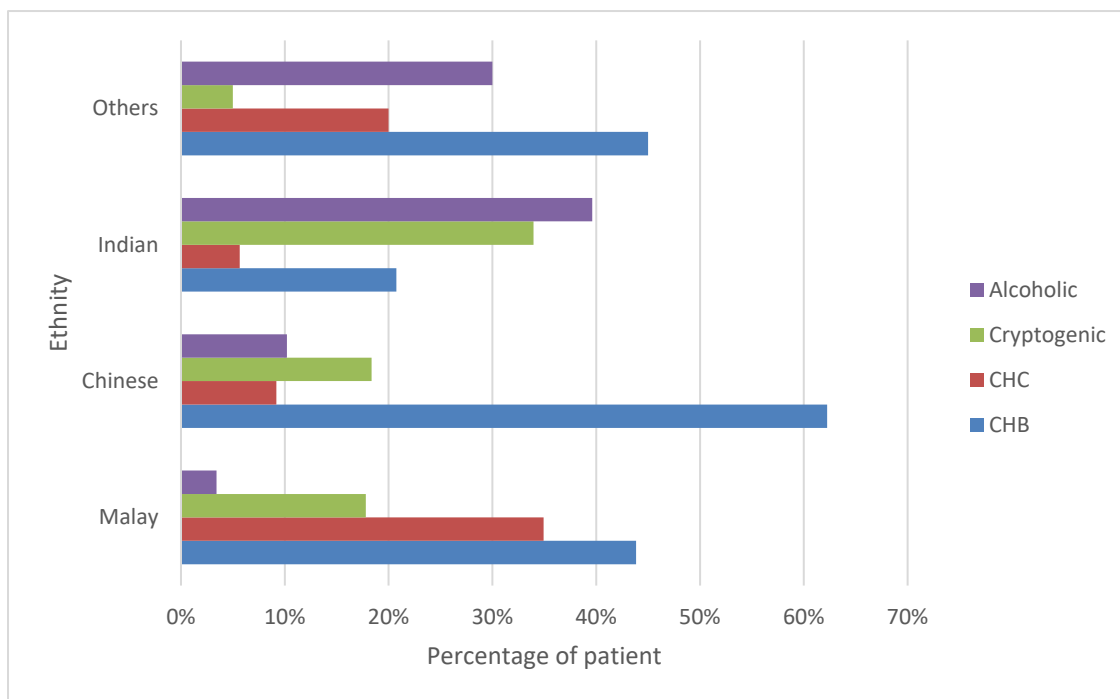
was found to be the leading cause to develop liver cirrhosis.



**Figure 3** Distribution of aetiology among males and females. CHB= chronic hepatitis B; CHC=chronic hepatic C; NAFLD=non-alcoholic fatty liver disease; AIH=autoimmune hepatitis; PBC=primary biliary cirrhosis

The four leading causes of liver cirrhosis namely CHB, CHC, cryptogenic liver diseases, and alcoholic were analysed on their distribution among the major races in this study. As shown in Fig. 4, CHB was the predominant aetiology among Chinese, contributing to 62.2%. For Malay, CHB was also the most common cause but with lower contribution (43.8%) as compared with that of Chinese. Besides, CHC was the second most

common cause (34.9%) among Malay. On the other hand, alcohol consumption (39.6%) and cryptogenic liver diseases (34.0%) were the major causes among Indian patients. With regard to other races, CHB was again the major cause (45%), followed by alcohol consumption (30%). However, these variations were without statistical significance ( $p=0.4262$ ).



**Figure 4** Distribution of aetiology among races. CHB= CHB=chronic hepatitis B; CHC=chronic hepatic C; NAFLD=non-alcoholic fatty liver disease; AIH=autoimmune hepatitis; PBC=primary biliary cirrhosis

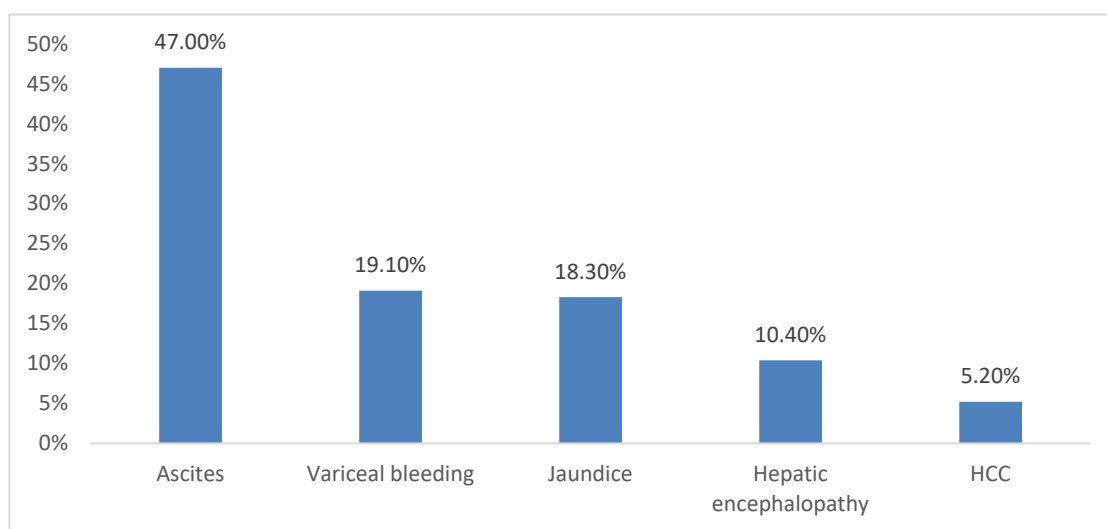
Staging or severity of cirrhosis at the time of diagnosis

61.9% of the patients had compensated cirrhosis with Child-Pugh A (least severe). This was followed by 23.8% with Child-Pugh B (moderate severe), and 14.3% with Child-Pugh C (most severe).

80.4% (N=287) of the cirrhotic patients had performed at least one OGDS surveillance, with

28.6% (82/287) of them had endoscopic evidence of portal hypertension.

About one third (115 out of 357, 32.2%) of cirrhotic patients had at least one hospitalisation due to complication during this study period (See Fig. 5). Among the complications, ascites was the most common (47.0%).



**Figure 5** Presenting complications of liver cirrhosis requiring hospitalizations

During the clinic follow up, 41 of these 357 liver cirrhosis patients (11.5%) had developed concurrent HCC. The initial causes of liver cirrhosis

for these 41 patients were CHB, CHC, CHB+CHC, cryptogenic and alcoholic liver diseases (Table 1).

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**Table 1** Incidence of HCC together with the aetiology during the clinic follow up

Aetiology	n of HCC/n of cirrhosis (%) (n=41/357, 11.5%)
CHB	23/145 (15.9%)
CHC	4/67 (6.0%)
CHB+CHC	1/5 (20%)
Cryptogenic	8/63 (12.7%)
Alcoholic	5/42 (11.9%)

## DISCUSSION

According to our study findings (Fig. 1), 60.8% of cirrhotic patients were caused by viral hepatitis, with CHB as the most common cause of cirrhosis. This was consistent with other Malaysian studies.<sup>19, 20</sup> In 2018, the incidence rate of CHB in Malaysia had increased from 2.26 per 100,000 in 2010 to 14.52 per 100,000 population, while the incidence rate of CHC was 8.65 per 100,000.<sup>21</sup> Although hepatitis B immunization coverage among the new-borns in Malaysia was reported up to 99.16% in 2018<sup>21</sup>, and some patients with CHC were able to receive the highly effective antiviral treatment at few Malaysian government hospitals since 2018, we can expect the rising trend of viral hepatitis related chronic liver disease (CLD) in the near future. Adults are more likely to have acute viral hepatitis infection through certain activities, such as tattooing, unprotected sexual activities, and intravenous drug use (IVDU). However, their low Hepatitis B vaccination coverage may continue to increase the incidence rate of CHB. In 2017, 0.3% of foreign workers in Malaysia were reported to have Hepatitis B infection.<sup>22</sup> The dramatic increasing population of foreign workers, especially those who are illegal, in this country may carry hepatitis virus, and continue to spread the disease silently. Although access to antiviral treatment is improving, it was estimated that only small proportion of patients with hepatitis C in Malaysia were treated with antiviral drugs.<sup>23</sup> Therefore, viral hepatitis will remain to be the major cause of CLD in the near future.

Interestingly, cryptogenic liver disease was the third commonest cause of cirrhosis after CHB, CHC and alcoholic in this study. Literatures suggested that some cryptogenic liver diseases were believed probably due to NAFLD. We noticed that cryptogenic liver diseases were commoner among females, elders and Indian patients, which was also happened in NAFLD. Cryptogenic liver disease is mainly diagnosed when other aetiologies had been excluded. Despite routine blood tests and ultrasound scan, liver biopsy was not routinely performed in most of our cirrhotic patient's prior the making diagnosis of cryptogenic liver disease. Therefore, this could be one of the limitations of our study.

The current study found that majority of cirrhotic patients were 40-59 years old with the mean age of 54 years (Fig. 2). This corresponded to

Qua et al's study that the mean age of cirrhotic patients in Malaysia was 58.8 years old.<sup>19</sup> In our study, we observed that the prevalence of CHB infection among cirrhotic patients increased with age. Few reasons could explain this finding. Firstly, national vaccination programme was only launched in Malaysia starting 1989, hence those who were current above thirty-year-old of age may had never received vaccination before. Therefore, CHB is expected still to be the leading cause of cirrhosis for next twenty years and there will be a decline in incidence perhaps thirty years from now. Secondly, the increasing rate of CHB infection among adults suggested the horizontal transmission is commoner during the adulthood. However, the prevalence of CHC infection was commoner among cirrhotic patients of 18-59 years old, but lower in the age group above 60 years old. This was different with some other countries such as Italy<sup>24</sup> and Japan<sup>25</sup>, where they observed the lower prevalence of CHC infection among young adults, but increasing prevalence during aging. This suggested that risk of being infection by hepatitis C virus is the greatest among those of reproductive age in which IVDU was the most common risk factor in Malaysia.<sup>26, 27</sup>

Male made up the majority of alcoholic cirrhosis cases (78.6%) and CHC cirrhosis cases (74.6%) (Fig. 3). It is evident from this study that more heavy alcohol drinking occurred among males, which was consistent with National Health and Morbidity Survey 2017. Besides, male preponderance among patients with CHC was likewise reported at Kuala Lumpur<sup>28</sup> and Kedah.<sup>29</sup> IVDU was most likely the risk factor for CHC infection among male patients.

By further studying the epidemiology of liver cirrhosis according to ethnicity (Fig 4), CHB was found to be the predominant aetiology of cirrhosis among Chinese due to their highest prevalence of CHB;<sup>19</sup> CHC cirrhosis was more common among Malays,<sup>22</sup> which could be explained by more drug abusers were Malays, and IVDU was reported as the major route of HCV transmission in Malaysia;<sup>26,27</sup> whereas alcohol was the main aetiology among Indians, presumably Indians consume alcohol at a larger amount and more frequently. However, it is crucial to rule out NAFLD occurring in those with excessive alcohol consumption.

61.9% of the patients had compensated cirrhosis with Child-Pugh A at the time of diagnosis. About one third of patients had at least one hospitalisation due to decompensation or complication during this study period (Fig. 5). Abdominal distension due to ascites was the commonest complication. This was similarly reported in existing literatures.<sup>30, 31</sup> However, no documentation regarding the attempt of abdominal paracentesis or prevalence of spontaneous peritonitis (SBP) in our study. Our preliminary data showed that majority of the cirrhotic patients had received at least one OGDS evaluation. However, only 28.6% of them had endoscopic finding of portal hypertension. This was lower than other literatures that reported gastroesophageal varices were detected in about half of the cirrhotic patients.<sup>13, 14</sup>

Patients with cirrhosis are at significant risk of developing HCC.<sup>32</sup> Our observations (Table 1) confirmed that cirrhotic patients associated with CHB were at high risk for developing HCC, which was comparable to previous studies.<sup>33-35</sup> This could be the reflection of existing significant CHB disease burden itself.

There were several practical limitations to our study. This was the single centre experience, which may not reflect the real situation of nationwide liver disease. The diagnostic criteria were not perfect, in which patients with more than one overlapping aetiology were categorized based on the predominant aetiology. Besides, histological assessment should be made compulsory in all the cirrhotic patients during making diagnosis of cryptogenic liver cirrhosis or NAFLD. Adherence to HCC surveillance should be further evaluated in the future study.

## CONCLUSION

We showed that CHB remains the most common etiologic factor among the cirrhotic patients attending a tertiary hospital in Selangor, Malaysia. Current study shared a useful sketch of the aetiologies, and clinical patterns of CLD in Malaysia. Compulsory vaccination among infants and improving Hepatitis B vaccination coverage in high-risk population groups include HCWs, contacts of HBsAg-positive persons, and foreign workers should be prioritized. Larger cohort studies on the aetiology of cirrhosis from other states in Malaysia are required to improve the understanding of liver cirrhosis aetiology in this region.

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## CONFLICT OF INTEREST

There is no conflict of interests regarding the publication of this article.

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