Viral and non-viral causes in patients with hepatocellular carcinoma in Arifin Achmad General Hospital, Riau Province during 2013-2017

Arfianti,1* Zulfatta Dwi Putra,2 Ekral Delhaldita,2 Ligat Pribadi Sembiring,3 Hendra Asputra3

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide. Recent reports have suggested increasing prevalence of HCC without evidence of hepatitis B and C infection (non-viral HCC). This study aimed to describe the distribution of viral and non-viral risk causes of hepatocellular carcinoma cases at Arifin Achmad General Hospital (AAGH).

Methods: This study using a cross-sectional approach conducted at Arifin Achmad General Hospital (AAGH), Riau Province from 2013 to 2017. Data were obtained from medical records of HCC patients using total sampling method.

Results: We included 129 cases of whom 64 (49.6%) were associated with viral causes, and 65 (50.4%) were non-viral HCC. Bivariate analyses showed that there was no age difference between viral and non-viral HCC patients, but the prevalence of non-viral HCC was significantly higher in females than males (OR: 3.12; 95% CI: 1.2-8.1; p=0.016). In addition, patients with alpha-fetoprotein (AFP) <400 ng/mL were more frequently associated with non-viral HCC compared with those with elevated AFP 400 ng/mL (OR: 3.71; 95% CI: 1.49-9.26; p=0.004).

Conclusion: There was an equal distribution of viral and non-viral causes in HCC cases at AAGH, Riau Province during 2013-2017. This suggests changing etiologies of HCC that may impact HCC surveillance.

Keywords: alpha-fetoprotein, gender, hepatitis B, hepatitis C, HCC surveillance, non-viral

INTRODUCTION

Liver cancer is the sixth most common cancer and the fourth leading cause of cancer mortality worldwide in 2018. Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancer. According to GLOBOCAN 2018, 841,000 new cases of liver cancer are diagnosed annually and causing 782,000 deaths. The most liver cancer burden is found in developing countries which makes up approximately 85% of the reported cases. In Indonesia, the liver cancer burden is estimated to be 18,468 new cases (5.3%) and causes 18,148 deaths in 2018.1 This indicates the dismal prognosis of patients with liver cancer in Indonesia.

The main risk factors for HCC are hepatitis B virus (HBV), hepatitis C virus infection (HCV) and alcohol consumption. Asia, including Indonesia, is an endemic area for HBV infection. Therefore 60% of HCC cases in Asia is related to HBV infection, 20% to HCV infection, alcohol consumption and other less common risk factors such as aflatoxin contamination and hereditary hemochromatosis. Despite the decreasing prevalence of chronic hepatitis B in most countries in Asia due to the success of universal vaccination and the advance of antiviral treatment, the incidence of HCC remains the same, except in Singapore where the incidence of HCC has declined significantly over the last 30 years.2,3

Interestingly, changing trends in the epidemiology of HCC have been documented globally. There have been accumulating reports on the rising of HCC cases without evidence of HBV or HCV infection (non-viral HCC). In Japan, where HCV is the most common cause of HCC, the incidence of HCV-related HCC has gradually declined in recent years. This likely reflects the success of a government-funded HCV treatment program. In contrast, non-viral HCC cases have substantially increased.4 The successful implementation of universal hepatitis B vaccination programmes in Asia has substantially decreased the proportion of HBV-related HCC. Several studies from Japan show that patients with non-viral HCC are increasing more than those with HCV and HBV infection.5 Currently, there are limited data on the prevalence of non-viral HCC in Indonesia.

The incidence and mortality of HCC are two-three times greater among men than women.6 The sex disparity on HCC risk is possibly associated with differences in prevalence of established risk factors, smoking habit, and also intrinsic factors.

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such as sex hormones and prevalence of metabolic disorders. HCC is usually diagnosed at age between 30 and 50 years, although age distribution of HCC varies by sex, geography and risk factor. It remains unclear if age and sex distribution are different between viral and non-viral HCC.

Currently, HCC surveillance is recommended for the population at risks such as patients with cirrhosis and chronic viral infection. In conjunction with abdominal ultrasound (US), alpha-fetoprotein (AFP) has been commonly used as a non-invasive marker to screen patients at risk for HCC. As epidemiology of HCC has been changed in many parts of the world, it is very important to explore the clinical characteristic of viral and non-viral HCC in order to develop strategies for prevention and treatment of patients with HCC. This study was aimed to determine the distribution of viral and non-viral risk factors in patients with HCC.

**METHODS**

This study was a cross-sectional study. Demographics and laboratory data were obtained from patients’ medical record at the Arifin Achmad General Hospital (AAGH), Riau Province, during 2013-2017 using the total sampling technique. The study was conducted in January 2019.

The inclusion criteria were patients who were diagnosed with hepatoma based on imaging modalities (CT scan, ultrasound, or MRI) at the AAGH in the period 2013-2017 and aged 18 years. HBV and HCV infection status was determined based on a positive HBsAg and anti-HCV test, respectively. Serum AFP was categorized as <400 ng/mL and 400 ng/mL.

Statistical analysis was conducted using SPSS Version 23.0. Age distribution was presented as mean SD, whereas categorical data (sex and AFP) were presented as proportion. Chi-square analysis was used to compare sex and age distribution between viral and non-viral HCC. Students T-test was used to determine significant differences in age between viral and non-viral HCC.

**RESULTS**

A total of 129 HCC cases met the inclusion criteria and were included in this study, of whom 64 cases were related to HBV/HCV infection, and the remaining 65 cases were not related with HBV/HCV infection. The mean age of HCC patients was 54 ± 12 years (range: 20-87 years) and composed of 104 males (86.8%) and 25 females (19.4%). HCC was mainly diagnosed by US in 112 cases (86.8%) while only 17 HCC cases used CT-scan as a diagnostic tool.

The Distribution of HCC cases in AAGH during 2013-2017 is presented in Figure 1. The number of HCC cases increased from 12 cases in 2013 to 30 cases in 2014, whereas it was comparable from 2014 to 2017. Also, the number of non-viral HCC cases was similar to those of viral HCC in 2013 and 2015, but it was less in 2016 and 2017. Non-viral HCC cases outnumbered viral HCC cases in 2014.

Table 2 showed the differences in age, gender and AFP levels between viral HCC and non-viral HCC cases. Although subjects in viral HCC were younger than those in non-viral HCC group, this difference was not statistically significant. Females were three times more likely to suffer from non-viral HCC than males (95% Confidence Interval [CI] 1.2-8.1, p=0.016). Furthermore, AFP levels greater than 400 ng/mL were more frequently found in

**Table 1 Sample characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCC cases (n=129)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV/HCV</td>
<td>64</td>
<td>49.6</td>
</tr>
<tr>
<td>Non-viral</td>
<td>65</td>
<td>50.4</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD years</td>
<td>54.4±12.4</td>
<td></td>
</tr>
<tr>
<td>Min-max years</td>
<td>20-87</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>104</td>
<td>80.6</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>19.4</td>
</tr>
<tr>
<td><strong>Diagnostic tools</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>112</td>
<td>86.8</td>
</tr>
<tr>
<td>CT-scan</td>
<td>17</td>
<td>13.2</td>
</tr>
<tr>
<td><strong>AFP</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;400 ng/ml</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>≥400 ng/ml</td>
<td>42</td>
<td>32.5</td>
</tr>
<tr>
<td>No data</td>
<td>47</td>
<td>36.5</td>
</tr>
</tbody>
</table>

**Figure 1** HCC cases in GHAA from 2013-2017
Table 2  Differences in age, gender, and AFP levels between viral and non-viral HCC cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>HBV/HCV-HCC (n=64)</th>
<th>Non-viral-HCC (n=65)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean±SD years)</td>
<td>52.84 ± 11.5</td>
<td>55.95 ± 13.1</td>
<td>0.154</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>57 (54.8 %)</td>
<td>47 (45.2 %)</td>
<td>0.016†</td>
<td>3.12 (1.2-8.1)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (28 %)</td>
<td>18 (72 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400 ng/mL</td>
<td>14 (35 %)</td>
<td>26 (65 %)</td>
<td>0.004†</td>
<td>3.71 (1.5-9.3)</td>
</tr>
<tr>
<td>≥400 ng/mL</td>
<td>28 (66.7 %)</td>
<td>14 (33.3 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Statistically significant if p<0.05

viral HCC than non-viral HCC cases (OR 3.71; 95% CI 1.5-9.3; p=0.004).

**DISCUSSION**

This study showed that from 2013-2017, there were 49.6% of HCC cases related to HBV/HCV infection, whereas the remaining 50.4% cases were non-viral HCC. Also, the distribution of viral and non-viral HCC was comparable during 2013-2017. The proportion of non-viral HCC in the present study was much higher than in previous studies from Indonesia. In Cipto Mangunkusumo hospital as the top referral hospital in Indonesia, non-viral accounted for 17.5% causes for HCC cases while in Dharmais hospital, 25.8% of HCC was associated with non-viral factors. Whether these results suggest that the prevalence of non-viral HCC has increased in Indonesia needs further studies as few studies have been done so far. However, several reports from developed countries have indicated that non-viral HCC is becoming a significant subgroup of HCC. In Japan, the proportion of HCV-HCC was decreased, but non-viral HCC tended to increase from 6.8%-10% in 2000 to 17.3%-19% in 2009. In Taiwan, where HBV was highly endemic, approximately 10% of HCC patients were categorised as non-viral HCC. Whether these results suggest that the prevalence of non-viral HCC has increased in Indonesia needs further studies as few studies have been done so far. However, several reports from developed countries have indicated that non-viral HCC is becoming a significant subgroup of HCC. In Japan, the proportion of HCV-HCC was decreased, but non-viral HCC tended to increase from 6.8%-10% in 2000 to 17.3%-19% in 2009. In Taiwan, where HBV was highly endemic, approximately 10% of HCC patients were categorised as non-viral HCC. In the USA and Europe, non-viral HCC has been the main etiology for cryptogenic cirrhosis and liver transplantation. Taken together, these data suggest that the incidence of non-viral HCC is rising globally.

The global epidemic of obesity and its associated metabolic consequences, including diabetes and non-alcoholic fatty liver disease (NAFLD) has been associated with the rising prevalence of non-viral HCC. In the USA, obesity, diabetes and metabolic syndromes contribute to 36.6% of HCC cases. NAFLD, the major hepatic manifestation of obesity, encompasses a pathological spectrum of liver disease ranging from a benign form of simple steatosis with no evidence of hepatocellular injury to NASH and cirrhosis. The increasing incidence of HCC mirrors the rising prevalence of NAFLD in western and Asian countries. Hence, the increased risk for HCC in obese and diabetic may well be mediated by the development of NAFLD.

A retrospective study from Japan showed that patients with non-viral HCC have a median survival of 1,553 days compared to 2,304 days for HCV-HCC patients, indicating a poorer prognosis among non-viral-HCC patients compared with HCV-HCC. This study also revealed that the advanced stage of tumour presentation was one of the significant prognostic factors contributing to overall survival of non-viral HCC. This data suggest that HCC surveillance should be applied more rigorously to this group of patients to increase the availability of curative treatments and eventually prolong the overall survival.

The mean age of HCC patients in this study was 54 years (range 20-87 years), and there was no significant difference between viral and non-viral HCC concerning age. This finding was in agreement with a recent study from Taiwan showing no age difference between viral and non-viral HCC patients, although the median age of non-viral HCC patients was younger (66 years old) than those from our study. In contrast, a large prospective study of 1079 HCC patients from Australia reported that HCC patients with non-viral factors were significantly older than those with HBV and HCV infection. They also found that HCC patients with viral causes were more likely to be enrolled in HCC surveillance program and thus may be diagnosed at a younger age. Whether age has a modifying effect on the natural course of HCC is still unclear.

It has been well established that men have a risk of approximately two to four times than that of women to develop HCC. This gender disparity in HCC risk may be influenced by behavioural risk factors, metabolic features, sex hormone, and tumour biology. In our study, females were more likely to suffer from non-viral HCC with risk of three times as high as male patients. In contrast, a retrospective study from Japan comparing non-viral HCC and HCV-HCC found that men had a greater risk for developing non-viral HCC than women, five whereas a study from Australia reported no difference in risk for developing non-viral HCC between females and males. These contradictory results may be due to differences in ethnicities, a geographic variation of etiological factors, and curative treatment options.
Serum AFP is a tumor marker used to diagnose HCC and together with ultrasound (US) was recommended as a method of screening in HCC surveillance.24,32 Previous studies showed that AFP level was an independent risk predictor of pathological grade, progression, and survival of HCC patients.31,26 AFP concentration >400 ng/mL is generally considered a prognostic predictor of poor survival of HCC.10,11 According to the present study, HCC patients with AFP level □400 ng/mL were more frequently found in viral HCC than non-viral HCC patients, suggesting that HCC patients with non-viral etiologies were more commonly presented with AFP concentration <400 ng/mL.

CONCLUSION
The proportion of patients with viral HCC was comparable with non-viral HCC, suggesting that non-viral factors were becoming significant etiologies of HCC in AAGH. Females had a greater risk to develop non-viral HCC than males and AFP levels <400 ng/mL were more commonly presented by non-viral HCC patients. Given the global epidemic of obesity and diabetes, this study suggests that this group of patients should be included in HCC surveillance program.

ETHICAL CLEARANCE
This study was approved by the Ethical Committee of the Faculty of Medicine University Riau.

CONFLICT OF INTEREST
All authors declare no conflict of interest related to this study.

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AUTHOR CONTRIBUTIONS
All of the authors contributed in this study from concept and designed the study, funding, data collection from the medical record, statistical analysis, drafted and finalised the manuscript.

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