HCC in south region of Java

by Thianti3 Thianti3

Submission date: 27-Apr-2023 07:55PM (UTC+0700)
Submission ID: 2077126645
File name: Gumilas_2019_J._Phys.__Conf._Ser._1246_012013.pdf (519K)
Word count: 3782
Character count: 18476

Hepatitis B as hepatocellular carcinoma (HCC) risk factor in the south region of Java, Indonesia

IOP Conf. Series: Journal of Physics: Conf. Series **1246** (2019) 012013 doi:10.1088/1742-6596/1246/1/012013

Hepatitis B as hepatocellular carcinoma (HCC) risk factor in the south region of Java, Indonesia

Nur Signa A Gumilas[1], Ika M Harini[1], Thianty Sylviningrum[2], Wahyu Djatmiko[3], Lantip Rujito[4]

[1] Department of Histology, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia
[2] Department of Dermatology and Venereology, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia
[3] Department of Internal Medicine, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia
[4] Department of Molecular Biology, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia

E-mail: nur.gumilas@unsoed.ac.id

Abstract. Hepatocellular carcinoma (HCC) is a liver cancer caused by uncontrolled growth of hepatocytes. Many factors relate to the incidence of hepatocellular carcinoma whether it is internal or external factors. This study aimed to determine the risk factors of HCC South Region of Central Java, Indonesia. The study design used a case-control approach using the population of HCC patients from Margono Soekarjo Banyumas Hospital as a referring hospital in a Southern part of Central Java. Samples were considered as total sampling criteria using patient's database from the hospital. Statistical analysis was Chi-square and Fisher test. The study found that the age and hepatitis B infection have an association with the prevalence of HCC. Individuals infected with hepatitis B were at higher risk of HCC, compared with individuals not infected with hepatitis B. Younger age was a protective factor against HCC. As a conclusion, there was a significant relationship between age and hepatitis B infection with HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is a liver cancer caused by uncontrolled growth of the primary cells of the liver (derived from hepatocytes /liver cells) [1]. The incidence of HCC in the late 70s was about 1.4 cases / 100.00 cases /year, and in 2011 it increased to 6.2 cases / 100,000 cases. HCC is more common in men than women, with a ratio of 2.4 [2]. Asia Pacific region stated that the HCC is the third most common cancer that causes death [3]. Data and studies in Indonesia concerning about the risk factors are still minimal. Data in RS Dr. Kariadi Semarang Indonesia, during the year 2013-2015, obtained as many as 205 people suffer from HCC [4], while in RS Immanuel Bandung Indonesia from January 2013 until December 2014, the prevalence of HCC was 46 patients [5].

Epidemiological studies suggest that HCC has an association with several risk factors including the host, like gender and genetic, and the environmental factors including the hepatitis B and C virus infection, alcohol consumption, smoking, as well as aflatoxin [6]. Another study also suggests that liver cirrhosis is one of a high-risk factor for HCC [7]. It has a change in liver cirrhosis to develop HCC up to 70-90% [8]. Data in RS Dr. Kariadi Semarang Indonesia, from 205 HCC patients in 2013-2015, there were 103 patients (50.24%) infected by hepatitis B. Another research by Wang et al. [9] in

4 countries, Indonesia as one them, mentioned that chronic liver disease (hepatitis and cirrhosis) was a significant factor causing HCC. Infection by hepatitis B virus was 21%, and hepatitis C was 40%.

HCC risk factor research is still very little done in Indonesia, especially in the South Region of Central Java, Banyumas Indonesia. This study was useful to know the risk factors that cause HCC based on local characters in Banyumas.

2. Methods

The study used a case-control design to determine the factors affecting the incidence of HCC in Banyumas Indonesia. Data were taken from HCC patients at Margono Soekarjo General Hospital from April to October 2017. After obtaining the approval, subjects underwent the interview, and medical record was taken from the hospital.

The subjects were divided into two groups, cases, and controls. The case group was HCC patients registered, while the control group was not HCC patient or non-malignant patient. Both of them were from the Margono Soekarjo General Hospital. The HCC group was 25 patients, while the control group was 28 patients.

Risk factors studied were hepatitis B and C infection, liver cirrhosis, alcohol consumption, and smoking. Hepatitis B infection was examined using HBsAg; hepatitis C infection was examined using anti-HCV. The diagnosis of liver cirrhosis was determined based on the patient's medical record and the result of a CT scan or ultrasound. Alcohol and smoking by using interviews and questionnaires. HCC diagnosis is established by history, physical examination, and ultrasound investigation and CT scan.

Determination of the effect of hepatitis B, hepatitis C, liver cirrhosis, alcohol consumption, and smoking was achieved using the Chi-square test and Fisher test. The exposure ratio between the case group and control group then was measured using Odds Ratio (OR) formulas with Confidence Interval (CI) of 95%.

3. Results

The characteristics of HCC patients and controls can be observed in Table 1. The characteristics of gender, age and HCC risk factors such as liver cirrhosis, hepatitis B, hepatitis C, alcohol consumption and smoking in patients with HCC and controls can be observed in Table 1. Most HCC patients were men, 20 patients (80 %), while female patients were 5 (20%). Comparison between men and women is 4. For ages, the majority of HCC patients are older than 40 years (84%), while the age of 20-40 years is 16%. The youngest age is 24 years old, while the oldest age is 74 years old (data are not shown).

There was one person (4%) of HCC patients with a history of liver cirrhosis, while 24 (96%) had no history of liver cirrhosis. HCC patients infected with hepatitis B were 14 patients (56%), while uninfected were 11 patients (44%). In this study, hepatitis C infection in HCC patients was only one person (4%), while 24 (96%) were not infected. Alcohol consumption and smoking were obtained from questionnaire-based interviews. HCC patients who consumed alcohol were four patients (16%), while those who did not consume alcohol were 21 patients (84%). HCC patients who smoked were 12 patients (48%), while 13 other patients (52%) did not smoke.

In the control group, sex and age differences did not differ substantially. Comparison of men with women is 1.15 (15/13 people). The comparison between the ages of 20-40 with age > 40 years is 0.75 (12/16 people). In this study, none of the controls had a history of liver cirrhosis (0%) and hepatitis C infection (0%). Hepatitis B infection, alcohol consumption and smoking in the control group were 3 (10.7%), 4 (14.3%) and 7 (25%), respectively.

Table 2 showed that the age ($p = 0.041$) and hepatitis B infection ($p = 0.001$) were associated with HCC. Individuals infected with hepatitis B (OR = 10.6) have a greater risk of developing HCC than individuals uninfected with hepatitis B. Individuals aged 20-40 (OR = 0.25) are more protected from HCC than individuals over 40 years of age.

However, sex ($p = 0.043$; OR = 3.47; 95% CI = 1.01 - 11.86), liver cirrhosis ($p = 0.472$), hepatitis C infection ($p = 0.472$), alcohol consumption ($p = 1.000$; OR = 1.14; 95% CI = 0.25 - 5.15) and smoking ($p = 0.081$; OR = 2.8; 95% CI = 0.87 - 8.84) respectively, were not HCC risk factors.

4. Discussions

This study aims to determine the risk factors of HCC in Banyumas Regency, a southern part of Java, Indonesia. The study design used case-control studies, grouped into 2, consisting of case groups (HCC) and control groups, consisting of 25 patients and 28 controls, respectively. In Table 1, HCC patients were more male than female, with a ratio of 4. However, statistical analysis showed that men were not a risk factor for HCC. Results of male and female patient ratios were consistent with the previous study which states that the ratio of men and women is 2.4 and that the ratio is more significant in areas of high incidence [10]. It was explained that HCC is more common in men than in women and the largest ratio occurs in Europe (> 4: 1). It may be because men are more exposed to HBV infection, consume alcohol and smoke [11]. Another study conducted by Yuan et al. in China showed an association between testosterone levels and HCC risk. It shows that men are more at risk of developing HCC [12]. Also, the hormone estrogen acts as a protective factor of HCC, which inhibits IL-6, inactivates STAT3, and inhibits tumor-associated macrophage [13].

Table 1. Characteristics of HCC patients and controls.

Characteristics	HCC		Controls		Total	
	n = 24	%	n = 28	%	n	%
Gender						
Male	20	80.0	15	53.6	35	66.0
Female	5	20.0	13	46.4	18	34.0
Age (years)						
20 - 40	4	16.0	12	42.9	16	30.2
>40	21	84.0	16	57.1	37	69.8
Liver cirrhosis						
Yes	1	4.0	0	0.0	1	1.9
No	24	96.0	28	100.0	52	98.1
Hepatitis B						
Yes	14	56.0	3	10.7	17	32.1
No	11	44.0	25	89.3	36	67.9
Hepatitis C						
Yes	1	4.0	0	0.0	1	1.9
No	24	96.0	28	100.0	52	98.1
Alcohol consumption						
Yes	4	16.0	4	14.3	8	15.1
No	21	84.0	24	85.7	45	84.9
Smoke						
Yes	12	48.0	7	25.0	19	35.8
No	13	52.0	21	75.0	34	64.2

In this study, age was associated with HCC, and young age was a protective factor. The previous study stated that HCC is progressively increased with age. In old age there is an accumulation of aging cells, creating a micro-environment in tissues that support the development and occurrence of cancer [14]. Also, aging cells trigger cancer initiation [15]. HBV immunization may also play a role in the incidence of HCC. The protective effect of HBV immunization causes a decrease in the incidence of HBV infection at a young age, and this has implications for the lack of cases of HCC at a young age [16]. However, the result of this study is different from that of Niu et al. which uses 314 HCC and 346 controls. His study used the age less than 50 years and over 50 years. These different results may be due to differences in sample size and age distribution [17].

Table 2. HCC risk factors.

Characteristics	HCC		Controls		Total		OR	p
	n = 24	%	n = 28	%	n	%	95% CI	
Gender								
Male	20	80.0	15	53.6	35	66.0	3.47	0.043
Female	5	20.0	13	46.4	18	34.0	1.01 – 11.86	
Age (years)								
20 - 40	4	16.0	12	42.9	16	30.2	0.25	0.041*
>40	21	84.0	16	57.1	37	69.8	0.07 – 0.94	
Liver cirrhosis								
Yes	1	4.0	0	0.0	1	1.9		0.472
No	24	96.0	28	100.0	52	98.1		
Hepatitis B								
Yes	14	56.0	3	10.7	17	32.1	10.6	0.001*
No	11	44.0	25	89.3	36	67.9	2.53 – 44.52	
Hepatitis C								
Yes	1	4.0	0	0.0	1	1.9		0.472
No	24	96.0	28	100.0	52	98.1		
Alcohol consumption								
Yes	4	16.0	4	14.3	8	15.1	1.14	1.000
No	21	84.0	24	85.7	45	84.9	0.25 – 5.15	
Smoke								
Yes	12	48.0	7	25.0	19	35.8	2.8	0.081
No	13	52.0	21	75.0	34	64.2	0.87 – 8.84	

HCC patients with cirrhosis found only one case. Liver cirrhosis was not associated with HCC (p = 0.472). This result differs from the study by Schutte et al. which states that cirrhosis of the liver occurs in HCC, which is 70-90%. However, if liver cirrhosis is not present, this is probably because the level of hepatocellular toxicity has not been achieved, but its carcinogenic effect has been able to induce HCC [8]. The mechanism of cirrhosis of the liver to HCC is a multistep mechanism. There is a gradual change of cirrhosis into low-grade dysplastic nodules (LGDN) → high-grade dysplastic nodules (HGDN) → early HCC → HCC progression → advanced HCC [18]. The mechanism is likely to have implications on the results of this study, in which the stage of cancer development of HCC patients in this study is already in the advanced HCC.

Hepatitis B is a risk factor for HCC in this study. A study suggests that hepatitis B infection is a significant contributing disease to HCC in Asia, especially in Southeast Asia, which is over 50% [19]. In hepatitis B infection, insertion of DNA virus into the host's hepatocyte cells, followed by multiplication of infected cells and induced host genomic instability, resulting in mutagenesis. Long-expressed viral proteins (wild-type and mutant HBx) cause cellular transcription dysregulation, proliferative control changes and facilitate hepatocytes to be sensitized to carcinogenic factors. Also, epigenetic changes in tumor expression of suppressor genes and the role of HBx viral proteins cause changes in chromatin at specific gene loci [20]. These results also show the high rates of infection and transmission of hepatitis B virus in Banyumas. Hepatitis B is transmitted through blood and semen. The transmission mechanism is through pregnant women to infants, sexual activity, injection equipment such as syringes, blood transfusions, and hemodialysis, also contamination of operating equipment and contamination of equipment for dental procedures [21]. In Indonesia, data on how hepatitis B transmission has never been done. More research is needed on this matter.

Hepatitis C found only 1 case in 28 cases of HCC, while the control group did not have hepatitis C. It revealed that hepatitis C infection is less than hepatitis B infection. Another study mentioned that 12% of hepatitis B patients are coinfected with hepatitis C. It shows that in Indonesia, the number of hepatitis C cases is less than hepatitis B [22]. Hepatitis B is more endemic in Indonesia, although the mechanism of transmission of hepatitis B and hepatitis C are the same. In Egypt, high rates of hepatitis C are associated with anti-Schistosoma therapy [23]. Another assumption that causes less hepatitis C than hepatitis B is due to viral characteristics and geographic conditions of Indonesia. It needs further research on this statement.

The study also revealed that alcohol and smoking were not a risk factor for HCC. The comparison of HCC patients with the control group who consumed alcohol was a comparable/balance, causing the results of the statistical analysis to be meaningless. A study by Jurgen Rehm et al. and WHO recorded that alcohol consumption per capita in 2005 in Indonesia was < 2.5 liters of pure alcohol, in individuals aged over 15 years [24]. This figure is small compared to countries in East Asia, Europe, and America. The low rate of alcohol consumption in Indonesia is probably due to religious, cultural and behavioral factors. Need further study on this matter. However, the study of the association of alcohol with HCC suggests that the onset of HCC may be indirect (genotoxic) and indirect (liver cirrhosis). Mechanisms that occur are hepatocyte DNA damage by acetaldehyde, ROS (reactive oxygen species) and RNS (reactive nitrogen species) production, hepatocyte DNA damage by ethanol and decreased immune system monitoring [25].

Smoking is also not a risk factor for HCC. The number of HCC patients who smoked compared with HCC patients who did not smoke was a comparable/balance, resulting in no significant difference. In Indonesia, the prevalence of smoking in men is very high [26]. The result was not significant because as many as 80% of HCC patients were male and the number of smokers and nonsmokers in HCC was balanced. Also, five women of HCC patients in this study, none of whom smoked (data not shown).

The limitations of this study are the small sample size and limited sampling time. It needs to be compared with research using larger sample quantities.

5. Conclusions

It can be concluded that there was a significant relationship between age and hepatitis B infection with HCC. Young age was a protective factor, and hepatitis B was a risk factor for HCC.

6. References

[1] Mu X, Español-Suñer R, Mederacke I, Affò S, Manco R, Sempoux C, Lemaigre F P, Adili A, Yuan D, Weber A, Unger K, Heikenwälder M, Leclercq I A and Schwabe R F 2015 Hepatocellular carcinoma originates from hepatocytes and not from the progenitor/biliary compartment *J. Clin. Invest.* **125** 3891–903

[2] Ghouri Y, Mian I and Rowe J 2017 Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis *J. Carcinog.* **16** 1

[3] Zhu R X, Seto W-K, Lai C-L and Yuen M-F 2016 Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region *Gut Liver* **10** 332–9

[4] Nadhim RP M, Ch. Suharti C S and Hardian H 2016 Distribusi Geografis Dan Tingkat Keparahan Pasien Karsinoma Hepatocellular Etiologi Virus Hepatitis B Di RS.Dr Kariadi *J Kedokt Diponegoro* **5** 1291–302

[5] Permadi A ., H. Ratnawati T . and Wargasetia 2016 Prevalence and Characteristics of Liver Cancer Patients in Immanuel Hospital Bandung within January 2013 until December 2014 Period *J Med Heal.* **1** 351–7

[6] Bosetti C, Turati F and La Vecchia C 2014 Hepatocellular carcinoma epidemiology *Best Pract. Res. Clin. Gastroenterol.* **28** 753–70

[7] Ramakrishna G, Rastogi A, Trehanpati N, Sen B, Khosla R and Sarin S K 2013 From Cirrhosis to Hepatocellular Carcinoma: New Molecular Insights on Inflammation and Cellular Senescence *Liver Cancer* **2** 367–83

[8] Schütte K, Bornschein J and Malfertheiner P 2009 Hepatocellular Carcinoma – Epidemiological Trends and Risk Factors *Dig. Dis.* **27** 80–92

[9] Wang B-E, Ma W-M, Sulaiman A, Noer S, Sumoharjo S, Sumarsidi D, Tandon B N, Nakao K,

Mishiro S, Miyakawa Y, Akahane Y and Suzuki H 2002 Demographic, clinical, and virological characteristics of hepatocellular carcinoma in Asia: Survey of 414 patients from four countries *J. Med. Virol.* **67** 394–400
[10] Ashtari S, Pourhoseingholi M A, Sharifian A and Zali M R 2015 Hepatocellular carcinoma in Asia: Prevention strategy and planning *World J. Hepatol.* **7** 1708–17
[11] Lafaro K J, Demirjian A N and Pawlik T M 2015 Epidemiology of Hepatocellular Carcinoma *Surg. Oncol. Clin.* **24** 1–17
[12] Yuan J-M, Ross R K, Stanczyk F Z, Govindarajan S, Gao Y-T, Henderson B E and Yu M C 2018 A cohort study of serum testosterone and hepatocellular carcinoma in Shanghai, China *Int. J. Cancer* **63** 491–3
[13] Shi L, Feng Y, Lin H, Ma R and Cai X 2014 Role of estrogen in hepatocellular carcinoma: is inflammation the key? *J. Transl. Med.* **12** 93
[14] Pascual S, Herrera I and Irurzun J 2016 New advances in hepatocellular carcinoma *World J. Hepatol.* **8** 421–38
[15] Mowla S N, Lam E W and Jat P S 2014 Cellular senescence and aging: the role of B-MYB *Aging Cell* **13** 773–9
[16] Goh G B-B, Chang P-E and Tan C-K 2015 Changing epidemiology of hepatocellular carcinoma in Asia *Best Pract. Res. Clin. Gastroenterol.* **29** 919–28
[17] Niu J, Lin Y, Guo Z, Niu M and Su C 2016 The Epidemiological Investigation on the Risk Factors of Hepatocellular Carcinoma: A Case–Control Study in Southeast China ed K He. *Medicine (Baltimore).* **95** e2758
[18] Zucman-Rossi J, Villanueva A, Nault J-C and Llovet J M 2015 Genetic Landscape and Biomarkers of Hepatocellular Carcinoma *Gastroenterology* **149** 1226–1239.e4
[19] de Martel C, Maucort-Boulch D, Plummer M and Franceschi S 2015 World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma *Hepatology* **62** 1190–200
[20] Levrero M and Zucman-Rossi J 2016 Mechanisms of HBV-induced hepatocellular carcinoma *J. Hepatol.* **64** S84–101
[21] Trépo C, Chan H L Y and Lok A 2014 Hepatitis B virus infection *Lancet* **384** 2053–63
[22] Lusida, M. I., Surayah, , Sakugawa, H. , Nagano-Fujii, M. , Soetjipto, , Mulyanto, , Handajani, R. , Boediwarsono, , Setiawan, P. B., Nidom, C. A., Ohgimoto, S. and Hotta H 2013 Genotype and Subtype Analyses of Hepatitis B Virus (HBV) and Possible Co-Infection of HBV and Hepatitis C Virus (HCV) or Hepatitis D Virus (HDV) in Blood Donors, Patients with Chronic Liver Disease and Patients on Hemodialysis in Surabaya, Indonesia *Microbiol. Immunol.* **47** 969–75
[23] Cuadros D F, Branscum A J, Miller F D and Abu-Raddad L J 2014 Spatial epidemiology of hepatitis C virus infection in Egypt: Analyses and implications *Hepatology* **60** 1150–9
[24] Rehm, J., C. Mathers, S. Popova, M. Thavorncharoensap, Y. Teerawattananon J P 2009 Alcohol and Global Health 1, Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* **373** 2223–33
[25] Purohit V, Rapaka R, Kwon O S and Song B J 2013 Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma *Life Sci.* **92** 10.1016/j.lfs.2012.10.009
[26] Sreeramareddy C T, Pradhan P M S, Mir I A and Sin S 2014 Smoking and smokeless tobacco use in nine South and Southeast Asian countries: prevalence estimates and social determinants from Demographic and Health Surveys *Popul. Health Metr.* **12** 22

Acknowledgments
Acknowledgments are submitted to Lembaga Penelitian dan Pengabdian Kepada Masyarakat (LPPM) of Jenderal Soedirman University who has funded this research through the Competence Improvement Research Grant of 2017.

HCC in south region of Java

ORIGINALITY REPORT

5%	4%	3%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

MATCH ALL SOURCES (ONLY SELECTED SOURCE PRINTED)

< 1%

★ Masao Omata, Laurentius A. Lesmana, Ryosuke Tateishi, Pei-Jer Chen et al. "Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma", Hepatology International, 2010

Publication

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		