



PROFILE OF CHRONIC HEPATITIS B IN LIVER AND NON LIVER MALIGNANCIES AT DR. SAIFUL ANWAR MALANG GENERAL HOSPITAL

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Abstrak

Latar belakang: Infeksi virus hepatitis B (HBV) merupakan masalah dunia yang berhubungan dengan morbiditas dan mortalitas. Virus hepatitis B (HBV) diidentifikasi sebagai faktor risiko utama karsinoma, salah satunya terkait dengan karsinoma hepatoseluler. Tujuan: Penelitian ini bertujuan untuk mengetahui profil penderita hepatitis B dengan keganasan di Poliklinik Gastroenterohepatologi RSUD Saiful Anwar. Metode: Penelitian ini merupakan penelitian observasional dengan desain cross sectional. Data dikumpulkan dari tahun 2013 hingga 2018. Pasien hepatitis B kronis ditemukan di poliklinik Gastroenterohepatologi. Data yang dikumpulkan berupa data sekunder, meliputi data demografi pasien meliputi umur, jenis kelamin, dan jenis obat. Hasilnya dideskripsikan secara deskriptif dan disajikan dalam bentuk tabel/persentase. Hasil: Dari hasil penelitian, jumlah penderita hepatitis B kronis dengan keganasan sebanyak 218 orang. Sebagian besar pasien berusia 20-60 tahun dengan rata-rata usia $49,7 \pm 12,6$ tahun. Sebagian besar subjek adalah laki-laki, 78,0%. Sebagian besar terapi yang diberikan kepada pasien adalah tenofovir 300 mg (93,2%). Kasus didominasi keganasan hati (52,8%). Sebagian besar pasien yang memiliki keganasan non-hati didiagnosis dengan *ca mammae* (37,0%). Kesimpulan: Infeksi virus hepatitis B kronis dapat berpotensi merusak jaringan hati yang dapat menyebabkan keganasan. Prevalensi keganasan hati dan non hati pada pasien hepatitis B kronis pada penelitian ini masing-masing adalah 52,8% dan 47,3%.

Kata Kunci: *Hepatitis B, karsinoma hepatoselular, sirosis hati.*

Abstract

*Background: Hepatitis B virus (HBV) infection is a worldwide problem associated with morbidity and mortality. Hepatitis B virus (HBV) was identified as a major risk factor for carcinoma, one of them is associated with hepatocellular carcinoma. Aim: This study aims to determine the profile of hepatitis B patients with malignancy at the Gastroenterohepatology Outpatient Polyclinic at Saiful Anwar Regional General Hospital. Methods: This research is an observational study with a cross-sectional design. Data was collected from 2013 to 2018. The chronic hepatitis B patients were found in the Gastroenterohepatology polyclinic. Data was collected in the form of secondary data, including patient demographic data including age, sex, and type of drug. The results are described descriptively and presented in tables/percentages. Results: From the results of the study, the total number of chronic hepatitis B patients with malignancy in was 218 people. Most of the patients were aged 20-60 years with an average age of 49.7 ± 12.6 years. Most of the subjects were male, 78.0%. Most of the therapy given to patients was tenofovir 300 mg (93.2%). Cases were dominated by liver malignancy (52.8%). Most of the patients who had non-liver malignancy were diagnosed with *ca mammae* (37.0%). Conclusion: Chronic hepatitis B virus infection may have the potential to damage liver tissue which can lead to malignancy. The prevalence of liver and non-liver malignancies in chronic hepatitis B patients in this study were 52.8% and 47.3%, respectively.*

Keywords: *Hepatitis B, hepatocellular carcinoma, liver cirrhosis.*

@Jurnal Ners Prodi Sarjana Keperawatan & Profesi Ners FIK UP 2023

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INTRODUCTION

Hepatitis B virus (HBV) infection affects more than two billion people worldwide (Song et al., 2019). Chronic HBV infection is a global health burden, especially in China. In China, the prevalence of HBV infection is much higher than United States and Western Europe, affecting 97 million people (Feng et al., 2021).

Chronic infection with HBV, a hepadnavirus, causes persistent damage to hepatocytes, leading to dysfunctional estrogen inactivation. High levels of free estrogen in the bloodstream can increase the prevalence of breast cancer and trigger advanced cancer (Fentiman, 2018). Transmission in highly endemic areas is horizontal both before birth and during childhood (Valsamakis, 2007). This type of transmission is associated with the increased development of chronic HBV infection.

HBV infection is associated with an increased risk of several malignancies (Feng et al., 2021). Chronic HBV infection increases the risk of developing cirrhosis and hepatocellular carcinoma (HCC) by up to 40% (Bozza et al., 2016). HBV carrier patients can experience other malignancies that are not related to the hepatitis virus, hence chemotherapy is indicated. Chemotherapy-induced immunosuppression can lead to HBV reactivation and can lead to hepatitis and liver failure, discontinuation of anticancer treatment, and death (Song et al., 2019).

The HBV was identified as a major risk factor for HCC. The HBV causes 80% of HCC cases, common in Chinese and African populations. The virus optimizes its life cycle for long-term persistence in liver tissue by forming plasmid-like closed circular covalent DNA (cccDNA) forms. immunity, and advanced cancer (Levrero & Zucman-Rossi, 2016).

Several clinical case studies detected HBV in several non-hepatic tissue types, indicating a potential role of HBV in the oncogenesis of non-hepatic cancer. Several population-based prospective studies have observed an association between chronic HBV infection and various non-liver cancers, but these findings are inconsistent.

A lack of detailed patient information leads to minimal control. The prognostic impact of HBV infection is still unclear in cervical cancer (Feng et al., 2021). Based on this background, this study aim to evaluate the association between chronic HBV infection and the risk of all types of cancer in the Saiful Anwar Hospital.

METHOD

Research design

The research conducted using a descriptive observational method with a cross-sectional design.

Data collection

Data was obtained from the medical records of Hepatitis B patients at the outpatient polyclinic of Saiful Anwar Hospital Malang from 2013 to 2018.

Data sources

The sample in this study were outpatients at the Gastroenterohepatology polyclinic at dr. Saiful Anwar Malang Hospital with a diagnosis of hepatitis B with malignancy. The inclusion criteria is patients diagnosed with Hepatitis B with liver and non-liver malignancy and the exclusion criteria are there are no supporting laboratory results needed both at baseline and follow-up for data analysis (HBV DNA, SGOT, SGPT, HbsAg), patients diagnosed with Hepatitis C, and there is incomplete supporting data.

Data analysis

Data were analyzed descriptively to describe data sets from the observations. The data will be presented in the form of tables and percentages

RESULTS AND DISCUSSION

Based on the results of the study, a total of 218 chronic hepatitis B patients with malignancy in Gastroenterohepatology were obtained for 5 years. Based on the type of malignancy, patients who experience non-liver malignancy are mostly diagnosed with Ca Mammae, which was 38 patients (37.0%). The data distribution of subject characteristics based on the type of malignancy is described in Table 1.

Table 1. Diagnosis of malignancy in patients

Diagnosis	n	%
Hepatoma	115	52,7
Breast cancer	38	17,4
Colon cancer	32	14,7
Malignant lymphoma	17	7,7
Lung cancer	14	6,4
Ovarian cancer	2	0,9
Total	218	100,0

Based on the age category, most of the patients were 20 - 60 years old (152 patients (69.7%)) with the overall average of patient's age was 49.7 ± 12.6 years. In addition, most of the subjects are male (170 patients (78.0%)). The most therapy given to patients was Tenofovir 300 mg in 203 patients (93.2%). In addition, a comparative bivariate analysis was carried out to evaluate the relationship between variables by assessing the difference in the proportion of each basic characteristic between the liver and non-liver malignancy groups. Based on the Chi Square test, there was a significant relationship between age, gender, and treatment with the type of malignancy with a p-value of 0.000; 0.006; and 0.000

respectively. The data distribution of the basic characteristics of the subject is described in Table 2.

Tabel 2. Baseline Characteristics of patients

Variable	Type of malignancy				Total		p
	Liver		Non Liver		n	%	
	n	%	n	%			
Age							
<20 years	0	0,0	17	16,5	17	7,8	0,000*
20–60 years	90	78,2	62	60,2	152	69,7	
>60 years	25	21,7	24	23,3	49	22,5	
Sex							
Male	107	93,0	63	61,2	170	78,0	0,006*
Female	8	7,0	40	38,8	48	22,0	
Therapy							
Tenofovir	13	11,3	2	2,0	15	6,9	0,000*
Lamivudine	102	88,7	101	98	203	93,2	
Total	115	100,0	103,0	100	218	100,0	

*significant value (p<0,05)

Based on the results of the non-parametric binomial test, there was no difference in prevalence between liver and non-liver malignancies in chronic hepatitis B patients (p>0.05). The prevalence of liver malignancy in chronic hepatitis B patients is 52.8%. Meanwhile, the prevalence of non-liver malignancy in chronic hepatitis B patients was 47.3%. The results of the analysis are described in Table 3.

Table 3. Non Parametric Binomial Test

Chronic Hepatitis B	Type of malignancy				Total		p
	Liver		Non Liver		n	%	
	n	%	n	%			
Yes	11	52.	10	47.	21	10	0.45
No	5	8	3	2	8	0	6

DISCUSSIONS

Based on the results of this study, it was found that most of the chronic hepatitis B patients had liver malignancy (52.8%). Similar results were also obtained in a previous study which reported that as many as 127 out of 251 cases of patients with chronic hepatitis B had hepatocellular carcinoma (Takano et al., 1995). Other studies also state that hepatitis B is one of the most common causes of hepatocellular carcinoma worldwide with ages of occurrence and prognoses that vary between regions (Anugwom et al., 2021). Other studies also reported that chronic hepatitis B infection is an important cause of hepatocellular carcinoma. The study also reported that the

prevalence of hepatocellular carcinoma in patients with chronic hepatitis B was 23.2%. Chronic hepatitis B patients with hepatocellular carcinoma were also found to have more cirrhosis than patients who did not suffer from hepatocellular carcinoma (Intaraprasong et al., 2016). The immune response in Hepatitis B infection is associated with liver injury, especially the high oncogenic potential leading to hepatoma. HBV induces hepatoma development through direct and indirect mechanisms. Hepatomas can progress through repeated cycles of cell death and regeneration, as well as initiation of inflammatory cascades that allow the propagation of oncogenic mutations. The HBV genome can integrate into host genes which can provide a growth advantage for the host cell at the DNA level. HBV has been found to integrate into cancer-associated genes, such as TERT, MLL4, and CCNE1, all of which have been shown to be upregulated in tumors. HBV has also been found to integrate into many other genes that can promote hepatoma (Pandeyarajan et al., 2021).

In this study, the most common non-liver malignancy found in chronic hepatitis B patients was breast cancer of 17.4%. Previous studies reported that breast, cervical, uterine, thyroid, lung, and skin cancers were found to be significantly associated with hepatitis B virus infection. Data analysis in these studies also showed that there was a significant relationship between hepatitis B virus infection and the incidence of lymphoma and cancer. bile. This study also suggests that it is necessary to consider screening for hepatitis B virus in cancer patients and monitoring cancer patients with hepatitis B virus infection (An et al., 2018). In addition, there is a potential mechanism for indirect oncogenesis of HBV in causing ca mammae. through its persistence as infection and continuous replication with long-term liver damage. Estrogen is mainly deactivated in the liver and long-term necro-inflammatory damage to the liver can lead to persistently high levels of estrogen, which is the dominant risk factor for breast cancer. HBV can also directly affect breast cells through the cis and trans effects of HBx which can act as an oncoprotein (Adhikari et al., 2016).

Chronic Hepatitis B is associated with liver and non-liver malignancies. Liver malignancy in HBsAg seropositive individuals are >15 times higher risk than individuals who are not HBV infected. HBX protein expression and anti-HBc protein expression were higher in cancer cells than in healthy specimen sections in the majority of patients with cancer. HBV may be stored in non-liver cells which can cause local inflammation. Chronic inflammation caused by HBV infection may play a role in cancer development. The

oncogenic viral protein HBX may play a direct role in cancer development. A lower association between HBV infection and nonliver cancer when compared with liver cancer was observed in the present study. Immunohistochemical results showed that HBX protein and anti-HBc protein were only expressed in the cytoplasm but not in the nucleolus. The low level of detectable cccDNA also suggests that HBV may be inactively replicating in non-liver tissue. However, further functional tests are needed to elucidate the mechanism of this action potential (Song et al., 2019). The results of this study have different results from several previous studies. A study by An et al (2018) found that chronic HBV infection is significantly related to non-liver malignancies including lymphoma, bile, cervix, uterus, breast, thyroid, lung, and skin cancer (An et al., 2018). Active replication of HBV and viral integration into the human genome in intra-hepatic cholangiocarcinoma (IHCC) tumors may provide a basic effect due to the presence of HBV DNA in IHCC tissue specimens based on molecular genetic research (Perumal et al., 2006) (Nakamura et al., 2015). Recent experiments have also shown that progenitor cells can differentiate into human hepatocytes and cholangiocytes, therefore HBV can induce cholangiocyte carcinogenesis by the same mechanism as hepatocyte carcinogenesis (C. H. Lee et al., 2009) (Tanaka et al., 2010). The difference in the results of this study may be due to differences in the study design, the population studied, the prevalence of cancer or hepatitis, and the period when the observations were made (An et al., 2018). Another study by Song et al (2009) showed that HBV infection is associated with the risk of non-liver cancer, especially digestive system cancer in Chinese adults. Another study in China also showed that HBV infection is positively associated with gastric cancer, especially in patients without a family history of gastric cancer (Wei et al., 2015).

A cohort study in Europe suggested that the rates of pancreatic cancer and lymphoma were not higher in HBV-infected patients compared to individuals who were not infected with HBV.7 Six other cancer sites are at increased risk in patients with HBV, including cancer of the upper aerodigestive tract, lung, kidney, skin (squamous cell carcinoma), thyroid gland, and leukemia. Patients with HBV are at increased risk for colorectal, gallbladder, kidney, and ovarian cancer.8,9 HBV is an important and relevant risk factor for cirrhosis and liver cancer development. These cancers are known as immunogenic tumors due to the interaction of the local tumor microenvironment with the innate immune system. Stress and the resulting physiological responses not only enable carcinogenesis by inducing

inflammation but also enable tumor development through suppressed immunity and dysregulation. Individuals who are better at coping with stress may be at lower risk of HBV-related liver cancer (Noverati et al., 2022).

The mechanisms underlying the association between chronic hepatitis B infection and malignancy have not been identified, but several biological phenomena may be relevant. First, the integration of HBV and human papillomavirus (HPV) into the same site on the human genome, as well as the inappropriate response of human leukocyte and lymphocyte antigens to the virus.23 Second, the prolonged association of the hepatitis virus with chronic inflammation against other organ damage that causes chronic obstructive pulmonary disease, autoimmune thyroiditis, and lichen planus on the skin with malignancy potential (Fallahi et al., 2014). Third, detection of HBV and HBV DNA surface antigens in skin tissue and breast milk (de Oliveira et al., 2009). These process may be related to the mechanism of the association between HBV and malignancy, but the specific processes between them are still not understood (An et al., 2018).

In this study, it was found that most of the patients were aged 20–60 years (69.7%) with an overall mean of 49.7 ± 12.6 years and were male (78.0%). In addition, this study also found that male patients were found to have more incidents of hepatocellular carcinoma, whereas in women more were found to have non-liver malignancies. Similar results were reported in a previous study, namely of the 474 patients included, the majority of patients were men with a mean age of 41.05 ± 13.93 years.26. Similar results were also obtained in other studies which reported that the majority of patients were male (55%) with an age range of 20–82 (average 46) years (Mahmoud et al., 2018). Other studies also reported that the risk of developing hepatocellular carcinoma increased with age with an adjusted HR (aHR) of 1.97 (95% CI, 0.99–3.87) for ages 40–49 years, aHR 3.00 (95% CI, 1.55–5.81) for ages 50–59 years; and aHR 4.02 (95% CI, 2.03–7.94) for ages over 60 years to less than 40 years.28 Men are known to have a higher risk of developing hepatocellular carcinoma compared to women (E.-Y. Lee et al., 2015) (Liu et al., 2017). Women have a lower incidence of hepatocellular carcinoma because being a woman, especially young women, has a protective effect that is thought to be a protective role of estrogen against the development of hepatocellular carcinoma (Mittal et al., 2018) (Davis et al., 2010). However, there is also a potential mechanism of indirect oncogenesis from hepatitis B infection to the development of mammary glands in which long-term necro-inflammatory damage to the liver can result in persistently high levels of estrogen

being the dominant risk factor for breast cavities in women (Adhikari et al., 2016).

However, this study has several limitations. The number of samples in this study was relatively small due to the incomplete medical record data that was desired and observed. This reduces the number of research samples and is feared not representative of the study population. In addition, this study did not record complete follow-up data. Statistical analysis cannot assess the risk of chronic HBV to liver and non-liver malignancies because they are in the same category.

CONCLUSION

Most of the patients were male and aged 20 – 60 years with an overall patient mean of 49.7 ± 12.6 years. The most therapy given to patients was tenofovir 300 mg (93.2%). The prevalence of liver malignancy in chronic hepatitis B patients is 52.8%. Meanwhile, the prevalence of non-liver malignancy in chronic hepatitis B patients was 47.3%. Further research is needed regarding the success of hepatitis B therapy in the RSSA gastroenterohepatology outpatient polyclinic with a larger number of samples and more complete data are needed to assess virological, serological and biochemical responses.

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