Factors Associated with Surveillance for Early Detection of Hepatocellular Carcinoma in Liver Cirrhosis Patients

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ABSTRACT

Background: *The minimal number of hepatocellular carcinoma (HCC) patients diagnosed through surveillance is proposed as the cause of persistently low number of survival. It is important to identify the proportion of surveillance for early detection of HCC in patients with liver cirrhosis and related factors. This study aimed to determine the proportion of surveillance for early detection of HCC in patients with liver cirrhosis and related factors.*

Method: *A cross-sectional study of patients with liver cirrhosis at Cipto Mangunkusumo Hospital from January to December 2013. The data was obtained from medical records and confirmed by telephone. Surveillance was required for abdominal ultrasound with or without AFP at least once a year within 3 years after that period. Factors studied were gender, ethnicity, education level, income level, availability of medical insurance, location of residence, surveillance education, cirrhosis aetiology, and severity of cirrhosis. Then, logistic regression test was used in the multivariate analysis.*

Results: *From 200 patients, 50 patients (25,0%) underwent surveillance, 150 patients (75,0%) did not. Bivariate analysis revealed 4 variables with p < 0.25, gender (p = 0,056), ethnicity (p = 0, 231), surveillance education (p = 0,005), and severity of cirrhosis (p = 0, 005). Multivariate analysis showed that the risk factors for surveillance were surveillance education (OR = 2,598; CI 95% (1,325 - 5,094), p = 0,005) and severity of cirrhosis (OR = 1.815; CI 95% = 1,210-2,724; p = 0,004).*

Conclusion: *Surveillance education and severity of cirrhosis were the factors associated with surveillance for early detection of HCC in liver cirrhosis patients.*

Keywords: *chirrosis of the liver, surveillance, related factors*

ABSTRAK

Latar belakang: *Sedikitnya pasien karsinoma hepato seluler (KHS) yang didiagnosis melalui surveilans diduga merupakan penyebab terus rendahnya angka kesintasan, sehingga penting untuk diketahui proporsi pelaksanaan surveilans untuk deteksi dini KHS pada pasien sirosis hati dan faktor-faktor yang berhubungan. Tujuan penelitian ini adalah mengetahui proporsi pelaksanaan surveilans untuk deteksi dini KHS pada pasien sirosis hati dan faktor-faktor yang berhubungan.*

Metode: Studi potong lintang pasien sirosis hati di RS Cipto Mangunkusumo periode Januari - Desember 2013. Data didapatkan dari rekam medis dan dikonfirmasi ulang dengan telepon. Surveilans disyaratkan USG abdomen dengan atau tanpa AFP minimal satu kali setahun dalam 3 tahun setelah periode tersebut. Faktor-faktor yang diteliti adalah jenis kelamin, suku bangsa, tingkat pendidikan, tingkat penghasilan, ketersediaan jaminan pengobatan, lokasi tempat tinggal, edukasi surveilans, etiologi sirosis, serta derajat beratnya sirosis. Uji regresi logistik digunakan untuk mengetahui faktor-faktor yang berhubungan dengan pelaksanaan surveilans.

Hasil: Dari 200 pasien sirosis hati, 50 pasien (25,0%) menjalani surveilans, 150 pasien (75,0%) tidak menjalani surveilans. Analisis bivariat menghasilkan 4 variabel dengan nilai p < 0,25 yaitu jenis kelamin (p = 0,056), suku bangsa (p = 0,231), edukasi surveilans (p = 0,005), dan derajat beratnya sirosis (p = 0,005). Analisis multivariat menghasilkan faktor risiko terlaksananya surveilans adalah edukasi surveilans (OR = 2,615; 95% CI: 1,332-5,134; p = 0,005) dan derajat beratnya sirosis (OR = 2,766, 95% CI: 1,413-5,415; p = 0,003).

Simpulan: Edukasi surveilans dan derajat beratnya sirosis merupakan faktor-faktor yang berhubungan dengan pelaksanaan surveilans untuk deteksi dini KHS pada pasien sirosis hati.

Kata kunci: Sirosis hati, surveilans, faktor yang berhubungan.

INTRODUCTION

Hepatocellular carcinoma (HCC) has poor prognosis because it is usually diagnosed in advanced stage, which makes the curative therapy can only be directed to a small number of patients.[1,2] A study by Mulyana et al in year 1998 – 1999 found as many as 93.5% HCC patients came in advanced stage, and in year 2013-2014 Loho et al found as much as 56.2% patients came in advanced stage.[3,4] The survival rate of HCC in Cipto Mangunkusumo Hospital between the period of 1998-1999 with the period of 2013-2014 did not differ as much, which are 24.1% and 29.4%, respectively. The small number of HCC patients who were diagnosed through surveillance was suggested to be the main cause of no difference of 1-year survival rates in both periods.[4]

A study by Davila et al in liver cirrhosis patients found only 17.1% patients underwent surveillance consistently. Some factors being analysed to significantly play role in the accomplishment of surveillance include sex, ethnic group, education level, income level, location of residence, surveillance education, aetiology of cirrhosis, and the severity degree of cirrhosis.[5] In the study by Webb et al, it was found that surveillance was performed in 21.6% patients and was reported that age and HCC aetiologies were the affecting factors.[6] Further, in study by Kohli et al, it was found that surveillance was performed in 60.9% patients and factor considered to play role was the severity degree of cirrhosis.[7]

There is no data regarding the proportion rate of surveillance performed for early detection of HCC and its associating factors in Indonesia or in Cipto Mangunkusumo Hospital. Therefore, this study was aimed to elucidate the proportion of surveillance being performed for early detection of HCC in liver cirrhosis patients and its associating factors.

METHOD

This study was performed using retrospective cohort design from secondary data of patients with liver cirrhosis who visited Cipto Mangunkusumo Hospital for treatment in the period of January to December 2013. Sample collection was performed in a consecutive manner based on database of Cipto Mangunkusumo Hospital medical records with diagnosis code of liver cirrhosis based on International Classification of Diseases and Related Health Problems 10th edition (ICD-10).

Inclusion criteria included patients aged ≥ 18 years old, diagnosed with live

cirrhosis within the determined period, and underwent treatment in outpatient or inpatient ward in Cipto Mangunkusumo Hospital during diagnosis. Exclusion criteria were missing medical records, patients who had been diagnosed with HCC when diagnosed with liver cirrhosis for the first time, and patients who finally could not be contacted. Characteristics of study subjects were identified and classified into consistent surveillance which included patients who underwent abdominal ultrasonography (USG) with or without AFP twice a year, inconsistent surveillance which included patients who underwent abdominal USG with or without AFP at least 1 time per year, and non-surveillance which included patients who did not undergo abdominal USG with or without AFP 1 time per year. Observations of complications of liver cirrhosis and influencing factors, such as: sex, ethnic

group, level of education, level of income, availability of health insurance, location of residence, HCC surveillance education, aetiology of liver cirrhosis, and severity degree of liver cirrhosis. Chi-Square test was used in bivariate analysis and logistic regression was employed for multivariate analysis.

RESULTS

Based on ICD-10, there were 396 patients diagnosed with liver cirrhosis who underwent treatment in Cipto Mangunkusumo Hospital in that period. From that

Table 1. Characteristics of study subjects

Variable	Total
Sex	
Female	66 (33.0)
Male	134 (67.0)
Age, average in years old (standard deviation)	58.25 (SD 12.13)
< 60	110 (55.0)
≥ 60	90 (45.0)
Ethnic group	
Javanese	70 (35.0)
Sundanese	39 (19.5)
Batak	23 (11.5)
Malay	32 (16.0)
Tionghoa (Chinese)	3 (1.5)
East Indonesia	33 (16.5)
Level of education	
< Senior high school	47 (23.5)
≥ Senior high school	153 (76.5)
Level of income	
< IDR 3 million	85 (42.5)
≥ IDR 3 million	115 (57.5)
Availability of health insurance	
Not available	33 (16.5)
Available	167 (83.5)
Location of residence	
Outside Jakarta	83 (41.5)
In Jakarta	117 (58.5)
HCC surveillance education	
Not educated	129 (64.5)
Educated	71 (35.5)
Aetiology of liver cirrhosis	
Non B non C	40 (20.0)
Hepatitis B	89 (44.5)
Hepatitis C	52 (26.0)
Hepatitis B and C	19 (9.5)
Severity degree of liver cirrhosis	
Child Pugh A	70 (35.0)
Child Pugh B	50 (25.0)
Child Pugh C	80 (40.0)
Complications of liver cirrhosis	
Ascites	47 (23.5)
Hepatic encephalopathy	17 (8.5)
Variceal rupture	28 (14.0)
Spontaneous bacterial peritonitis	13 (6.5)
Hepatorenal syndrome	5 (2.5)
Ascites + hepatic encephalopathy	12 (6.0)
Variceal rupture + hepatic encephalopathy	10 (5.0)
Spontaneous bacterial peritonitis + hepatic encephalopathy	4 (2.0)
Hepatorenal syndrome + hepatic encephalopathy	3 (4.0)
No complications	61 (30.5)

number, those who fulfilled inclusion criteria and were not included in exclusion criteria were 200 patients. Patients who underwent consistent surveillance were 33 patients (16.5%), inconsistent surveillance were 17 patients (8.5%), with a total of 50 patients who underwent surveillance (25,0%), while 150 patients did not undergo surveillance (75.0%).

In this study, we found 4 HCC cases diagnosed through consistent surveillance. Two cases of HCC BCLC A treated with RFA, 1 case of HCC BCLC B treated with PEIT, and 1 case of HCC BCLC C treated with TACE. It was found that 3 cases of HCC were diagnosed through inconsistent surveillance. Two cases of HCC BCLC B were treated with TACE, and 1 case of HCC BCLC C received sorafenib treatment.

Univariate analysis found that majority of patients were male as many as 67.0%. As many as 35.0% patients were Javanese, 76.5% had education level ≥ senior high school, 57.5% had income level ≥ 3 million Indonesian Rupiah (IDR), 83.5% had health insurance, 58.5% lived in Jakarta. As many as 64.5% were not educated to perform surveillance consistently, 49.5% patients had liver cirrhosis due to Hepatitis B, 40.0% patients were categorised to suffer from liver cirrhosis Child Pugh C, and 23.5% patients suffered from ascites as the most common complication of liver cirrhosis.

Characteristics of study subjects can be seen in Table 1 and 2.

The results of bivariate analysis indicated 2 variables were statistically significant (p < 0.05) as factors associated with surveillance accomplishment, including education of surveillance and the severity degree of cirrhosis. Bivariate analysis on the factors associated with the accomplishment of HCC surveillance can be seen in Table 3.

Table 2. Complications of liver cirrhosis based on surveillance

Variable	Surveillance	Not surveillance
Complications of liver cirrhosis		
Ascites	6 (12.0)	41 (27.4)
Hepatic encephalopathy	5 (10.0)	12 (8.0)
Variceal rupture	3 (6.0)	25 (16.6)
Spontaneous bacterial peritonitis	1 (2.0)	12 (8.0)
Hepatorenal syndrome	1 (2.0)	4 (2.6)
Ascites + hepatic encephalopathy	3 (6.0)	9 (6.0)
Variceal rupture + hepatic encephalopathy	2 (4.0)	8 (5.4)
Spontaneous bacterial peritonitis + hepatic encephalopathy	0 (0.0)	4 (2.6)
Hepatorenal syndrome + hepatic encephalopathy	0 (0.0)	3 (2.0)
No complications	29 (58.0)	32 (21.4)

Table 3. Bivariate analysis of factors associated with the accomplishment of Hepatocellular Carcininoma (HCC) surveillance

Variable	Surveillance	Not surveillance	P	PR	95% CI
Sex					
Female	22 (33,3)	44 (66,7)	0,056	1,893	0,979 - 3,662
Male	28 (20,9)	106 (79,1)			
Ethnic group					
Javanese	21 (30,0)	49 (70,0)	0,231	1,493	0,774 - 2,880
Non-Javanese	29 (22,3)	101 (77,7)			
Level of education					
≥ Senior high school	38 (24,8)	115 (75,2)	0,923	0,964	0,455 - 2,043
< Senior high school	12 (25,5)	35 (74,5)			
Level of income					
≥ 3 million Rupiah	29 (25,2)	86 (74,8)	0,934	1,028	0,537 - 1,965
< 3 million Rupiah	21 (24,7)	64 (75,3)			
Availability of health insurance					
Available	43 (25,7)	124 (74,3)	0,582	1,288	0,522 - 3,180
Not available	7 (21,2)	26 (78,8)			
Location of residence					
In Jakarta	31 (26,5)	86 (73,5)	0,562	1,214	0,630 - 2,341
Outside Jakarta	19 (22,9)	64 (77,1)			
HCC surveillance education					
Educated	26 (36,6)	45 (63,4)	0,005	2,528	1,312 - 4,869
Not educated	24 (18,6)	105 (81,4)			
Aetiology of liver cirrhosis					
Hepatitis virus	42 (26,3)	118 (73,7)	0,414	1,424	0,608 - 3,334
Non Hepatitis Virus	8 (20,0)	32 (80,0)			
Severity degree of liver cirrhosis					
Child Pugh C	29 (36,2)	51 (63,8)	0,003	2,681	1,392 - 5,163
Child Pugh A & B	21 (17,5)	99 (82,5)			

The multivariate analysis revealed that factors associated with the accomplishment of HCC surveillance in patients with liver cirrhosis were the HCC surveillance education with odds ratio (OR) = 2.615 and confidence interval (95% CI) 1.332 – 5.134, and the severity degree of liver cirrhosis with OR = 2.766 and 95% CI: 1.413 – 5.415. Results of logistic regression can be seen in Table 4.

Table 4. Multivariate analysis of factors associated with the accomplishment of hepatocellular carcinoma (HCC) surveillance

Variable	p	OR	(95% CI)
Step 1			
Sex	0.093	1.811	0.906 – 3.621
Ethnic group	0.231	1.389	0.692 – 2.788
Success rate of education surveillance	0.006	2.614	1.320 – 5.174
Severity degree of cirrhosis	0.004	2.703	1.368 – 5.340
Step 2			
Sex	0.083	1.842	0.924 – 3.673
Success rate of education surveillance	0.006	2.582	1.308 – 5.098
Severity degree of cirrhosis	0.003	2.772	1.407 – 5.461
Step 3			
Success rate of education surveillance	0.005	2.615	1.332 – 5.134
Severity degree of cirrhosis	0.003	2.766	1.413 – 5.415

DISCUSSION

From 200 study subjects, the proportion of male participants was high, which was 67.0%. It was similar to a study performed by Davila et al in which the proportion of male was 65.7%.[5] Several studies also showed comparable results.[6-8] This may occur as a result of oestrogen in female that could prevent the accumulation of fat in the adipose tissue which further prevents fatty liver.[9] Oestrogen can also inhibit stellate cells and activate hematopoietic stem cells which finally prevent the development of liver fibrosis.[10] From the study on alcohol consumption habit in patients with alcoholic liver disease, it was found that males consumed more alcohol compared to females with a ratio of 2:1 in the age ≥ 26 years old; therefore, this will further increase the number of male alcoholic liver cirrhosis patients.[10]

The average age of this study subjects was 58.25 years old with standard deviation of 12.13 years old. Similar result was reported in the study by Kohli et al with the average age of 58 years old and standard deviation of 9.6 years old.[7] Study conducted by Singal et al reported a lower median age of 52 years old (range 23-82 years old)[7]. This is caused by the aetiology of liver cirrhosis in western country, such as the United States, was mainly affected by the life style of alcohol and high fat food consumption in young age; thus,

patients were diagnosed with liver cirrhosis in younger age.[11] Patients with income above minimum regional salary (≥ 3 million Rupiah) in this study was 57.5%, This is different from the study by Davila et al which reported that the income level above minimum regional salary (>$ 32,500) were 73.1%. This is different as United State is a developed country, while Indonesia is a developing country.[5]

Subjects who underwent HCC surveillance were 50 (25.0%) patients, 33 of whom (16.5%) underwent consistent HCC surveillance and the remaining 17 (8.5%) patients performed inconsistent HCC surveillance. Meanwhile, there were 150 (75%)

patients who did not undergo HCC surveillance. Likewise, in a study by Webb et al, it was found that the surveillance rate was 21.6%.[6] In the study performed by Davila et al, the surveillance rate was reported to be 17.1%.[5] This could be caused by the assessment of surveillance in the previous 20 years period; this study classified the observation time into 1994-1996, 1997-1999, and 2000-2002 to evaluate the development of surveillance rate, and performed in private practice until tertiary hospital with all possible limited facilities and infrastructures.[5] Study by Kohli et al found that the surveillance rate was 60,9%.[7] This higher number of surveillance was caused by the study method being used which was retrospective cohort control, in which patients who had been diagnosed with HCC, a number of patients were included to receive surveillance but not for variable comparisons.[7] Study by Singal et al found patients who received surveillance was 61.3%.[8] This was also caused by the method being used in this study, which was a prospective cohort whereby a number of patients had been appointed to either receive surveillance or not.[8]

This study found that factors, such as sex, ethnic group, education level, income level, availability of health insurance, location of residency, and aetiology of liver cirrhosis were not associated with the success of HCC surveillance in patients with liver cirrhosis.

On the contrary, the education of HCC surveillance and the severity degree of liver cirrhosis were both associated with the accomplishment of HCC surveillance in liver cirrhosis. A study by Singal et al revealed that patients who received adequate education from a gastroentero-hepatologist would undergo surveillance significantly. This is caused by in primary health care, doctor usually does not educate patients correctly. The limited infrastructures to notify the patients in HCC surveillance periodically, supporting examinations in the suspicion of HCC, and curative

treatment in primary care also play roles.[8] According to a qualitative review in 102 studies performed by Jin et al, patients did not perform surveillance routinely because they did not understand completely about the disease, prevention plan, or treatment. Patients did not know the risk they are facing of neglecting the surveillance, the advantage of regular treatment visit regardless of their clinical symptoms, or only thought that the disease would merely require treatment in one period of time and would not need further monitoring. Therefore, education to patients are really important to increase adherence.[12] Studies by Kohli et al and Davila et al reported statistically significant results on analysis of subjects with high severity of liver cirrhosis influence the consistency of HCC surveillance compared to those with lower severity of liver cirrhosis.[5,7] It was stated that the more severe the clinical symptoms suffered by the subject, the more adherent they are to the surveillance and routine treatment. Conversely, if the clinical symptoms are mild, patients would feel that they did not need to undergo HCC surveillance.[5,7]

CONCLUSION

In conclusion, this study showed that the proportion of surveillance accomplishment for early detection of HCC in patients with liver cirrhosis were 25%. Factors associated with accomplishment of surveillance for early detection of HCC were education on surveillance and degree of severity of cirrhosis; while sex, ethnic group, education level, income level, availability of health insurance, location of residence, and aetiology of cirrhosis did not show any significant correlation.

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